Weight Loss and Weight Loss Maintenance in Type 2 Diabetes

KIRSTEN BERK

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Cover: painting made by Jasper Gersen of art gallery 'De Brugspin' in Ter Aar. Remake of the work 'Still life with almonds' of Maurice de Vlaminck (1907). With the addition of an insulin pen, it symbolizes the continuous struggle of a person with diabetes to balance his or her nutrition and medication, in order to achieve optimal blood glucose levels.

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Chapter 1

General introduction

THE INTERTWINED EPIDEMICS OF DIABETES AND OBESITY

The problem of overweight and obesity is vastly growing worldwide, with devastating consequences on health. For the Caucasian population, the definition of overweight is having a Body Mass Index (BMI) of 25-30 kg/m^2, and with a BMI > 30 kg/m^2 a person is considered obese (1). The World Health Organization estimated that in 2014 out of 5 billion adults worldwide nearly 2 billion were overweight or obese (figure 1) (2).

In Europe, this problem is even bigger with over 50% of both men and women being overweight or obese, and the Netherlands are unfortunately no exception (4, 5). From 1981 till 2015, the percentage of overweight Dutch adults increased from 33% to over 50%, and the percentage of adults with obesity even increased threefold to 13.7% (figure 2) (4). One of the targets of the World Health Organization for 2025 is to halt the rise in the prevalence of obesity (6), since it's a major risk factor for many other diseases such as cancers, heart diseases and in particular type 2 diabetes (T2D) (7). Persons who are overweight or obese have a three times and seven times greater risk of developing T2D, compared to those with a healthy weight (i.e. BMI 20-25 kg/m^2) (8). It is estimated that 82-87% of all people with T2D are overweight or obese (9). Worldwide, 1 in every

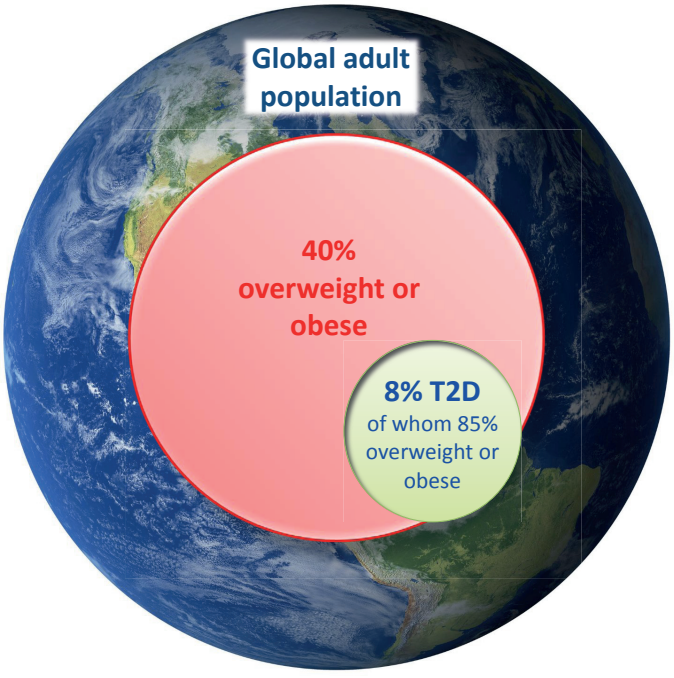

Figure 1. The global prevalence of obesity and type 2 diabetes
Source: data of the Global Nutrition Report 2016 (3)

12 adults has T2D (figure 1) (2). In the past decades, it has become more and more clear that the rise in prevalence of T2D goes alongside with the obesity epidemic (10).

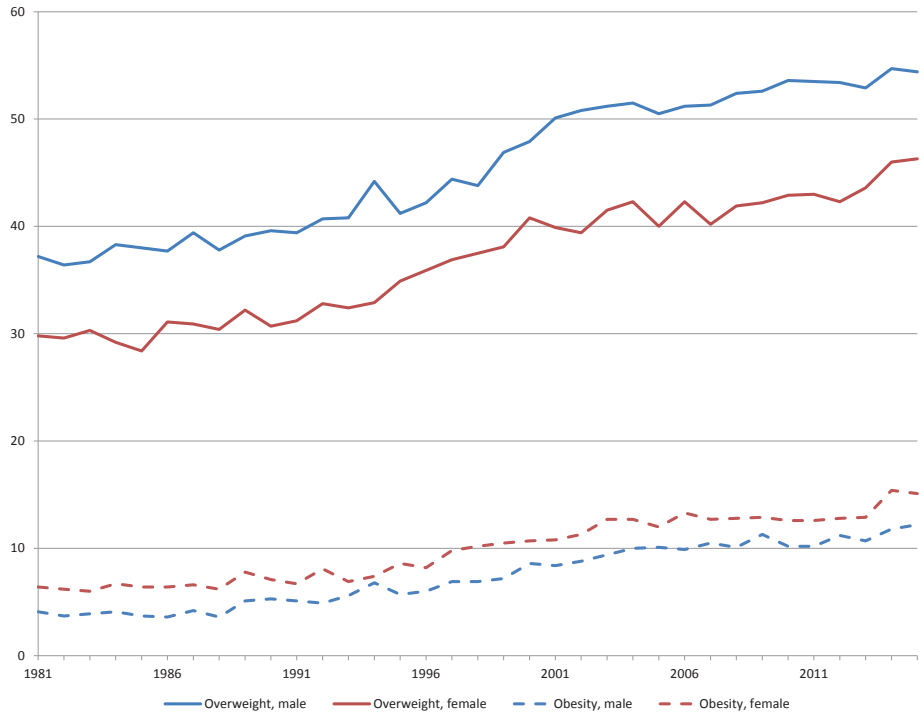

Figure 2. Percentage of adults with overweight and obesity in The Netherlands from 1981-2015 (Source: RIVM) (4).

WHAT LINKS OBESITY TO TYPE 2 DIABETES?

Since obesity and T2D are so closely related, the term 'diabesity' has been adopted by researchers in this field (11). There are several factors associated with both obesity and T2D, including over-nutrition, lack of exercise, sleep deprivation, changes in gut microbiota, changes in hormones, etc. The transition from obesity to diabetes is characterized by a progressive augmentation in insulin resistance (a decreased tissue response to insulin) coupled with a deficit in insulin secretion (figure 3). It has been well documented that an increase in white adipose tissue results in elevated plasma free fatty acids (FFA) levels (12-14). Via multiple pathways, these FFAs induce hyperinsulinemia, which is one of the first steps towards diabetes (15). Moreover, adipose tissue excretes pro-inflammatory cytokines, inducing a state of chronic inflammation typical for obesity.

This chronic inflammation and the accompanied oxidative stress also contribute to the development of insulin resistance (12-14). Moreover, oxidative stress and chronic inflammation may cause beta cell dysfunction (16). The beta cells of the pancreas will initially respond to the state of insulin resistance by increasing the production of insulin. When ultimately this compensation fails because of beta cell dysfunction, insulin insufficiency and consequently hyperglycemia will occur and the person will be diagnosed with T2D. Importantly, insulin resistance can locally induce endothelial dysfunction, eventually leading to vascular complications (figure 4) (17).

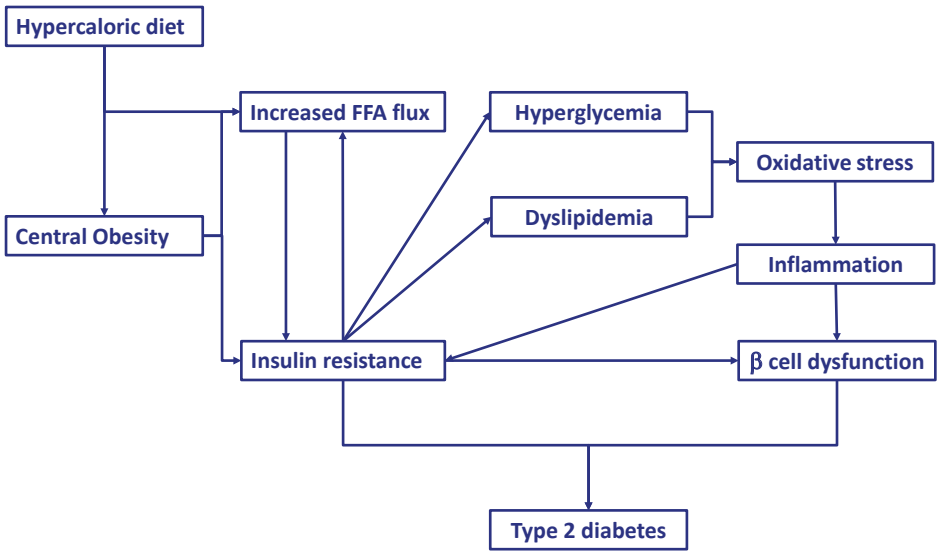

Figure 3. The effects of obesity on metabolism, leading to type 2 diabetes
Visceral adipose tissue ('central obesity') releases free fatty acids (FFA) easily into the bloodstream. A hyper caloric diet also leads to an increase in FFA. This increased FFA flux into liver and muscle promotes insulin resistance, leading to hyperglycemia and dyslipidemia, and stimulates the production of radical oxygen species inducing cell damage ('oxidative stress'), leading to a chronic low-grade inflammation. This low-grade inflammation, typical for obesity, also induces insulin resistance. Oxidative stress and chronic inflammation may cause β cell dysfunction which together with increasing insulin resistance contributes to the development of type 2 diabetes.

WHAT ARE THE CONSEQUENCES OF OBESITY?

BMI is associated with coronary heart disease and stroke: for each 5 kg/m^2 increase in BMI (above a BMI of 20 kg/m^2), the risk of developing coronary heart disease is 1.27 times higher and the risk of stroke is 1.18 times higher. These increased risks are largely mediated by high levels of cholesterol, glucose, and blood pressure (19). Obesity increases mortality and reduces healthy life years, a finding which is consistent over

four continents (20). It has been estimated that in obese people aged 20-39 years, 6 years of life are lost from diabetes and cardiovascular disease (CVD), with smaller losses in the elderly. The loss of *healthy* life years has been estimated as 2 to 4 times higher than the total life years lost (21). Moreover, adults with diabetes with an increased BMI have more vascular complications and increased mortality than those with a normal BMI (22-24). In the Swedish National Diabetes Register, 81% of the obese individuals with T2D had hyperlipidemia and 88% hypertension, both independent CVD risk factors. BMI is an independent predictor of these risk factors (25). In a large Japanese cohort study, persons with T2D and obesity were 2.2 times more likely to have diabetic nephropathy (chronic kidney disease) compared to normal weight T2D individuals, and even past obesity almost doubled the risk of nephropathy (22, 23).

Apart from health problems and the accompanied loss of quality of life, obesity and diabetes also induce loss of income for the affected individual (26, 27). For society, the economic effects of obesity and its related diseases are detrimental: in the US, direct medical costs associated with obesity were estimated to have reached 114 billion

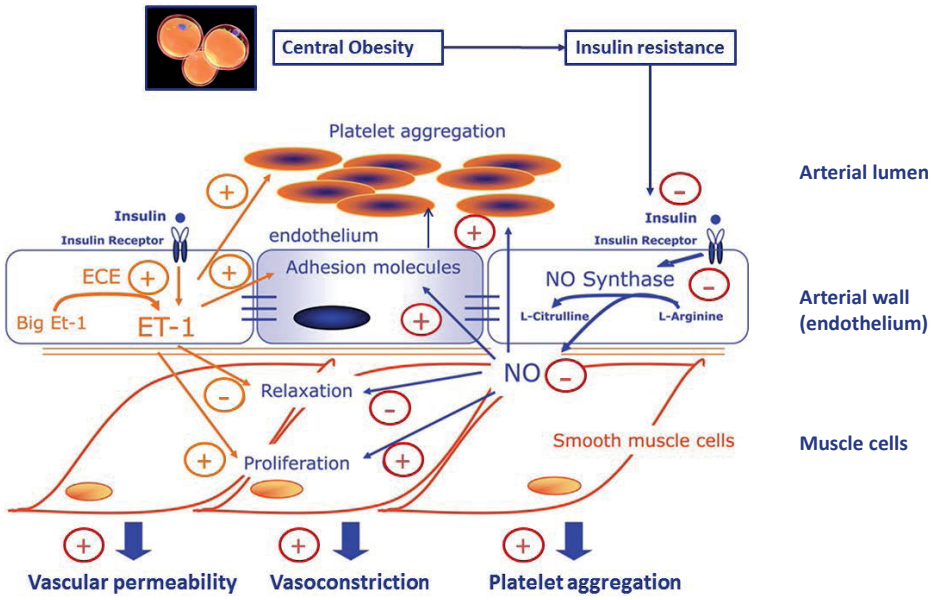

Figure 4. The effects of obesity on vascular function. Adapted from: Potenza et al. (18)
Central obesity induces insulin resistance. Local insulin resistance of the endothelium decreases the production of nitric oxide (NO) and stimulates the secretion of endothelin-1 (ET-1) from endothelial cells. As a result, the endothelium produces more adhesion molecules (for example soluble vascular cell adhesion molecule 1 (sVCAM-1) and soluble intercellular adhesion molecule 1 (sICAM-1)) and molecules enhancing platelet aggregation, like von Willebrand Factor (vWF), leading to an enhanced permeability of the endothelium, and more vasoconstriction and platelet aggregation. These changes can eventually lead to vascular complications and cardiovascular disease.

dollars annually in 2008 (28). For the Netherlands in 2016, the direct medical costs of overweight, obesity and related diseases were estimated to be 1.7 billion euro (29). The largest part of this amount was spent on cardiovascular diseases and diabetes (29, 30).

Taken together, it is utterly important to reduce the global burden of obesity as well as diabetes. Unfortunately, recent global reports show that the rise in BMI still continues and that 'the probability of meeting the global obesity target is virtually zero' (31).

WHAT CAN BE DONE ABOUT OBESITY AND OBESITY-RELATED TYPE 2 DIABETES?

Lifestyle interventions

Since obesity and overweight are caused by an energy imbalance due to an increase in food intake and a decrease in physical activity, it seems logical to search for interventions in nutrition and exercise. There is strong and consistent evidence that weight loss via diet and/or exercise can delay the onset of T2D (32, 33). In obesity-related T2D, lifestyle interventions aimed at weight loss have been shown to improve hyperglycemia, hyperlipidemia, hypertension, proteinuria, obstructive sleep apnea and quality of life, and to reduce the need for medications (34-41). In a prospective study in 4970 overweight individuals with diabetes, intentional weight loss was associated with a 25% reduction in overall mortality compared with weight stable individuals (42). However, in the only RCT conducted investigating the effect of an intensive lifestyle intervention on cardiovascular events (the Look AHEAD trial), no effect has been shown (43). This study has several limitations, potentially diminishing the effect, such as the non-blinded design, the higher use of cardio protective drugs in the control arm and the modest weight loss difference between the study arms because of weight regain. Behavioral lifestyle interventions typically include a diet with an energy-deficit of at least 500 kcal a day, daily exercise and behavioral interventions. Effective weight loss diets include low-fat diets, low-carbohydrate diets, high-protein diets and Mediterranean diets (43-47). In the guideline 'obesity management for the treatment of T2D' of the American Diabetes Association (48) it is stated that all these diets are equally effective if they create the same energy deficit. It was also stated that very low-calorie diets (VLCDs; a diet with an energy-intake limited to 450-800 kcal per day (49)) produce the greatest energy deficit, and thus the most weight loss, and are safe to use in T2D with close medical monitoring (48). These VLCDs normally consist of 2 or 3 meal replacements per day and at least 50 grams of protein and daily requirements of vitamins and minerals. A VLCD is typically low in carbohydrates as well as in fat content. In a recent meta-analysis, the authors found that VLCDs induce more weight loss in obese people with T2D compared to usual care or compared to low calorie diets, with similar levels of adherence (50). Remarkably, a

VLCD has been shown to normalize both beta cell function and hepatic insulin sensitivity, hereby reversing the abnormalities underlying T2D (51).

Anti-obesity drugs and bariatric surgery

Over the past decades, researchers have tried to find a pharmaceutical treatment for obesity and diabetes. Long term interventions with anti-obesity medications showed that they are modestly effective in reducing weight and CVD risk factors, at the expense of side effects such as gastro-intestinal complaints, raised blood pressure and pulse rate, and mood disorders (52, 53). Many of these drugs have already been withdrawn from the market because of safety concerns. New anti-diabetes treatments as glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidylpeptidase IV (DPP-4) inhibitors and sodium glucose cotransporter-2 (SGLT-2) inhibitors are very promising, achieving positive effects on both weight and glucose control in adults with diabetes (54). But also in obese individuals without T2D, GLP-1 receptor agonists have been shown to effectively decrease weight and reverse the pre-diabetes state (55).

Bariatric surgery is a therapeutic option for individuals with obesity and obesity-related T2D, resulting in favorable long-term outcomes on weight, diabetes remission and CVD risk profile (56-58). The gastric bypass procedure shows better results on weight and blood glucose levels than the gastric sleeve and gastric banding procedure (59, 60). Long-term data on survival, mental health and complications are currently lacking, making gastric surgery not the first treatment option for obese persons. For persons with T2D in the Netherlands, bariatric surgery is only reimbursed by the health insurers in case of severe obesity (BMI > 35).

INDIVIDUAL DIFFERENCES IN THE EFFECTIVENESS OF WEIGHT LOSS DIETS

Although energy restricted diets are successful in reducing weight in obesity-related T2D, not all individuals equally benefit. There is a tremendous intra-individual variability in the effect of weight loss interventions: a substantial percentage of individuals is unsuccessful in reducing weight via lifestyle interventions (61). Although the exact mechanisms underlying this variance are unknown, a number of predictors of weight loss have been identified over the past decades. However, these predictors only explain 20-30% of the variance in weight loss (62). Moreover, these predictors have been studied in the obese non-diabetic population, and obviously without including variables specific for diabetes. Since obesity-related T2D is a complex multifactorial disorder, a combination of psychological and physiological predictors of weight loss is hypothetically needed to explain a larger part of the variance of the efficacy of weight loss programs.

THE EFFECT OF WEIGHT LOSS DIETING ON CARDIOVASCULAR DISEASE RISK FACTORS

Classical cardiovascular disease (CVD) risk factors, such as high blood pressure, high blood glucose levels and an unfavorable lipid profile, are independently associated with both obesity and CVD, but they do not fully explain the association between overweight or obesity and cardiovascular disease (19). In addition to these classic CVD risk factors, atherosclerosis may be aggravated by other factors, such as systemic inflammation and endothelial dysfunction, which are typical for overweight and obese individuals (17, 63). Visceral fat mass secretes pro-inflammatory cytokines and induces a free fatty acid (FFA) flux, subsequently leading to oxidative stress, insulin resistance and endothelial dysfunction (figure 3 and 4) (12). Impaired vascular function is an independent predictor of adverse cardiovascular outcomes (64, 65). In T2D, endothelial dysfunction and systemic inflammation have been linked to vascular complications and mortality (17, 66-72).

Diet-induced weight loss improves the classical CVD risk factors in overweight and obese adults with and without T2D (35-38). Moreover, weight loss improves vascular function and alleviates the inflammatory state (44, 63, 73-79). Individuals with T2D often receive multiple cardio-protective agents, such as metformin, statins and ACE-inhibitors, which also have been shown to improve endothelial function and chronic inflammation (17). It is unknown whether diet-induced weight loss still has an effect on endothelial function in T2D adults, who are on (maximum) cardio-protective medical treatment. Moreover, it is unknown if weight loss still has beneficial effects on endothelial function and inflammation at progressed stages of the disease.

A number of new candidate biomarkers for CVD risk have emerged and the effect of weight loss on these markers is fully unknown. Among them is lipoprotein(a) [lp(a)], an LDL-like particle with an additional apolipoprotein(a) molecule attached to it. High plasma Lp(a) concentration is an independent CVD risk factor, especially in individuals with T2D (80-85). Another example of a new biomarker for vascular impairment is low density lipoprotein receptor-relative with 11 ligand-binding repeats (LR11, also called SorLA or SORL1). LR11 is a type I membrane protein, which after proteolytic cleavage sheds a large soluble extracellular part called sLR11 into the circulation. LR11 and sLR11 have been shown to play a role in energy metabolism, atherosclerosis, and plaque formation (86-90). Increased plasma levels of sLR11 correlate with BMI and overall adipose tissue mass. In T2D, sLR11 correlates with coronary artery disease and retinopathy (91-93). The effect of weight loss on plasma levels of sLR11 has not been investigated before.

THE PROBLEM OF WEIGHT REGAIN

As abovementioned, diet-induced weight loss improves CVD risk factors in overweight and obese individuals with T2D. However, in the Look AHEAD trial an intensive lifestyle intervention did not result in any effect on CVD events after 10 years of follow-up in adults with T2D, despite short-term favorable effects on CVD risk factors. Possible explanations of this lack of effect might have been the gradual regain of weight during follow-up or the use of cardio protective medication (43).

Weight regain after successful weight loss is a substantial problem in the treatment of obesity (94, 95). Almost anyone who has ever lost weight can confirm that it is more difficult to maintain weight loss than to lose weight. After a successful weight loss diet, only 20-50% of the dieters manages to maintain a clinically relevant weight loss of 5-10% for more than 1 year (96, 97). Physiological reasons for weight regain include a decline in resting energy expenditure (98), increase of specific neural signals in the brain, leading to increased appetite and decreased non-resting energy expenditure (99-101), and changes in hormones like leptin, ghrelin and insulin, increasing hunger signals and promoting energy storage (95, 97).

Apart from these physiological explanations for the difficulty of weight loss maintenance, also environmental and behavioral barriers have been identified (61, 95). We live in an 'obesogenic' environment, in which overconsumption of energy-dense foods is encouraged by their abundant availability, oversized portions and aggressive marketing (102). Above this, inactivity has become the standard due to our sedentary jobs, mechanized labor and motorized transportation (103). Successful weight loss maintainers have been shown to continue exercising on a daily basis and consuming an energy-balanced diet, even after they have reached their weight loss goal (104). Personal motivation, self-efficacy (the belief that one is able to successfully change one's behavior) and behavioral techniques as self-monitoring and planning have been shown very important in that respect (105, 106). In the conventional treatment of obesity, dietitians personalize a weight loss diet to the individual needs and wishes, while applying different kinds of behavioral techniques, such as self-monitoring, planning, peer support, goal setting, etc. (107). Nonetheless, the adherence to the prescribed lifestyle regimen often decreases over time, possibly because the perceived 'costs' eventually outweigh the perceived 'benefits' of the lifestyle change (61). A permanent behavioral change is needed, and therefore, behavioral therapy is an important part of long-term weight management programs.

COGNITIVE BEHAVIORAL THERAPY IN WEIGHT LOSS AND MAINTENANCE

In this thesis, I focus on Cognitive Behavioral Therapy (CBT). CBT is a psychological approach to behavior change, aimed at identifying and changing aversive thinking patterns and mood states using behavioral experiments and challenges. It is widely used in the treatment of psychological disorders including eating disorders (108-110). Cognitive approaches to weight loss and maintenance focus on identifying dysfunctional cognitions and beliefs that affect lifestyle, like thoughts regarding self-image, diet, exercise, unrealistic goal-setting and prior relapses. In cognitive behavioral (group) therapy (CB(G)T), these thoughts are identified and modified in order to facilitate behavioral change and subsequently weight loss and maintenance. For example, all-or-nothing thinking ('I ate one cookie, so my diet is ruined for today. I might as well eat the whole lot') is a common dysfunctional thinking pattern of unsuccessful dieters (111, 112). With cognitive restructuring, these thoughts can be challenged and replaced by more realistic ones, ultimately facilitating behavior leading to weight loss. CB(G)T has been shown to effectively reduce weight in obese individuals without diabetes, mostly when combined with diet and/or exercise (36, 111, 113-121). In international clinical guidelines for the management of obesity, CBT or 'cognitive restructuring' is recommended as a behavioral treatment option to facilitate weight loss (122, 123). Also in adults with type 2 diabetes, one prospective and one retrospective cohort study showed favorable effects of CBGT on long-term weight loss, when combined with other lifestyle interventions (124, 125). Other specific cognitive behavioral strategies as Proactive Coping and Problem Solving Therapy have also been shown to enable weight loss (126, 127). CBT can be provided one-on-one or in a group. The advantages of individual therapy are more personal attention and possibly less drop-out, while group therapy provides social support and is less costly. In obesity research, individual CBT has been shown equally or less effective than CBGT (128-131).

Apart from promoting weight loss, there is some evidence that CBGT is effective in maintaining weight, or reducing weight regain, after losing weight via diet (116, 117). Sbrocco et al. (117) showed that in 24 obese women, who lost weight via an intervention focusing on diet and exercise, weight regain occurred in the group randomized to traditional behavioral treatment (control condition), while in the group with a CBGT-based intervention, a continued slow weight loss was seen during follow-up. In the study of Werrij et al. (116), 204 overweight and obese participants lost on average 5% of their bodyweight via diet. Subsequently, they were randomly assigned to diet plus CBGT or diet plus exercise (control). After a 1-year follow-up, CBGT was effective in maintaining diet-induced weight loss, while exercise alone was not. Abovementioned studies were conducted in non-diabetic obese participants only, so whether a CBGT

intervention is effective in reducing weight regain after weight loss dieting in adults with T2D is unknown.

THE CURRENT THESIS: LONG-TERM EFFECTIVENESS OF CBGT ON WEIGHT MAINTENANCE IN T2D

In this thesis, I studied whether CBGT is effective in preventing weight regain during 2 years after VLCD-induced weight loss in overweight and obese adults with T2D. Further, I determined which physiological and psychological factors predict successful diet-induced weight loss in overweight and obese T2D individuals, and the effect of short-term weight loss on specific CVD risk markers and the interaction with cardio-protective medication.

Aims of this thesis

The primary aim of the current thesis is:

- To determine the effect of cognitive behavioral group therapy on maintaining weight during 2 years of follow-up after weight loss via a very low-calorie diet in overweight and obese adults with type 2 diabetes.

The secondary aims are:

- To evaluate the effects of cognitive behavioral group therapy on cardiovascular risk factors and psychological wellbeing during 2 years of follow-up after weight loss via a very low-calorie diet.
- To determine which individuals benefit most from a very low-calorie diet.
- To determine the short-term effect of diet-induced weight loss on glycemic parameters and cardiovascular disease risk factors.

To this end, we set up the Prevention Of Weight Regain (POWER) trial, which is a 2-phase study in overweight and obese adults with T2D from a single tertiary center, the Erasmus Medical Center, Rotterdam, the Netherlands. During the first phase, participants followed a very low-calorie diet (VLCD) for 8 weeks. The participants, who successfully lost weight via the VLCD, entered the second phase with a duration of 2 years. At the start of the second phase, the participants were randomized to CBGT or usual care. After the first phase, all participants continued with a low-calorie diet (LCD) for 12 weeks, and thereafter a diet aiming at weight maintenance was advised. At the end of the first phase, we examined which characteristics best predicted successful weight loss, and assessed the effect of the diet-induced weight loss on glycemic parameters and CVD risk factors. During and at the end of the second phase, we determined the effect of CBGT on weight regain.

Outline of this thesis

Chapter 2 examines which physiological and psychological variables predict short term diet-induced weight loss, and whether a prediction model of VLCD-induced weight loss in T2D can be developed.

In chapter 3, I report the effect of diet-induced weight loss on classical cardiovascular risk factors and biomarkers of endothelial dysfunction and inflammation in overweight and obese adults with T2D. In addition, we investigated whether this effect was influenced by the use of cardio-protective drugs (statins, ACE inhibitors, metformin) and the duration of T2D.

The effects of diet-induced weight loss on sLR11 and Lp(a) in T2D are unknown. Chapter 4 focusses on the effect of diet-induced weight loss on plasma sLR11 levels in overweight and obese individuals with T2D.

In chapter 5, we examine the effect of weight loss via diet or bariatric surgery on Lp(a) levels in overweight and obese individuals with and without T2D. The effect of diet was assessed in the participants of the POWER trial, in an independent cohort of overweight and obese subjects with T2D, and in a cohort of obese subjects without T2D. The effect of bariatric surgery was assessed in a cohort of obese subjects without T2D.

Chapter 6 is the protocol of the Prevention Of Weight Regain (POWER) trial, in which we describe the rationale of the study, the interventions, sample size calculations, randomization, methods of statistical analyzation and pilot data.

In chapter 7, I report the results of the POWER trial, in which we investigated the 2-years efficacy of CBGT compared to usual care, in preventing weight regain after a VLCD in overweight and obese adults with T2D.

In chapter 8, I discuss the main findings of this thesis and place them in a broader perspective: methodological considerations, potential clinical implications, including the results of an implementation study of VLCD, and future research are the main topics.

REFERENCES

1. World Health Organization. BMI classifications 2016 [Available from: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html].
2. World Health Organization. Obesity and Overweight 2016 [updated June 2016. Available from: www.who.int/mediacentre/factsheets/fs311/en/].
3. International Food Policy Research Institute. Global Nutrition Report 2016: From Promise to Impact: Ending Malnutrition by 2030. Washington, DC: 2016.
4. RIVM. Overgewicht volwassenen: Volksgezondheidszorg.info; 2015 [Available from: https://www.volksgezondheidenzorg.info/onderwerp/overgewicht/cijfers-context/huidige-situatie].
5. World Health Organization. Obesity: data and statistics: WHO; 2016 [Available from: http://www.euro.who.int/en/health-topics/noncommunicable-diseases/obesity/data-and-statistics].
6. World Health Organization. Global Status Report on Noncommunicable Diseases 2014 [Available from: http://apps.who.int/iris/bitstream/10665/148114/1/9789241564854_eng.pdf?ua=1].
7. Field AE, Coakley EH, Must A, Spadano JL, Laird N, Dietz WH, et al. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. Arch Intern Med. 2001;161(13):1581-6.
8. Abdullah A, Peeters A, de Courten M, Stoelwinder J. The magnitude of association between overweight and obesity and the risk of diabetes: a meta-analysis of prospective cohort studies. Diabetes Res Clin Pract. 2010;89(3):309-19.
9. Bays HE, Chapman RH, Grandy S, Group SI. The relationship of body mass index to diabetes mellitus, hypertension and dyslipidaemia: comparison of data from two national surveys. Int J Clin Pract. 2007;61(5):737-47.
10. Gregg EW, Cheng YJ, Narayan KM, Thompson TJ, Williamson DF. The relative contributions of different levels of overweight and obesity to the increased prevalence of diabetes in the United States: 1976-2004. Prev Med. 2007;45(5):348-52.
11. Astrup A, Finer N. Redefining type 2 diabetes: 'diabesity' or 'obesity dependent diabetes mellitus'? Obes Rev. 2000;1(2):57-9.
12. McArdle MA, Finucane OM, Connaughton RM, McMorrow AM, Roche HM. Mechanisms of obesity-induced inflammation and insulin resistance: insights into the emerging role of nutritional strategies. Front Endocrinol (Lausanne). 2013;4:52.
13. Abranches MV, Oliveira FC, Conceicao LL, Peluzio MD. Obesity and diabetes: the link between adipose tissue dysfunction and glucose homeostasis. Nutr Res Rev. 2015;28(2):121-32.
14. Verma S, Hussain ME. Obesity and diabetes: An update. Diabetes Metab Syndr. 2016.
15. Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP. Prospective analysis of the insulin-resistance syndrome (syndrome X). Diabetes. 1992;41(6):715-22.
16. Khodabandehloo H, Gorgani-Firuzjaee S, Panahi G, Meshkani R. Molecular and cellular mechanisms linking inflammation to insulin resistance and beta-cell dysfunction. Transl Res. 2016;167(1):228-56.
17. Tousoulis D, Papageorgiou N, Androulakis E, Siasos G, Latsios G, Tentolouris K, et al. Diabetes mellitus-associated vascular impairment: novel circulating biomarkers and therapeutic approaches. J Am Coll Cardiol. 2013;62(8):667-76.
18. Potenza MA, Addabbo F, Montagnani M. Vascular actions of insulin with implications for endothelial dysfunction. Am J Physiol Endocrinol Metab. 2009;297(3):E568-77.

19. Global Burden of Metabolic Risk Factors for Chronic Diseases C, Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, et al. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants. Lancet. 2014;383(9921):970-83.
20. Global BMI Mortality Collaboration. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet. 2016;388(10046):776-86.
21. Grover SA, Kaouache M, Rempel P, Joseph L, Dawes M, Lau DC, et al. Years of life lost and healthy life-years lost from diabetes and cardiovascular disease in overweight and obese people: a modelling study. Lancet Diabetes Endocrinol. 2015;3(2):114-22.
22. Tanaka S, Tanaka S, Iimuro S, Ishibashi S, Yamashita H, Moriya T, et al. Maximum BMI and microvascular complications in a cohort of Japanese patients with type 2 diabetes: the Japan Diabetes Complications Study. J Diabetes Complications. 2016;30(5):790-7.
23. Tanaka S, Tanaka S, Iimuro S, Yamashita H, Katayama S, Akanuma Y, et al. Predicting macro- and microvascular complications in type 2 diabetes: the Japan Diabetes Complications Study/the Japanese Elderly Diabetes Intervention Trial risk engine. Diabetes Care. 2013;36(5):1193-9.
24. Tobias DK, Pan A, Jackson CL, O'Reilly EJ, Ding EL, Willett WC, et al. Body-mass index and mortality among adults with incident type 2 diabetes. N Engl J Med. 2014;370(3):233-44.
25. Ridderstrale M, Gudbjornsdottir S, Eliasson B, Nilsson PM, Cederholm J, Steering Committee of the Swedish National Diabetes R. Obesity and cardiovascular risk factors in type 2 diabetes: results from the Swedish National Diabetes Register. J Intern Med. 2006;259(3):314-22.
26. Su W, Huang J, Chen F, Iacobucci W, Mocarski M, Dall TM, et al. Modeling the clinical and economic implications of obesity using microsimulation. J Med Econ. 2015;18(11):886-97.
27. Tunceli K, Bradley CJ, Nerenz D, Williams LK, Pladevall M, Elston Lafata J. The impact of diabetes on employment and work productivity. Diabetes Care. 2005;28(11):2662-7.
28. Tsai AG, Williamson DF, Glick HA. Direct medical cost of overweight and obesity in the USA: a quantitative systematic review. Obes Rev. 2011;12(1):50-61.
29. Lette M, Bemelmans WJ, Breda J, Slobbe LC, Dias J, Boshuizen HC. Health care costs attributable to overweight calculated in a standardized way for three European countries. Eur J Health Econ. 2016;17(1):61-9.
30. in 't Panhuis-Plasmans M. Zorgkosten van ongezond gedrag. RIVM, 2012.
31. Collaboration NCDRF. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet. 2016;387(10026):1377-96.
32. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346(6):393-403.
33. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001;344(18):1343-50.
34. Look Ahead Research Group. Eight-year weight losses with an intensive lifestyle intervention: the look AHEAD study. Obesity (Silver Spring). 2014;22(1):5-13.
35. Anderson JW, Kendall CW, Jenkins DJ. Importance of weight management in type 2 diabetes: review with meta-analysis of clinical studies. J Am Coll Nutr. 2003;22(5):331-9.

36. Norris SL, Zhang X, Avenell A, Gregg E, Brown TJ, Schmid CH, et al. Long-term non-pharmacologic weight loss interventions for adults with type 2 diabetes. Cochrane Database Syst Rev. 2005(2):CD004095.
37. Tzotzas T, Evangelou P, Kiortsis DN. Obesity, weight loss and conditional cardiovascular risk factors. Obes Rev. 2011;12(5):e282-9.
38. Wing RR, Lang W, Wadden TA, Safford M, Knowler WC, Bertoni AG, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care. 2011;34(7):1481-6.
39. Kuna ST, Reboussin DM, Borradaile KE, Sanders MH, Millman RP, Zammit G, et al. Long-term effect of weight loss on obstructive sleep apnea severity in obese patients with type 2 diabetes. Sleep. 2013;36(5):641-9A.
40. Navaneethan SD, Yehnert H, Moustarah F, Schreiber MJ, Schauer PR, Beddhu S. Weight loss interventions in chronic kidney disease: a systematic review and meta-analysis. Clin J Am Soc Nephrol. 2009;4(10):1565-74.
41. Redmon JB, Bertoni AG, Connelly S, Feeney PA, Glasser SP, Glick H, et al. Effect of the look AHEAD study intervention on medication use and related cost to treat cardiovascular disease risk factors in individuals with type 2 diabetes. Diabetes Care. 2010;33(6):1153-8.
42. Williamson DF, Thompson TJ, Thun M, Flanders D, Pamuk E, Byers T. Intentional weight loss and mortality among overweight individuals with diabetes. Diabetes Care. 2000;23(10):1499-504.
43. Look Ahead Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med. 2013;369(2):145-54.
44. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, et al. Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. Jama. 2004;292(12):1440-6.
45. Metz JA, Stern JS, Kris-Etherton P, Reusser ME, Morris CD, Hatton DC, et al. A randomized trial of improved weight loss with a prepared meal plan in overweight and obese patients: impact on cardiovascular risk reduction. Arch Intern Med. 2000;160(14):2150-8.
46. Krebs JD, Elley CR, Parry-Strong A, Lunt H, Drury PL, Bell DA, et al. The Diabetes Excess Weight Loss (DEWL) Trial: a randomised controlled trial of high-protein versus high-carbohydrate diets over 2 years in type 2 diabetes. Diabetologia. 2012;55(4):905-14.
47. Larsen RN, Mann NJ, Maclean E, Shaw JE. The effect of high-protein, low-carbohydrate diets in the treatment of type 2 diabetes: a 12 month randomised controlled trial. Diabetologia. 2011;54(4):731-40.
48. American Diabetes Association. 7. Obesity Management for the Treatment of Type 2 Diabetes. Diabetes Care. 2017;40(Suppl 1):S57-S63.
49. Baker S, Jerums G, Proietto J. Effects and clinical potential of very-low-calorie diets (VLCDs) in type 2 diabetes. Diabetes Res Clin Pract. 2009;85(3):235-42.
50. Rehackova L, Arnott B, Araujo-Soares V, Adamson AA, Taylor R, Sniehotta FF. Efficacy and acceptability of very low energy diets in overweight and obese people with Type 2 diabetes mellitus: a systematic review with meta-analyses. Diabet Med. 2016;33(5):580-91.
51. Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Diabetologia. 2011;54(10):2506-14.
52. Patel D. Pharmacotherapy for the management of obesity. Metabolism. 2015;64(11):1376-85.

53. Padwal R, Li SK, Lau DC. Long-term pharmacotherapy for obesity and overweight. Cochrane Database Syst Rev. 2003(4):CD004094.

54. Scheen AJ, Van Gaal LF. Combating the dual burden: therapeutic targeting of common pathways in obesity and type 2 diabetes. Lancet Diabetes Endocrinol. 2014;2(11):911-22.

55. Iepsen EW, Torekov SS, Holst JJ. Therapies for inter-relating diabetes and obesity - GLP-1 and obesity. Expert Opin Pharmacother. 2014;15(17):2487-500.

56. Eliasson B, Liakopoulos V, Franzen S, Naslund I, Svensson AM, Ottosson J, et al. Cardiovascular disease and mortality in patients with type 2 diabetes after bariatric surgery in Sweden: a nation-wide, matched, observational cohort study. Lancet Diabetes Endocrinol. 2015;3(11):847-54.

57. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Brethauer SA, Navaneethan SD, et al. Bariatric surgery versus intensive medical therapy for diabetes–3-year outcomes. N Engl J Med. 2014;370(21):2002-13.

58. Courcoulas AP, Yanovski SZ, Bonds D, Eggerman TL, Horlick M, Staten MA, et al. Long-term outcomes of bariatric surgery: a National Institutes of Health symposium. JAMA Surg. 2014;149(12):1323-9.

59. Demaria EJ, Winegar DA, Pate VW, Hutcher NE, Ponce J, Pories WJ. Early postoperative outcomes of metabolic surgery to treat diabetes from sites participating in the ASMBS bariatric surgery center of excellence program as reported in the Bariatric Outcomes Longitudinal Database. Ann Surg. 2010;252(3):559-66; discussion 66-7.

60. Lee WJ, Chong K, Ser KH, Lee YC, Chen SC, Chen JC, et al. Gastric bypass vs sleeve gastrectomy for type 2 diabetes mellitus: a randomized controlled trial. Arch Surg. 2011;146(2):143-8.

61. MacLean PS, Wing RR, Davidson T, Epstein L, Goodpaster B, Hall KD, et al. NIH working group report: Innovative research to improve maintenance of weight loss. Obesity (Silver Spring). 2015;23(1):7-15.

62. Stubbs J, Whybrow S, Teixeira P, Blundell J, Lawton C, Westenhoefer J, et al. Problems in identifying predictors and correlates of weight loss and maintenance: implications for weight control therapies based on behaviour change. Obes Rev. 2011;12(9):688-708.

63. Brook RD. Obesity, weight loss, and vascular function. Endocrine. 2006;29(1):21-5.

64. Widlansky ME, Gokce N, Keaney JF, Jr., Vita JA. The clinical implications of endothelial dysfunction. J Am Coll Cardiol. 2003;42(7):1149-60.

65. Verma S, Buchanan MR, Anderson TJ. Endothelial function testing as a biomarker of vascular disease. Circulation. 2003;108(17):2054-9.

66. Stehouwer CD, Gall MA, Twisk JW, Knudsen E, Emeis JJ, Parving HH. Increased urinary albumin excretion, endothelial dysfunction, and chronic low-grade inflammation in type 2 diabetes: progressive, interrelated, and independently associated with risk of death. Diabetes. 2002;51(4):1157-65.

67. Kanai A, Kawamura T, Umemura T, Nagashima M, Nakamura N, Nakayama M, et al. Association between future events of brain infarction and soluble levels of intercellular adhesion molecule-1 and C-reactive protein in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract. 2008;82(2):157-64.

68. Schillinger M, Exner M, Amighi J, Mlekusch W, Sabeti S, Rumpold H, et al. Joint effects of C-reactive protein and glycated hemoglobin in predicting future cardiovascular events of patients with advanced atherosclerosis. Circulation. 2003;108(19):2323-8.

69. Schulze MB, Rimm EB, Li T, Rifai N, Stampfer MJ, Hu FB. C-reactive protein and incident cardiovascular events among men with diabetes. Diabetes Care. 2004;27(4):889-94.

70. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, 3rd, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003;107(3):499-511.

71. Frankel DS, Meigs JB, Massaro JM, Wilson PW, O'Donnell CJ, D'Agostino RB, et al. Von Willebrand factor, type 2 diabetes mellitus, and risk of cardiovascular disease: the framingham offspring study. Circulation. 2008;118(24):2533-9.

72. Eringa EC, Serne EH, Meijer RI, Schalkwijk CG, Houben AJ, Stehouwer CD, et al. Endothelial dysfunction in (pre)diabetes: characteristics, causative mechanisms and pathogenic role in type 2 diabetes. Rev Endocr Metab Disord. 2013;14(1):39-48.

73. Bigornia SJ, Farb MG, Tiwari S, Karki S, Hamburg NM, Vita JA, et al. Insulin status and vascular responses to weight loss in obesity. J Am Coll Cardiol. 2013;62(24):2297-305.

74. Raitakari M, Ilvonen T, Ahotupa M, Lehtimaki T, Harmoinen A, Suominen P, et al. Weight reduction with very-low-caloric diet and endothelial function in overweight adults: role of plasma glucose. Arterioscler Thromb Vasc Biol. 2004;24(1):124-8.

75. Barzilay JI, Forsberg C, Heckbert SR, Cushman M, Newman AB. The association of markers of inflammation with weight change in older adults: the Cardiovascular Health Study. Int J Obes (Lond). 2006;30(9):1362-7.

76. Belza A, Toubro S, Stender S, Astrup A. Effect of diet-induced energy deficit and body fat reduction on high-sensitive CRP and other inflammatory markers in obese subjects. Int J Obes (Lond). 2009;33(4):456-64.

77. Hamdy O, Ledbury S, Mullooly C, Jarema C, Porter S, Ovalle K, et al. Lifestyle modification improves endothelial function in obese subjects with the insulin resistance syndrome. Diabetes Care. 2003;26(7):2119-25.

78. Wycherley TP, Brinkworth GD, Noakes M, Buckley JD, Clifton PM. Effect of caloric restriction with and without exercise training on oxidative stress and endothelial function in obese subjects with type 2 diabetes. Diabetes Obes Metab. 2008;10(11):1062-73.

79. Thompson D, Walhin JP, Batterham AM, Stokes KA, Cooper AR, Andrews RC. Effect of diet or diet plus physical activity versus usual care on inflammatory markers in patients with newly diagnosed type 2 diabetes: the Early ACTivity In Diabetes (ACTID) randomized, controlled trial. J Am Heart Assoc. 2014;3(3):e000828.

80. Hopewell JC, Seedorf U, Farrall M, Parish S, Kyriakou T, Goel A, et al. Impact of lipoprotein(a) levels and apolipoprotein(a) isoform size on risk of coronary heart disease. J Intern Med. 2014;276(3):260-8.

81. Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. Circulation. 2008;117(2):176-84.

82. Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Elevated lipoprotein(a) and risk of aortic valve stenosis in the general population. J Am Coll Cardiol. 2014;63(5):470-7.

83. Bennet A, Di Angelantonio E, Erqou S, Eiriksdottir G, Sigurdsson G, Woodward M, et al. Lipoprotein(a) levels and risk of future coronary heart disease: large-scale prospective data. Arch Intern Med. 2008;168(6):598-608.

84. Hiraga T, Kobayashi T, Okubo M, Nakanishi K, Sugimoto T, Ohashi Y, et al. Prospective study of lipoprotein(a) as a risk factor for atherosclerotic cardiovascular disease in patients with diabetes. Diabetes Care. 1995;18(2):241-4.

85. Waldeyer C, Makarova N, Zeller T, Schnabel RB, Brunner FJ. Lipoprotein(a) and the Risk of Cardiovascular Disease in the European Population – Results from the BiomarCaRE Consortium. European Heart Journal. 2017 Apr 24. doi: 10.1093/eurheartj/ehx166.

86. Ohwaki K, Bujo H, Jiang M, Yamazaki H, Schneider WJ, Saito Y. A secreted soluble form of LR11, specifically expressed in intimal smooth muscle cells, accelerates formation of lipid-laden macrophages. Arterioscler Thromb Vasc Biol. 2007;27(5):1050-6.

87. Zhu Y, Bujo H, Yamazaki H, Hirayama S, Kanaki T, Takahashi K, et al. Enhanced expression of the LDL receptor family member LR11 increases migration of smooth muscle cells in vitro. Circulation. 2002;105(15):1830-6.

88. Zhu Y, Bujo H, Yamazaki H, Ohwaki K, Jiang M, Hirayama S, et al. LR11, an LDL receptor gene family member, is a novel regulator of smooth muscle cell migration. Circ Res. 2004;94(6):752-8.

89. Jiang M, Bujo H, Ohwaki K, Unoki H, Yamazaki H, Kanaki T, et al. Ang II-stimulated migration of vascular smooth muscle cells is dependent on LR11 in mice. J Clin Invest. 2008;118(8):2733-46.

90. Whittle AJ, Jiang M, Peirce V, Relat J, Virtue S, Ebinuma H, et al. Soluble LR11/SorLA represses thermogenesis in adipose tissue and correlates with BMI in humans. Nat Commun. 2015;6:8951.

91. Takahashi M, Bujo H, Jiang M, Noike H, Saito Y, Shirai K. Enhanced circulating soluble LR11 in patients with coronary organic stenosis. Atherosclerosis. 2010;210(2):581-4.

92. Takahashi M, Bujo H, Shiba T, Jiang M, Maeno T, Shirai K. Enhanced circulating soluble LR11 in patients with diabetic retinopathy. Am J Ophthalmol. 2012;154(1):187-92.

93. Ogita M, Miyauchi K, Dohi T, Tsuboi S, Miyazaki T, Yokoyama T, et al. Increased circulating soluble LR11 in patients with acute coronary syndrome. Clin Chim Acta. 2013;415:191-4.

94. Dombrowski SU, Knittle K, Avenell A, Araujo-Soares V, Sniehotta FF. Long term maintenance of weight loss with non-surgical interventions in obese adults: systematic review and meta-analyses of randomised controlled trials. Bmj. 2014;348:g2646.

95. Greenway FL. Physiological adaptations to weight loss and factors favouring weight regain. Int J Obes (Lond). 2015;39(8):1188-96.

96. Wing RR, Phelan S. Long-term weight loss maintenance. Am J Clin Nutr. 2005;82(1 Suppl):222S-5S.

97. Anastasiou CA, Karfopoulou E, Yannakoulia M. Weight regaining: From statistics and behaviors to physiology and metabolism. Metabolism. 2015;64(11):1395-407.

98. Schwartz A, Doucet E. Relative changes in resting energy expenditure during weight loss: a systematic review. Obes Rev. 2010;11(7):531-47.

99. Maclean PS, Bergouignan A, Cornier MA, Jackman MR. Biology's response to dieting: the impetus for weight regain. Am J Physiol Regul Integr Comp Physiol. 2011;301(3):R581-600.

100. Rosenbaum M, Kissileff HR, Mayer LE, Hirsch J, Leibel RL. Energy intake in weight-reduced humans. Brain Res. 2010;1350:95-102.

101. Sumithran P, Proietto J. The defence of body weight: a physiological basis for weight regain after weight loss. Clin Sci (Lond). 2013;124(4):231-41.

102. Vermeer WM, Steenhuis IH, Poelman MP. Small, medium, large or supersize? The development and evaluation of interventions targeted at portion size. Int J Obes (Lond). 2014;38 Suppl 1:S13-8.

103. Kohl HW, 3rd, Craig CL, Lambert EV, Inoue S, Alkandari JR, Leetongin G, et al. The pandemic of physical inactivity: global action for public health. Lancet. 2012;380(9838):294-305.

104. Phelan S, Wyatt HR, Hill JO, Wing RR. Are the eating and exercise habits of successful weight losers changing? Obesity (Silver Spring). 2006;14(4):710-6.

105. Milsom VA, Middleton KMR, Perri MG. Successful long-term weight loss maintenance in a rural population. Clin Interv Aging. 2011;6:303-9.

106. Thomas JG, Bond DS, Phelan S, Hill JO, Wing RR. Weight-loss maintenance for 10 years in the National Weight Control Registry. Am J Prev Med. 2014;46(1):17-23.

107. American Diabetes Association. 6. Obesity Management for the Treatment of Type 2 Diabetes. Diabetes Care. 2016;39 Suppl 1:S47-51.

108. Vanderlinden J, Adriaensen A, Vancampfort D, Pieters G, Probst M, Vansteelandt K. A cognitive-behavioral therapeutic program for patients with obesity and binge eating disorder: short- and long- term follow-up data of a prospective study. Behav Modif. 2012;36(5):670-86.

109. Brownley KA, Berkman ND, Sedway JA, Lohr KN, Bulik CM. Binge eating disorder treatment: a systematic review of randomized controlled trials. Int J Eat Disord. 2007;40(4):337-48.

110. Thoma N, Pilecki B, McKay D. Contemporary Cognitive Behavior Therapy: A Review of Theory, History, and Evidence. Psychodyn Psychiatry. 2015;43(3):423-61.

111. Van Dorsten B, Lindley EM. Cognitive and behavioral approaches in the treatment of obesity. Med Clin North Am. 2011;95(5):971-88.

112. Fabricatore AN. Behavior therapy and cognitive-behavioral therapy of obesity: is there a difference? J Am Diet Assoc. 2007;107(1):92-9.

113. Painot D, Jotterand S, Kammer A, Fossati M, Golay A. Simultaneous nutritional cognitive–behavioural therapy in obese patients. Patient Educ Couns. 2001;42(1):47-52.

114. Stahre L, Hallstrom T. A short-term cognitive group treatment program gives substantial weight reduction up to 18 months from the end of treatment. A randomized controlled trial. Eat Weight Disord. 2005;10(1):51-8.

115. Stahre L, Tarnell B, Hakanson CE, Hallstrom T. A randomized controlled trial of two weight-reducing short-term group treatment programs for obesity with an 18-month follow-up. Int J Behav Med. 2007;14(1):48-55.

116. Werrij MQ, Jansen A, Mulkens S, Elgersma HJ, Ament AJ, Hospers HJ. Adding cognitive therapy to dietetic treatment is associated with less relapse in obesity. J Psychosom Res. 2009;67(4):315-24.

117. Sbrocco T, Nedegaard RC, Stone JM, Lewis EL. Behavioral choice treatment promotes continuing weight loss: preliminary results of a cognitive-behavioral decision-based treatment for obesity. J Consult Clin Psychol. 1999;67(2):260-6.

118. Liao KL. Cognitive-behavioural approaches and weight management: an overview. J R Soc Promot Health. 2000;120(1):27-30.

119. Dennis KE, Pane KW, Adams BK, Qi BB. The impact of a shipboard weight control program. Obes Res. 1999;7(1):60-7.

120. Tuomilehto H, Seppa J, Uusitupa M. Obesity and obstructive sleep apnea–clinical significance of weight loss. Sleep Med Rev. 2013;17(5):321-9.

121. Annesi JJ, Johnson PH, Porter KJ. Bi-Directional Relationship Between Self-Regulation and Improved Eating: Temporal Associations With Exercise, Reduced Fatigue, and Weight Loss. J Psychol. 2015;149(6):535-53.

122. Garvey WT, Mechanick JI, Brett EM, Garber AJ, Hurley DL, Jastreboff AM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive

Clinical Practice Guidelines for Medical Care of Patients with Obesity. Endocr Pract. 2016;22 Suppl 3:1-203.

123. National Institute for Health and Care Excellence (NICE). Obesity: identification, assessment and management. NICE guidelines [CG189]. 2014.

124. Forlani G, Lorusso C, Moscatiello S, Ridolfi V, Melchionda N, Di Domizio S, et al. Are behavioural approaches feasible and effective in the treatment of type 2 diabetes? A propensity score analysis vs. prescriptive diet. Nutr Metab Cardiovasc Dis. 2009;19(5):313-20.

125. Mottalib A, Sakr M, Shehabeldin M, Hamdy O. Diabetes Remission after Nonsurgical Intensive Lifestyle Intervention in Obese Patients with Type 2 Diabetes. J Diabetes Res. 2015;2015:468704.

126. Thoolen B, De Ridder D, Bensing J, Maas C, Griffin S, Gorter K, et al. Effectiveness of a self-management intervention in patients with screen-detected type 2 diabetes. Diabetes Care. 2007;30(11):2832-7.

127. Perri MG, Nezu AM, McKelvey WF, Shermer RL, Renjilian DA, Viegener BJ. Relapse prevention training and problem-solving therapy in the long-term management of obesity. J Consult Clin Psychol. 2001;69(4):722-6.

128. Katzman MA, Bara-Carril N, Rabe-Hesketh S, Schmidt U, Troop N, Treasure J. A randomized controlled two-stage trial in the treatment of bulimia nervosa, comparing CBT versus motivational enhancement in Phase 1 followed by group versus individual CBT in Phase 2. Psychosom Med. 2010;72(7):656-63.

129. Minniti A, Bissoli L, Di Francesco V, Fantin F, Mandragona R, Olivieri M, et al. Individual versus group therapy for obesity: comparison of dropout rate and treatment outcome. Eat Weight Disord. 2007;12(4):161-7.

130. Paul-Ebhohimhen V, Avenell A. A systematic review of the effectiveness of group versus individual treatments for adult obesity. Obes Facts. 2009;2(1):17-24.

131. Renjilian DA, Perri MG, Nezu AM, McKelvey WF, Shermer RL, Anton SD. Individual versus group therapy for obesity: effects of matching participants to their treatment preferences. J Consult Clin Psychol. 2001;69(4):717-21.

Chapter 2

Predictors of diet-induced weight loss in overweight adults with type 2 diabetes

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ABSTRACT

Background and Aims

A very low calorie diet improves the metabolic regulation of obesity related type 2 diabetes, but not for all patients, which leads to frustration in patients and professionals alike. The aim of this study was to develop a prediction model of diet-induced weight loss in type 2 diabetes.

Methods

192 patients with type 2 diabetes and BMI>27 kg/m^2 from the outpatient diabetes clinic of the Erasmus Medical Center underwent an 8-week very low calorie diet. Baseline demographic, psychological and physiological parameters were measured and the C-index was calculated of the model with the largest explained variance of relative weight loss using backward linear regression analysis. The model was internally validated using bootstrapping techniques.

Results

Weight loss after the diet was 7.8±4.6 kg (95%CI 7.2-8.5; p<0.001) and was independently associated with the baseline variables fasting glucose (B=-0.33 (95%CI -0.49, -0.18), *p*=0.001), anxiety (HADS; B=-0.22 (95%CI -0.34, -0.11), *p*=0.001), numb feeling in extremities (B=1.86 (95%CI 0.85, 2.87), *p*=0.002), insulin dose (B=0.01 (95%CI 0.00, 0.02), *p*=0.014) and waist-to-hip ratio (B=6.79 (95%CI 2.10, 11.78), *p*=0.003). This model explained 25% of the variance in weight loss. The C-index of this model to predict successful (≥5%) weight loss was 0.74 (95%CI 0.67-0.82), with a sensitivity of 0.93 (95% CI 0.89-0.97) and specificity of 0.29 (95% CI 0.16-0.42). When only the obese T2D patients (BMI≥30 kg/m^2; n = 181) were considered, age also contributed to the model (B=0.06 (95%CI 0.02, 0.11), *p*=0.008), whereas waist-to-hip ratio did not.

Conclusions

Diet-induced weight loss in overweight adults with T2D was predicted by five baseline parameters, which were predominantly diabetes related. However, failure seems difficult to predict. We propose to test this prediction model in future prospective diet intervention studies in patients with type 2 diabetes.

INTRODUCTION

The metabolic regulation of obesity-related type 2 diabetes improves with diet-induced weight loss. A very low calorie diet is successful in that respect, but unfortunately not in all patients, which leads to feelings of failure and reduction of cost-effectiveness of the treatment. A prediction model of weight loss can assist selecting those individuals that will benefit most.

The dramatic rise in the world-wide prevalence of obesity has led to a rising prevalence of T2D. It is estimated that 82-87% of the T2D population are overweight or obese (1). In patients with T2D, a high BMI and waist circumference are associated with increased mortality (2, 3). Conversely, moderate weight loss improves glycaemic control, lipid profile and blood pressure in these individuals and has been associated with reduced mortality (4-6). Therefore, weight loss is an important aspect of treatment of T2D. Weight loss of more than 5% results in important health benefits and reduces health care costs (7, 8). However, not all individuals that are overweight or obese achieve and maintain 5% weight loss or more with lifestyle interventions (6, 9). Predictors of weight loss may be very helpful in optimizing individualized weight loss strategies and in selecting those individuals who will benefit most from a diet, ultimately improving treatment outcome and reducing health care costs. In adults with obesity, a number of physiological and psychological predictors of weight loss have been identified. These include sex, previous dieting for weight loss, initial weight, motivation, self-efficacy, self-esteem and exercise (10, 11). However, these predictors of weight loss have not been studied in subjects with T2D, and diabetes-specific variables have not been included in previous research in this field. Both psychological and physiological factors are most probably of importance, as obesity-related T2D is a complex multifactorial disease.

Therefore, the purpose of the present study was to identify which factors predict diet-induced weight loss in overweight and obese adults with T2D, using psychological, physiological as well as diabetes-related variables.

MATERIALS AND METHODS

We enrolled participants of the run-in phase of the Prevention Of Weight Regain (POWER) trial of which the protocol has been published previously (12). This study was approved by the Medical Ethics Committee of the Erasmus Medical Center in Rotterdam (reference number MEC-2009-143/NL26508.078.09), in compliance with the Helsinki Declaration. All participants provided written informed consent before participating in this study.

Study population

Patients with T2D having BMI>27 kg/m^2, whose age was 18-75 years, were recruited from the outpatient diabetes clinic of the Erasmus Medical Center, Rotterdam from 2010-2013. Exclusion criteria were pregnancy, lactation, severe psychiatric problems, significant cardiac arrhythmias, unstable angina, decompensated congestive heart failure, major organ system failure, untreated hypothyroidism, and end-stage renal disease. Patients who had a myocardial infarction, cerebrovascular accident or major surgery during the previous 3 months were also excluded.

Diet intervention and data collection

Intervention

After signing informed consent, participants followed a Very Low Calorie Diet (VLCD) for a period of 8 weeks. The VLCD consisted of 2 commercially available meal replacements per day (Glucerna SR®, Abbott Nutrition BV), plus 75 grams of lean meat, one skimmed milk product and vegetables. Daily intake was approximately 750 kcal. Participants received oral and written instructions on how to follow this diet at home. Before the start of the diet the anti-diabetes medication was lowered to prevent hypoglycaemia: oral anti-diabetic agents (except metformin) and short-acting insulin analogues were discontinued, while the doses of long-acting insulin analogues and biphasic mixtures were halved. GLP-1 analogues and DPP-4 inhibitors were continued. One week after starting the diet, participants received a phone call of the research team. A structured discussion about blood glucose measurements, questions about the diet, problems with adherence to the diet, and complaints was performed. Participants were encouraged to follow the dietary recommendations of the study and to weekly email their blood glucose measurements. The insulin dose was adjusted during the diet period based on these daily glucose measurements.

Measures and outcomes

The primary outcome was weight loss, expressed as a percentage of baseline bodyweight. At baseline and at the end of the diet intervention bodyweight was measured. Weight loss was considered 'successful' if ≥5% reduction of baseline body weight was achieved. Moderate weight loss of ≥5% is considered by the American Diabetes Association and the European Association of the Study of Diabetes to produce significant health benefits (13, 14).

Besides age and sex, the baseline variables were as follows:

1. Weight and BMI
   Weight was measured to the nearest 0.1 kg using the same Seca 888 compact digital flat scale after removal of shoes. Height was measured to the nearest 0.5 cm without shoes using a Seca stadiometer.
2. Waist circumference and waist-to-hip ratio
   Waist circumference (cm) was measured at the level midway between the lowest rib margin and the aliac crest. Hip circumference was measured at the widest point over the buttocks. Both waist- and hip circumference were measured by the nearest 0,5 cm, using a tape-measure. Subsequently, waist-hip ratio (WHR) was calculated.
3. Glycemic control
   a. Fasting glucose, measured using standard laboratory techniques
   b. Hemoglobin A1c (HbA1c), measured using standard laboratory techniques
   c. Total daily insulin dose (IU/day)
   d. Total daily metformin dose (mg/day)
4. Physical complaints related to diabetes
   a. Polyuria (yes/no)
   b. Pruritus (yes/no)
   c. Eye problems (yes/no)
   d. Numbness in extremities (yes/no)
5. Exercise
   Days per week ≥30 minutes of exercise
6. History of dieting for weight loss
   Number of weight loss attempts
7. Fatigue
   Measured by the Checklist Individual Strength (CIS) (15), which consists of 20 statements for which the respondent has to indicate on a 7-point scale (from true to false) to what extent the particular statement applies to him or her. The statements refer to four fatigue aspects: (1) subjective fatigue (2) reduced motivation (3) reduced activity and (4) reduced concentration. People with a score above 76 are at increased risk of long-term sickness absence.
8. Depression and anxiety
   Measured by the Hospital Anxiety and Depression scale (HADS). The HADS consists of a 7-item Anxiety scale and a 7-item Depression Scale. Each item is scored from 0 to 3. A total score on either scale below 8 excludes anxiety or depression, respectively. A score of 8–10 and 11-21 indicates a possible and probable anxiety/depression, respectively (16).

9. Quality of life
   Measured by the EQ-5D VAS score, ranging from 0 (death) to 100 (perfect health) (17, 18)
10. Self-esteem
    Measured by the Rosenberg Self-esteem Scale (RSE), which is a 10-item questionnaire that measures global self-esteem. Items are scored on a 4-point scale. A higher score indicates a more positive self-esteem. Scores below 21 indicate low self-esteem (19)
11. Eating disorders
    a. Measured by the Eating Disorder Examination-Questionnaire (EDE-Q), a 36 item questionnaire that measures concerns about shape, weight and eating, restraint and binge eating. Total EDE-Q score range between 0–6. A higher score indicates more severe eating psychopathology (20).
    b. Binge eating disorder (BED), measured by use of the DSM-V criteria (yes/no)

All data were filed in a database using a trial management system (OpenClinica®).

Statistical Analysis

Variables at baseline were expressed as number with percentage or mean with standard deviation. Prior to analysis, missing data were imputed using regression imputation. Participants with more than 50% missing data were excluded. For 7 participants, whose body weight at the end of the diet intervention was not available due to attrition, we assumed 0% weight loss. We analysed the data according to the intention-to-treat as well as the per-protocol principle, leaving those 7 patients out of the analysis. The average weight loss was analysed using a paired samples t-test. The difference between groups at baseline was tested with a Chi-Square test, an independent samples t-test or a Mann-Whitney U test, depending on normality of the data. Potential predictors were identified by univariate regression analyses with percentage weight loss as dependent variable. Subsequently, all variables were entered into a multiple regression analysis. The least informative covariates were successively removed from the model in a backward stepwise elimination procedure based on the Akaike information criterion (AIC)(21). We accepted a maximum Variance Inflation Factor of 5 to exclude multicollinearity problems. Each step of the backward regression analysis was internally validated using bootstrapping (22). In short, 1000 bootstrap cohorts (of equal size as the original dataset) were randomly drawn, with replacement, from the cases in the original dataset. Logistic regression was applied to predict successful (≥ 5% = 1) and unsuccessful (< 5% = 0) weight loss. The relationship between false positives (1 - specificity) and true positives (sensitivity) of this prediction was presented in a ROC (Receiving Operating Characteristic) curve. For the dichotomized prediction, the sensitivity, specificity and positive predictive value were

calculated. Statistical significance was set at $p < 0.05$. All data processing and analyses were carried out in SPSS (version 21).

RESULTS

From March 2010 to May 2013, we assessed 296 patients with BMI>27 kg/m^2 and T2D from our out-patient diabetes clinic, of whom 276 were eligible and 206 were willing to participate in this study (Fig 1). Individuals who declined to participate were older (58.0 (49.8-64.0) years vs. 53.5 (47.0-61.8) years, p=0.04) and more often male (61% vs. 42%, p=0.005) than the individuals who were willing to participate in this study. Ethnicity did not differ. The main reasons for the declined participation were work related and lack of time. Fourteen participants did not fill out the questionnaires and did not provide blood samples, hence we collected data from 192 participants.

Table 1 shows baseline characteristics of our study population, of which 58% were female. Of the participants, 181 (94.3%) had a BMI>30 kg/m^2, thus qualified as obese. Mean HbA1c and fasting glucose levels were well above target levels despite antidiabetic medication. Sixty-two percent of the participants used insulin (62.0±63.9 IU/day). According to the HADS norm, 18% had a clinical depression and 20% a clinical anxiety disorder. Twelve participants (6.3%) used antidepressants (self-reported).

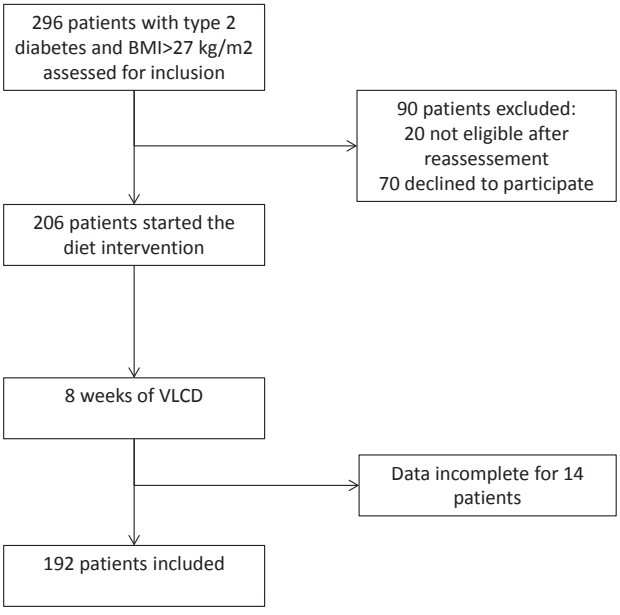

Figure 1. Study flow chart

Table 1. General baseline characteristics (n = 192)

Characteristics	Value, mean ± SD (range)
Age (y)	54.2 ± 10.6 (26-75)
Sex, female (n (%))	112 (58%)
Exercise (weekly days ≥30 min. exercise)	5.3 ± 2.3 (0-7)
Physiological variables:	
Weight (kg)	106.0 ± 19.0 (69.4-169.2)
BMI (kg/m^2)	37.0 ± 5.6 (27.3-62.6)
Waist circumference (cm)	120.2 ± 13.3 (90-163)
Waist-to-hip ratio	1.0 ± 0.1 (0.8 -1.3)
HbA1c (mmol/mol)	63.9 ± 15.2 (32-126)
HbA1c (%)	8.0 ± 1.4 (5.1-13.7)
Fasting glucose (mmol/l)	9.5 ± 3.2 (3.2-21.1)
Insulin dose (IU)*	100.1 ± 52.7 (8-248)
and users (n (%))	119 (62%)
Metformin dose (mg)*	1774.8 ±754.2 (500-3000)
and users (n (%))	154 (80%)
Numb feeling in extremities (n (%))	96 (50%)
Polyuria (n (%))	57 (30%)
Pruritus (n (%))	37 (19%)
Diabetes-related eye problems (n (%))	45 (23%)
Psychological variables:	
Depression score (HADS 0-20);	7.0 ± 4.0 (0-20)
Clinical depression (n (%))	35 (18%)
Anxiety score (HADS 0-20);	6.6 ± 4.3 (0-20)
Clinical anxiety disorder (n (%))	38 (20%)
Self-esteem (RSE 0-40)	30.6 ± 5.6 (13-40)
Quality of life (EQ5D VAS 1-100)	58.8 ± 21.0 (10-100)
Fatigue (CIS total score 20-140)	80.9 ± 23.8 (25-133)
Eating disorders (EDE-Q total score 0-6)	2.2 ± 1.2 (0-5.4)
Binge eating disorder (DSM V, n (%))	11 (6%)
Diet history (no. of weight loss attempts)	1.0 ± 1.1 (0-5)

*dose only in users

After 8 weeks of VLCD, participants had lost 7.8±4.6 kg (95%CI 7.2-8.5; $p<0.001$). Twenty-five percent of the participants lost less than 5%, 28% lost 5-7.5%, 21% lost 7.5-10% and 26% lost more than 10% of their bodyweight. Compared with the successful weight loss group, the unsuccessful weight loss group (i.e. <5%) showed higher levels of HbA1c and fasting glucose, and were more likely to have pruritus and a lower self-esteem ($p<0.01$).

Table 2. Univariate linear regression analysis of relative weight loss with baseline variables

Covariate	B	SE	β	*p*
Age (y)	0.086	0.026	0.237	0.001
Sex (female)	-1.908	0.547	-0.246	0.001
Exercise (weekly days ≥ 30 min. exercise)	0.137	0.119	0.083	0.251
Physiological variables:				
Weight (kg)	0.014	0.015	0.071	0.325
Waist circumference (cm)	0.040	0.021	0.137	0.058
Waist-to-hip ratio	10.160	2.927	0.244	0.001
Fasting glucose (mmol/l)	-0.311	0.085	-0.257	<0.001
HbA1c (mmol/mol)	-0.046	0.018	-0.181	0.012
Insulin dose (IU)	0.008	0.004	0.131	0.070
Insulin dose change during diet (IU)	-0.019	0.006	-0.245	0.001
Metformin dose (mg)	<0.0001	<0.0001	0.007	0.922
Numbness in extremities (n=0/y=1)	1.792	0.540	0.234	0.001
Polyuria (n=0/y=1)	0.019	0.608	0.002	0.976
Pruritus (n=0/y=1)	-1.732	0.693	-0.178	0.013
Diabetes-related eye problems (n=0/y=1)	-0.648	0.654	-0.072	0.324
Psychological variables:				
Depression score (HADS 0-20)	-0.132	0.070	-0.136	0.060
Anxiety score (HADS 0-20)	-0.223	0.062	-0.252	<0.001
Self-esteem (RSE 0-40)	0.126	0.049	0.184	0.011
Quality of life (EQ5D VAS 1-100)	0.024	0.013	0.131	0.071
Fatigue (CIS total score 20-140)	-0.011	0.012	-0.065	0.371
Eating disorders (EDE-Q total score 0-6)	-0.276	0.238	-0.084	0.247
Binge eating disorder (DSM V, n=0/y=1)	0.049	1.189	0.003	0.967
Diet history (no. of weight loss attempts)	-0.111	0.248	-0.032	0.656

In univariate regression analyses (table 2), age, waist-to-hip ratio, numb feeling in extremities, and self-esteem were all positively associated with relative weight loss, while female sex, fasting glucose, HbA1c, pruritus and anxiety were negatively associated with relative weight loss.

Table 3 shows the results of the multiple linear regression analysis. Since both fasting glucose and HbA1c, and waist circumference and waist-to-hip ratio were strongly correlated ($p<0.001$), we included only fasting glucose and waist-to-hip ratio in the multivariate analysis to avoid multicollinearity problems. In the backward stepwise elimination multiple regression analysis (using bootstrapping), the final model contained 5 baseline variables which were independently associated with relative weight loss: the higher the

reported numb feeling in extremities (B=1.86 (95%CI 0.85, 2.87), p=0.002), insulin dose (B=0.01 (95%CI 0.00, 0.02), p=0.014) and waist-to-hip ratio (B=6.79 (95%CI 2.10, 11.78), p=0.003), and the lower the fasting glucose level (B=-0.33 (95%CI -0.49, -0.18), p=0.001) and anxiety score (HADS; B=-0.22 (95%CI -0.34, -0.11), p=0.001), the greater the relative weight loss. These five parameters together explained 25% of the variance of relative weight loss (R^2 = 0.25, $F(5)$ = 12.54, p<0.001). In Fig 2, we show the ROC curve of our intention-to-treat model in discriminating unsuccessful (<5%) from successful (≥5%) weight loss, which had a C-index of 0.74 (95%CI 0.67-0.82). The logistic model had 0.80 (95% CI 0.74-0.86) post-test likelihood of predicting successful weight loss and 0.58 (95% CI 0.39-0.78) post-test likelihood of predicting unsuccessful weight loss. The model yielded 134 true positive, 34 false positive, 10 false negative and 14 true negative predictions. Hence, the sensitivity of this model was 0.93 (95% CI 0.89-0.97) and the specificity was 0.29 (95% CI 0.16-0.42). When we corrected this model for change in insulin dose during the diet, the five baseline variables remained significantly associated with relative weight loss; the model now explained 30% of the variance of weight loss (R^2 = 0.30, $F(6)$ = 13.31, p<0.001) and discriminated successful from unsuccessful weight loss with a C-index of 0.75. However, the VIF statistics for insulin dose and insulin change was 7, indicating possible multicollinearity problems.

We conducted the multivariate regression analysis in a backward stepwise manner, to obtain the optimal model. Alternatively, putting all the univariately associated variables (p<0.1) in the multivariate regression model only marginally affected the performance of the model (R^2 = 0.29, $F(11)$ = 6.53, p<0.001; C-index = 0.77).

Variables entered into the model: age; sex; weight; waist-to-hip ratio; fasting glucose; total daily insulin dose; total daily metformin dose; physical complaints related to diabetes (polyuria, pruritus, eye problems, numbness in extremities, all yes/no); exercise (days per week ≥30 minutes of exercise); history of weight loss dieting (number of different diets); fatigue (Checklist Individual Strength); depression and anxiety (Hospital Anxiety and Depression scale); quality of life (EQ-5D VAS score); self-esteem (Rosenberg self-esteem); eating disorders (EDE-Q); and binge eating disorder (DSM-V criteria, yes/no).

When we excluded the 7 participants who did not finish the diet intervention (per protocol analysis), the model slightly improved, as indicated by the additional contribution of the variables pruritus and quality of life (EQ5D VAS). The lower the reported pruritus and the higher the perceived quality of life, the greater was the weight loss. This model explained 30% of the variance of relative weight loss (R^2 = 0.30, $F(8)$ = 9.29, p<0.001) and discriminated successful from unsuccessful weight loss with a C-index of 0.79.

We also performed the analysis for the obese subgroup (BMI≥30 kg/m^2; n=181) only. Compared to the entire study population, age now also contributed to the model (B=0.06 (95%CI 0.02, 0.11), p=0.008), whereas waist-to-hip ratio was removed from

Table 3. Multiple linear regression model (backward stepwise elimination using bootstrapping) of relative weight loss with baseline variables

Variable	B	95%CI Lower	95%CI Upper	R^2	*p*
Fasting glucose (mmol/l)	-0.332	-0.485	-0.180	0.078	0.001
Insulin dose (IU)	0.010	0.002	0.018	0.032	0.014
Waist-to-hip ratio	6.790	2.096	11.775	0.025	0.003
Numbness in extremities	1.860	0.853	2.874	0.065	0.002
Anxiety (HADS)	-0.219	-0.344	-0.111	0.056	0.001

Explained variance in this model R^2 = 0.25, F(5) = 12.54, p<0.001; C-index = 0.74

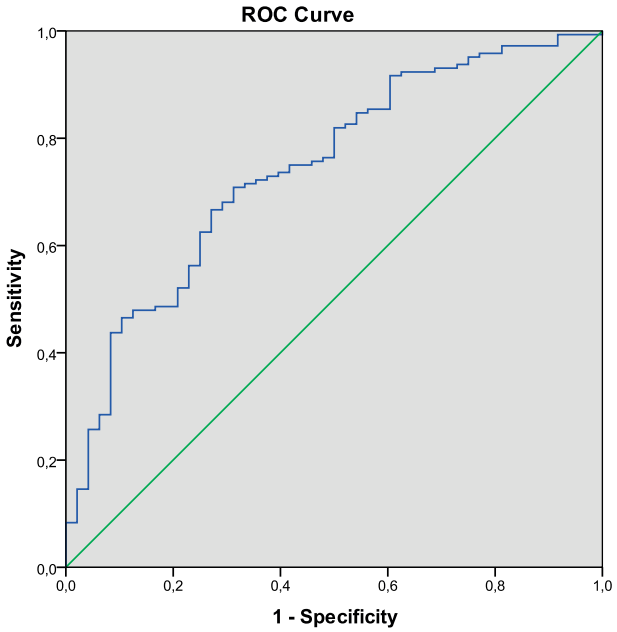

Figure 2. ROC Curve of multiple logistic regression model of successful relative weight loss (≥5%) Variables included in the multiple linear regression model: fasting glucose level, insulin dose, waist-to-hip ratio, numb feeling in extremities and anxiety score.

the model in the backward elimination procedure. The model containing fasting glucose, insulin dose, age, numb feeling in extremities and anxiety score explained 25% of the variance of relative weight loss (R^2 = 0.25, *F*(5) = 11.84, *p*<0.001), and discriminated successful from unsuccessful weight loss with a C-index of 0.73.

DISCUSSION

In this pragmatic explorative study, we found that successful diet-induced weight loss can be predicted in overweight adults with T2D by the baseline variables fasting glucose, anxiety, numb feeling in extremities, insulin dose and waist-to-hip ratio. However, failure seems more difficult to predict. Surprisingly, the 'usual suspects' in predicting weight loss in individuals with obesity but without T2D, such as initial weight, diet history, self-esteem and exercise, did not contribute to the model. Remarkably, 3 out of 5 predictors in the model were related to diabetes. This suggests that diabetes control is of major importance for overweight and obese patients with T2D, who aim at losing weight, more than factors that are most relevant in non-diabetic persons with obesity.

Our data showed that participants with a higher baseline fasting glucose and, hence, worse diabetes control were less successful in achieving weight reduction. One could speculate that controlling diabetes might require skills that are also important in controlling weight. A recent review by Ahola, et al. found that factors associated with good management of diabetes included individual issues such as self-efficacy, motivation, coping and problem-solving skills, as well as issues related to the environment such as social support and socio-economic factors (23). All of these factors have been linked with successful weight loss as well (10). Alternatively, participants with a high fasting glucose may lose energy through glycosuria. Losing weight reduces blood glucose levels in T2D (6) and subsequently the energy deficit due to glycosuria may disappear, leading to a disadvantage in weight loss for participants with a very high fasting glucose at baseline.

We identified anxiety as an unexpected negative predictor for weight loss. Among our participants with T2D, the prevalence of anxiety disorder was as high as 20%. This is higher than the prevalence of anxiety disorder in the Dutch population (7.7% for males and 12.5% for females (24)), and in line with previous studies in T2D (25). While anxiety has not been extensively studied in the context of weight control, it has been correlated with a defensive coping style: avoiding problems rather than solving them (26). In diabetes, an anxious, defensive coping style has been associated with decreased adherence to therapy (27). Similarly, in our study anxiety could have led to a decreased adherence to the diet. A more autonomous coping strategy has been shown to correlate better with the capability to lose weight than a defensive coping style (11, 28). It would be interesting to test whether treating anxiety prior to the diet intervention would improve the success rate of a weight loss diet.

Baseline insulin dose was positively associated with weight loss. Before starting with the VLCD, we reduced the insulin dose by more than 50% to avoid hypoglycaemic events. Insulin use has been associated with weight gain due to the stimulation of lipogenesis and a reduction of lipolysis and glycosuria (29). Lowering the insulin dose could have had the opposite effect, where participants on a high baseline dose could

have had more benefit from the greater absolute reduction of insulin dose. Reducing the insulin dose before a weight loss attempt is important to prevent hypoglycaemia, but it may also enhance weight loss. Indeed, baseline insulin dose and change in insulin dose were highly correlated (r=-0.929, $p<0.001$), so the association of baseline insulin with weight loss could very well have been the effect of lowering the insulin dose. However, when we corrected the model for change in insulin dose, baseline insulin dose was still significantly associated with relative weight loss.

Experiencing a numb feeling in extremities was positively associated with the relative weight loss. Of the participants who lost less than 5% weight, 35% reported this complaint, compared with 55% in the successful weight loss group. A numb feeling in extremities could be associated with diabetic neuropathy. Indeed, numbness was significantly correlated with a history of diabetic neuropathy (data not shown) and therefore probably with the severity of complications. Complications or perceiving more complaints could be a motivational trigger for patients to adhere to the diet regimen, although this has not been studied previously.

Participants with a higher waist-to-hip ratio and to a lesser extent waist circumference, i.e. more abdominal fat, were more prone to lose weight in our study population. Moderate weight loss, particularly by a VLCD, has been shown to result in preferential loss of visceral fat mass (30). Visceral fat mass is associated with reduced insulin sensitivity and increased systemic low-grade inflammation (2, 31). Men tend to have a higher waist-to-hip ratio than women, as was the case in our population (1.07±0.07 vs. 0.94±0.06, $p<0.001$). Since males have a higher energy expenditure compared to women, and the diet intervention was the same for both men and women, the association we found could be explained by the higher energy deficit for the male participants. Accordingly, the univariate analysis showed that women lost significantly less weight than men, suggesting that men will benefit most from weight reduction and preferential abdominal fat mass loss. However, in the multiple linear regression analysis, sex no longer contributed significantly to weight loss while waist-to-hip ratio remained an independent contributor. Waist-to-hip ratio is a stronger predictor for weight loss success than sex.

A number of covariates, such as baseline bodyweight, self-motivation, diet history and self-esteem have previously been associated with diet-induced weight loss in individuals with obesity (10, 11). However, they did not predict relative weight loss in the present study. Self-esteem was positively associated with weight loss in the univariate analysis, but no longer in the multiple analysis. In concordance with most other studies on predictors of weight loss in subjects with obesity (10, 32), binge eating disorders and baseline exercise behaviour were not associated with weight loss. In previous studies, depression or other measures of psychological well-being were not predictive for weight loss (33), as was the case in the present study, or were negatively associated with weight loss (34).

Limitations and strengths

The present study is a pragmatic and explorative before-after study in the run-in phase of a trial. We internally validated our results using statistical techniques (bootstrapping), however, future prospective replication studies are required in order to confirm our findings. With the baseline variables that were included in our study, 25% of the variance of weight loss could be explained, leaving a large part unexplained. Future studies could build further on the model presented here in an independent patient cohort, including other possible predictors like plasma hormone levels or genomic profiles. A limitation of this study is the relatively low number of participants with unsuccessful weight loss, diminishing the discriminating power of the model. Due to the academic hospital setting, our study population may not be representative of the general population with T2D and overweight. However, a substantial percentage of our population had been referred to us by the general practitioner with participation in our study as exclusive purpose, leading to a relatively heterogeneous patient cohort in a 'real life' clinical setting. Finally, we studied the short-term effect of the diet intervention only. However, a relatively quick success of the intervention in terms of weight loss and improved glycemic control may motivate the patients with obesity and diabetes to change lifestyle necessary to achieve long term health benefit. Additional studies are required to determine whether the model also predicts long-term maintenance of weight loss. Strengths of the current study are the prospective design, the relative large cohort of patients with T2D, the low attrition rate (3%) and the consideration of psychological as well as physiological variables.

Conclusion and clinical implications

The current study suggests that diet-induced weight loss can be predicted by five easily measurable psychological and physiological variables, with a positive post-test probability of 80%. Diabetes specific variables were better at predicting successful weight loss during a VLCD than the predictors known from non-T2D obese cohorts. Future prospective studies in the T2D population are needed in order to replicate these findings. Restricting a VLCD to individuals with a high post-test likelihood of successful weight loss seems attractive as it might increase efficacy and improve the cost-effectiveness. Such screening of patients and predicting their treatment success will bring us one step closer to personalized treatment of diabetes.

REFERENCES

1. Bays HE, Chapman RH, Grandy S, Group SI. The relationship of body mass index to diabetes mellitus, hypertension and dyslipidaemia: comparison of data from two national surveys. Int J Clin Pract. 2007;61(5):737-47.
2. Katzmarzyk PT, Hu G, Cefalu WT, Mire E, Bouchard C. The importance of waist circumference and BMI for mortality risk in diabetic adults. Diabetes Care. 2013;36(10):3128-30.
3. Tobias DK, Pan A, Jackson CL, O'Reilly EJ, Ding EL, Willett WC, et al. Body-mass index and mortality among adults with incident type 2 diabetes. N Engl J Med. 2014;370(3):233-44.
4. Williamson DF, Thompson TJ, Thun M, Flanders D, Pamuk E, Byers T. Intentional weight loss and mortality among overweight individuals with diabetes. Diabetes Care. 2000;23(10):1499-504.
5. Anderson JW, Kendall CW, Jenkins DJ. Importance of weight management in type 2 diabetes: review with meta-analysis of clinical studies. J Am Coll Nutr. 2003;22(5):331-9.
6. Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med. 2013;369(2):145-54.
7. Klein S, Burke LE, Bray GA, Blair S, Allison DB, Pi-Sunyer X, et al. Clinical implications of obesity with specific focus on cardiovascular disease: a statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. Circulation. 2004;110(18):2952-67.
8. Espeland MA, Glick HA, Bertoni A, Brancati FL, Bray GA, Clark JM, et al. Impact of an intensive lifestyle intervention on use and cost of medical services among overweight and obese adults with type 2 diabetes: the action for health in diabetes. Diabetes Care. 2014;37(9):2548-56.
9. Franz MJ, Boucher JL, Rutten-Ramos S, VanWormer JJ. Lifestyle Weight-Loss Intervention Outcomes in Overweight and Obese Adults with Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. J Acad Nutr Diet. 2015;115(9):1447-63.
10. Stubbs J, Whybrow S, Teixeira P, Blundell J, Lawton C, Westenhoefer J, et al. Problems in identifying predictors and correlates of weight loss and maintenance: implications for weight control therapies based on behaviour change. Obes Rev. 2011;12(9):688-708.
11. Teixeira PJ, Going SB, Sardinha LB, Lohman TG. A review of psychosocial pre-treatment predictors of weight control. Obes Rev. 2005;6(1):43-65.
12. Berk KA, Buijks H, Ozcan B, Van't Spijker A, Busschbach JJ, Sijbrands EJ. The Prevention Of WEight Regain in diabetes type 2 (POWER) study: the effectiveness of adding a combined psychological intervention to a very low calorie diet, design and pilot data of a randomized controlled trial. BMC Public Health. 2012;12:1026.
13. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012;35(6):1364-79.
14. Klein S, Sheard NF, Pi-Sunyer X, Daly A, Wylie-Rosett J, Kulkarni K, et al. Weight management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies: a statement of the American Diabetes Association, the North American Association for the Study of Obesity, and the American Society for Clinical Nutrition. Diabetes Care. 2004;27(8):2067-73.
15. Bultmann U, de Vries M, Beurskens AJ, Bleijenberg G, Vercoulen JH, Kant I. Measurement of prolonged fatigue in the working population: determination of a cutoff point for the checklist individual strength. J Occup Health Psychol. 2000;5(4):411-6.

16. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med. 1997;27(2):363-70.
17. Brooks R. EuroQol: the current state of play. Health Policy. 1996;37(1):53-72.
18. Lamers LM, Stalmeier PF, McDonnell J, Krabbe PF, van Busschbach JJ. [Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff] Kwaliteit van leven meten in economische evaluaties: het Nederlands EQ-5D-tarief. Ned Tijdschr Geneeskd. 2005;149(28):1574-8.
19. Rosenberg M. Society and The Adolescent Self-Image. Princeton, NJ: Princeton University Press. 1965.
20. Fairburn CG, Beglin SJ. Assessment of eating disorders: interview or self-report questionnaire? Int J Eat Disord. 1994;16(4):363-70.
21. Akaike H. A new look at the statistical model identication. IEEE Transactions on Automatic Control AC. 1974;19:716-23.
22. Steyerberg EW, Harrell FE, Jr., Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. J Clin Epidemiol. 2001;54(8):774-81.
23. Ahola AJ, Groop PH. Barriers to self-management of diabetes. Diabet Med. 2013;30(4):413-20.
24. de Graaf R, ten Have M, Tuithof M, van Dorsselaer S. First-incidence of DSM-IV mood, anxiety and substance use disorders and its determinants: results from the Netherlands Mental Health Survey and Incidence Study-2. J Affect Disord. 2013;149(1-3):100-7.
25. Fisher L, Skaff MM, Mullan JT, Arean P, Glasgow R, Masharani U. A longitudinal study of affective and anxiety disorders, depressive affect and diabetes distress in adults with Type 2 diabetes. Diabet Med. 2008;25(9):1096-101.
26. Wu LM, Sheen JM, Shu HL, Chang SC, Hsiao CC. Predictors of anxiety and resilience in adolescents undergoing cancer treatment. J Adv Nurs. 2013;69(1):158-66.
27. Garay-Sevilla ME, Porras JS, Malacara JM. Coping strategies and adherence to treatment in patients with type 2 diabetes mellitus. Rev Invest Clin. 2011;63(2):155-61.
28. Elfhag K, Rossner S. Who succeeds in maintaining weight loss? A conceptual review of factors associated with weight loss maintenance and weight regain. Obes Rev. 2005;6(1):67-85.
29. Malone M, Alger-Mayer SA, Anderson DA. Medication associated with weight gain may influence outcome in a weight management program. Ann Pharmacother. 2005;39(7-8):1204-8.
30. Chaston TB, Dixon JB. Factors associated with percent change in visceral versus subcutaneous abdominal fat during weight loss: findings from a systematic review. Int J Obes (Lond). 2008;32(4):619-28.
31. Tousoulis D, Papageorgiou N, Androulakis E, Siasos G, Latsios G, Tentolouris K, et al. Diabetes mellitus-associated vascular impairment: novel circulating biomarkers and therapeutic approaches. J Am Coll Cardiol. 2013;62(8):667-76.
32. Sherwood NE, Jeffery RW, Wing RR. Binge status as a predictor of weight loss treatment outcome. Int J Obes Relat Metab Disord. 1999;23(5):485-93.
33. Hainer V, Hlavata K, Gojova M, Kunesova M, Wagenknecht M, Kopsky V, et al. Hormonal and psychobehavioral predictors of weight loss in response to a short-term weight reduction program in obese women. Physiol Res. 2008;57 Suppl 1:S17-27.

34. Wolf S, Foley S, Budiman-Mak E, Moritz T, O'Connell S, Jelinek C, et al. Predictors of weight loss in overweight veterans with knee osteoarthritis who participated in a clinical trial. J Rehabil Res Dev. 2010;47(3):171-81.

Chapter 3

Diet-induced weight loss and markers of endothelial dysfunction and inflammation in treated patients with type 2 diabetes

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ABSTRACT

Background and Aims

Overweight and obesity increase cardiovascular mortality in patients with type 2 diabetes (T2D). In a recent trial, however, diet-induced weight loss did not reduce the cardiovascular risk of patients with T2D, possibly due to the parallel intensive medical treatment. We investigated the effect of diet-induced weight loss on cardiovascular risk factors in overweight and obese patients with T2D, and whether this effect was influenced by the use of statins, ACE inhibitors, metformin and duration of T2D.

Methods

Patients with T2D and BMI > 27 were subjected to an energy-restricted diet during 4 months. Before and after intervention, plasma levels of sICAM-1, sVCAM-1, hsCRP, vWF and classical biomarkers were measured. The association of the change in biomarker levels with medication use and T2D history, corrected for age, sex and change in insulin dose, was tested by matched linear regression analyses.

Results

In 131 patients, the diet resulted in weight loss of 10.2 kg (95%CI 9.2, 11.3; $p<0.001$), improved median levels of $HbA1_c$ (-7.0 mmol/mol (95%CI -8.5, -5.0); p<0.001), LDL cholesterol (-0.2 mmol/L (95%CI -0.4, -0.1); p<0.001), sICAM-1 (-22.4 ng/mL (95%CI -37.1, -8.7); p=0.001), vWF (-3.9 IU/mL (95%CI -6.4, -1.4); p=0.003) and hs-CRP (-0.6 mg/L (95%CI -1.2, -0.2); p=0.007), but did not affect sVCAM-1 levels (1.6 ng/mL (95%CI -41.5, 48.6); p=0.949). Duration of T2D and medical treatment were not associated with these effects, except for an association between statin use and change in sVCAM-1, where statin users improved more.

Conclusion

Diet-induced weight loss reduced the levels of biomarkers of endothelial dysfunction and inflammation in overweight and obese patients with T2D independently of medication use and T2D duration. Even on intensive medical drug treatment as well as after a long history of T2D, patients may still profit from diet-induced weight reduction.

INTRODUCTION

Cardiovascular disease is a feared complication of type 2 diabetes (T2D), as it is often fatal in persons with T2D (1). Overweight and obesity enhance cardiovascular mortality in T2D (2). In early asymptomatic stages, the insulin resistance typical for T2D has already detrimental effects on endothelial function (3). This endothelial dysfunction is characterized by decreased vasodilation, increased vasoconstriction, insufficient or excessive angiogenesis, reduced barrier function, pro-coagulant activity, and a pro-inflammatory status, which are all associated with cardiovascular disease (4). The soluble vascular cell adhesion molecule 1 (sVCAM-1), soluble intercellular adhesion molecule 1 (sICAM-1) and von Willebrand factor (vWF) are biomarkers of endothelial function. These markers are elevated in patients with T2D and have been linked to vascular complications and mortality in T2D (3, 5-9). The systemic inflammation marker high-sensitivity C-reactive protein (hs-CRP) is also associated with endothelial dysfunction, atherosclerosis as well as visceral adipose tissue mass (10, 11). The hs-CRP levels are clinically used to stratify cardiovascular risk (12).

Moderate intentional weight loss in overweight persons with and without T2D improves insulin sensitivity, blood pressure, lipid profile, endothelial function, and alleviates the pro-inflammatory state (13-19). However, weight loss resulting from a lifestyle intervention did not reduce the cardiovascular risk of patients with T2D in the Look AHEAD trial (20). The use of well-established, cardio-protective drugs such as statins, angiotensin-converting enzyme (ACE) inhibitors and metformin, which are commonly prescribed in T2D, might have reduced the contrast between the groups in this study. Alternatively, pathological changes might have become irreversible after a long history of T2D.

In this study, we have investigated the effect of diet-induced weight loss on biomarkers of endothelial dysfunction and inflammation in overweight and obese patients with T2D. Subsequently, we determined the associations between the change in biomarkers and the use of cardio-protective medication and the time since diagnosis of T2D.

MATERIALS AND METHODS

The present study is a pragmatic before-after study in the run-in phase of the Prevention Of Weight Regain (POWER) trial of which the protocol has been published previously (21). This study was approved by the Medical Ethics Committee of the Erasmus Medical Center in Rotterdam (reference number MEC-2009-143/NL26508.078.09), in compliance with the Helsinki Declaration. All participants provided informed consent.

Study population

Overweight and obese T2D patients (BMI>27 kg/m^2) aged 18-75 years were recruited from the outpatient diabetes clinic of the Erasmus Medical Center, Rotterdam from 2010-2013. Exclusion criteria were pregnancy, lactation, severe psychiatric problems, significant cardiac arrhythmias, unstable angina, decompensated congestive heart failure, major organ system failure, untreated hypothyroidism, and end-stage renal disease, and a myocardial infarction, cerebrovascular accident or major surgery during the previous 3 months. For all participants in the present study, antidiabetic and cardio protective medication was constant for at least 3 months prior to the intervention.

Diet intervention and data collection

The participants started with a very low-calorie diet (VLCD) of 750 kcal per day for a period of 8 weeks. The VLCD consisted of 2 commercially available meal replacements (Glucerna SR, Abbott Nutrition B.V.) per day plus 75 grams of lean meat, 150 ml of skimmed milk, and low-carbohydrate vegetables ad libitum. Subsequently, participants followed a low calorie diet of 1100-1300 kcal/day for another 12 weeks. After 20 weeks, the participants used a 1300 kcal/day diet based on national health recommendations. During the diet program, 60 minutes of daily exercise was encouraged. To reduce the risk of hypoglycemia, the doses of sulfonylurea-derivatives and insulin were lowered before start of the dietary intervention but after baseline measurements. During the dietary intervention, insulin dose was adjusted based on glucose levels. Since insulin was adjusted during the intervention, we did not analyze the interaction of insulin use with the diet-effect, but in all the analyses diet-induced effects were corrected for the insulin change during the intervention. The doses of metformin, statins and ACE inhibitors were maintained during the intervention.

Plasma samples were obtained after an overnight fast, and samples were stored at -80°C until further analysis. Of the 206 patients, who followed the dietary intervention, blood samples were obtained before as well as immediately after the dietary intervention of 131 patients. To enable participants to serve as their own control, only these 131 patients were enrolled in the current study. The other 75 patients did not differ significantly from the enrolled patients with respect to age, sex, baseline weight, baseline $HbA1_c$ or diabetes complications (data not shown). We recorded demographic variables, duration of diabetes, smoking status and medication use, and measured weight (kg), waist circumference (cm) and blood pressure of all participants before and after the dietary intervention. The combined use of statins, ACE inhibitors and metformin was defined as 'maximum treatment'. Glycated hemoglobin ($HbA1_c$ (mmol/mol)), fasting glucose (mmol/l) and plasma lipids (mmol/l) were measured using routine lab techniques. Physical activity was measured using the Short Questionnaire to Assess Health Enhancing

Physical Activity (SQUASH) (22). The study was monitored and documented with the trial management system OpenClinica (Waltham, MA).

Measurement of biomarkers of endothelial dysfunction and inflammation

Biomarker levels were measured in plasma by enzyme-linked immunosorbent assays (ELISA). sICAM-1, sVCAM-1 and hs-CRP were measured using DuoSet ELISA Development Systems (R&D Systems, Minneapolis, MN) and vWF was measured using Von Willebrand Factor BioAssay ELISA (USBiological Life Sciences, Salem, MA). All assays were performed according to the manufacturer's instructions. For each patient, samples collected before and after intervention were analyzed on the same ELISA plate.

Statistical analysis

We calculated that a sample size of 120 patients would give a power of 80% to detect a small effect (Cohen's d=0.20) with an alpha of 0.05 and an inter-correlation of 0.70 between the two measurements. Normality of the data and homogeneity of variances were tested using the Shapiro-Wilks test and Levene's test. Variables before and after the dietary intervention were expressed as mean with standard deviation or median with inter-quartile range and tested for statistical significance using a two-sided paired samples t-test or a Wilcoxon ranking test plus Hodges-Lehman median difference test, depending on presence or absence of normality of data. Wilcoxon ranking tests were used to compare the distribution of participants across CRP based CVD-risk groups before and after the intervention. Matched linear regression analyses were performed to test the association of the change in biomarkers with medication use and T2D history, corrected for age, sex and change in insulin dose. To analyze the interaction between the biomarkers before and after dietary intervention and medication use, we used repeated measurements MANOVA analyses. The variables used in the regression analyses and repeated measurements MANOVA were Blom-transformed to meet with the assumption of normally distributed residuals. Statistical significance was considered at p-values of <0.05. All statistical analyses were carried out using IBM SPSS statistics version 21.

RESULTS

Baseline characteristics

Table 1 summarizes the characteristics of our study population. At baseline, the BMI was 36.8±5.6 kg/m^2. The median period after T2D diagnosis was 10.0 years and ranged from 0.4 to 39.0 years. Of the 131 participants, 62.6% were treated with insulin, 75.6% with metformin and 20.6% with a sulfonylurea-derivative, while only two participants were treated with incretins and none with thiazolidinediones. 72.5% of

the participants used statins, whereas 58.8% of the participants used ACE inhibitors, 35.9% beta blockers, 21.4% calcium antagonists, 48.1% diuretics and 3.1% alpha-2 antagonists. Microvascular and macrovascular complications were evident in 60.3% and 27.6% of the participants. While on medication, the median baseline $HbA1_c$ level was 61.0 mmol/mol and the median baseline LDL cholesterol level was 2.5 mmol/l. Nineteen participants (15.4%) were current smokers; during the intervention period three started and two stopped smoking.

Table 1. Characteristics of the study population (n=131) before and after dietary intervention

Variables*	Before	After	p-value**
Age (y, range)	54 (26-74)		
Sex (% female)	57.3		
Years after diagnose T2D	10.0 (3.0, 15.0)		
Insulin users (%)	62.6	57.6	
Insulin dose among users (IU/day)	108.0 (68.0, 136.0)	31.0 (16.8, 52.5)	<0.001
Metformin users (%)	75.6	unchanged	
Metformin dose among users (mg/day)	1700 (1000, 2550)	unchanged	
Statin users (%)	72.5	unchanged	
ACE inhibitor users (%)	58.8	unchanged	
Microvascular disease (%)	60.3	unchanged	
Macrovascular disease (%)	27.6	unchanged	
Physical Activity (SQUASH score)	3360 (1440, 6270)	3960 (1800, 7680)	0.395
Weight (kg)	105.0±19.1	94.5±17.3	<0.001
BMI (kg/m²)	36.8±5.6	33.1±5.2	<0.001
Waist circumference (cm)	119.8±12.9	110.8±11.9	<0.001
Systolic blood pressure (mmHg)	138.0 (127.8, 157.3)	139.0 (128.0, 150.0)	0.405
$HbA1_c$ (mmol/mol)	61.0 (52.0, 71.0)	53.0 (43.0, 66.0)	<0.001
Fasting glucose (mmol/l)	8.8 (6.9, 10.8)	7.3 (6.1, 9.3)	<0.001
Total cholesterol (mmol/l)	4.4 (3.7, 5.1)	4.1 (3.5, 4.8)	<0.001
LDL cholesterol (mmol/l)	2.5 (2.1, 3.1)	2.4 (1.8, 2.9)	<0.001
HDL cholesterol (mmol/l)	1.1 (1.0, 1.3)	1.2 (1.0, 1.4)	0.002
Triglycerides (mmol/l)	1.8 (1.2, 2.6)	1.4 (1.0, 2.0)	<0.001
sICAM-1 (ng/ml)	175.0 (133.1, 257.5)	158.2 (113.4, 222.5)	0.001
sVCAM-1 (ng/ml)	451.3 (324.3, 636.5)	432.5 (292.0, 682.1)	0.949
hs-CRP (mg/l)	3.9 (1.6, 13.0)	3.4 (1.1, 8.5)	0.007
vWF (IU/ml)	31.3 (24.1, 43.6)	30.2 (20.5, 40.7)	0.003

**Mean±SD or median (interquartile range), **Paired samples T-test or Wilcoxon ranking test*

At baseline, the statin users had a lower median LDL cholesterol (2.4 mmol/L (2.0, 3.0) vs. 2.9 mmol/L (2.3, 3.6), p=0.007), lower hs-CRP (3.3 g/mL (1.3, 10.0) vs. 6.9 g/mL

(1.8, 18.9), p=0.035) and lower vWF levels (30.6 IU/mL (23.1, 41.3) vs. 36.2 IU/mL (27.5, 57.7), p=0.028) than the non-statin users. Compared to participants not using ACE inhibitors, users were older (56.0 y (50.0, 63.0) vs. 53.0 y (42.5, 59.0), p=0.018) and had a higher systolic blood pressure (141.0 mmHg (130.0, 162.5) vs. 132.0 mmHg (122.5, 148.5), p=0.009). Participants on metformin treatment did not differ at baseline from those not using metformin. Participants on 'maximum treatment' using the combination of statins, ACE inhibitors and metformin (n=48) showed a lower hs-CRP level than the other participants (2.7 g/mL (1.1, 7.1) vs. 4.8 g/mL (2.3, 16.6), p=0.015).

Effect of the dietary intervention

The effects of the dietary intervention on metabolic and endothelial markers are shown in table 1. During the 4-month dietary intervention, participants lost 10.2 kg (95%CI 9.2, 11.3; p <0.001), which is 9.8±5.2% of their initial bodyweight. The median plasma levels of $HbA1_c$ (-7.0 mmol/mol (95%CI -8.5, -5.0); p<0.001), LDL cholesterol (-0.2 mmol/L (95%CI -0.4, -0.1); p<0.001) and other plasma lipids (p<0.01) improved, while systolic blood pressure did not change (p=0.405). The median plasma levels of sICAM-1 (-22.4 ng/mL (95%CI -37.1, -8.7); p=0.001), vWF (-3.9 IU/mL (95%CI -6.4, -1.4); p=0.003) and hs-CRP (-0.6 mg/L (95%CI -1.2, -0.2); p=0.007) decreased during the weight loss intervention, while sVCAM-1 levels were unchanged (1.6 ng/mL (95%CI -41.5, 48.6); p=0.949). The change in these biomarkers was not correlated with change in physical activity nor with the prevalence of microvascular and macrovascular disease (data not shown).

Only for CRP levels, a cut-off point for high CVD risk has been defined as equal to or above 3 mg/L, while CRP levels <1 mg/L reflect a low risk for CVD (12). The distribution of patients over the three risk categories shifted significantly towards the lower CVD-risk categories during the diet intervention (p<0.001): at baseline, 58.3% of our population had a CRP level above 3 mg/ml, which decreased to 50.8% after the dietary intervention (p=0.033). The proportion of patients with a low-risk CRP level increased from 12.1% to 23.5% during the diet intervention (p<0.001).

Associations of the change in biomarkers with duration of T2D

To determine whether the diet-induced changes in biomarkers were associated with the time since diagnosis of T2D, we conducted univariate linear regression analyses, corrected for age, sex and change in insulin dose. At baseline, sVCAM-1 levels were positively associated with duration of T2D (β=0.245, p=0.005), while sICAM-1 (β=0.104, p=0.237), vWF (β=0.065, p=0.460) and hs-CRP levels (β=-0.021, p=0.811) were not. The diet-induced changes in sICAM-1 (β=-0.044, p=0.621), sVCAM-1 (β=0.013, p=0.886), vWF (β=-0.005, p=0.952) and hs-CRP (β=-0.012, p=0.887) were not related to the duration of T2D.

Table 2. The interaction between diet-induced weight loss and medication on markers of endothelial function and inflammation

Biomarker:	Before diet:	After diet:	Before diet:	After diet:	P_{time}*	$P_{interaction}$**
	No statins (n=36)		Statins (n=95)			
sICAM-1 (ng/mL)	182.9 (127.7, 281.0)	150.2 (110.6, 258.0)	174.7 (134.0, 249.1)	158.2 (116.0, 216.8)	.002	.711
sVCAM-1 (ng/mL)	409.0 (325.0, 588.6)	474.9 (339.2, 724.5)	459.7 (323.4, 686.0)	424.3 (276.7, 635.9)	.667	.079
hs-CRP (g/mL)	6.9 (1.8, 18.9)	3.8 (1.4, 11.7)	3.3 (1.3, 10.0)	2.6 (0.9, 7.5)	.001	.232
VWF (IU/mL)	36.2 (27.5, 57.7)	31.8 (21.9, 49.9)	30.6 (23.1, 41.3)	29.3 (18.6, 38.1)	.012	.657
	No ACE inhibitors (n=54)		ACE inhibitors (n=77)			
sICAM-1 (ng/mL)	181.1 (134.9, 258.2)	193.6 (127.0, 251.0)	171.1 (128.3, 251.6)	145.4 (107.7, 200.5)	.003	.053
sVCAM-1 (ng/mL)	420.6 (303.6, 579.2)	438.8 (294.8, 736.4)	476.1 (333.7, 663.6)	432.5 (274.2, 675.7)	.854	.220
hs-CRP (g/mL)	3.8 (1.8, 13.1)	3.5 (1.5, 8.6)	4.4 (1.3, 12.6)	2.7 (0.8, 8.6)	.003	.253
VWF (IU/mL)	31.9 (27.1, 39.9)	31.4 (25.0, 41.2)	31.3 (22.6, 48.4)	28.4 (17.9, 39.2)	.018	.247
	No metformin (n=32)		Metformin (n=99)			
sICAM-1 (ng/mL)	217.8 (138.0, 298.6)	204.8 (130.0, 285.6)	171.1 (127.8, 231.1)	146.8 (109.1, 202.6)	.020	.248
sVCAM-1 (ng/mL)	484.5 (306.4, 730.0)	441.9 (339.2, 918.8)	429.3 (327.1, 614.4)	424.4 (276.7, 680.4)	.988	.478
hs-CRP (g/mL)	5.4 (2.4, 17.0)	5.3 (1.7, 22.7)	3.6 (1.3, 11.6)	2.6 (0.9, 7.4)	.047	.094
VWF (IU/mL)	33.0 (24.5, 56.5)	32.2 (15.6, 48.1)	31.0 (24.1, 42.7)	29.9 (20.5, 39.8)	.027	.948
	No maximum treatment (n=83)		Maximum treatment (n=48)			
sICAM-1 (ng/mL)	186.9 (133.8, 285.7)	189.8 (125.5, 262.2)	161.9 (128.6, 207.9)	142.6 (98.0, 168.1)	.001	.093
sVCAM-1 (ng/mL)	432.3 (317.5, 610.7)	439.1 (335.2, 736.2)	461.0 (332,6, 669.1)	420.6 (248.4, 568.9)	.353	.047
hs-CRP (g/mL)	4.8 (2.3, 16.6)	4.0 (1.6, 11.7)	2.7 (1.1, 7.1)	2.0 (0.7, 7.0)	.002	.887
VWF (IU/mL)	33.7 (26.2, 43.6)	31.3 (22.4, 42.9)	28.1 (21.5, 45.9)	28.0 (17.8, 38.1)	.007	.515

Median (interquartile range) of the biomarkers are reported.

Repeated measurements MANOVA analyses were performed on normalized outcome values, we reported the *time effect and **interaction effect.

Associations of the change in biomarkers with cardio-protective medication

Firstly, we studied the association of medication with the diet-induced change in the vascular biomarker levels via a matched linear regression analysis corrected for age, sex and change in insulin dose. Changes in the biomarkers were not associated with the use of statins, ACE inhibitors or metformin, except for a negative association between statin use and change in sVCAM-1 (β=-0.23, p=0.020).

We also performed a formal interaction study. In table 2 we present the difference in effect of the dietary intervention on the measured vascular biomarkers, according to medication use. There were no significant interactions between the vascular biomarker levels before and after diet and the use of statins, ACE inhibitors and metformin. We found a borderline significant interaction between sVCAM-1 before and after diet with maximum medical treatment (statin plus ACE inhibitor plus metformin). Participants on maximum medical treatment showed a decrease in sVCAM-1 while the other participants showed an increase in sVCAM-1 (between-group difference p=0.047). Similar results were obtained after adjusting for age, sex, weight change and insulin use.

DISCUSSION

We found that diet-induced weight loss not only improved glycemic state and lipid parameters, but also reduced biomarkers of endothelial dysfunction and inflammation in overweight and obese patients with T2D. These effects of weight loss were not associated with the duration of T2D or with the use of statins, ACE inhibitors, and metformin.

The beneficial effect of diet-induced weight loss on classical cardiovascular risk factors such as hypercholesterolemia and hyperglycemia in obese T2D patients is well established (20, 23) and confirmed in this study. Our results on biomarkers of endothelial function and inflammation are in concordance with previous studies on weight loss dieting in obese subjects with and without T2D (16, 19, 24-27). The biomarkers for endothelial function used in this study play an important role in the adhesion of leukocytes to the endothelium, coagulation processes and vascular inflammation (28, 29). In subjects with T2D, each of these biomarkers is strongly associated with cardiovascular outcome (3, 7-11), and a lowering of sICAM-1, vWF and hs-CRP may therefore reduce the risk of vascular complications. To illustrate, the proportion of patients shifting from the medium or high CVD risk group to the low CVD risk group, according to their hs-CRP level, was almost doubled. However, the changes in biomarker levels induced by our short term diet-induced weight loss program are relatively small, and follow-up studies are required to determine the clinical relevance.

We found that statin use and diet-induced weight loss are additive in reducing hs-CRP levels in T2D patients, which is in line with the results of the Look AHEAD trial (24). Although the dietary intervention in our study was of shorter duration, the same magnitude of weight loss was observed as in the Intensive Lifestyle Intervention arm of the Look AHEAD trial after 1 year (20). Unlike the Look AHEAD group, we directly compared the statin-treated with the non-statin treated participants. Adjustments of the statin doses made during the dietary intervention period were a limitation of the Look Ahead study. In our study, medication doses were maintained during the intervention. We found no interaction of statin use with improvements in hs-CRP levels, nor in sICAM-1 and vWF levels. The only interaction between diet and medication was observed in patients receiving the combination of a statin, ACE inhibitor and metformin versus the other patients, which showed a diet-induced improvement of sVCAM1 levels when on maximal treatment. The lack of effect on cardiovascular endpoints in the Look AHEAD trial (20) may therefore not be the result of the increasingly intensive medical treatment of the participants, but possibly of the gradual regain of weight during the follow-up period. Taken together, lifestyle interventions aimed at long-term weight reduction may still be a therapeutic option on top of medication in overweight and obese T2D patients.

The wide range of T2D history in our study group (0.4-39.0 years since T2D was diagnosed) gave us a good opportunity to study the influence of duration of T2D on the effect of a weight loss intervention. One could argue that in a late stage of disease many pathological changes have become irreversible and therefore the vasculature may not benefit from weight loss anymore (30). However, we found that the effect of weight loss on surrogate vascular endpoints was independent of T2D duration, suggesting that patients with a long history of T2D still benefit from a weight loss intervention similar to newly diagnosed patients. Our results are in line with results from patients with a relatively short history of T2D. In the ACTID trial (26) the levels of sICAM-1, CRP and IL-6 decreased significantly during diet and in another small trial brachial flow-mediated dilatation (FMD) improved, although the microvascular reactivity and vWF did not change significantly in this latter trial (19).

Strengths and limitations of the study

The present study is a pragmatic before-after study in the run-in phase of a randomized trial. As a consequence, we cannot fully exclude that other factors than the dietary intervention have contributed to the described effects. Physical activity did not change significantly and did not correlate with the change in biomarkers (data not shown), medication use was tightly monitored and no major changes in medical status are to be expected during the 4-month intervention period. However, patient compliance to medication or dietary treatment could not be checked. Future randomized controlled replication studies are required in order to confirm our findings. One could argue that the

medication subgroups were small and that the chance of a type 2 error was considerable for the interaction analysis. However, the linear regression analyses are more robust and were in concordance with the interaction study. Another limitation is the use of change scores in the regression analyses, which may be sensitive to regression toward the mean. Finally, our study was limited to the endothelial role in inflammation and thrombosis using surrogate markers. We have no data available for vasomotor, barrier and angiogenic function. The effect of diet-induced weight loss on long-term endothelial function and cardiovascular endpoints in this patient population awaits further study. Strengths of the present study were the prospective design, structured information about medication use and a strict medication protocol during the intervention. Furthermore, we were able to collect a cohort with a wide range of T2D history, making the results generalizable to the overweight and obese T2D population.

CONCLUSIONS

Our findings support a beneficial effect of diet-induced weight reduction on biomarkers of endothelial dysfunction and inflammation irrespective of intensive medical drug treatment and a long history of T2D. Replication in long term follow-up studies is needed in order to establish the effect of diet-induced weight loss and the interaction with cardio protective medication on cardiovascular endpoints.

REFERENCES

1. Barr EL, Zimmet PZ, Welborn TA, Jolley D, Magliano DJ, Dunstan DW, et al. Risk of cardiovascular and all-cause mortality in individuals with diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance: the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). Circulation. 2007;116(2):151-7.
2. Katzmarzyk PT, Hu G, Cefalu WT, Mire E, Bouchard C. The importance of waist circumference and BMI for mortality risk in diabetic adults. Diabetes Care. 2013;36(10):3128-30.
3. Tousoulis D, Papageorgiou N, Androulakis E, Siasos G, Latsios G, Tentolouris K, et al. Diabetes mellitus-associated vascular impairment: novel circulating biomarkers and therapeutic approaches. J Am Coll Cardiol. 2013;62(8):667-76.
4. Eringa EC, Serne EH, Meijer RI, Schalkwijk CG, Houben AJ, Stehouwer CD, et al. Endothelial dysfunction in (pre)diabetes: characteristics, causative mechanisms and pathogenic role in type 2 diabetes. Rev Endocr Metab Disord. 2013;14(1):39-48.
5. Steiner M, Reinhardt KM, Krammer B, Ernst B, Blann AD. Increased levels of soluble adhesion molecules in type 2 (non-insulin dependent) diabetes mellitus are independent of glycaemic control. Thromb Haemost. 1994;72(6):979-84.
6. Meigs JB, Hu FB, Rifai N, Manson JE. Biomarkers of endothelial dysfunction and risk of type 2 diabetes mellitus. Jama. 2004;291(16):1978-86.
7. Stehouwer CD, Gall MA, Twisk JW, Knudsen E, Emeis JJ, Parving HH. Increased urinary albumin excretion, endothelial dysfunction, and chronic low-grade inflammation in type 2 diabetes: progressive, interrelated, and independently associated with risk of death. Diabetes. 2002;51(4):1157-65.
8. Kanai A, Kawamura T, Umemura T, Nagashima M, Nakamura N, Nakayama M, et al. Association between future events of brain infarction and soluble levels of intercellular adhesion molecule-1 and C-reactive protein in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract. 2008;82(2):157-64.
9. Frankel DS, Meigs JB, Massaro JM, Wilson PW, O'Donnell CJ, D'Agostino RB, et al. Von Willebrand factor, type 2 diabetes mellitus, and risk of cardiovascular disease: the framingham offspring study. Circulation. 2008;118(24):2533-9.
10. Schillinger M, Exner M, Amighi J, Mlekusch W, Sabeti S, Rumpold H, et al. Joint effects of C-reactive protein and glycated hemoglobin in predicting future cardiovascular events of patients with advanced atherosclerosis. Circulation. 2003;108(19):2323-8.
11. Schulze MB, Rimm EB, Li T, Rifai N, Stampfer MJ, Hu FB. C-reactive protein and incident cardiovascular events among men with diabetes. Diabetes Care. 2004;27(4):889-94.
12. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, 3rd, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003;107(3):499-511.
13. Look Ahead Research Group. Effect of a long-term behavioural weight loss intervention on nephropathy in overweight or obese adults with type 2 diabetes: a secondary analysis of the Look AHEAD randomised clinical trial. Lancet Diabetes Endocrinol. 2014;2(10):801-9.
14. Wing RR, Reboussin D, Lewis CE, Look ARG. Intensive lifestyle intervention in type 2 diabetes. N Engl J Med. 2013;369(24):2358-9.
15. Gregg EW, Chen H, Wagenknecht LE, Clark JM, Delahanty LM, Bantle J, et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. Jama. 2012;308(23):2489-96.

16. Raitakari M, Ilvonen T, Ahotupa M, Lehtimaki T, Harmoinen A, Suominen P, et al. Weight reduction with very-low-caloric diet and endothelial function in overweight adults: role of plasma glucose. Arterioscler Thromb Vasc Biol. 2004;24(1):124-8.

17. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, et al. Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. Jama. 2004;292(12):1440-6.

18. Bigornia SJ, Farb MG, Tiwari S, Karki S, Hamburg NM, Vita JA, et al. Insulin status and vascular responses to weight loss in obesity. J Am Coll Cardiol. 2013;62(24):2297-305.

19. Hamdy O, Ledbury S, Mullooly C, Jarema C, Porter S, Ovalle K, et al. Lifestyle modification improves endothelial function in obese subjects with the insulin resistance syndrome. Diabetes Care. 2003;26(7):2119-25.

20. Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med. 2013;369(2):145-54.

21. Berk KA, Buijks H, Ozcan B, Van't Spijker A, Busschbach JJ, Sijbrands EJ. The Prevention Of WEight Regain in diabetes type 2 (POWER) study: the effectiveness of adding a combined psychological intervention to a very low calorie diet, design and pilot data of a randomized controlled trial. BMC Public Health. 2012;12:1026.

22. Wendel-Vos GC, Schuit AJ, Saris WH, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epidemiol. 2003;56(12):1163-9.

23. Anderson JW, Kendall CW, Jenkins DJ. Importance of weight management in type 2 diabetes: review with meta-analysis of clinical studies. J Am Coll Nutr. 2003;22(5):331-9.

24. Belalcazar LM, Haffner SM, Lang W, Hoogeveen RC, Rushing J, Schwenke DC, et al. Lifestyle intervention and/or statins for the reduction of C-reactive protein in type 2 diabetes: from the look AHEAD study. Obesity (Silver Spring). 2013;21(5):944-50.

25. Clifton PM, Keogh JB, Foster PR, Noakes M. Effect of weight loss on inflammatory and endothelial markers and FMD using two low-fat diets. Int J Obes (Lond). 2005;29(12):1445-51.

26. Thompson D, Walhin JP, Batterham AM, Stokes KA, Cooper AR, Andrews RC. Effect of diet or diet plus physical activity versus usual care on inflammatory markers in patients with newly diagnosed type 2 diabetes: the Early ACTivity In Diabetes (ACTID) randomized, controlled trial. J Am Heart Assoc. 2014;3(3):e000828.

27. Buscemi S, Cosentino L, Rosafio G, Morgana M, Mattina A, Sprini D, et al. Effects of hypocaloric diets with different glycemic indexes on endothelial function and glycemic variability in overweight and in obese adult patients at increased cardiovascular risk. Clin Nutr. 2013;32(3):346-52.

28. Tousoulis D, Hatzis G, Papageorgiou N, Androulakis E, Bouras G, Giolis A, et al. Assessment of acute coronary syndromes: focus on novel biomarkers. Curr Med Chem. 2012;19(16):2572-87.

29. Tousoulis D, Kampoli AM, Tentolouris C, Papageorgiou N, Stefanadis C. The role of nitric oxide on endothelial function. Curr Vasc Pharmacol. 2012;10(1):4-18.

30. Johansen OE. Interpretation of cardiovascular outcome trials in type 2 diabetes needs a multiaxial approach. World J Diabetes. 2015;6(9):1092-6.

Chapter 4

Levels of the soluble LDL receptor-relative LR11 decrease in overweight individuals with Type 2 Diabetes upon diet-induced weight loss

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ABSTRACT

Background and Aims

Cardiovascular disease (CVD) is a major complication in patients with type 2 diabetes (T2D), especially in those with obesity. Plasma soluble low density lipoprotein receptor-relative with 11 ligand-binding repeats (sLR11) plays a role in the development of atherosclerosis and has been linked with the metabolism of triglyceride-rich lipoproteins, adiposity, and vascular complications in T2D. We aimed to determine the effect of diet-induced weight loss on plasma sLR11 levels in overweight and obese individuals with T2D.

Methods

Plasma sLR11 levels were determined in 64 individuals with T2D and BMI > 27 kg/m^2 before and after a 20-week weight loss diet. As a reference, sLR11 levels were also determined in 64 healthy, non-obese controls, matched as a group for age and sex.

Results

Median plasma sLR11 levels of the T2D study-group at baseline (15.4 ng/mL (IQR 12.9-19.5)) were higher than in the controls (10.2 (IQR: 8.7-12.2) ng/mL; p=0.001). The diet resulted in a weight loss of 9.7±5.2% (p=0.001) and improved CVD risk factors. sLR11 levels were reduced to 13.3 ng/mL (IQR 11.0-17.1; p=0.001). Changes in sLR11 levels positively associated with changes in non-HDL cholesterol (B=1.54, R^2=0.17, p=0.001) and HbA1c (B=0.07, R^2=0.11, p=0.007), but not with weight loss (B=0.04, R^2=0.05, p=0.076). The changes in non-HDL cholesterol and HbA1c together explained 24% of the variance of sLR11 reduction (p=0.001).

Conclusions

Weight loss dieting in overweight and obese individuals with T2D resulted in a reduction in plasma sLR11 levels, that was associated with improvements in lipid-profile and glycemic state.

INTRODUCTION

Type 2 diabetes (T2D) and obesity are major risk factors for cardiovascular disease (CVD) (1-4). The risk of cardiovascular disease (CVD) is higher in obese than in lean individuals with T2D (1). Weight loss has been shown to improve multiple cardiovascular risk factors in obese patients with T2D, e.g. lipid profile, glycemic control, blood pressure and systemic inflammation (5-9).

Low density lipoprotein receptor-relative with 11 ligand-binding repeats (LR11, also called SorLA or SORL1) is a type I membrane protein, which after proteolytic cleavage sheds a large soluble extracellular part called sLR11 into the circulation (10, 11). LR11 is highly expressed in intimal smooth muscle cells of atheromatous lesions in experimental animal models (12-14). LR11 and sLR11 have been shown to play a role in the development of atherosclerosis and plaque formation by increasing vascular smooth muscle cell proliferation and migration from media to intima layer, and by causing macrophage infiltration of the arterial wall (10, 11, 15, 16). In mouse models, LR11 expression in adipose tissue and sLR11 plasma levels are upregulated by a high-fat diet (17). In HepG2 and smooth muscle cell cultures, LR11 expression and sLR11 release are stimulated by triglyceride-rich lipoproteins (TGRL) (18), which typically are increased in subjects with T2D (19, 20). Compared to healthy controls, levels of sLR11 are higher in individuals with T2D (21, 22) and are correlated with hemoglobin A1c (HbA1c) levels (21, 23, 24). Individuals with T2D complicated by coronary stenosis, acute coronary syndrome, or retinopathy display increased plasma sLR11 levels, suggesting a link with the severity of vascular complications in these patients (21, 23, 25). In humans, LR11 expression in white adipose tissue (WAT) positively correlated with BMI (26), and plasma levels of sLR11 correlated with BMI and overall adipose tissue mass (17). In mouse models, sLR11 has been shown to act as a negative regulator of adipose tissue energy expenditure (17), and LR11 expression in WAT exacerbated diet-induced adiposity and decreased lipolysis in WAT by promoting cell surface recycling of internalized insulin receptors (26). The decrease in BMI and visceral and subcutaneous fat tissue induced by bariatric surgery in obese subjects was accompanied by a marked reduction in sLR11 levels (17). We therefore hypothesized that diet-induced weight loss will reduce sLR11 levels in patients with T2D.

The aim of the current study was to determine whether diet-induced weight loss affects sLR11 levels in a cohort of overweight and obese patients with T2D. In addition, we investigated the association between plasma sLR11 levels and other CVD risk factors in relation with diet-induced weight loss.

MATERIALS AND METHODS

Study Population and Design

In this study, we enrolled the first 64 participants of the run-in phase of the Prevention of Weight Regain (POWER)-trial (27). The latter study was aimed at studying long term weight maintenance after the run-in diet phase. Participants were overweight and obese subjects (BMI > 27 kg/m^2) with established T2D from the outpatient clinic of the Erasmus Medical Center, Rotterdam, the Netherlands. Exclusion criteria were pregnancy (or lactating), severe psychiatric problems, significant cardiac arrhythmias, unstable angina, decompensated congestive heart failure, major organ system failure, untreated hypothyroidism, end-stage renal disease, or a cerebrovascular event, myocardial infarction or major surgery in the last 3 months.

The participants were subjected to a very low calorie diet for 8 weeks, using a diabetes-specific meal replacement (Glucerna SR, Abbott Nutrition BV) for breakfast and lunch combined with a light dinner, providing approximately 750 kcal/day in total, including 67 g carbohydrates, 54 g protein and 32 g fat (of which 16 g was monounsaturated fatty acid), and micronutrients as recommended by the national nutritional guidelines (27). In the next 12 weeks, a low calorie diet according to the national nutritional guidelines (approx. 1300 kcal/day), was gradually reintroduced.

At baseline and after the diet intervention, outcome parameters were measured and filed in a database using the OpenClinica® trial management system. We recorded demographic variables, exercise (days per week with minimum of 30 minutes of exercise), diabetes complications and medication use. Statin medication was converted into statin equivalent score (scale 0-7) (28). We measured bodyweight, height, waist circumference and blood pressure, and determined glycated hemoglobin (HbA1c), fasting glucose, fasting insulin, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and hs-CRP by standard clinical laboratory assays. Non-HDL cholesterol was calculated as the difference between total and HDL cholesterol. HOMA-IR was calculated using the formula: HOMA-IR = [glucose (mmol/L) * insulin (μU/mL)/22.5] (29), but analyzed separately for insulin users and non-insulin users.

A healthy control group was used as a reference for the sRL11 level. The controls were matched as a group for age and sex to the T2D group but did not undergo dieting. The healthy controls (n = 64) were recruited via an advertisement in the Rotterdam region.

All participants provided written informed consent. This research was approved by the Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam, the Netherlands (reference number MEC-2009-143/NL26508.078.09), in compliance with the Helsinki Declaration.

Blood sample analysis

Fasting blood samples were obtained from the patients with T2D before and after the 20-week dieting period, and from the healthy controls. After centrifugation, plasma samples were stored at -80°C until analysis. Lipid and glycemic parameters were measured by standard biochemical techniques. Soluble LR11 was measured using a sandwich enzyme-linked immunosorbent assay (ELISA) with two specific monoclonal antibodies against human LR11 (Sekiaui Medical, Ryugasaki Japan) as previously described (30). In brief, 50 ml of plasma diluted with sample buffer were incubated with the capture monoclonal antibody M3 and then incubated with biotinylated reporter monoclonal antibody R14. The LR11-antibody complex was quantitated with horseradish-peroxidase-conjugated streptavidin. A standard curve was constructed using purified LR11 protein. The lower detection limit for sLR11 was 0.1 ng/mL.

Statistical Analysis

This was a post hoc analysis of data obtained in the run-in phase of a randomized trial, with long term weight loss as the primary endpoint (27). Normality of the data and homogeneity of variances were tested using the Shapiro-Wilks test and Levene's test. Variables before and after the diet intervention period were expressed as ratio (%), mean ± standard deviation or median (inter-quartile range). Differences were tested for statistical significance using a two-sided paired samples t-test or a Wilcoxon ranking test, depending on the normality of data. Changes were calculated as value after intervention minus baseline value. Differences between two (sub)groups were tested for significance using either a two-sided t-test or a Mann-Whitney U test. Potential outliers were identified using Cook's Distance statistics (31). Correlations at baseline were determined using Spearman correlation analysis. We performed univariate linear regression analyses to identify potential contributors to the diet-induced changes in sLR11 levels. The change in sLR11 was log transformed to obtain a normal distribution of the residuals of the regression analyses and perform statistical testing. Subsequently, all significant co-variables were included in multivariate analysis. All data were analyzed using IBM SPSS v 21.0 software.

RESULTS

Baseline measurements

The general characteristics of the 64 patients with T2D are shown in Table 1. Sixty-two (96.9%) out of the 64 patients were obese (BMI> 30 kg/m2). At inclusion, 43 (67%) of the participants presented with microvascular complications and 16 (25%) had experienced macrovascular complications. Forty-five patients (70%) used insulin. The median HOMA-IR for insulin-users and non-insulin-users was 80.6 (39.7-225.9) and 42.6 (23.9-73.0), respectively (p=0.016).

Table 1. Characteristics of the participants before and after diet (n=64)

	Baseline	After diet	*p*
Male sex *N* (%)	28 (44)		
Age (y)	53.0 (46.3-62.0)		
Ethnicity (cau) *N* (%)	39 (61)		
Microvascular complications *N* (%)	43 (67)		
Macrovascular complications *N* (%)	16 (25)		
30 minutes of exercise (days/week)	7.0 (4.0-7.0)	7.0 (5.0-7.0)	0.583
Weight (kg)	106.7±19.5	96.3±17.7	<0.001
BMI (kg/m^2)	37.2±5.3	33.6±5.0	<0.001
Waist circumference (cm)	121.7±12.6	112.2±11.9	<0.001
Systolic blood pressure (mmHg)	141.6±18.1	139.8±21.2	0.509
Diastolic blood pressure (mmHg)	80.1±10.7	79.5±9.4	0.637
sLR11 (ng/mL)	15.4 (12.9-19.5)	13.3 (11.0-17.1)	<0.001
Total cholesterol (mmol/L)	4.5 (3.9-5.5)	4.3 (3.6-5.0)	0.003
HDL cholesterol (mmol/L)	1.1 (1.0-1.3)	1.2 (1.0-1.4)	0.003
LDL cholesterol (mmol/L)	2.5 (2.1-3.1)	2.5 (1.8-2.9)	0.035
Non-HDL cholesterol (mmol/L)	3.3 (2.7-4.1)	3.0 (2.5-3.8)	<0.001
Triglyceride (mmol/L)	1.9 (1.3-2.9)	1.5 (1.0-2.2)	<0.001
hs-CRP (mg/L)	2.8 (1.3-17.7)	2.3 (1.0-10.6)	0.055
HbA1c (%)	7.8 (7.2-8.6)	7.2 (6.3-8.3)	<0.001
HbA1c (mmol/mol)	62.0 (55.0-70.0)	55.0 (45.3-67.8)	<0.001
Fasting glucose (mmol/L)	8.8 (7.2-10.4)	7.2 (6.0-9.4)	<0.001
Insulin users *N* (%)	45 (70)	41 (64)	0.046
Insulin dose among users (IU/day)	100.0 (57.0-136.0)	34.0 (19.0-50.0)	<0.001
Metformin users *N* (%)	46 (72)	48 (75)	0.157
Metformin dose among users (mg/day)	1700 (1375-2550)	1700 (1000-2550)	0.602
Statin users *N* (%)	47 (73)	45 (70)	0.705
Statin equivalent dose (scale 0-7)	4.0 (3.0-4.0)	4.0 (3.0-4.0)	0.839
ACE inhibitor users *N* (%)	38 (59)	34 (53)	0.637

[a]Data are mean±SD or median (IQR)

The healthy controls had a significantly lower BMI (25.7±3.8 kg/m^2) compared to the T2D patients (p<0.001). The median sLR11 level at baseline was 15.4 (IQR: 12.9-19.5) ng/mL for the T2D group, which was significantly higher than the median sLR11 level of the healthy controls (10.2 (IQR: 8.7-12.2) ng/mL, p<0.001).

In the T2D group, baseline levels of sLR11 correlated with levels of HDL cholesterol (r=-0.269, p=0.034), non-HDL cholesterol (r=0.274, p=0.031), ApoB (r=0.324, p=0.010), triglycerides (r=0.303, p=0.016), HbA1c (r=0.254, p=0.045) and fasting glucose (r=0.319, p=0.012). sLR11 levels correlated with HOMA-IR in the non-insulin-

users (r=0.511, p=0.030), but not in the insulin-users (r=0.131, p=0.402). sLR11 was not significantly correlated with weight (r=0.054, p=0.672), BMI (r=0.196, p=0.120), waist circumference (r=0.232, p=0.065) or statin dose (r=-0.219, p=0.082). Similar results were found after exclusion of the two non-obese T2D patients. In the combined T2D and healthy control group, sLR11 levels were significantly correlated with BMI at baseline (r=0.602, p<0.001), but no longer after correcting for fasting glucose levels (r=0.113, p=0.210).

Effect of diet-induced weight loss

After a 20-week dietary intervention, the participants lost 10.5 ± 6.1 kg body weight, which was 9.7% (range +1.7% to -20.7%) of the initial body weight (p<0.001, Table 1). Waist circumference, HDL cholesterol, non-HDL cholesterol, triglyceride, HbA1c, fasting glucose and HOMA-IR all improved significantly (p<0.001). At the end of the diet intervention, the number of participants using insulin was reduced from 45 (70%) to 41 (64%; p=0.046), and among insulin users, the median dose was significantly reduced by 66 units per day (p<0.001). The number of patients on metformin, statin and ACE inhibitors, and prescribed doses, did not change significantly during the intervention period.

After the diet intervention, median plasma sLR11 levels were 13.3 (IQR 11.0-17.1) ng/mL, which was significantly lower than baseline levels (p<0.001). The effect of the diet on plasma sLR11 levels varied markedly among the participants, as shown in Figure 1. Of the 64 participants, 44 exhibited decreased plasma sLR11 levels, 7 remained stable (defined as a change below the intra-assay coefficient of variation of 3%), and the other 13 participants displayed increased plasma sLR11 levels. The participants with decreased sLR11 levels had lost significantly more weight than the other 20 participants (-11.7 kg vs. -7.7 kg, p=0.009).

In Table 2, the results of the univariate regression analyses with the change in sLR11 are shown. The change in sLR11 was not associated with sex, age and weight loss. Significant associations were observed with change in non-HDL cholesterol (B=0.59, R^2=0.17, p=0.001) and HbA1c (B=0.03, R^2=0.11, p=0.007). The change in HbA1c strongly correlated with weight loss (r=0.456, p<0.001), while non-HDL cholesterol levels did not (r=0.209, p=0.105).

In a multiple linear regression model, the change in non-HDL cholesterol and HbA1c remained independently associated with sLR11 change (p=0.003 and p=0.023, Table 3). The model with changes in non-HDL cholesterol and HbA1c explained 24% of the variance of sLR11 change (p<0.001). Adding baseline sLR11 to this model did not affect the point estimates, p-value and the explained variance.

Using Cook's distance analysis (31), we identified four possible outliers with strongly increased sLR11 levels. These four cases showed a moderate influence on the outcomes (Cook's distance 0.08-0.19). Excluding these participants from the analysis yielded the

same independent contributors to the change in sLR11, where the change in non-HDL cholesterol (B=1.48, *p*=0.001) and HbA1c (B=0.08, *p*=0.002) explained 35% of the variance of sLR11 reduction (17% and 18% for change in non-HDL cholesterol and HbA1c, respectively).

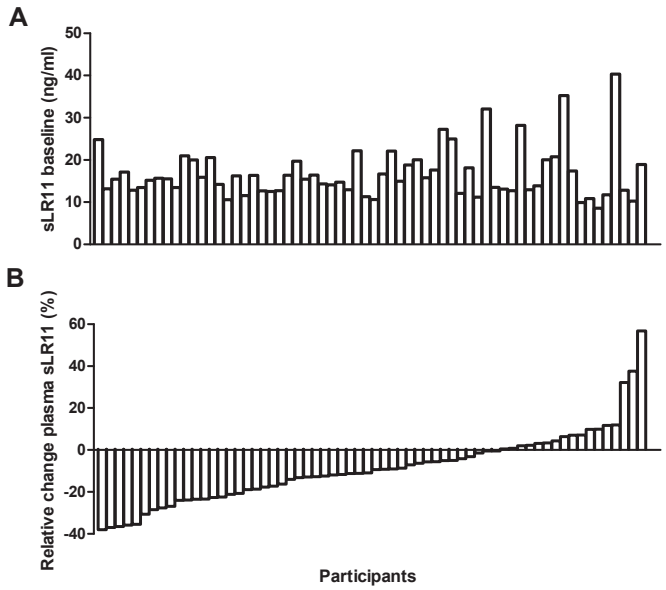

Figure 1. Baseline sLR11 levels and change (%) in plasma sLR11 levels during 20 weeks of diet in individual participants.
(A) Baseline sLR11 levels and (B) change (%) in plasma sLR11 levels during 20 weeks of diet in individual participants 1 till 64. Participants were arranged according to relative change in plasma sLR11 levels.

Table 2. Univariate regression analysis of (log-transformed) change in plasma sLR11 levels and age, sex, baseline sLR11 and changes in other co-variables.

Univariate	B	95%CI	R^2	*p*
Age	0.01	-0.01-0.04	0.02	0.292
Sex	0.13	-0.43-0.69	0.00	0.644
Baseline sLR11	0.02	-0.03-0.07	0.01	0.413
ΔWeight	0.04	-0.01-0.09	0.05	0.076
ΔWaist circumference	0.03	-0.02-0.09	0.02	0.243
ΔHDL cholesterol	0.32	-1.03-1.66	0.00	0.639
Δnon-HDL cholesterol	0.59	0.25-0.93	0.17	0.001
ΔTriglyceride	0.01	-0.14-0.15	0.00	0.917
ΔCRP	-0.02	-0.04-0.01	0.02	0.245
ΔHbA1c	0.03	0.01-0.05	0.11	0.007
ΔFasting glucose	0.10	-0.01-0.22	0.05	0.082

Table 3. Matched multiple regression analysis of (log-transformed) changes in plasma sLR11 levels and changes in co-variables.

Multivariate	B	95%CI	Partial R^2	*p*
ΔNon-HDL cholesterol	0.53	0.19-0.86	0.15	0.003
Δ$HbA1_C$	0.02	0.003-0.04	0.09	0.023
Explained variance			0.24	

DISCUSSION

The present study shows that plasma sLR11 levels were significantly reduced in overweight and obese individuals with T2D upon a 20-week weight loss diet. The reduction in plasma sLR11 was independently associated with reductions in non-HDL cholesterol and HbA1c, but not with weight loss or the reduction in waist circumference or BMI. The observed reduction in sLR11 during weight loss may have clinical relevance as it is in the same order of magnitude as the previously reported increase in sLR11 upon coronary stenting in response to vascular injury (32). Since patients with T2D are prone to develop atherosclerosis, and sLR11 has been shown to facilitate the atherosclerotic process (10, 11, 15, 16), the reduction in sLR11 may be beneficial in delaying the development of vascular complications.

A decrease of sLR11 levels after weight loss has also been described in morbidly obese individuals, who underwent bariatric surgery (17). At 12 months post-surgery, the decrease in sLR11 and BMI was 37 % and 28%, respectively. In our study, 20 weeks of weight loss dieting resulted in a more modest decrease in sLR11 and BMI of 9% and 10%, but the decrease in sLR11 relative to that in BMI was similar in both studies. In the bariatric surgery study, the decrease in sLR11 was strongly associated with the loss of adipose tissue mass, but not with the reduction in BMI. In our study, the change in sLR11 levels was also not related to change in BMI, nor with change in weight or waist circumference. However, we did not include measurements of adipose tissue mass. Obviously, the effects of bariatric surgery go beyond weight reduction, and include changes in peptide hormones (like GLP-1 and leptin), bile acid flow and gut bacteria, all potentially affecting sLR11 levels (33). Whether these factors are also affected by diet-induced weight loss is unknown. Nonetheless, we show for the first time that the potentially beneficial reduction in sLR11 levels seen after bariatric surgery can also be achieved through weight loss dieting.

The average baseline sLR11 level in the overweight and obese subjects with T2D was significantly higher than in healthy, non-obese controls. Comparable high sLR11 levels (mean: 16.8 ng/ml) have been reported in morbidly obese individuals (17), suggesting that the high sLR11 level in our participants is related to their prominent obesity. However, in our T2D study group sLR11 levels were not correlated with baseline

BMI, weight and waist circumference. Whittle et al. found that circulating sLR11 levels were positively correlated with BMI in 156 subjects with sleep apnea and in 25 subjects with type 2 diabetes or glucose intolerance (17). The participants in their sleep apnea study group were mostly non-obese, and also in their glucose-intolerant study group half of the participants were non-obese, resulting in a BMI ranging from morbidly obese to underweight values. When we included our healthy, mostly normal weight controls in the analysis, we indeed found a strong correlation between BMI and sLR11. Since this correlation disappeared after correcting for baseline fasting glucose levels, it could be argued that the increase of sLR11 with BMI is secondary to decreased glucose tolerance. In line with this, sLR11 levels have previously been shown to be associated with HbA1c levels in diabetic as well as the non-diabetic patient groups (21, 23, 24).

The mechanism by which sLR11 decreases during weight loss-dieting or bariatric surgery remains to be clarified. There is evidence that circulating sLR11 originates from the vasculature (34); however, brown and white adipose tissue highly express LR11 and therefore may also contribute (17). High-fat feeding significantly increased and fasting decreased LR11 mRNA expression in adipose tissue of mice (17). Similarly, we have previously reported that high-fat feeding upregulates liver LR11 expression and circulating sLR11 levels in mice (18). We have also shown that postprandial TGRL enhance the expression of LR11 in hepatocytes (18), as it does in endothelial cells (35). Consequently, the decline in sLR11 levels in the overweight subjects with T2D upon dieting may also be due to reduced levels of TGRL during the dieting period. Accordingly, our data show that changes in sLR11 levels associated with changes in non-HDL cholesterol. These changes in non-HDL cholesterol predominantly reflect altered levels of TGRL, because LDL-C levels were hardly affected by the diet (Table 1). Non-HDL cholesterol level is a known CVD risk factor and a strong predictor of CVD and death in patients with T2D (36, 37). Modulation of sLR11 levels may contribute to the mechanisms by which non-HDL cholesterol affects CVD risk.

sLR11 has recently been identified as a negative regulator of brown adipose tissue (BAT) activity (17). It is tempting to speculate that BAT activity increased, possibly contributing to weight loss and improved metabolic profile, as a result of the decreased sLR11 levels in our study population. The association of sLR11 levels with the glycemic state of the participants, as reflected by HbA1c, has been reported previously for the diabetic as well as the non-diabetic population (21, 23, 24). In mouse models, the increased thermogenic activity in brown and white adipose tissue that is associated with decreased sLR11 levels, has been shown to improve insulin sensitivity and the glycemic state (17). Interestingly, in a recent study mice lacking LR11 expression showed improved insulin sensitivity when fed a high-fat diet, although LR11 was shown to augment insulin receptor signaling in adipocytes by recycling internalized receptor molecules to the cell surface (26). Possibly, the plasma sLR11 levels are only remotely related to LR11 expression in

adipose tissue, or the effects of LR11 on systemic glucose tolerance are mainly mediated by circulating sLR11. Alternatively, glucose transporter type 4 (GLUT4)-storage vesicles were found to be enriched in LR11 (38) suggesting a possible role for LR11 in GLUT4 trafficking. Whether sLR11 has a direct effect on glucose metabolism needs further study.

Study limitations and strengths

Diet-induced weight loss induces a wide range of metabolic changes, making it difficult to pinpoint the precise mechanisms responsible for the observed effect on sLR11 levels. Therefore, it remains to be established to which aspect of the dietary intervention the reduction of sLR11 and its associations can be attributed. We did not study the effect on visceral and subcutaneous fat mass, which in part may account for the unexplained variance in sLR11 change. Moreover, we have conducted a before-after study in which we analyzed weight loss in a continuous way. As a consequence, we cannot fully exclude that lifestyle changes other than the dietary intervention have contributed to the weight reduction. Physical activity, however, did not change significantly. Another limitation is the use of change scores in the regression analyses, which may be sensitive to regression toward the mean, although adding baseline levels to the regression analyses did not change our results. Strengths of this study are the prospective design, the relatively large study population of overweight and obese subjects with T2D, and the relatively long duration of the diet intervention.

In conclusion, circulating sLR11 levels were significantly reduced during weight loss dieting. The reduction in sLR11 was associated with reduction in HbA1c and non-HDL cholesterol levels, and respectively pointing at improved glycemic control and reduced cardiovascular risk. The reduced sLR11 levels may contribute to the mechanism by which diet modulates CVD risk. Further research is warranted to elucidate the direct interactions between sLR11 and glucose, cholesterol and triglyceride metabolism in patients with T2D.

REFERENCES

1. Ridderstrale M, Gudbjornsdottir S, Eliasson B, Nilsson PM, Cederholm J. Obesity and cardiovascular risk factors in type 2 diabetes: results from the Swedish National Diabetes Register. J Intern Med. 2006;259(3):314-22.
2. Dhaliwal SS, Welborn TA. Central obesity and multivariable cardiovascular risk as assessed by the Framingham prediction scores. Am J Cardiol. 2009;103(10):1403-7.
3. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. J Am Coll Cardiol. 2009;53(21):1925-32.
4. Mazzone T, Chait A, Plutzky J. Cardiovascular disease risk in type 2 diabetes mellitus: insights from mechanistic studies. Lancet. 2008;371(9626):1800-9.
5. Maggio CA, Pi-Sunyer FX. The prevention and treatment of obesity. Application to type 2 diabetes. Diabetes Care. 1997;20(11):1744-66.
6. Williamson DF, Thompson TJ, Thun M, Flanders D, Pamuk E, Byers T. Intentional weight loss and mortality among overweight individuals with diabetes. Diabetes Care. 2000;23(10):1499-504.
7. Anderson JW, Kendall CW, Jenkins DJ. Importance of weight management in type 2 diabetes: review with meta-analysis of clinical studies. J Am Coll Nutr. 2003;22(5):331-9.
8. Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med. 2013;369(2):145-54.
9. Baker S, Jerums G, Proietto J. Effects and clinical potential of very-low-calorie diets (VLCDs) in type 2 diabetes. Diabetes Res Clin Pract. 2009;85(3):235-42.
10. Ohwaki K, Bujo H, Jiang M, Yamazaki H, Schneider WJ, Saito Y. A secreted soluble form of LR11, specifically expressed in intimal smooth muscle cells, accelerates formation of lipid-laden macrophages. Arterioscler Thromb Vasc Biol. 2007;27(5):1050-6.
11. Zhu Y, Bujo H, Yamazaki H, Ohwaki K, Jiang M, Hirayama S, et al. LR11, an LDL receptor gene family member, is a novel regulator of smooth muscle cell migration. Circ Res. 2004;94(6):752-8.
12. Bujo H, Saito Y. Markedly induced expression of LR11 in atherosclerosis. J Atheroscler Thromb. 2000;7(1):21-5.
13. Bujo H, Saito Y. Modulation of smooth muscle cell migration by members of the low-density lipoprotein receptor family. Arterioscler Thromb Vasc Biol. 2006;26(6):1246-52.
14. Kanaki T, Bujo H, Hirayama S, Ishii I, Morisaki N, Schneider WJ, et al. Expression of LR11, a mosaic LDL receptor family member, is markedly increased in atherosclerotic lesions. Arterioscler Thromb Vasc Biol. 1999;19(11):2687-95.
15. Zhu Y, Bujo H, Yamazaki H, Hirayama S, Kanaki T, Takahashi K, et al. Enhanced expression of the LDL receptor family member LR11 increases migration of smooth muscle cells in vitro. Circulation. 2002;105(15):1830-6.
16. Jiang M, Bujo H, Ohwaki K, Unoki H, Yamazaki H, Kanaki T, et al. Ang II-stimulated migration of vascular smooth muscle cells is dependent on LR11 in mice. J Clin Invest. 2008;118(8):2733-46.
17. Whittle AJ, Jiang M, Peirce V, Relat J, Virtue S, Ebinuma H, et al. Soluble LR11/SorLA represses thermogenesis in adipose tissue and correlates with BMI in humans. Nat Commun. 2015;6:8951.
18. Vongpromek R, Bujo H, Hoekstra M, Schneider WJ, van der Zee L, Schinkel AF, et al. LR11/SorLA links triglyceride-rich lipoproteins to risk of developing cardiovascular disease in FH patients. Atherosclerosis. 2015;243(2):429-37.

19. Curtin A, Deegan P, Owens D, Collins P, Johnson A, Tomkin GH. Alterations in apolipoprotein B-48 in the postprandial state in NIDDM. Diabetologia. 1994;37(12):1259-64.

20. Ginsberg HN, Zhang YL, Hernandez-Ono A. Regulation of plasma triglycerides in insulin resistance and diabetes. Archives of medical research. 2005;36(3):232-40.

21. Takahashi M, Bujo H, Shiba T, Jiang M, Maeno T, Shirai K. Enhanced circulating soluble LR11 in patients with diabetic retinopathy. Am J Ophthalmol. 2012;154(1):187-92.

22. Shiba T, Bujo H, Takahashi M, Sato Y, Jiang MZ, Hori Y, et al. Vitreous fluid and circulating levels of soluble lr11, a novel marker for progression of diabetic retinopathy. Graef Arch Clin Exp. 2013;251(12):2689-95.

23. Takahashi M, Bujo H, Jiang M, Noike H, Saito Y, Shirai K. Enhanced circulating soluble LR11 in patients with coronary organic stenosis. Atherosclerosis. 2010;210(2):581-4.

24. Nohara A, Kobayashi J, Kawashiri MA, Tada H, Inazu A, Jiang M, et al. Clinical significance of measuring soluble LR11, a circulating marker of atherosclerosis and HbA1c in familial hypercholesterolemia. Clin Biochem. 2014;47(13-14):1326-8.

25. Ogita M, Miyauchi K, Dohi T, Tsuboi S, Miyazaki T, Yokoyama T, et al. Increased circulating soluble LR11 in patients with acute coronary syndrome. Clin Chim Acta. 2013;415:191-4.

26. Schmidt V, Schulz N, Yan X, Schurmann A, Kempa S, Kern M, et al. SORLA facilitates insulin receptor signaling in adipocytes and exacerbates obesity. J Clin Invest. 2016;126(7):2706-20.

27. Berk KA, Buijks H, Ozcan B, Van't Spijker A, Busschbach JJ, Sijbrands EJ. The Prevention Of WEight Regain in diabetes type 2 (POWER) study: the effectiveness of adding a combined psychological intervention to a very low calorie diet, design and pilot data of a randomized controlled trial. BMC public health. 2012;12:1026.

28. Smith M, Lee N, Haney E. Drug Class Review: HMG-CoA Reductase Inhibitors (Statins) and Fixed-dose Combination Products Containing a Statin: Final Report Update 5. Portland (OR): Oregon Health & Science University; 2009.

29. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412-9.

30. Matsuo M, Ebinuma H, Fukamachi I, Jiang M, Bujo H, Saito Y. Development of an immunoassay for the quantification of soluble LR11, a circulating marker of atherosclerosis. Clin Chem. 2009;55(10):1801-8.

31. Cook RD. Detection of Influential Observation in Linear Regression. Technometrics. 1977;19(1):15-8.

32. Ogita M, Miyauchi K, Jiang M, Kasai T, Tsuboi S, Naito R, et al. Circulating soluble LR11, a novel marker of smooth muscle cell proliferation, is enhanced after coronary stenting in response to vascular injury. Atherosclerosis. 2014;237(1):374-8.

33. Chakravartty S, Tassinari D, Salerno A, Giorgakis E, Rubino F. What is the Mechanism Behind Weight Loss Maintenance with Gastric Bypass? Curr Obes Rep. 2015;4(2):262-8.

34. Bajari TM, Winnicki W, Gensberger ET, Scharrer SI, Regele H, Aumayr K, et al. Known players, new interplay in atherogenesis: Chronic shear stress and carbamylated-LDL induce and modulate expression of atherogenic LR11 in human coronary artery endothelium. Thromb Haemostasis. 2014;111(2):323-32.

35. Ting HJ, Stice JP, Schaff UY, Hui DY, Rutledge JC, Knowlton AA, et al. Triglyceride-rich lipoproteins prime aortic endothelium for an enhanced inflammatory response to tumor necrosis factor-alpha. Circulation Research. 2007;100(3):381-90.

36. Liu J, Sempos C, Donahue RP, Dorn J, Trevisan M, Grundy SM. Joint distribution of non-HDL and LDL cholesterol and coronary heart disease risk prediction among individuals with and without diabetes. Diabetes Care. 2005;28(8):1916-21.

37. Lu W, Resnick HE, Jablonski KA, Jones KL, Jain AK, Howard WJ, et al. Non-HDL cholesterol as a predictor of cardiovascular disease in type 2 diabetes: the strong heart study. Diabetes Care. 2003;26(1):16-23.

38. Jedrychowski MP, Gartner CA, Gygi SP, Zhou L, Herz J, Kandror KV, et al. Proteomic analysis of GLUT4 storage vesicles reveals LRP1 to be an important vesicle component and target of insulin signaling. The Journal of biological chemistry. 2010;285(1):104-14.

Chapter 5

Effect of diet-induced weight loss on lipoprotein(a) levels in obese individuals with and without type 2 diabetes

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ABSTRACT

Background and Aims

Elevated levels of lipoprotein(a) [Lp(a)] are an independent risk factor for cardiovascular disease (CVD), particularly in individuals with type 2 diabetes. Although weight loss improves conventional risk factors for CVD in type 2 diabetes, the effects on Lp(a) are unknown and may influence the long-term outcome of CVD after diet-induced weight loss. The aim of this clinical study was to determine the effect of diet-induced weight loss on Lp(a) levels in obese individuals with type 2 diabetes.

Methods

Plasma Lp(a) levels were determined by immunoturbidimetry in plasma obtained before and after 3-4 months of an energy-restricted diet in four independent study cohorts. The primary cohort consisted of 131 predominantly obese patients with type 2 diabetes (cohort 1), all participants of the Prevention Of Weight Regain in diabetes type 2 (POWER) trial. The secondary cohorts consisted of 30 obese patients with type 2 diabetes (cohort 2), 37 obese individuals without type 2 diabetes (cohort 3) and 26 obese individuals without type 2 diabetes who underwent bariatric surgery (cohort 4).

Results

In the primary cohort, the energy-restricted diet resulted in a weight loss of 9.9% (95% CI 8.9, 10.8) and improved conventional CVD risk factors such as LDL-cholesterol levels. Lp(a) levels increased by 14.8 nmol/l (95% CI 10.2, 20.6). In univariate analysis, the change in Lp(a) correlated with baseline Lp(a) levels (r=0.38, $p<0.001$) and change in LDL-cholesterol (r=0.19, $p=0.033$). In cohorts 2 and 3, the weight loss of 8.5% (95% CI 6.5, 10.6) and 6.5% (95% CI 5.7, 7.2) was accompanied by a median increase in Lp(a) of 13.5 nmol/l (95% CI 2.3, 30.0) and 11.9 nmol/l (95% CI 5.7, 19.0), respectively (all $p<0.05$). When cohorts 1-3 were combined, the diet-induced increase in Lp(a) correlated with weight loss (r=0.178, $p=0.012$). In cohort 4, no significant change in Lp(a) was found (-7.0 nmol/l; 95% CI -18.8, 5.3) despite considerable weight loss (14.0%; 95% CI 12.2, 15.7).

Conclusions

Diet-induced weight loss was accompanied by an increase in Lp(a) levels in obese individuals with and without type 2 diabetes while conventional CVD risk factors for CVD improved. This increase in Lp(a) levels may potentially antagonise the beneficial cardiometabolic effects of diet-induced weight reduction.

INTRODUCTION

Cardiovascular disease (CVD) is the main cause of morbidity and mortality in obese individuals with and without type 2 diabetes [1-3]. The risk of CVD in obese patients with type 2 diabetes has been attributed to age, smoking, hyperglycaemia, hypertension and dyslipidaemia [2]. Weight loss via lifestyle programmes, consisting of diet and physical activity, results in an improvement in conventional CVD risk factors and is first-line therapy to slow down the development of type 2 diabetes and the progression of its complications in overweight or obese individuals [4, 5].

Lipoprotein (a) [Lp(a)] is an independent risk factor for CVD [6-12]. Lp(a) consists of an LDL-like particle with an additional apolipoprotein (a) [apo(a)] attached to it. Plasma Lp(a) concentrations vary highly between individuals and are largely genetically determined by the number of copies of kringle-IV type 2 (KIV-2) in the Apo(a) protein (apo(a) isoform) [13-16]. A low number of copies of KIV-2, associated with elevated levels of Lp(a), has been shown to increase the risk of CVD [17]. A recent prospective population-based cohort of 56,367 participants showed a significantly higher contribution of Lp(a) levels to CVD and risk of myocardial infarction in patients with type 2 diabetes than in control participants without type 2 diabetes [18]. About 25% of the variance in Lp(a) levels has been attributed to lifestyle [19]. Weight loss in obese individuals has been reported to affect Lp(a) levels, but the results are controversial [20-23]. The effect of weight loss on plasma Lp(a) levels in type 2 diabetes has not yet been determined.

The aim of the current study was to determine the effect of diet-induced weight loss on Lp(a) levels in obese patients with type 2 diabetes. In order to confirm our findings we also examined the effect of weight loss on Lp(a) levels in three independent cohorts of obese patients with or without type 2 diabetes. As a secondary aim, we assessed the influence of Apo(a) isoforms on diet-induced changes in Lp(a) level in individuals with type 2 diabetes.

METHODS

Participants and interventions

The effect of weight loss was examined in four independent cohorts. The primary cohort (cohort 1, n=131) consisted of overweight and obese individuals (BMI >27 kg/m^2, 93% obese) with type 2 diabetes who participated in the run-in phase of the Prevention Of Weight Regain (POWER) trial (trial registration no. NTR2264) [24]. This trial aimed to study long-term weight maintenance after the run-in diet phase. The sample size of 131 patients was sufficient to find a difference of 10.6 nmol/l (5 mg/dl) in Lp(a) level with a baseline-to-end correlation of 0.95 between the measurements, an a of 0.05

and a power of 0.90. The diet started with 8 weeks of a diet very low in energy (very low calorie diet [VLCD]) of approximately 3000 kJ (750 kcal) per day, consisting of two meal replacements (Glucerna SR, Abbott Nutrition, Lake Forest, Illinois, USA) and a small dinner daily. Thereafter, energy intake was slowly increased up to approximately 5500 kJ (1300 kcal) per day (a low-energy diet) over 12 weeks. Some of the baseline characteristics and effect of the diet on body weight in cohort 1 have previously been reported [25].

Cohort 2 (n=30) also consisted of overweight and obese patients (80% obese) with type 2 diabetes, who were recruited after the POWER trial had finished, to study the implementation of a VLCD for weight loss in type 2 diabetes. The participants underwent the same dietary intervention as the patients in the primary cohort. Cohorts 1 and 2 were both recruited from the outpatient diabetes clinic of the Erasmus Medical Center, Rotterdam, the Netherlands. To reduce risk of hypoglycaemia, doses of insulin and sulfonylurea derivates were lowered before the start of the diet but after baseline measurements had been made. During the diet, the insulin dose was regularly adjusted to achieve optimal glycaemic control. Metformin use was continued. Only two participants were taking glucagon-like peptide 1 (GLP-1) receptor agonist treatment, which was continued during the intervention period. Statin treatment was kept unchanged during the study.

Cohort 3 consisted of 37 obese individuals without type 2 diabetes, who were recruited at the Obesity Center 'Centrum voor Gezond Gewicht' of the Erasmus Medical Center. They underwent a 3 month dietary intervention consisting of a 2000 kJ (500 kcal) per day reduction in intake relative to baseline (low-energy diet), with macronutrient and micronutrient content in line with national dietary guidelines, while exercise was encouraged.

Cohort 4 consisted of 26 obese individuals without type 2 diabetes who underwent gastric banding (n=10) or a gastric bypass procedure (n=16). These participants were recruited at the Leiden University Medical Center, Leiden, the Netherlands. No specific diet was recommended beyond a staged meal progression during the first 3 months after surgery. Analyses were performed at baseline and 3 months after surgery.

The dietary intervention studies and Lp(a) analysis of previously collected clinical samples were approved by the Medical Ethics Committee of the Erasmus Medical Center (reference numbers MEC-2009-143, MEC-2014-090 and MEC 2016-604). The bariatric surgery study and use of the samples was approved by the Medical Ethics Committee of the Leiden University Medical Center (reference number MEC P08.215). All investigations were carried out in accordance with the principles of the declaration of Helsinki (2008). All participants provided written informed consent.

Measurements

Blood samples were obtained after an overnight fast and were stored at -80°C until further analysis. Demographic variables were recorded, and weight, height and waist circumference (except for cohort 4) were measured. Ethnicity was expressed as white or non-white. HbA_{1c}, fasting glucose, total cholesterol, LDL-cholesterol, HDL-cholesterol and triacylglycerol were measured using standard laboratory techniques.

Lp(a) measurement

Plasma Lp(a) concentrations were measured using a particle-enhanced immunoturbidimetric assay, which was largely independent of Apo(a) KIV repeat number (Diagnostic System #171399910930; DiaSys Diagnostic System, GmbH, Holzheim, Germany) [26]. Plasma samples were stored at -80°C for 0.5-5 years and thawed for the first time prior to this analysis. For each individual, levels at baseline and after intervention were measured in the same run. The detection limit of the assay was 6 nmol/l, and the mean intra-assay variability was 2.8%. Interference of triacylglycerol with Lp(a) measurements was minimal, as measured Lp(a) levels were less than 5% affected by the addition of plasma containing different concentrations of triacylglycerol (ranging from 0 to 12 mmol/l) to plasma with a relatively high Lp(a) concentration (169 or 338 nmol/l). Repeated sampling in 27 healthy control individuals at an interval of 2-6 months did not reveal significant differences in median Lp(a): 29.3 nmol/l (interquartile range [IQR] 17.5-87.8) vs 26.4 nmol/l (IQR 12.4-60.3), p=0.087, for day 0 and after 2-6 months, respectively.

In the primary cohort (cohort 1), the Apo(a) KIV repeat number was determined by immunoblotting, as previously described [27, 28]. When two distinct Apo(a) isoforms were present, the band representing the smaller isoform showed the strongest intensity in most cases and was used as a continuous variable. Apo(a) KIV repeat numbers were stratified in two groups as previously described [28]: low molecular weight (mass) (LMW) when at least one isoform with 22 or fewer KIV repeats was present, and high molecular weight (mass) (HMW) when only isoforms with more than 22 repeats were present.

Statistical analysis

Normality of the data and homogeneity of variances were tested using the Shapiro–Wilk test and Levene's test. Variables were expressed as mean ± SD or as median with IQR, and were tested for statistical significance using a two-sided paired-sample *t* test or a Wilcoxon ranking test, depending on the normality of the data. Medians and 95% CIs were calculated using ratio statistics, and median differences were analysed using a related-samples Hodges–Lehman test. Owing to the low numbers in cohorts 2, 3 and 4, in-depth analyses were performed only for cohort 1. We determined Spearman correla-

tions of both baseline Lp(a) levels and change in Lp(a) with different variables of weight loss and glycaemic control.

Mann–Whitney U tests were used to analyse the difference in baseline Lp(a) levels between the LMW and HMW subgroups. Repeated-measurements multivariate ANOVA (MANOVA) analysis (on Blom-transformed outcome variables) was used to analyse the difference in change in Lp(a) between subgroups. SPSS version 21.0 (IBM corp., Armonk, New York, USA) and GraphPad Prism version 5 (GraphPad Software, La Jolla, California, USA) were used for the statistical analyses.

RESULTS

Effect of diet on obese patients with type 2 diabetes (cohort 1)

The characteristics of the primary cohort (cohort 1) at baseline and after intervention are shown in Table 1. The 131 individuals were predominantly obese, as 93% had a BMI greater than 30 kg/m^2. The remainder had a BMI >27 and ≤30 kg/m^2. This cohort had a mixed ethnic background (56% white, and 44% non-white: South-Asian and African). Baseline Lp(a) levels correlated negatively with Apo(a) KIV repeat number (r=-0.53, p<0.001), baseline weight (r=-0.18, p=0.046), HbA_{1c} (r=-0.20, p=0.022), fasting triacylglycerol (r=-0.19, p=0.032) and ethnicity (r=-0.34, p<0.001), and positively with LDL-cholesterol (r=0.18, p=0.038). We found no correlation of baseline Lp(a) levels with sex (r=0.08, p=0.389), fasting glucose (r=-0.17, p=0.057) or fasting insulin levels (r=-0.06, p=0.494). Participants of white origin had lower baseline Lp(a) levels than non-white participants: median 25.7 nmol/l (IQR 5.7-120.1) vs 122.0 nmol/l (IQR 34.0-214.6) (p<0.001).

The diet resulted in a weight loss of 10.2 kg (95% CI 9.2, 11.3), which was equivalent to 9.9% (95% CI 8.9, 10.8) of initial body weight. Both BMI and waist circumference decreased significantly (p<0.001 for all). HbA_{1c} and fasting glucose levels decreased (p<0.001 for both), indicating improved glycaemic control. Lipid variables also improved during the dietary intervention (p<0.01 for all, Table 1).

Lp(a) levels increased significantly from 40.9 nmol/l (IQR 13.9-159.5) to 55.9 nmol/l (IQR 23.0-201.1) (p<0.001, Table 1). Figure 1 shows a waterfall plot of the changes in Lp(a) per individual. Of the 131 participants, 49 showed an increase of over 21 nmol/l (10 mg/dl), and only six showed a decrease of 21 nmol/l or more (10 mg/dl). The median increase in Lp(a) levels in cohort 1 was 14.8 nmol/l (95% CI 10.2, 20.6).

The change in Lp(a) correlated with baseline Lp(a) levels (r=0.38, p<0.001) and with the change in fasting glucose (r=-0.17, p=0.049) and LDL-cholesterol (r=0.19, p=0.033). The correlations with change in fasting glucose and LDL-cholesterol disappeared after correction for baseline Lp(a) levels. The change in Lp(a) did not correlate

Table 1 Characteristics of the study cohorts before and after intervention

Variables	Cohort 1 (n=131)		Cohort 2 (n=30)		Cohort 3 (n=37)		Cohort 4 (n=26)	
	Before	After	Before	After	Before	After	Before	After
Age, years (range)	54 (26-74)	–	55 (34-70)	–	42 (18-63)	–	48 (34-59)	–
Sex, n (%) female	75 (57%)	–	15 (50%)	–	29 (78%)	–	26 (100%)	–
Years after diagnosis of type 2 diabetes	10.0 (3.0-15.0)	–	5.0 (2.0-10.0)	–	–	–	–	–
Weight (kg)	105.0±19.1	94.5±17.3***	103.2±23.3	94.2±21.7***	111.4±17.1	104.3±16.7***	124.0±11.8	106.6±11.2***
BMI (kg/m²)	36.8±5.6	33.1±5.2***	34.8±6.6	31.8±6.6***	38.4±4.7	35.9±4.5***	43.7±3.2	37.4±3.5***
Waist circumference (cm)	119.8±12.9	110.8±11.9***	113.1±12.3	106.0±12.3**	106.2±15.1	98.3±13.8***	–	–
HbA_{1c} (%)	7.7 (6.9-8.6)	7.0 (6.1-8.2)***	7.5 (7.0-8.2)	6.6 (6.0-8.2)**	5.5 (5.3-5.8)	5.4 (5.2-5.7)**		
HbA_{1c} (mmol/mol)	61.0 (52.0-71.0)	53.0 (43.0-66.0)***	58.0 (53.0-65.8)	49.0 (42.0-66.0)**	37.0 (34.0-39.5)	36.0 (33.0-38.5)**	–	–
Fasting glucose (mmol/l)	8.8 (6.9-10.8)	7.3 (6.1-9.3)***	8.7 (7.0-10.5)	7.4 (6.5-9.3)	5.3 (5.0-5.8)	5.1 (4.8-5.4)**	5.1 (4.7-5.2)	4.9 (4.4-5.3)
Total cholesterol (mmol/l)	4.4 (3.7-5.1)	4.1 (3.5-4.8)***	3.9 (3.6-5.1)	4.2 (3.5-5.5)	5.2 (4.3-5.7)	4.6 (4.1-5.2)***	4.7 (3.8-5.8)	4.0 (3.5-4.9)**
LDL-cholesterol (mmol/l)	2.5 (2.1-3.1)	2.4 (1.8-2.9)***	2.4 (2.0-3.2)	2.2 (1.7-3.3)	3.4 (3.0-4.0)	3.1 (2.7-3.6)***	2.8 (2.3-3.6)	2.3 (1.8-3.0)**
HDL-cholesterol (mmol/l)	1.1 (1.0-1.3)	1.2 (1.0-1.4)**	1.2 (1.0-1.5)	1.2 (1.1-1.5)	1.3 (1.1-1.4)	1.2 (1.1-1.4)**	1.1 (1.0-1.3)	1.0 (0.9-1.2)**
Triacylglycerol (mmol/l)	1.8 (1.2-2.6)	1.4 (1.0-2.0)***	1.5 (1.1-2.5)	1.4 (0.9-2.0)	1.3 (1.0-1.8)	1.1 (0.9-1.4)*	1.2 (0.9-1.8)	1.2 (1.0-1.4)
Lp(a) (nmol/l)	40.9 (13.9-159.5)	55.9 (23.0-201.1)***	56.9 (12.4-148.9)	61.5 (20.4-185.9)*	27.0 (2.1-75.2)	45.2 (22.7-94.5)**	36.4 (17.2-91.5)	20.6 (6.3-104.1)

Data are mean±SD, or median (IQR); *p<0.05, **p<0.01, ***p<0.001; difference before–after intervention

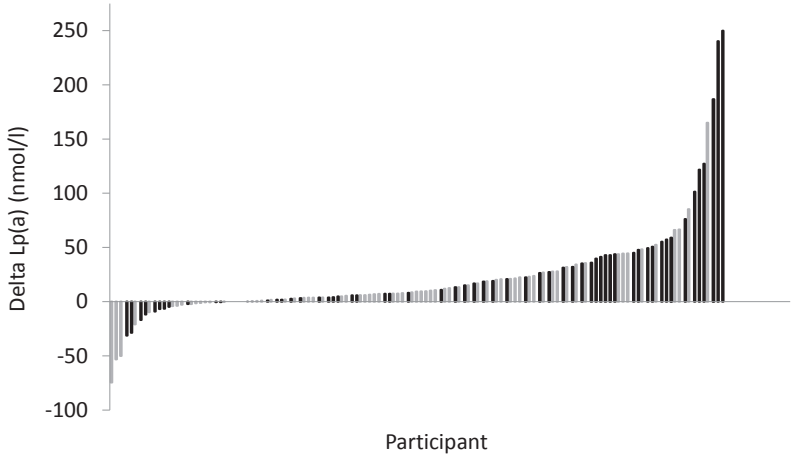

Figure 1. Diet-induced changes in Lp(a) level per individual in cohort 1 (n=131)
Individual participants (x-axis) are arranged according to the diet-induced change in Lp(a) level. Grey bars, white participants; black bars, non-white participants

with sex (r=-0.04, p=0.543) or change in weight (r=-0.14, p=0.116). The change in Lp(a) also correlated with ethnicity (white vs non-white: r=-0.17, p=0.048), although this did not happen after correction for baseline Lp(a) levels. The Lp(a) response to the diet did not differ between white and non-white individuals in a repeated-measurements MANOVA ($F_{(1;129)}$=0.199, p=0.656). In cohort 1, 95 out of the 131 (73%) participants used statins; the diet-induced change in Lp(a) levels was similar whether or not statins were used ($F_{(1;129)}$=0.669, p=0.415).

Excluding two possible outliers, who had an increase in Lp(a) level of ≥211 nmol/l, did not alter the outcome.

Effect of Apo(a) isoform on diet-induced changes in Lp(a) levels in cohort 1

Forty-three participants had an LMW and 88 an HMW Apo(a) isoform. As expected, baseline Lp(a) levels were significantly higher in the LMW than the HMW subgroup (148.8 nmol/l [IQR 26.6-297.9] vs 30.6 nmol/l [IQR 6.5-119.4]; p<0.001). Lp(a) levels increased during the dietary intervention to 182.7 nmol/l (IQR 37.3-327.5; p<0.001) in the LMW subgroup and to 41.6 nmol/l (IQR 15.4-139.9; p<0.001) in the HMW subgroup (Fig. 2). The diet-induced effect on Lp(a) did not significantly differ between the LMW and the HMW subgroup ($F_{(1;129)}$=1.68, p=0.197). The alteration in Lp(a) levels correlated strongly with baseline Lp(a) level in the HMW subgroup (r=0.43, p<0.001) but not in the LMW subgroup (r=0.24, p=0.118).

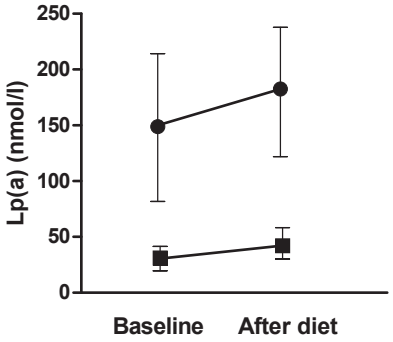

Figure 2. The effect of the dietary intervention on Lp(a) level in the Apo(a) isoform subgroups in cohort 1. Medians and 95% CIs of Lp(a) levels before and after the dietary intervention for the LMW Apo(a) isoform group (circles, n=43) and the HMW Apo(a) isoform group (squares, n=88)

Long-term effect

Of the 131 participants in cohort 1, 69 consented to provide an additional blood sample 20 months after finishing the dietary intervention. This subgroup was older (55.6 vs 51.8 years, p=0.016), had a longer history of type 2 diabetes (12.2 vs 8.8 years, p=0.017) and had lost more weight during the intervention (12.1 vs 8.6 kg, p=0.001), but did not differ from the other participants in sex distribution, ethnicity, baseline Lp(a), BMI, HbA_{1c} and LDL-cholesterol, nor in change in Lp(a) during the diet. In this subgroup, Lp(a) levels increased from 40.9 nmol/l (IQR 15.6-151.7) to 55.1 nmol/l (IQR 24.7-200.2) during the dietary intervention. Twenty months after the diet, patients had regained an average of 6.8±5.5 kg of body weight but were still 5.2±6.0 kg below baseline weight. Lp(a) levels decreased to 43.9 nmol/l (IQR 12.2-157.8), which was no longer statistically different from baseline levels (p=0.050). Weight regain was not correlated with the decrease in Lp(a) levels from the end of the intervention to 20 months after the intervention (r=-0.06, p=0.626).

Effect of weight loss on Lp(a) levels in secondary cohorts

The characteristics of the cohorts 2–4 at baseline and after the intervention are shown in Table 1. Cohort 2, consisting predominantly of obese patients with type 2 diabetes, showed effects of the diet similar to the primary cohort. Weight loss was 9.0 kg (95% CI 6.7, 11.3), or 8.5% (95% CI 6.5, 10.6) of initial body weight, and both BMI and waist circumference decreased significantly (p<0.01 for all). HbA_{1c} level also decreased (p=0.001), but changes in fasting glucose and lipid variables (total cholesterol, triacylglycerol, LDL-cholesterol and HDL-cholesterol) did not reach statistical significance in this small group (Table 1). During dieting, Lp(a) increased from 56.9 nmol/l (IQR 12.4-148.9) to 61.5 nmol/l (IQR 20.4-185.9) (p=0.018; Table 1). The median increase in Lp(a) was 13.5 nmol/l (95% CI 2.3, 30.0).

In cohort 3, which consisted of obese individuals without type 2 diabetes, the dietary intervention led to a weight loss of 7.1 kg (95% CI 6.3, 8.0), or 6.5% (95% CI 5.7, 7.2) of initial body weight, and to significant reductions in BMI and waist circumference (p<0.001 for all). Although these participants did not have type 2 diabetes, HbA_{1c} and fasting glucose levels improved in this group (p=0.002 and p=0.003, respectively). In addition, lipid variables improved significantly (p<0.05 for all). Lp(a) levels increased from 27.0 nmol/l (IQR 2.1-75.2) to 45.2 nmol/l (IQR 22.7-94.5) (p=0.001; Table 1). The median increase in Lp(a) was 11.9 nmol/l (95% CI 5.7, 19.0).

Cohort 4 consisted of obese individuals without type 2 diabetes who underwent bariatric surgery and were followed up for 3 months. This intervention resulted in a weight loss of 17.4 kg (95% CI 15.0, 19.8), or 14.0% (95% CI 12.2, 15.7) of initial body weight (p<0.001). During this period, most lipid variables improved significantly (Table 1). Lp(a) levels were lower after the intervention than before (falling from 36.4 nmol/l [IQR 17.2-91.5] to 20.6 nmol/l [IQR 6.3-104.1]), but this result did not reach statistical significance in this small group (Table 1). The median difference in Lp(a) level was -7.0 nmol/l (95% CI -18.8, 5.3).

Figure 3 summarises the results obtained for the four independent cohorts. The relationship between weight loss and increase in Lp(a) levels was similar for the first three cohorts. When cohorts 1-3 were considered together, the increase in Lp(a) correlated with the diet-induced weight loss (n=198, r=-0.18, p=0.012). This relationship was not observed for cohort 4, which consisted of individuals who lost weight after bariatric surgery.

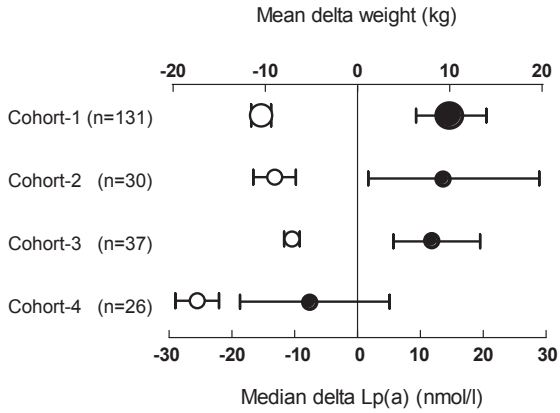

Figure 3. ΔLp(a) and Δweight in the four independent study cohorts.
Means and 95% CI for Δweight (white circles) and medians with 95% CIs for ΔLp(a) (black circles) in the four cohorts. The size of the symbols reflects the number of participants

DISCUSSION

Our data show that diet-induced weight loss increased Lp(a) levels in overweight and obese individuals irrespective of the presence or absence of type 2 diabetes. Repeated sampling in healthy control participants at an interval of 2-6 months showed that the increase in Lp(a) levels was not explained by general environmental changes over time or by assay artefacts. In patients with type 2 diabetes, the extent of the increase in Lp(a) was mainly determined by baseline Lp(a) level, with the highest increase seen in individuals with the highest baseline levels. This effect on Lp(a) was independent of the Apo(a) isoform. Such an increase in Lp(a) levels was not observed in individuals who underwent bariatric surgery, suggesting that weight loss per se does not increase Lp(a) levels.

Previous studies have not shown a change in Lp(a) levels in obese adults after various dietary interventions aimed at weight loss [21-23]. In these studies, weight-reducing drugs and diets different from ours were tested, and patients with type 2 diabetes were not included. One study reported a decrease in Lp(a) levels in obese children [20]. This discrepancy in relation to our study may be explained by different age-related hormonal states or by differences in dietary composition. The type and content of fat in the diet may be an important determinant of the dietary effect on Lp(a) levels. An increased intake of total and saturated fat has been found to decrease Lp(a) levels, while an increased intake of monounsaturated fatty acids tended to increase Lp(a) levels in healthy individuals and those with metabolic dysregulation [29-31]. Faghihnia et al [30] have suggested that a low-fat diet results in an increase in Lp(a) levels that may be due to an altered metabolism of Lp(a) particles. The dietary interventions used in our cohorts 1-3 were all based on a low intake of total and saturated fat, while no specific dietary restrictions were prescribed for the participants in the cohort who underwent bariatric surgery. We previously reported that, in a random subset of participants in cohort 1, our dietary intervention lowered plasma levels of the soluble form of the LDL receptor relative sLR11 [32]. However, diet-induced changes in sLR11 and Lp(a) levels did not correlate with each other ($r=-0.07$, $p=0.635$). In participants in cohort 1 from whom blood samples were available at 20 months of follow-up, Lp(a) levels had almost returned to baseline values, whereas the initial weight reduction was only partially reversed by weight regain. This suggests that the increase in Lp(a) levels was an acute effect of the diet. Unfortunately, we do not have information about the diet during the prolonged follow-up. Future studies on the effect on Lp(a) of weight-reducing diets with different fat contents in obese patients with and without type 2 diabetes are warranted.

High Lp(a) levels have consistently been associated with an increased risk of coronary heart disease [6, 9], and results from genetic studies indicate a causal association between high Lp(a) levels and CVD [17, 33, 34]. The risk of CVD associated with high Lp(a) levels is notably higher in individuals with than without type 2 diabetes [18]. The

dose–response relationship of Lp(a) levels with CVD risk has been shown to be curvilinear in shape, with no evidence of a threshold [35]. This suggests that the increase in Lp(a) levels induced by weight loss dieting observed in our study might increase the risk of CVD. This could potentially reduce the beneficial cardiometabolic effects that result from the improvement in conventional CVD risk factors after diet-induced weight loss. In the Look AHEAD (Action for Health in Diabetes) study (NCT00017953), the incidence of CVD was not reduced by a low-energy, low-fat diet and physical activity in patients with type 2 diabetes after 10 years of follow-up, despite an improvement in conventional risk factors for CVD [5]. Hypothetically, a parallel increase in Lp(a) levels could be one of the explanations why CVD events were not reduced by this lifestyle change. However, effects on Lp(a) levels were not reported in the Look AHEAD trial. Randomised clinical trials addressing the effect of alterations in Lp(a) levels with lifestyle changes or medication on hard clinical endpoints or CVD risk are needed. Recently, the short-term efficacy and safety of two specific Lp(a)-lowering agents has been reported [36]. Long-term effects on cardiovascular endpoints are awaited.

In participants who underwent bariatric surgery, weight loss was not accompanied by an increase in Lp(a) level. Two previous studies have shown that bariatric surgery-induced weight loss in obese individuals was accompanied by a decrease in Lp(a) levels [37, 38], whereas another study found no significant effect [39]. The effects of bariatric surgery on bile acid flow and signalling, inflammation, release of gastrointestinal hormones, the gut microbiome and the wound healing processes may all have had an impact on Lp(a), resulting in the absence of a weight loss-induced increase in Lp(a) levels [40-44].

The baseline Lp(a) levels in our two cohorts with type 2 diabetes (cohorts 1 and 2) were relatively high compared with the two cohorts without type 2 diabetes (cohorts 3 and 4), whereas in the Women's Health Study and Copenhagen City Heart Study the Lp(a) levels in participants with diabetes were significantly lower than the Lp(a) levels in the control participants [45, 46]. Non-white individuals, in particular those of South-Asian ancestry, display markedly higher Lp(a) levels than white individuals [47-49], and are over-represented in our cohorts with type 2 diabetes. The change in Lp(a) during the diet was correlated with ethnicity. However, in the repeated-measurements analysis we found no difference between the white and non-white populations in ΔLp(a). This suggests that non-white individuals have higher baseline Lp(a) levels, and therefore show the highest absolute change in Lp(a) levels on dieting, but that the relative change is similar to that in white individuals.

The strengths of this study are its prospective design and the use of four independent cohorts for investigating the effect of weight loss on Lp(a), which more than doubled the total number of participants who have so far been studied in relation to this topic. Our study is descriptive in nature. Future studies should clarify the mechanisms underlying the increase in Lp(a) levels on diet-induced weight loss, as well as the consequence of weight

loss for the functionality of Lp(a). As all the participants had been referred to a tertiary centre, our findings may not be applicable to the entire population of overweight and obese patients with or without type 2 diabetes. We found that the effect of diet-induced weight loss on Lp(a) levels occurred irrespective of the presence or absence of type 2 diabetes. However, some of the individuals in cohorts 3 and 4 may have had impaired glucose tolerance, since the classification was based on fasting glucose level and not on an oral glucose tolerance test. Finally, a long-term follow-up study is required to determine whether elevated Lp(a) levels after weight loss dieting affect the incidence of CVD in obese patients with and without type 2 diabetes.

In conclusion, Lp(a) levels increased significantly in obese individuals with and without type 2 diabetes during diet-induced weight loss, but not in individuals who underwent bariatric surgery. This may hypothetically reduce the beneficial cardiometabolic effects of a diet-induced weight loss. Therefore, Lp(a) may be an additional target in overweight and obese individuals on a energy-restricted diet to reduce the risk of CVD. Long-term follow-up studies are required to establish whether adding a specific Lp(a)-lowering agent to a dietary intervention will improve long-term CVD outcome in obese individuals with and without type 2 diabetes.

REFERENCES

1. Costanzo P, Cleland JG, Pellicori P et al. (2015) The obesity paradox in type 2 diabetes mellitus: relationship of body mass index to prognosis: a cohort study. Ann Intern Med 162: 610-618
2. Joseph JJ, Golden SH (2014) Type 2 diabetes and cardiovascular disease: what next? Curr Opin Endocrinol Diabetes Obes 21: 109-120
3. Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration, Lu Y, Hajifathalian K et al. (2014) Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants. Lancet 383: 970-983
4. Anderson JW, Kendall CW, Jenkins DJ (2003) Importance of weight management in type 2 diabetes: review with meta-analysis of clinical studies. J Am Coll Nutr 22: 331-339
5. Wing RR, Bolin P, Brancati FL et al. (2013) Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. The New England journal of medicine 369: 145-154
6. Bennet A, Di Angelantonio E, Erqou S et al. (2008) Lipoprotein(a) levels and risk of future coronary heart disease: large-scale prospective data. Arch Intern Med 168: 598-608
7. Kamstrup PR (2010) Lipoprotein(a) and ischemic heart disease—a causal association? A review. Atherosclerosis 211: 15-23
8. Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG (2008) Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. Circulation 117: 176-184
9. Hopewell JC, Seedorf U, Farrall M et al. (2014) Impact of lipoprotein(a) levels and apolipoprotein(a) isoform size on risk of coronary heart disease. J Intern Med 276: 260-268
10. Hiraga T, Kobayashi T, Okubo M et al. (1995) Prospective study of lipoprotein(a) as a risk factor for atherosclerotic cardiovascular disease in patients with diabetes. Diabetes Care 18: 241-244
11. James RW, Boemi M, Sirolla C, Amadio L, Fumelli P, Pometta D (1995) Lipoprotein (a) and vascular disease in diabetic patients. Diabetologia 38: 711-714
12. Emerging Risk Factors Collaboration, Erqou S, Kaptoge S et al. (2009) Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. Jama 302: 412-423
13. Boerwinkle E, Leffert CC, Lin J, Lackner C, Chiesa G, Hobbs HH (1992) Apolipoprotein(a) gene accounts for greater than 90% of the variation in plasma lipoprotein(a) concentrations. J Clin Invest 90: 52-60
14. Kraft HG, Kochl S, Menzel HJ, Sandholzer C, Utermann G (1992) The apolipoprotein (a) gene: a transcribed hypervariable locus controlling plasma lipoprotein (a) concentration. Human genetics 90: 220-230
15. Lackner C, Cohen JC, Hobbs HH (1993) Molecular definition of the extreme size polymorphism in apolipoprotein(a). Hum Mol Genet 2: 933-940
16. Scanu AM, Fless GM (1990) Lipoprotein (a). Heterogeneity and biological relevance. J Clin Invest 85: 1709-1715
17. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG (2009) Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. Jama 301: 2331-2339
18. Waldeyer C, Makarova N, Zeller T, Schnabel RB, Brunner FJ. (2017) Lipoprotein(a) and the Risk of Cardiovascular Disease in the European Population – Results from the BiomarCaRE Consortium. European Heart Journal. Apr 24. doi: 10.1093/eurheartj/ehx166

19. Kronenberg F, Utermann G (2013) Lipoprotein(a): resurrected by genetics. J Intern Med 273: 6-30
20. Brandstatter A, Lingenhel A, Zwiauer K, Strobl W, Kronenberg F (2009) Decrease of Lp(a) during weight reduction in obese children is modified by the apo(a) kringle-IV copy number variation. Int J Obes (Lond) 33: 1136-1142
21. Corsetti JP, Sterry JA, Sparks JD, Sparks CE, Weintraub M (1991) Effect of weight loss on serum lipoprotein(a) concentrations in an obese population. Clin Chem 37: 1191-1195
22. Kiortsis DN, Tzotzas T, Giral P, et al. (2001) Changes in lipoprotein(a) levels and hormonal correlations during a weight reduction program. Nutr Metab Cardiovasc Dis 11: 153-157
23. Yamashita T, Sasahara T, Pomeroy SE, Collier G, Nestel PJ (1998) Arterial compliance, blood pressure, plasma leptin, and plasma lipids in women are improved with weight reduction equally with a meat-based diet and a plant-based diet. Metabolism 47: 1308-1314
24. Berk KA, Buijks H, Ozcan B, Van't Spijker A, Busschbach JJ, Sijbrands EJ (2012) The Prevention Of WEight Regain in diabetes type 2 (POWER) study: the effectiveness of adding a combined psychological intervention to a very low calorie diet, design and pilot data of a randomized controlled trial. BMC Public Health 12: 1026
25. Berk KA, Oudshoorn TP, Verhoeven AJM et al. (2016) Diet-induced weight loss and markers of endothelial dysfunction and inflammation in treated patients with type 2 diabetes. Clinical Nutrition ESPEN 15: 101-106
26. Mujibul Haq AM, AS MG, Huque MM (2011) Serum total homocysteine and lipoprotein (a) levels in acute myocardial infarction and their response to treatment with vitamins. J Coll Physicians Surg Pak 21: 266-270
27. Vongpromek R, Bos S, Ten Kate GJ et al. (2015) Lipoprotein(a) levels are associated with aortic valve calcification in asymptomatic patients with familial hypercholesterolaemia. J Intern Med 278: 166-173
28. Kronenberg F, Kuen E, Ritz E et al. (2000) Lipoprotein(a) serum concentrations and apolipoprotein(a) phenotypes in mild and moderate renal failure. J Am Soc Nephrol 11: 105-115
29. Clevidence BA, Judd JT, Schaefer EJ et al. (1997) Plasma lipoprotein (a) levels in men and women consuming diets enriched in saturated, cis-, or trans-monounsaturated fatty acids. Arterioscler Thromb Vasc Biol 17: 1657-1661
30. Faghihnia N, Tsimikas S, Miller ER, Witztum JL, Krauss RM (2010) Changes in lipoprotein(a), oxidized phospholipids, and LDL subclasses with a low-fat high-carbohydrate diet. J Lipid Res 51: 3324-3330
31. Berglund L, Lefevre M, Ginsberg HN et al. (2007) Comparison of monounsaturated fat with carbohydrates as a replacement for saturated fat in subjects with a high metabolic risk profile: studies in the fasting and postprandial states. Am J Clin Nutr 86: 1611-1620
32. Berk KA, Vongpromek R, Jiang M et al. (2016) Levels of the soluble LDL receptor-relative LR11 decrease in overweight individuals with type 2 diabetes upon diet-induced weight loss. Atherosclerosis 254: 67-72
33. Clarke R, Peden JF, Hopewell JC et al. (2009) Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med 361: 2518-2528
34. Tregouet DA, Konig IR, Erdmann J et al. (2009) Genome-wide haplotype association study identifies the SLC22A3-LPAL2-LPA gene cluster as a risk locus for coronary artery disease. Nat Genet 41: 283-285

35. Nordestgaard BG, Chapman MJ, Ray K et al. (2010) Lipoprotein(a) as a cardiovascular risk factor: Current status. European Heart Journal 31: 2844-2853

36. Viney NJ, van Capelleveen JC, Geary RS et al. (2016) Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials. Lancet 388: 2239-2253

37. Williams DB, Hagedorn JC, Lawson EH et al. (2007) Gastric bypass reduces biochemical cardiac risk factors. Surg Obes Relat Dis 3: 8-13

38. Ram E, Vishne T, Magazanik A et al. (2007) Changes in blood lipid levels following silastic ring vertical gastroplasty. Obes Surg 17: 1292-1296

39. Woodard GA, Peraza J, Bravo S, Toplosky L, Hernandez-Boussard T, Morton JM (2010) One year improvements in cardiovascular risk factors: a comparative trial of laparoscopic Roux-en-Y gastric bypass vs. adjustable gastric banding. Obes Surg 20: 578-582

40. Chennamsetty I, Claudel T, Kostner KM et al. (2011) Farnesoid X receptor represses hepatic human APOA gene expression. J Clin Invest 121: 3724-3734.

41. Huang M, Gong Y, Grondolsky J, Hoover-Plow J (2014) Lp(a)/apo(a) modulate MMP-9 activation and neutrophil cytokines in vivo in inflammation to regulate leukocyte recruitment. Am J Pathol 184: 1503-1517.

42. Nielsen LB, Stender S, Kjeldsen K, Nordestgaard BG (1996) Specific accumulation of lipoprotein(a) in balloon-injured rabbit aorta in vivo. Circ Res 78: 615-626

43. von Zychlinski A, Kleffmann T, Williams MJ, McCormick SP (2011) Proteomics of Lipoprotein(a) identifies a protein complement associated with response to wounding. J Proteomics 74: 2881-2891

44. Yano Y, Shimokawa K, Okada Y, Noma A (1997) Immunolocalization of lipoprotein(a) in wounded tissues. J Histochem Cytochem 45: 559-568

45. Kamstrup PR, Nordestgaard BG (2013) Lipoprotein(a) concentrations, isoform size, and risk of type 2 diabetes: a Mendelian randomisation study. Lancet Diabetes Endocrinol 1: 220-227

46. Mora S, Kamstrup PR, Rifai N, Nordestgaard BG, Buring JE, Ridker PM (2010) Lipoprotein(a) and risk of type 2 diabetes. Clin Chem 56: 1252-1260

47. Enkhmaa B, Anuurad E, Berglund L (2016) Lipoprotein (a): impact by ethnicity and environmental and medical conditions. J Lipid Res 57: 1111-1125.

48. Banerjee D, Wong EC, Shin J, Fortmann SP, Palaniappan L (2011) Racial and ethnic variation in lipoprotein (a) levels among Asian Indian and Chinese patients. J Lipids 2011:291954..

49. Hoogeveen RC, Gambhir JK, Gambhir DS et al. (2001) Evaluation of Lp[a] and other independent risk factors for CHD in Asian Indians and their USA counterparts. J Lipid Res 42: 631-638.

Chapter 6

The Prevention Of WEight Regain in diabetes type 2 (POWER) study: the effectiveness of adding a combined psychological intervention to a very low calorie diet, design and pilot data of a randomized controlled trial

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ABSTRACT

Background and Aims

Obesity is of major pathogenic importance to type 2 diabetes, it contributes to poor glycaemic control and increases the risk of cardiovascular disease. Over 80% of patients with diabetes type 2 are overweight. To achieve a more favourable risk profile, changes in diet and lifestyle are needed. However, current treatment programs for obese DM type 2 patients are not effective in the long term. In this RCT, we compare the effectiveness of a Combined Psychological Intervention (CPI) and usual care in maintaining the favourable effects on weight and risk profile during 2 years of follow-up after a Very Low Calorie Diet (VLCD).

Methods

In a randomised parallel group intervention study, 140 patients with type 2 diabetes and overweight (BMI>27 kg/m2) will be recruited from the outpatient department of the Erasmus Medical Centre. After obtaining ≥5% of weight loss with a VLCD, participants will be randomly assigned to CPI or usual care for 10 weeks. CPI consists of cognitive behaviour therapy, problem solving therapy and proactive coping. Primary outcome measure is weight change (kg). Other outcome measures are Body Mass Index (BMI = weight (kg)/length (m)2), waist circumference (cm), systolic blood pressure (mmHg), HbA1c (mmol/mol), lipid levels (LDL, HDL, TG (mmol/l) and chol/HDL-ratio), antidiabetic agents and doses, cardiovascular risk profile (UKPDS), lifestyle and quality of life (EuroQol EQ-5D). Psychosocial parameters are also studied, as secondary outcomes as well as determinants for weight loss. When successful, we want to conduct an analysis of the cost effectiveness of the intervention as compared to usual care.

Discussion

We expect that a CPI after a VLCD will be effective in maintaining weight loss and improving cardiovascular risk and glycaemic control, while being cost-effective and improving quality of life in patients with type 2 diabetes.

INTRODUCTION

Diabetes has become a worldwide epidemic: the estimated global prevalence was 2.8% in 2000 and is expected to rise up to 4.4% in 2030. In the year 2000 the excess global mortality attributable to diabetes was 5.2% making diabetes the fifth leading cause of death (1). The increase in prevalence is associated with aging of the population, the increasing prevalence of obesity in combination with physical inactivity. Cardiovascular disease is the major cause of death among patients with diabetes. An intensive pharmaceutical and behavioural therapy treatment has been estimated to reduce the risk of cardiovascular and micro vascular events by approximately 50% (2). Approximately 80% of the people with type 2 diabetes are overweight. Losing weight is the cornerstone of prevention and treatment of type 2 diabetes: it decreases the resistance to insulin, improves glycaemic control and reduces hypertension and lipid abnormalities (3-5). Weight loss interventions thus may contribute to a reduction of cardiovascular risk and is shown to reduce mortality in patients with type 2 diabetes and obesity (6). Unfortunately, interventions aimed at weight reduction have only a limited effect in the long run because of regain of the initial weight loss. The required long-term lifestyle change seems difficult to achieve (7). A meta-analysis of weight loss interventions in adults with type 2 diabetes showed that multi-component interventions including Very Low Calorie Diets may hold promise for achieving weight loss (7,8). However, trials with long follow-up periods are lacking and the most effective type of psychological intervention remains unclear.

In the present study, we determine the effect of an integrated multi-model cognitive group therapy, in obtaining and maintaining favourable effects on weight and cardiovascular risk profile during 2 years of follow-up after a Very Low Calorie Diet.

Very Low-Calorie Diet

A Very Low Calorie Diet (VLCD) is a diet of less than 800 kilocalories (kcal) daily [4]. The very low intake of fat and carbohydrates, but normal amount of proteins (0.8 g/kg ideal bodyweight per day) enhances lipolysis and ketosis while preventing a negative nitrogen balance, sparing lean body mass (9). The most commonly used VLCD's are commercially available mixed-formula diets, containing various amounts of carbohydrate, fat and high quality protein, and have proven safety for use in patients with type 2 diabetes (9,10). The short-term effects (i.e. < 6 months) of a VLCD in overweight patients with type 2 diabetes are favourable on weight, glycaemic control, hypertension and dyslipidaemia (11-15). However, study outcomes are less positive in the long term (i.e. > 1 year follow-up): patients regain most of the lost weight and HbA1c returns to the same value as prior to the intervention. Nonetheless, participants often needed less anti-diabetic agents (16-18). The study of Jazet, et al (19) seems to be a positive exception: 18 months after a 30-day VLCD period, favourable effects on weight, blood pressure and dyslipidaemia

were maintained in 18 obese patients with diabetes type 2, but with no effect on HbA1c. The authors indicated that the success was based on the strong motivation of the patients to prevent a need for insulin and a slow reintroduction of normal diet. Limitations of this study, however, were the small intervention group and the lack of a control group.

Taken together, randomized controlled trials of sufficient duration focused on prevention of weight gain after a VLCD in DM type 2 patients are required to improve the effectiveness of VLCDs.

Weight maintenance

To achieve weight maintenance after successful weight loss, a permanent behaviour change is needed. For this purpose, a variety of psychological interventions have been implemented in weight reduction programmes. Behaviour therapy and cognitive behaviour therapy (CBT) are potential psychological interventions facilitating better maintenance of weight loss (20). CBT is used to describe a wide range of techniques to change thinking patterns and behaviours. As a result, interventions are heterogeneous and the findings are difficult to compare. We identified three promising psychological interventions to attain better results in sustaining weight loss: cognitive (behaviour) therapy, problem solving therapy and proactive coping. In the current study, we propose to combine them into an integrated weight maintenance programme.

Cognitive behavioural therapy

Within cognitive psychology, humans are regarded as information processing systems, where knowledge is organized in so-called schemas. Cognitive schemas are activated by incoming information, leading to cognitions (thoughts), emotions and subsequently to behaviour. According to the founding father of the cognitive therapy, Aaron Beck, emotional disorders such as depression and anxiety disorders result from dysfunctional schemas. Cognitive therapy focuses on changing dysfunctional schemas and cognitions, using behavioural experiments and challenges (21). In eating disorders, the cognitive model was first used to treat bulimia nervosa by adjusting overvaluation of weight and shape based on low self-esteem (22,23). In the treatment of obesity, this model is combined with the cognitive model for addiction, which is based on the assumption that addictive behaviour is enhanced by dysfunctional cognitions during exposure to external stimuli like the smell or sight of food (24). In a Cochrane review (20) concerning the effect of psychological interventions in the treatment of overweight and obese patients, positive effects of cognitive behaviour treatment on weight loss were described, particularly when combined with diet and/or physical activity. In a number of studies, weight loss was enhanced significantly by the addition of the cognitive component to an intervention of diet and/or exercise (25-28). Moreover, it was found that a longer duration of the intervention and more frequent clinical contact was associated with an increased effect.

However, studies with substantial follow-up (i.e. > 1 year) are lacking. In patients with type 2 diabetes, psychotherapy (especially CBT) improves glycaemic control (HbA1c –1.0%) and psychological well-being (29). Surprisingly, CBT did not appear to affect weight control in this patient group. Perhaps this was caused by too short duration of the studies (i.e. <6 months), as CBT may encourage long-term behavioral changes (29).

Problem solving therapy

Problem Solving Therapy (PST) is defined as the self-directed cognitive-behavioural process by which a person attempts to identify effective or adaptive solutions for specific problems encountered in everyday living (30,31) PST is recognized as an effective treatment of depression (32,33). The problem-solving model for obesity treatment was first described by Perri, Nezu and Viegener in 1992 (34). and proposes that active problem solving efforts by a health care provider can help the obese person encounter everyday problems in their weight management. Perri, et al. found significantly greater long-term weight reductions in participants, who completed a PST-intervention, compared to participants receiving behavioural therapy (35). Moreover, a recent study showed that people with better problem-solving skills lost more weight and were more compliant to therapy (36).

Proactive coping

Proactive coping (PC), directed at an upcoming instead of an ongoing stressor, is a new focus in positive psychology research. PC consists of efforts undertaken in advance of a potentially stressful event to prevent it or modify its form before it occurs. The theory described by Aspinwall and Taylor consists of five stages: PC starts with the 'accumulation of resources' such as time, money, planning or organizational skills and social support, so that one is prepared as much as possible to deal with future threats. 'Recognition' refers to the ability to see a potential stressful event coming, followed by 'initial appraisal' (what is this and should I be worried about this?). The next stage consists of 'initial coping efforts': activities undertaken to prevent or minimize a recognized or suspected stressor. Finally, the 'use of feedback' involves the evaluation of the stressful event itself and the effects of one's preliminary efforts (37). Schwarzer and Taubert described PC as a way of aspiring a positive future by accumulating resources and realistic goal setting (38). A recent publication has shown that the pursuit of goals was related to improved wellbeing, while preventing a negative future was not (39). A study of the effects of PC on the self-care behaviours of newly diagnosed DM patients revealed that the treatment was highly appreciated and even after 9 months improvements in eating and exercising habits were seen. In addition, the intervention was effective in reducing both weight and blood pressure after 9 months, but had no effect on $HbA1_c$ or lipid profile (40).

In the current randomized study, we compare the effect of a Combined Psychological Intervention (CPI) with usual care on weight maintenance after a Very Low Calorie Diet.

Hence, we do not compare the effectiveness of Cognitive Behaviour Therapy with neither Problem Solving Therapy nor Proactive Coping, but combine these three therapies into an integrated multi-model program.

Objectives

The primary objective of this study is to determine if an integrated multi-model cognitive group therapy, is more effective in preventing weight regain after a Very Low Calorie Diet compared to usual care.

The secondary objectives are to investigate whether an integrated multi-model cognitive group therapy following a VLCD has an effect on glycaemic control, cardiovascular risk profile, psychological variables and quality of life, and subsequently to determine which patient group benefits most of the intervention.

The tertiary objective is to determine whether the intervention is cost-effective.

Ethical approval

This research is approved by the Medical Ethics Committee of the Erasmus Medical Centre in Rotterdam (reference number MEC-2009-143/NL26508.078.09), in compliance with the Helsinki Declaration.

METHODS/DESIGN

Design of the study

This study is a randomized controlled parallel group intervention trial. When patients lose equally or more than 5% of their bodyweight in the first 8 weeks of the VLCD, they are included in the intervention trial testing CPI. This arbitrary cut-off value was chosen because of its relatively large effect on the risk profile (3). Moreover, we need a relevant weight loss to investigate weight maintenance after weight reduction. After randomization, stratified to the achieved weight loss at 8 weeks, participants are assigned to one of the following conditions:

1. VLCD + conventional treatment
2. VLCD + conventional treatment + CPI

The duration of the diet period will be 20 weeks: 8 weeks of VLCD (<800 kcal/day) followed by 12 weeks of slowly reintroducing a normal, mildly energy-restricted diet (1300 kcal/day). During week 10 of the diet, the intervention group starts with a total of 17 sessions of CPI. The first 10 sessions are weekly sessions; followed by two 2-weekly sessions, two monthly sessions, two 3-monthly sessions and 1 session with an interval of 6 months.

Outcome measurements are assessed at baseline, after finishing the intensive CPI-period at 4 months and subsequently at 1 year, 1.5 years and 2 years after randomization. At 8

weeks (randomization after VLCD), only the primary outcome (weight) will be measured. Figure 1 shows the design of the study.

The study started in May 2010 with a pilot and inclusion will be completed in 2013. The follow-up will continue until 2015.

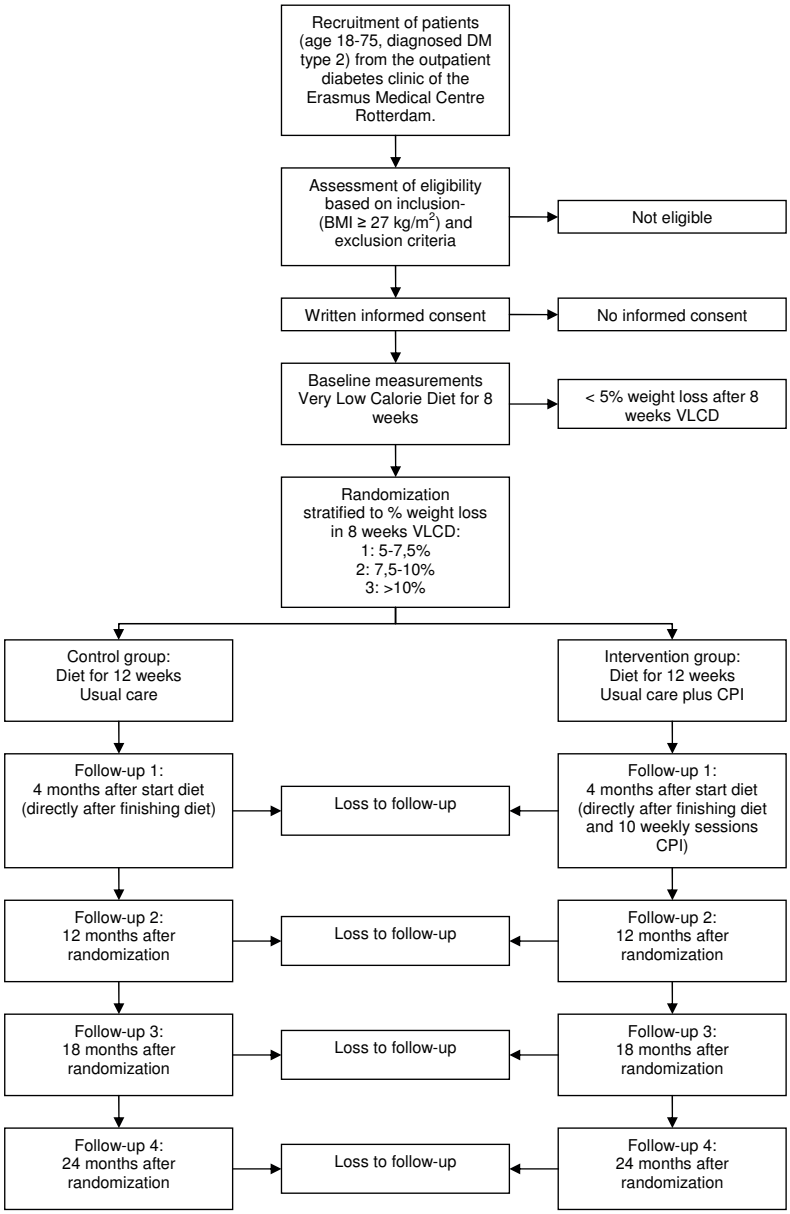

Figure 1. flow-chart of the study
VLCD = Very low-calorie diet, CPI = Combined Psychological Intervention

Study population

Patients are recruited from the outpatient diabetes clinic of the Erasmus Medical Centre in Rotterdam by the medical team, based on the in- and exclusion criteria shown in Table 1. In our hospital, a tertiary referral centre, we see both patients with only oral antidiabetic agents and patients treated with one or more insulin doses daily. In general, our patients will have more complex disease and more comorbidity compared to the average diabetic patient referred to a GP. However, GP's can also directly refer their eligible patients to our trial. Patients interested in participating in the study will receive an information letter and a questionnaire to be filled in at home. Two weeks later they will visit the outpatient clinic for an intake interview with the researcher (KACB). Eligibility will be checked again. After signing the informed consent form by the patient, the baseline measurements will be performed.

Patients with psychiatric disorders or major psychological disturbances are excluded from the trial. Patients with eating disorders (bulimia nervosa and binge eating disorder) or depression are not excluded, since it is expected that these conditions are common among patients with type 2 diabetes and previous research has shown that cognitive behaviour therapy can have beneficial effects in these patient groups (28,41-43). We will analyse the effect of these background variables on the outcome of the intervention.

Table 1. eligibility

Inclusion criteria:	
1	Diagnosed diabetes mellitus type 2
2	Age 18–75 years
3	BMI ≥ 27 kg/m^2
Exclusion criteria:	
6	Pregnancy or lactation during the study
7	Inadequate expression of the Dutch language (spoken and written)
8	Inability to lose ≥ 5% of bodyweight during the first 8 weeks of VLCD
9	Severe psychiatric problems
10	Significant cardiac arrhythmias, unstable angina, decompensated congestive heart failure, major organ system failure, untreated hypothyroidism and/or myocardial infarction, end-stage renal disease, cerebrovascular accident or major surgery in the last 3 months.

Randomization

Groups of 20 patients will start with a VLCD concomitantly. After 8 weeks of VLCD, the patients who lost ≥5% of bodyweight are randomly assigned to either or the intervention group (usual care + CPI) or the control group (usual care) with an allocation ratio of 1:1. The stratified randomization is computer controlled, carried out by a secretary and supervised by a statistician, who are both not involved in the trial. The reason for a strati-

fied randomization is to avoid an unsuccessful randomization with regard to weight loss during the VLCD. It is not possible to correct afterwards in the analysis, as it is the primary outcome measurement. We defined the following strata (based on clinical experience):

1. 5% - 7.5%
2. 7.5% - 10%
3. >10% weight loss after 8 weeks of VLCD.

The statistician generates the allocation sequence and hands it over to the secretary of the department of Medical Psychology and Psychotherapy, who is not involved in the study, to guarantee allocation concealment. The secretary assigns the participants to their group and makes a list for KACB, who will plan their study appointments.

Sample size calculation

After randomization of 75 participants, the sample size calculation was carried out by an independent statistician to base it on realistic data. Sample size was calculated with SPSS 17.0, using the mixed-model ANOVA procedure described by Aberson (44). Alpha was set at 0.05, power at 0.80 and the baseline-end correlation at 0.90. A clinically relevant difference between the treatment groups is 5% weight loss (3). Mean weight at the start of the treatment is about 110 kg, with a standard deviation of 22, this equals an effect size of d = 0.25 (45). With this power calculation we estimate that we need 52 patients in each group. Anticipating a dropout rate of 25%, we aim for a total sample size of 140.

For the most important secondary outcomes we calculated the detectable difference with the sample size of n=104, alpha 0.05 and power 0.80 (Table 2). The detectable differences are quite small, so the aimed sample size seems adequate to analyse at least these secondary outcomes.

Blinding

Given the nature of the intervention, it is impossible to blind the participants, CPI-therapist and researcher (KACB). Nevertheless, we will try to keep the intervention as separate as possible from the diabetes treatment, by giving participants strict instructions not to communicate about the intervention with their medical team. Patients are given the possibility to discuss problems related to the study with an independent medical doctor. The CPI group sessions will take place in another part of the hospital, outside the diabetes clinic, to ensure that patients and medical team will not run into each other. The VLCD is not a part of the intervention and can therefore be guided by the diabetes medical team. To avoid bias, measurements will be conducted by blinded medical assistants and analyses will be done by two analysts, independent of each other. The allocation sequence will be revealed to the researchers once recruitment, data collection and analyses are complete.

Table 2. Power calculation secondary outcomes

Secondary outcome:	SD:	Detectable difference:(n = 104, β=0.8 α=0.05)
Waist circumference	11	2.75 cm
Blood pressure sys/dias	20/20	5/5 mmHg
Total cholesterol	1.4	0.35 mmol/l
LDL cholesterol	1.0	0.25 mmol/l
HDL cholesterol	0.7	0.2 mmol/l
Triglyceride	3.0	0.75 mmol/l
HbA1c	12	3 mmol/mol
Insulin	50	12.5 IU
Depression (HADS score 0–21)	3	0.75
Anxiety (HADS score 0–21)	4	1.0
Self-esteem (RSE score 10–40)	5	1.25
Fatigue (CIS score 8–56)	13	3.25
Concentration (CIS score 5–35)	8.5	2.1
Motivation (CIS score 4–28)	6	1.5
Activity (CIS score 3–21)	5	1.25
Quality of life (EuroQol 5D score 1–3)	0.5	0.125
Quality of life (EuroQol VAS 1–100)	21	5.25

Interventions

Phase 0: very Low calorie diet

The first part of the study (before randomization) is the same for all participants and consists of a Very Low Calorie Diet (VLCD) for the duration of 8 weeks, with a phase-out of 12 weeks. When after 8 weeks of VLCD a loss of 5% or more of the initial bodyweight is reached, random allocation to the intervention- and control group will take place. Patients losing less than 5% of bodyweight in the first 8 weeks are excluded from the study and will receive usual care, including dietary advice. The use of a VLCD is an integrated part of the dietary treatment at our outpatient diabetes clinic. Normally, the patients are free to choose between the different types of weight reduction strategies. In the present study however, only one type of weight reduction therapy is used (VLCD). The product we use for this study is Glucerna SR®, a product specifically developed for patients with diabetes and based on a combination of slow released carbohydrates, a low-fat, high monounsaturated fatty acid content and the addition of dietary fibre. Various studies indicate that this product decreases the postprandial blood glucose levels, which may have a lowering effect on HbA1c. This diabetes-specific diet product is also used as a meal replacement for achieving weight reduction in people with type 2 diabetes, with positive effects on weight control, glycaemic control and lipid profile (46-48).We have chosen to use a twice a day regimen of meal replacements, together with a small dinner,

providing 750 kcal, 67 g carbohydrates, 54 g protein and 32 g fat (of which 16 g monounsaturated fatty acids (MUFA)) a day and RDA recommendations in micronutrients. We believe that enabling the participants to have dinner with their family during the VLCD will improve compliance.

We have developed a protocol for the use of a VLCD in patients with type 2 diabetes, where we describe the different aspects of the treatment. Oral anti-diabetic agents (except Metformin) and short-acting insulin analogues are discontinued, while the dosage of long-acting insulin analogues and biphasic mixtures is halved, to avoid severe hypoglycaemia. GLP-1 or DPP-4 inhibitors will be continued. During the VLCD and gradual transition to a normal diet, medication is adjusted by means of glucose self-control and frequent contact with diabetes nurses and dieticians. The dose of any antihypertensive medication is also adjusted during VLCD and follow-up, in consultation with the responsible physician. Re-alimentation takes place by slowly reintroducing normal food in 12 weeks' time, until participants use a lightly energy restricted diet (1300 kcal a day), according to national dietary guidelines.

Phase 1: control group

Following the VLCD-period and gradual reintroduction of normal diet, the control group receives usual care, provided by the diabetes team of the out-patient diabetes clinic of the Erasmus Medical Centre. Usual care consists of a 3-monthly visit to the physician and diabetes nurse, including medical examinations. Dietary treatment is part of usual care by referral to a specialized dietician. Patients are free to make additional appointments with their dietician in- or outside the hospital and they can choose to follow whatever diet they would like during the follow-up period. Both the number of visits to a dietician and the dieting methods, products and duration of the diet are noted during the follow-up period of 2 years. Dieticians in our hospital are all trained in motivational interviewing to motivate the patients in changing their lifestyle. All members of the diabetic team encourage the patients to get enough exercise, but we do not refer to an exercise programme. Patients in need of psychological help (ie psychological disorder, clinical depression, major eating disorder) are referred to a clinical psychologist in- or outside the hospital. In our population, these referrals are rare. Nonetheless, the number of visits to a psychologist as well as to other caregivers will be noted during this trial. CBT or techniques of PST and PC are no part of usual care.

Phase 1: intervention group

After 8 weeks of VLCD, the participants allocated to the intervention group start with CPI in groups of up to 10 patients, in addition to the basic treatment for diabetes and obesity, focusing on (self) regulation of blood glucose and the prevention/reduction of complications, according to national guidelines. The CPI sessions are guided by a

trained psychologist/psychotherapist, with experience in diabetes care. Two psychologists (HB and AVTS) are involved in this study, so we can investigate the 'therapist-effect'.

The first 10 weekly sessions consist of cognitive behaviour therapy, partly based on the method developed by Werrij and colleagues from the University of Maastricht (27). These CBT meetings are followed by 7 relapse prevention sessions. The aim of the first 10 sessions is to restructure dysfunctional cognitions on lifestyle, weight and body perception. Sessions 11–17 aim to prevent relapse by combining intervention techniques of CBT, PC and PST. Table 3 presents the treatment protocol in brief.

Table 3. Brief presentation of the treatment protocol

Weekly sessions	
Session 1	Introduction of the therapist and the group members
	Agreements on attendance, commitment, homework and privacy
	Setting realistic treatment goals
	Explaining the rationale of the cognitive treatment
	Introducing relevant concepts op CBT (situation, thoughts, emotions, behaviour) and the use of the diary
Sessions 2 – 4	Discussing rationale and the concepts of CBT
	Explaining unrealistic and automatic thoughts
	Identifying and challenging dysfunctional cognitions about eating, weight and shape (by Socratic dialogue)
	Homework: cognitive diaries
Sessions 5 – 8	Introducing the behavioural experiment
	Challenging dysfunctional cognitions by setting up a behavioural experiment
	Identifying and challenging 'core beliefs', the underlying self-schemas
	Homework: cognitive diaries and behavioural experiments
Sessions 9 – 10	Preparing for the oncoming ending of weekly sessions
	Identifying and challenging dysfunctional cognitions about relapse
	Introducing relapse prevention sessions
Relapse prevention sessions	
Session 11	Challenging dysfunctional cognitions about relapse
	Setting goals for the long term
	Explaining Problem Solving Treatment and Proactive Coping
Session 12 – 16	Implementing PST and PC in an individual plan
Session 17	Preparing for treatment ending
	Challenging dysfunctional cognitions about treatment ending
	Personal reminder in difficult times

After session 1, the structure of each session is as follows:

- time for questions following the previous session
- discussing home-assignments
- explaining and practicing of cognitive (behavioural) techniques
- discussing new home-assignments
- summary and evaluation of the session (by completing the Session Rating Scale)

In sessions 1–5 dysfunctional cognitions about eating, weight and shape are identified and challenged. Also exercise will be included in the sessions. Cognitive diaries are introduced and participants are encouraged to use these diaries at home to record personal critical situations and dysfunctional thoughts. They also score the credibility of their dysfunctional thoughts (0-100%). Furthermore, the validity of the dysfunctional thoughts is tested and alternative thoughts are generated. Guided by examples of the group, the group is acting as a research team, investigating the validity of dysfunctional cognitions and creating alternative and more realistic thoughts. The new thoughts are again scored on credibility (0-100%). Methods used for testing the validity of a person's thoughts are the Socratic dialogue and behavioural experiments. Behavioural experiments are set up during the session, carried out at home, and discussed in the next session. The underlying schemas ('core beliefs') are explored during sessions 6–10. The validity of self-schemas is tested in the same way as the other dysfunctional thoughts and recorded in the diary. Subsequently, 7 relapse prevention meetings are held to stabilize behaviour change, with increasing intervals until the end of the study (2 years). During these relapse prevention meetings, the acquired techniques will be repeated. In addition, techniques of Problem Solving Therapy are used to help participants coping with everyday problems they encounter while implementing their lifestyle changes. Based on individually set goals, experienced problems are identified and possible solutions will be put forward in a group brainstorm session. The participant will choose the most appropriate solution and creates and carries out an implementation plan. In this plan, the participant formulates the solution as a SMART (Specific, Measurable, Attainable, Realistic, Timely) goal and considers which steps should be taken to achieve this goal. Subsequently, the participants will be encouraged to identify barriers that may arise while trying to achieve their goals. Under guidance of the psychologist, activities will be defined which can be undertaken to prevent the occurrence or diminish the effect of these potentially threats (Proactive Coping).In following relapse prevention sessions, the implementation plan is evaluated and new (sub) problems are chosen to tackle. By linking Problem Solving Therapy to Proactive Coping and cognitive restructuring of (relapse) thoughts, we hope to have created a powerful intervention to provide participants skills to prevent and cope with relapse in their behaviour.

Outcome assessment

Outcome measurements (see below) are assessed at baseline (before start VLCD), and again at 4 months (after VLCD and 10 CPI sessions), 1 year, 1 ½ years and 2 years. Demographic variables are assessed at baseline by use of a self-administered questionnaire, which is checked during the intake interview with the investigator. All other secondary outcomes are assessed at baseline, after 4 months, 1 year, 1 ½ years and 2 years, using self-administered questionnaires, except of the Session Rating Scale, which is filled in after every CPI session. Data are managed by use of the trial management system 'EXPeRT Clinical' of OmniComm, USA.

Primary outcome

The primary endpoint with respect to the efficacy of CPI is the differential course of weight (kg) between both study groups, measured at 8 weeks and at 2 years follow-up. Weight is measured to the nearest 0.1 kg, after removal of shoes using a Seca 888 compact digital flat scale.

Secondary outcomes

1. Anthropometric measurements: Height is measured to the nearest 0.5 cm without shoes using a Seca stadiometer. Body Mass Index is calculated as weight divided by height squared (BMI = weight (kg)/height $(m)^2$). Waist circumference (cm) is measured at the level midway between the lowest rib margin and the aliac crest. Hip circumference is measured at the widest point over the buttocks. Both waist- and hip circumference are measured by the nearest 0.5 cm, using a tape-measure. Subsequently, waist-hip ratio (WHR) is calculated.
2. Cardiovascular risk profile by use of the UKPDS risk engine (49):

a. Systolic and diastolic blood pressure (mmHg) are measured twice in upright position, while the patient had rested for at least 5 minutes with an Omron M4-I Intelli-sense device. The second value will be used.
b. Blood samples are taken to asses total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides (mmol/l), measured on a Roche Modular P 800, reagents used from Roche, methods used from Roche are Cholesterol Chod-pap, HDL-c plus 3rd generation, LDL-c plus 2nd generation and Triglycerides GPO-PAP.

3. Glycaemic control:

a. HbA_{1c} (mmol/mol), measured on a Menarini HA-8160, reversed-phase action exchange chromatography.
b. HOMA-%S calculated by measuring fasting plasma glucose (mmol/l), (measured on a Roche Modular P 800, reagent used from Roche, method used from Roche is Glucose Hexokinase) and fasting insulin (mmol/l)
c. Glucose lowering medication (insulin (IU/day) and antidiabetic agents (mg/day))

4. Psychological measurements

a. Anxiety and depression are measured by the Hospital Anxiety and Depression Scale (HADS) (50,51). The HADS consists of a 7-item Anxiety scale and a 7-item Depression Scale. The items are scored from 0 to 3 and the range of scores is 0 – 21. A score between 0 and 7 excludes depression/anxiety. A score of 8–10 indicates a possible depression/anxiety. A score of 11–21 is indicative of a probable depression/anxiety.

b. Somatic symptoms are measured by the VOEG-13 ('Vragenlijst Onderzoek Ervaren Gezondheid') (52), a Dutch 13-item questionnaire used to measure the health of a population, often used in social science research. The items consist of somatic symptoms like headache, nervousness and lethargy and respondents indicate whether they have these symptoms or not. A higher score indicates more somatic symptoms and a worse perceived health.

c. Fatigue is measured by the Checklist Individual Strength (CIS) (53) which quantifies subjective fatigue and related behavioural aspects. The CIS consists of 20 statements for which the respondent has to indicate on a 7-point scale to what extent the particular statement applies to him or her (1 = Yes, that is true; to 7 = No, that is not true). The statements refer to four fatigue aspects: (1) subjective fatigue (2) reduced motivation (3) reduced activity and (4) reduced concentration. For the CIS a cut-off point of >76 has been established [54].. People with a score above this cut-off point are at an increased risk of long-term sickness absence.

d. Self-esteem is measured by the Rosenberg Self-Esteem Scale (RSE) (55). The RSE is a 10-item questionnaire that measures global self-esteem. Items are scored on a 4-point scale. A higher score indicates a more positive self-esteem. Scores below 21 indicate low self-esteem.

e. Eating disorders are measured by the Eating Disorder Examination-Questionnaire (EDE-Q) (56), a 36 item questionnaire that measures concerns about shape, weight and eating, restraint and binge eating. Subscale scores for restraint and shape, weight and eating concern range between 0–6. A higher score indicates more severe eating psychopathology. Because binge eating cannot be measured reliably by the EDE-Q, we use a questionnaire composed by Werrij, et al (28). for diagnosing binge eating disorder (BED), based on the DSM-IV criteria for BED. BED is diagnosed when respondents report eating binges twice a week or more.

f. Session rating. How the participants value the sessions is measured by the Session Rating Scale (SRS) (57). The SRS is an ultra-brief alliance measure designed specifically for every session clinical use. The SRS consists of four 10-cm visual analogue scales (relationship scale, goals and topic scale, approach or method scale, overall evaluation scale), with instructions to place a hash mark on a line (continuum) with negative responses depicted on the left and positive responses indicated on the

right. Based on a total possible score of 40, any score lower than 36 overall, or 9 on any scale, could be a source of concern and therefore prudent to invite the client to comment.

5. Lifestyle

a. We developed a lifestyle questionnaire on diet history, smoking, drinking habits, drug use and hours sleep.

b. Physical activity is measured using the SQUASH (Short Questionnaire to Assess Health Enhancing Physical Activity) (58). The SQUASH collects days per week, average time per day, and effort for physical activities such as commuting activities, leisure time and sport activities, household activities, and activities at work or school. Total minutes of activity are calculated for each question by multiplying frequency (days per week) by duration (minutes per day). Activity scores for separate questions are calculated by multiplying total minutes of activity by an intensity score (range 1–9). The total activity score is calculated by taking the sum of the activity scores for the separate questions.

6. Cost-effectiveness

a. Quality of life is measured by the EuroQol (EQ-5D) (59,60). The EQ-5D is 5-item self-report questionnaire on which participants report if they experience any problems in mobility, self-care, usual activities, pain and anxiety/depression. Each dimension has 3 levels: no problems, some problems and severe problems. The scores on the three dimensions can be combined into one co called 'utility' score, which represents the societal value of quality of life. The utility score has a range from 1.00 (the value of health without health problems) till 0.00 (the value of health problems as bad a death). This societal value of quality of life is used as input for so called Quality Adjusted Life Years (QALY) analysis, as the societal perspective is the preferred perspective in health economics. The EuroQol instrument contains also the EQ-VAS, a vertical visual analogue scale with the anchors best imaginable health (score of 100) and worst imaginable health (score of 0). This EQ–VAS represents the patient's perspective of quality of life.

b. Costs are measured by the Trimbos/iMTA Questionnaire for Costs associated with Psychiatric Illness (TiC-P) (61). The TiC-P measures direct medical costs due to health-care utilization during the past four weeks. Also, it registers the indirect non-medical costs due to productivity loss during the past two weeks.

Patient follow-up and compliance

Follow-up measurements will take place combined with evaluation group meetings. For patients in both groups, follow-up visits to the physician, diabetes nurse and dietician are registered. A common limitation of weight loss studies is a selective loss to follow-up: higher drop-out rates occur among patients, who do not achieve their weight loss goals.

We want to tackle this problem by use of incentives to keep all patients in the trial: motivating phone calls of the researcher, little gifts during the program, etc. Furthermore, we will perform a follow-up and analysis of the drop-outs after completion of the study and compare completers and drop-outs at base-line. For this purpose, the drop-outs will be interviewed by a medical student, who is not involved in the study. Compliance to the intervention is assessed by registration of the attendance to the CPI sessions: participants are considered non-compliant when they are absent on more than 8 sessions. Since we expect that the treatment will be less effective when more than 8 sessions are missed, this non-compliant participants will be considered drop-outs. We have conducted a pilot study to improve our research protocol. We will not perform interim analyses and we will not define stopping rules, since the intervention has no serious side-effects.

Data/results pilot study

In order to test the protocol we conducted a pilot study, in which we included 13 patients to assess the study design and logistic pathways of the VLCD-period and the first 10 weeks of CPI. In this pilot study, we found that the protocol was feasible and that no

Table 4. baseline characteristics pilot group

	Baseline (n=13)	
Sex (%)	Males	25%
	Females	75%
Age (y)		49.5
Insulin dependent (%)	Insulin dependent	75%
	Non-insulin dependent	25%

Table 5. Outcome measurements pilot group

	Baseline (n=13)	T1 = 4 months (n=13)	95%CI
Weight (kg)	114.8	106.0***	[5.2-12.4].
Waist circumference (cm)	121.4	113.7**	[3.2-12.2].
Systolic BP (mmHg)	144.6	127.9*	[1.1-32.2].
Diastolic BP (mmHg)	86.1	78.0	[–0.4-16.7].
Total cholesterol (mmol/l)	5.0	4.5	[–0.2-1.3].
HDL cholesterol (mmol/l)	1.7	1.3	[–0.3-1.3].
LDL cholesterol (mmol/l)	2.6	2.5	[–0.3-0.5].
Triglycerides (mmol/l)	3.6	2.6	[–1.1-3.0].
HbA1c (mmol/mol)	66.3	66.6	[–9.8-9.1].
Insulin (IU)	82.3	32.3*	[7.3-94.7].
Depression score (HAD) >8 = (sub)clinical	5.7	4.6	[–1.5-3.7].

Paired samples T-test *p<0.05 **p<0.01 ***p<0.001

major changes had to be done. The only change we made was in the lay-out of the questionnaires, making them better understandable to our participants. Results of this pilot study (baseline and T=4 months) are shown below (Table 4 and 5).

Statistical analyses

All analyses will be conducted according to the intention-to-treat as well as the on-treatment principle. We consider participants on-treatment when they miss less than 8 sessions CPI. At baseline, comparability between the control- and intervention group will be assessed to test the success of the randomization. As measures of central tendency for numerical data we will use the mean (in case of normal distribution) and median values (in case of non-normal distribution), with respectively the standard deviation and interquartile range as measures of dispersion. Mixed modelling, also known as random effect modelling, multilevel or hierarchical linear regression analyses will be applied for longitudinal analyses of the data. Mixed modelling can efficiently handle data with missing and unbalanced time-points. It corrects for bias when absence of data is dependent on characteristics that are present in the models (missing at random, MAR) (62). There will be two levels in the models. The patients constitute the upper level, their repeated measures the lower level. First, for each outcome variable a saturated model will be postulated, with the primary or secondary outcomes as dependent variables. The saturated models will include treatment group, time, quadratic time, logarithm of time and all treatment-time interactions as fixed effects. The deviance statistic (63) using restricted maximum likelihood (64) will be applied to determine the covariance structure. Next, using Wald tests, the saturated models will be reduced by eliminating insignificant fixed effects. The significance of the difference between the saturated models and the parsimonious final models will be determined with the deviance statistics using ordinary likelihood.

DISCUSSION

To our knowledge, this trial is the first randomized controlled trial to test the effects of an integrated multi-model cognitive group therapy in the battle against weight regain after a successful weight loss intervention (VLCD) in patients with type 2 diabetes. Weight regain is common in the obese population in general, but even more pronounced in the diabetes type 2 population, and with more devastating effects on their health outcomes. The strength of this study is the combined psychological intervention (CPI) of cognitive restructuring, problem solving treatment and proactive coping, which will provide powerful tools to the participants for maintaining behavioural change and improving health outcomes. We expect that adding CPI to a VLCD will be effective in maintaining weight

loss, improving lifestyle and, as a result, leading to improved glycaemic control and a reduction of cardiovascular risk.

We expect that a number of factors may influence the treatment effect, therefore we will also examine potential determinants of weight maintenance, such as depression, anxiety, self-esteem, fatigue, somatic symptoms, eating disorders and lifestyle. Apart from being predictive for the success of the intervention, these factors may be changed by the treatment itself and therefore will be followed over time as secondary outcome measurements.

It is expected that if the intervention is successful, it will also be cost effective since the costs of group counselling are relatively low and the expected reduction of medication, prevention or delay of complications and a reduction of hospital admissions are considered major cost savings. If the therapy is indeed effective, a formal cost effectiveness analysis will be performed.

Few studies have implemented interventions to sustain weight loss for longer than 18 months. In this study, we opt for a follow-up period of 2 years, enabling predictions on long-term behavioural change and weight maintenance. During the follow-up period, participants will have relapse-prevention group meetings with increasing intervals to stabilize behaviour. It is known that the effect of an intervention reduces when the contact with the therapist stops, and one can therefore expect that the participants experience a relapse in their behaviour after the follow-up period. The last session op CPI will be at 1,5 years after randomization, leaving the participants 6 months 'to themselves'. Obviously, our patients remain under supervision of the healthcare team after completion of the study and will be encouraged to continue their good habits. Nevertheless, after 5 years, we will try to repeat the assessment of the main outcome variables to determine the long-term effect.

Limitations

This trial is explanatory in design in relation to the measures of process but pragmatic in terms of the comparison with usual care rather than a specified alternative group. We chose this design to enable analysis of an additional intervention on top of usual care in a population already receiving multiple interventions. The pragmatic approach and planned economic analysis aim to facilitate implementation of the intervention when successful, but this design does not identify the optimal psychological therapy.

If the intervention is successful, it cannot be ascertained which of the 3 therapies involved determined the success. However, each of the treatments has been studied separately and is more or less proven effective in achieving weight reduction and maintenance (20,26,28-32,34-36,40). We expect that a diet with a combination of several forms of cognitive behaviour therapy together will have a greater impact than the individual factors.

Clearly the assumption is that the overlap of effects of the different types of interventions is negligible. This is not necessarily true. Hence, the present study is designed to study the effect of a combination therapy, but cannot identify the optimal combination of interventions.

Another limitation is the comparison to usual care only. One could argue that the participants in the intervention group may benefit from the attention they get, and not necessarily from the CPI. In our study design, it is impossible to distinguish between the effect of attention and the effect of the intervention itself. Our choice to compare our intervention on top of usual care with usual care only, is based on the fact that this kind of comparative effectiveness design has more clinical relevance. Such design is a necessary condition for a cost effectiveness analysis, as cost effectiveness is measured in relation to the dominant alternative treatment strategy. Moreover, the individual interventions have been shown effective in comparison with other psychological interventions, exercise or placebo as a control (27,35,40,65).

We are aware of the fact that our population is not generalizable to the entire group of overweight patients with type 2 diabetes.

One can speculate that patients, who agree to participate in the study and are able to achieve a 5% weight reduction in 8 weeks, are expected to be more motivated then patients, who refuse to participate or who fail to lose sufficient weight. Randomization will distribute this selection bias equally to the CPI and the control group. Nonetheless, our findings will solely be applicable to patients, who are motivated to reduce their body weight.

Our hospital is a tertiary referral centre and as a result the patients often have end stage disease with multiple complications. Due to this selection, motivation, compliance and treatment outcome are expected to be low, potentially resulting in underestimation of the effect. However, GP's will also be able to refer their eligible patients directly to the trial. Those patients often have less severe disease and complications.

Insufficient command of the Dutch language is an exclusion criterion of this investigation, because the cognitive training is given in Dutch and the workbook and homework assignments must be understood and carried out in Dutch as well. In this way, a part of the immigrant population is excluded and the study population will not reflect the entire diabetic population of the Erasmus MC.

We will use incentives (motivating phone calls, little booklets etc.) to minimize drop-out. This effect will be the same for the control group and the intervention group, not affecting the results. However, it will have an effect on the generalizability of the study because the less motivated participants are more likely to remain in the study where they would normally drop-out.

We are aware of the impact, especially on the control group, of the large measurement burden due to all the psychological questionnaires. We will discuss this with the

participants beforehand and expect that they find 5 times 30 minutes of completing questionnaires is acceptable in the light of the weight loss intervention they will receive.

Future implementation

If this intervention proves to be effective and cost-effective, we will promote implementation into diabetes care.

In the present study, we use a VLCD because it leads to quick and substantial weight loss, but off course the multi-model cognitive therapy can be combined with any weight loss intervention (i.e. low calorie diet, low carbohydrate diet, exercise), to sustain the effect.

The study will start in 2010 and the inclusion of patients will take approximately 3 years. After the follow-up period of 2 years, we expect the results to become available in 2015.

Abbreviations

BMI, Body Mass Index; CBT, Cognitive Behaviour Therapy; PST, Problem Solving Therapy; PC, Proactive coping; CPI, Combined Psychological Intervention; VLCD, Very Low Calorie Diet; LDL, Low Density Lipoprotein; HDL, High Density Lipoprotein

REFERENCES

1. Roglic G, Unwin N: Mortality attributable to diabetes: estimates for the year 2010. Diabetes Res Clin Pract 2010, 87(1):15-9.
2. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O: Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003, 348(5):383–393.
3. Anderson JW, Kendall CW, Jenkins DJ: Importance of weight management in type 2 diabetes: review with meta-analysis of clinical studies. J Am Coll Nutr 2003, 22(5):331–339.
4. Institute NHLaB: Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. Washington DC: National Institutes of Health; 1998.
5. Maggio CA, Pi-Sunyer FX: The prevention and treatment of obesity. Application to type 2 diabetes. Diabetes Care 1997, 20(11):1744–1766.
6. Williamson DF, Thompson TJ, Thun M, Flanders D, Pamuk E, Byers T: Intentional weight loss and mortality among overweight individuals with diabetes. Diabetes Care 2000, 23(10):1499–1504.
7. Norris SL, Zhang X, Avenell A, Gregg E, Brown TJ, Schmid CH, Lau J: Long-term non-pharmacologic weight loss interventions for adults with type 2 diabetes. Cochrane Database Syst Rev 2005, 18(2):CD004095.
8. Wing RR: Use of very-low-calorie diets in the treatment of obese persons with non-insulin-dependent diabetes mellitus. J Am Diet Assoc 1995, 95(5):569–572. quiz 573–564.
9. Amatruda JM, Richeson JF, Welle SL, Brodows RG, Lockwood DH: The safety and efficacy of a controlled low-energy ('very-low-calorie') diet in the treatment of non-insulin-dependent diabetes and obesity. Arch Intern Med 1988, 148(4):873–877.
10. Henry RR, Gumbiner B: Benefits and limitations of very-low-calorie diet therapy in obese NIDDM. Diabetes Care 1991, 14(9):802–823.
11. Capstick F, Brooks BA, Burns CM, Zilkens RR, Steinbeck KS, Yue DK: Very low calorie diet (VLCD): a useful alternative in the treatment of the obese NIDDM patient. Diabetes Res Clin Pract 1997, 36(2):105–111.
12. Jazet IM, Pijl H, Frolich M, Romijn JA, Meinders AE: Two days of a very low calorie diet reduces endogenous glucose production in obese type 2 diabetic patients despite the withdrawal of blood glucose-lowering therapies including insulin. Metabolism 2005, 54(6):705–712.
13. Rotella CM, Cresci B, Mannucci E, Rizzello SM, Colzi G, Galli G, Giannini S, Messeri G, Piani F, Vannini R, et al: Short cycles of very low calorie diet in the therapy of obese type II diabetes mellitus. J Endocrinol Invest 1994, 17(3):171–179.
14. Williams KV, Mullen ML, Kelley DE, Wing RR: The effect of short periods of caloric restriction on weight loss and glycemic control in type 2 diabetes. Diabetes Care 1998, 21(1):2–8.
15. Baker S, Jerums G, Proietto J: Effects and clinical potential of very-low-calorie diets (VLCDs) in type 2 diabetes. Diabetes Res Clin Pract 2009, 85(3):235–242.
16. Dhindsa P, Scott AR, Donnelly R: Metabolic and cardiovascular effects of very-low-calorie diet therapy in obese patients with Type 2 diabetes in secondary failure: outcomes after 1 year. Diabet Med 2003, 20(4):319–324.
17. Paisey RB, Frost J, Harvey P, Paisey A, Bower L, Paisey RM, Taylor P, Belka I: Five year results of a prospective very low calorie diet or conventional weight loss programme in type 2 diabetes. J Hum Nutr Diet 2002, 15(2):121–127.

18. Wing RR, Marcus MD, Salata R, Epstein LH, Miaskiewicz S, Blair EH: Effects of a very-low-calorie diet on long-term glycemic control in obese type 2 diabetic subjects. Arch Intern Med 1991, 151(7):1334–1340.
19. Jazet IM, de Craen AJ, van Schie EM, Meinders AE: Sustained beneficial metabolic effects 18 months after a 30-day very low calorie diet in severely obese, insulin-treated patients with type 2 diabetes. Diabetes Res Clin Pract 2007, 77(1):70–76.
20. Shaw K, O'Rourke P, Del Mar C, Kenardy J: Psychological interventions for overweight or obesity. Cochrane Database Syst Rev 2005, 18(2):CD003818.
21. Beck AT: Cognitive therapy and the emotional disorders. New York: International Universities Press; 1976.
22. Fairburn C: A cognitive behavioural approach to the treatment of bulimia. Psychol Med 1981, 11(4):707–711.
23. Wilson GT, Fairburn CG: Cognitive treatments for eating disorders. J Consult Clin Psychol 1993, 61(2):261–269.
24. Daansen PJ: Het obesitasprogramma: cognitieve gedragstherapie bij overgewicht. Den Haag: Parnassia; 2000.
25. Block J: Effects of rational emotive therapy on overweight adults. Psychotherapy: Theory, Research and Practice 1980, 17(3):277–280.
26. Cooper Z, Fairburn CG: A new cognitive behavioural approach to the treatment of obesity. Behav Res Ther 2001, 39(5):499–511.
27. Dennis KE, Pane KW, Adams BK, Qi BB: The impact of a shipboard weight control program. Obes Res 1999, 7(1):60–67.
28. Werrij MQ, Jansen A, Mulkens S, Elgersma HJ, Ament AJ, Hospers HJ: Adding cognitive therapy to dietetic treatment is associated with less relapse in obesity. J Psychosom Res 2009, 67(4):315–324.
29. Ismail K, Winkley K, Rabe-Hesketh S: Systematic review and meta-analysis of randomised controlled trials of psychological interventions to improve glycaemic control in patients with type 2 diabetes. Lancet 2004, 363(9421):1589–1597.
30. D'Zurilla TJ, Nezu AM: Problem-solving Therapies. In Handbook of Cognitive Behavioral Therapies. 2nd edition. Edited by Dobson KS: Guilford Press; 2001:211–245.
31. D'Zurilla TJ, Goldfried MR: Problem solving and behavior modification. J Abnorm Psychol 1971, 78(1):107–126.
32. Mynors-Wallis LM, Gath DH, Day A, Baker F: Randomised controlled trial of problem solving treatment, antidepressant medication, and combined treatment for major depression in primary care. BMJ 2000, 320(7226):26–30.
33. Mynors-Wallis LM, Gath DH, Lloyd-Thomas AR, Tomlinson D: Randomised controlled trial comparing problem solving treatment with amitriptyline and placebo for major depression in primary care. BMJ 1995, 310(6977):441–445.
34. Perri MG, Nezu AM, Viegener BJ: Improving the long-term management of obesity: Theory, research and clinical guidelines. New York: Wiley; 1992.
35. Perri MG, Nezu AM, McKelvey WF, Shermer RL, Renjilian DA, Viegener BJ: Relapse prevention training and problem-solving therapy in the long-term management of obesity. J Consult Clin Psychol 2001, 69(4):722–726.

36. Murawski ME, Milsom VA, Ross KM, Rickel KA, DeBraganza N, Gibbons LM, Perri MG: Problem solving, treatment adherence, and weight-loss outcome among women participating in lifestyle treatment for obesity. Eat Behav 2009, 10(3):146–151.

37. Aspinwall LG, Taylor SE: A stitch in time: self-regulation and proactive coping. Psychol Bull 1997, 121(3):417–436.

38. Schwarzer R, Taubert S: Tenacious goal pursuits and striving toward personal growth: Proactive coping. In Beyond Coping: Meeting Goals, Visions and Challenges. Edited by Fydenberg E. London: Oxford University Press; 2002:19–35.

39. Sohl SJ, Moyer A: Refining the Conceptualization of an Important Future-Oriented Self-Regulatory Behavior: Proactive Coping. Pers Individ Dif 2009, 47(2):139–144.

40. Thoolen B, De Ridder D, Bensing J, Maas C, Griffin S, Gorter K, Rutten G: Effectiveness of a self-management intervention in patients with screen-detected type 2 diabetes. Diabetes Care 2007, 30(11):2832–2837.

41. Agras WS, Telch CF, Arnow B, Eldredge K, Marnell M: One-year follow-up of cognitive-behavioral therapy for obese individuals with binge eating disorder. J Consult Clin Psychol 1997, 65(2):343–347.

42. Fairburn CG, Jones R, Peveler RC, Carr SJ, Solomon RA, O'Connor ME, Burton J, Hope RA: Three psychological treatments for bulimia nervosa. A comparative trial. Arch Gen Psychiatry 1991, 48(5):463–469.

43. Fava GA, Ruini C, Rafanelli C, Finos L, Conti S, Grandi S: Six-year outcome of cognitive behavior therapy for prevention of recurrent depression. Am J Psychiatry 2004, 161(10):1872–1876.

44. Aberson CL: Applied power analysis for the behavioral sciences. New York: Routledge; 2010.

45. Cohen J: Statistical power analysis for the behavioral sciences. New York: Academic; 1969.

46. Fix B, Low W, Cockram DW: Effects of a liquid nutritional supplement containing a novel carbohydrate system on glucose tolerance in subjects with type 2 diabetes (abstract). Ann Nutr Metab 2001, 45(suppl 1):277.

47. Gonzalez-Ortiz M, Martinez-Abundis E, Hernandez-Salazar E, Kam-Ramos AM, Robles-Cervantes JA: Effect of a nutritional liquid supplement designed for the patient with diabetes mellitus (Glucerna SR) on the postprandial glucose state, insulin secretion and insulin sensitivity in healthy subjects. Diabetes Obes Metab 2006, 8(3):331–335.

48. Sun J, Wang Y, Chen X, Chen Y, Feng Y, Zhang X, Pan Y, Hu T, Xu J, Du L, et al: An integrated intervention program to control diabetes in overweight Chinese women and men with type 2 diabetes. Asia Pac J Clin Nutr 2008, 17(3):514–524.

49. Stevens RJ, Kothari V, Adler AI, Stratton IM, United Kingdom Prospective Diabetes Study G: The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). Clin Sci (Lond) 2001, 101(6):671–679.

50. Bjelland I, Dahl AA, Haug TT, Neckelmann D: The validity of the hospital anxiety and depression scale. An updated literature review. J Psychosom Res 2002, 52(2):69–77.

51. Zigmond AS, Snaith RP: The hospital anxiety and depression scale. Acta Psychiatr Scand 1983, 67(6):361–370.

52. Dirken JM: Arbeid en stress: het vaststellen van aanpassingsproblemen in werksituaties. Vragenlijst voor onderzoek van de ervaren gezondheidstoestand (VOEG). Wolters-Noordhoff; Leiden: Nederlands Instituut voor Praeventieve Geneeskunde TNO; 1969.

53. Vercoulen J, Alberts M, Bleijenberg G: De Checklist Individual Strength (CIS). Gedragstherapie 1999, 32:131–136.

54. Bultmann U, de Vries M, Beurskens AJ, Bleijenberg G, Vercoulen JH, Kant I: Measurement of prolonged fatigue in the working population: determination of a cutoff point for the checklist individual strength. J Occup Health Psychol 2000, 5(4):411–416.

55. Rosenberg M: Society and The Adolescent Self-Image. Princeton, NJ: Princeton University Press; 1965.

56. Fairburn CG, Beglin SJ: Assessment of eating disorders: interview or self-report questionnaire? Int J Eat Disord 1994, 16(4):363–370.

57. Hafkenscheid A: The impact of psychotherapy sessions: internal structure of the Dutch Session Evaluation Questionnaire (SEQ). Psychol Psychother 2009, 82(Pt 1):99-111

58. Wendel-Vos GC, Schuit AJ, Saris WH, Kromhout D: Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epidemiol 2003, 56(12):1163–1169.

59. [No authors listed).: EuroQol–a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy 1990, 16(3):199–208.

60. Busschbach JJ, McDonnell J, Essink-Bot ML, van Hout BA: Estimating parametric relationships between health description and health valuation with an application to the EuroQol EQ-5D. J Health Econ 1999, 18(5):551–571.

61. IMTA: Vragenlijst over Zorggebruik, Ziekte en Werk (TIC-P). Rotterdam: Erasmus Medical Center; 2007.

62. Little RJA, Rubin DB: Statistical analysis with missing data. New York: John Wiley and Sons; 1987.

63. Singer JD, Willett JB: Applied longitudinal data analysis - modeling change and event occurrence. Oxford: Oxford University Press; 2003.

64. Verbeke G, Molenberghs G: Linear mixed models for longitudinal data. New York: Springer; 2000.

65. Goodrick GK, Poston WS 2nd, Kimball KT, Reeves RS, Foreyt JP: Nondieting versus dieting treatment for overweight binge-eating women. J Consult Clin Psychol 1998, 66(2):363–368.

Chapter 7

Efficacy of cognitive behavioral group therapy to prevent weight regain after dieting in type 2 diabetes: the 2-years, randomized controlled Prevention Of WEight Regain (POWER) trial.

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ABSTRACT

Objective

Weight loss programs for adults with type 2 diabetes are not effective in the long term due to regain of weight. Our aim was to determine the efficacy of cognitive behavioral group therapy (CBGT) in preventing weight regain after a very low-calorie diet (VLCD) in obese adults with type 2 diabetes.

Research design and methods

We randomized 158 obese adults (BMI 36.3 [32.5-40.0]) with type 2 diabetes, who achieved ≥5% weight loss with an 8-week VLCD, to usual care or CBGT (17 group sessions) to prevent weight regain, on top of usual care. The primary outcomes were the between-group differences after two years in (1) body weight and (2) weight regain. Secondary outcomes were HbA1c, insulin dose, plasma lipids, depression, anxiety, self-esteem, quality of life, fatigue, physical activity, eating disorders and related cognitions.

Results

The difference in body weight at two years was -1.2 [95% CI -7.7-5.3] kg (*P*=0.7). Weight regain was 4.7 [95% CI 3.0-6.3] kg for the control group and 4.0 [95% CI 2.3-5.6] kg for the CBGT group, with a between-group difference of -0.7 [95% CI -3.1-1.6] kg (*P*=0.6). None of the secondary outcomes differed between the two groups.

Conclusions

CBGT after diet-induced weight loss did not prevent weight regain, and did not improve cardiovascular risk factors and the psychological wellbeing in obese adults with type 2 diabetes. Our results suggest that there is no scientific justification for offering CBGT to optimize the long term effect of weight loss dieting in this patient group.

INTRODUCTION

Lifestyle interventions that reduce weight improve a number of cardiovascular disease risk factors in adults with type 2 diabetes (1, 2), but studies on hard endpoints have been disappointing. In the Look AHEAD trial, an intensive lifestyle intervention did not result in an effect on cardiovascular outcomes (3). Weight regain during follow-up in a substantial proportion of the participants has contributed to this unforeseen outcome (4, 5). Obviously, non-invasive weight loss interventions require strategies that prevent regain of body weight to achieve clinically relevant effects.

Cognitive behavioral group therapy (CBGT) has been shown effective in weight management and weight loss maintenance after dieting in obese adults without type 2 diabetes (6, 7). CBGT is a psychological intervention aimed at changing dysfunctional thoughts about self-image and behavior into more realistic, helpful thoughts, hereby facilitating long term behavioral change. In type 2 diabetes, only two observational studies have been conducted reporting favorable effects on weight loss of CBGT as part of weight loss programs (8, 9). The effect of CBGT on maintenance of weight loss has not been investigated in patients with type 2 diabetes.

The primary objective of the present study was to determine the efficacy of CBGT on maintaining weight during two years after diet-induced weight loss in overweight and obese adults with type 2 diabetes. The secondary objectives were to evaluate the effects of CBGT on cardiovascular risk factors and psychological wellbeing.

RESEARCH DESIGN AND METHODS

Study design

The protocol of the 'Prevention Of Weight Regain' (POWER) trial has been published previously (10). This study was a parallel-group, randomized clinical trial, conducted between March 2010 and May 2015, and was approved by the Medical Ethics Committee (MEC-2009-143/NL26508.078.09) in compliance with the Helsinki Declaration (2008). All participants provided written informed consent.

Study Population

Overweight and obese (BMI>27 kg/m^2) patients with type 2 diabetes aged 18-75 years were recruited from the outpatient diabetes clinic of the Erasmus MC. Our hospital is a tertiary referral center, but patients with severe comorbidity were excluded for this trial. Some of the eligible patients were referred by their GPs specifically for participation in our trial. Exclusion criteria were: pregnancy; lactation; inadequate understanding of the Dutch language (spoken and written); severe psychiatric problems; significant

cardiac arrhythmias; unstable angina; decompensated congestive heart failure; carcinomas; major organ system failure; untreated hypothyroidism; end-stage renal disease; myocardial infarction, cerebrovascular accident or major surgery during the previous 3 months. Of the subjects who met the criteria but declined to participate, we recorded age, sex and ethnic origin.

Weight loss dieting

After collection of baseline data, participants started with a very low-calorie diet (VLCD) of approximately 750 kcal/day for 8 weeks. Blocks of twenty participants started with the diet concomitantly. The daily diet consisted of 2 diabetes-specific meal replacements (Glucerna SR, Abbott Nutrition B.V.) plus 75 grams of lean meat, 150 ml of skimmed milk, and low-carbohydrate vegetables ad libitum. To reduce the risk of hypoglycemia, doses of sulfonylurea derivates and insulin were reduced at the start of the dietary intervention. After 8 weeks the diet was changed into a low-calorie diet of 1100-1300 kcal/day, gradually increasing the intake during the following 12 weeks. From then on, the participants used a diet based on national health recommendations, aiming at weight maintenance. During the entire study, 60 minutes of moderately intensive daily exercise was recommended, and antidiabetic medication and insulin doses were adjusted by the responsible physician based on plasma glucose levels. Other medication remained unchanged.

Randomization and Masking

After 8 weeks of the VLCD, the participants who lost >5% of bodyweight were randomly assigned to either the usual care group or the CBGT group with an allocation ratio of 1:1. The block randomization was stratified to weight loss: categories 5-7.5%, 7.5-10% and >10%. The participants, CBGT therapists and primary researcher (KAB) were not blinded for the intervention, whereas the medical team at the outpatient clinic was. Participants were not allowed to talk to their medical team about the CBGT sessions. The treatment of diabetes and its complications (according to the national guidelines) was not influenced by the allocation of the participants. Blinded medical assistants conducted the measurements (weight, waist circumference, blood pressure) and all statistical analyses were conducted by two researchers independently.

Control group: usual care

The control group received the usual care for diabetes regulation and cardiovascular risk management in our tertiary medical referral center. This consisted of scheduled visits every 3-6 months (often on separate occasions) to the internist and diabetes nurse, plus referral to a dietitian or psychologist when indicated. Additionally, during the diet period the participants using insulin frequently contacted the diabetes nurse by mail or telephone

to optimally adjust their insulin dose according to their glucose levels. The increased attention (during additional visits) given to the CBGT group was not compensated for in the control group.

Intervention group: cognitive behavioral group therapy (CBGT) added to usual care
After randomization, participants allocated to the intervention group started with CBGT with up to 10 participants per group. The first 10 sessions were weekly; these were followed by two fortnightly sessions, two monthly sessions, two 3-monthly sessions, and the last session took place 18 months after randomization. The CBGT sessions were given by a trained psychologist/psychotherapist (HB or AVTS) experienced in CBGT as well as in diabetes care.

The aim of the first 10 sessions, including 1 partner-session, was to restructure dysfunctional cognitions on lifestyle, weight and body perception, based on the method developed by Werrij and colleagues at the University of Maastricht (11). Sessions 11-17 were aimed at preventing relapse by combining intervention techniques of Cognitive Behavioral Therapy (CBT) with pro-active coping and problem solving therapy (12-14). A detailed description of the intervention has been published previously (10). The CBGT was given on top of usual care.

Outcome Measures

All primary and secondary outcome variables were pre-specified an described in more detail in the study protocol (10). Outcome variables were assessed at baseline, at randomization after eight weeks of VLCD (primary outcome only), and at 12 weeks (after the weekly CBGT sessions were finished), 52 weeks, 78 weeks and 104 weeks after randomization.

The primary endpoints were the differences between the study groups in body weight (kg) after two years of follow-up and in weight regain (kg) from randomization to two years. Weight was measured to the nearest 0.1 kg after removal of shoes, using a Seca 888 compact digital flat scale.

Secondary outcomes (all defined as between-group differences) were as follows: change in weight (kg) from baseline to two years of follow-up; two year estimates and change from baseline to two years in waist circumference (cm); systolic blood pressure (mmHg); total cholesterol (mmol/l), LDL-cholesterol (mmol/l), HDL cholesterol (mmol/l), triglycerides (mmol/l) and HbA1c (%/mmol/mol), all measured via routine laboratory techniques; insulin dose (IU/day); depression and anxiety (Hospital Anxiety and Depression Scale (HADS) (15, 16)); self-esteem (Rosenberg Self-Esteem Scale (RSE) (17)); quality of life (EuroQol EQ-5D (18, 19)); fatigue (Checklist Individual Strength (CIS) (20, 21)); physical activity (Short Questionnaire to Assess Health Enhancing Physical Activity (SQUASH) (22)); eating disorders (Eating Disorder Examination-Questionnaire

(EDE-Q) (23)) and related cognitions (EDE-Q sub scores eating restraint, eating concern, weight concern and shape concern, score range 0-6). In addition to the predefined outcome variables, we recorded the number of visits to physicians and paramedics at the diabetes out-patient clinic. We managed our data using the trial management system OpenClinica (Waltham, MA).

Sample Size

To base the sample size calculation on realistic eight-week weight loss data, an independent statistician carried out a blinded power-calculation after the first 75 participants completed the eight-week VLCD period, as was described in the protocol (10). Sample size was calculated with SPSS 17.0, using the mixed-model ANOVA procedure described by Aberson (24). Alpha was set at 0.05, power at 0.80 and the baseline-end correlation at 0.90. A clinically relevant difference between the treatment groups was set at 5% weight loss (25). This calculation yielded a necessity of 52 patients in each group. Anticipating a dropout rate of 25%, we aimed for a total sample size of 140. We also conducted a post-hoc power calculation. With an alpha of 0.05 and the true baseline-end correlation of 0.94, the power was 0.998 for the intention-to-treat analysis and 0.969 for the per-protocol analysis.

Statistical Analyses

Normality of the data and homogeneity of variances were tested using the Shapiro-Wilk test and Levene's test. Variables at baseline were expressed as number with percentage, mean with standard deviation or median with inter-quartile range. The difference between the control and intervention group at baseline was tested with a Chi-Square test, an independent samples t-test or a Mann-Whitney U test, depending on normality of the data. Linear mixed modelling was applied for the analyses of the between-group differences of the 2-year course of the primary and secondary outcomes. This method efficiently handles data with missing and unbalanced time-points, and corrects for selective dropout when missing is conditionally on variables incorporated in the model (missing at random) (26). The models included three levels: group membership as highest level, patients as intermediate level and their repeated measures as lower level. The need of the upper (group membership) level was determined with the deviance statistic (27). The fixed parts of the models included allocation arm, sex, linear, quadratic and logarithmic time effects and the interactions of allocation and sex with the time effects. Variance components matrices were applied for the covariance structures. All analyses were conducted according to the intention-to-treat and the per-protocol principle. Treatment was considered per-protocol when participants attended at least 9 CBGT sessions (10). Per-protocol analyses were restricted to the usual care group and the compliant participants in the CBGT group. The difference in number of visits to the outpatient clinic

during the study was analyzed using a Mann-Whitney U test. Results with p-values <0.05 were considered statistically significant. Analyses were carried out using IBM SPSS 21.0.

RESULTS

Patient Characteristics

Of the 296 patients who were assessed from March 2010 until May 2013, 276 were eligible to participate in our study and 206 gave written informed consent (Figure 1). Individuals who declined to participate were older (56.1 ± 10.3 years vs. 53.0 ± 10.8 years, *P* = 0.05) and more often male (61% vs. 43%, p=0.008) than those willing to participate in the study. The main reasons for refusal to participate were work-related and lack of time.

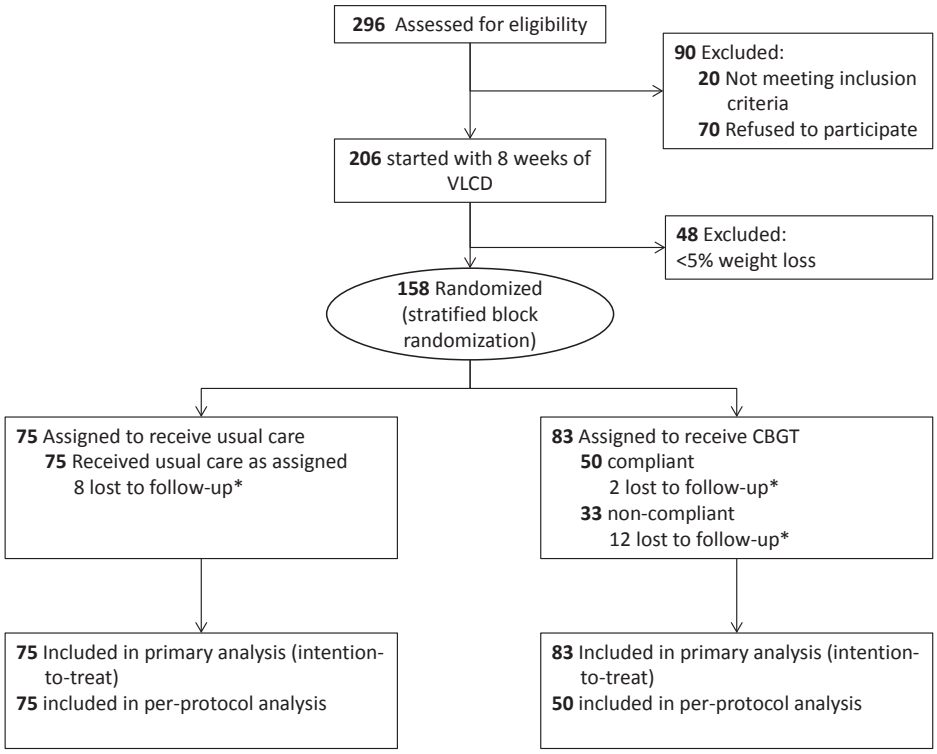

Figure 1. Study flow-chart

*Reasons for lost to follow-up: 3 got pregnant, 2 moved to other country, 2 moved to other hospital, 3 underwent bariatric surgery, 2 were diagnosed with carcinoma, 5 did no longer want to participate, 5 did no longer respond to invitation

BMI = body mass index; VLCD = very low-calorie diet; CBGT = cognitive behavioral group therapy

After the 8-week very low-calorie diet, 158 participants (77%) had lost ≥5 % of their bodyweight and were randomized to either the intervention (n=83) or the control group (n=75). Baseline characteristics of the participants that did and did not achieve ≥5 % weight loss are compared in supplemental table S1. The excluded individuals had significantly higher baseline levels of HbA1c (8.5 (7.6-10.0)%; 69.5 (59.3-86.3) mmol/mol vs. 7.6 (7.0-8.5)%; 60.0 (53.0-69.0) mmol/mol, P = 0.001) and a higher anxiety score (8.0 (4.0-11.0) vs. 6.0 (3.0-9.0), P = 0.038) than the included participants.

Baseline characteristics did not significantly differ between the control and intervention group (Table 1), except for the eating disorder score (EDE-Q; P = 0.021). Eight participants in the control group and 14 in the intervention group were lost to follow-up at different time points during the study (P = 0.358) (Figure 1). Those participants were kept in the analyses as data with missing time points.

The average numbers of usual care visits to the outpatient diabetes clinic during 2 years were similar in the CBGT and the control group: 12.0 (8.0-15.0) vs. 13.0 (8.0-17.0), respectively, P = 0.495. In addition to the visits for the usual care, the participants in the intervention group attended a median of 9.0 (5.0-14.0) CBGT sessions. Thirty-three participants missed more than 8 sessions and were considered non-compliant. Non-compliant participants attended a median of 4.0 (0.0-7.0) CBGT sessions, while compliant participants attended 14.0 (11.0-15.3) CBGT sessions. Non-compliant participants were significantly younger than compliant participants (49.0 (38.5-55.5) vs. 56.0 (49.5-63.0) years; P = 0.004). The main reasons mentioned for non-compliance were health problems and lack of time (work related). Twenty % of the participants in the CBGT group and 12% of the participants in the control group reported consulting an external psychologist (P = 0.187), with a median number of 3.5 (2.0-5.8) visits in the CBGT group and 4.0 (1.0-8.5) visits in the control group during two years (P = 0.978).

Weight change during the trial

During the initial 8-week of dieting a weight loss of 10.0 [95% CI 9.1-10.9] kg was observed in the control group while the CBGT group lost 9.2 [95% CI 8.4-10.0] kg. After 2-year of follow-up weight loss was 5.3 [95% CI 3.5-7.2] kg and 5.2 [95% CI 3.4-7.1] kg, respectively. Overall, 38.6% of the participants still had a weight loss of ≥5% after two years of follow-up, including 17.7% whose weight loss remained ≥10%. During the 2-year follow-up, 19.0% of the participants managed to fully maintain their lost weight. These percentages were similar in both study arms: χ^2=0.161, P = 0.688; χ^2=0.307, P = 0.580; and χ^2=0.077, P = 0.781, respectively.

Primary Outcome

We did not find a significant difference in body weight between the CBGT and control group at two years of follow-up (intention-to-treat analysis, table 2). The between-group

Table 1. Baseline participant characteristics

Characteristic*	Control (n=75)	CBGT (n=83)
Age (y)	55.2±9.3 range 32-73	52.3±11.3 Range 28-74
Female (No. (%))	44 (58.7)	44 (53.0)
Caucasian (No. (%))	45 (60.0)	42 (50.6)
Low education (No. (%))	25 (33.3)	21 (25.3)
Employed (No. (%))	24 (32.0)	36 (43.4)
Employment (days/week)	0 (0-3.3)	0 (0-5)
Years after diagnosis T2D	10.0 (3.0-15.0)	8.0 (3.5-16.0)
Weight (kg)	106.7±22.5	105.5±19.3
BMI (kg/m^2)	35.7 (32.9-40.9)	36.7 (31.7-39.4)
Waist circumference (cm)	120.4±12.9	119.4±14.2
Systolic blood pressure (mmHg)	145.0±20.9	138.6±18.6
Diastolic blood pressure (mmHg)	81.0±10.5	80.2±10.7
HbA1$_c$ (%)	7.7 (7.1-8.4)	7.5 (6.9-8.7)
HbA1$_c$ (mmol/mol)	61.0 (53.8-68.3)	58.0 (51.5-72.0)
Fasting glucose (mmol/l)	8.7 (6.9-10.5)	8.2 (6.8-10.8)
Total cholesterol (mmol/l)	4.4 (3.7-5.1)	4.5 (3.9-5.2)
LDL cholesterol (mmol/l)	2.5 (2.0-3.0)	2.6 (2.2-3.1)
HDL cholesterol (mmol/l)	1.2 (1.0-1.4)	1.1 (1.0-1.3)
Triglycerides (mmol/l)	1.7 (1.3-2.4)	2.0 (1.3-2.7)
Insulin users (No. (%))	49 (65.3)	52 (63.4)
Insulin dose among users (IU/day)	100.1±42.2	95.7±54.9
Statin users (No. (%))	50 (69.4)	59 (74.7)
Clinical depression (No. (%) with HADS score >10)	12 (16.4)	15 (18.8)
Clinical anxiety disorder (No. (%) with HADS score >10)	12 (16.4)	16 (20.0)
Self-esteem (RSE score)	32.0 (28.0-35.0)	32.5 (27.0-35.0)
Quality of life (EQ5D score)	0.78 (0.57-0.84)	0.81 (0.65-1.0)
Fatigue (CIS sub score 1)	37.0 (27.3-47.8)	36.5 (28.0-47.8)
Eating disorder (EDE-Q score)	1.9±1.0	2.4±1.2
Physical activity (SQUASH score)	2350 (1260-5355)	3495 (1440-5978)

**Data are mean±SD, median (interquartile range) or number (%).*
CBGT = cognitive behavioral group therapy group; T2D = type 2 diabetes; BMI = body mass index; HbA1$_c$ = glycated hemoglobin; LDL = low-density lipoprotein; HDL = high-density lipoprotein

difference was -1.2 [95% CI -7.7-5.3] kg (P = 0.717). In the per-protocol analysis the between-group difference was -3.8 [95% CI -11.5-3.8] kg (P = 0.323). Weight regain during follow-up was 4.7 [95% CI 3.0-6.3] kg for the control group and 4.0 [95% CI 2.3-5.6] kg for the CBGT group, with a between-group difference of -0.7 [95% CI

-3.1-1.6] kg (P = 0.556) in the intention-to-treat analysis and -0.6 [95% CI -3.3-2.0] kg (P = 0.635) in the per-protocol analysis. The deviance statistic of the linear mixed model indicated that a three-level model with a third upper 'group' level was not significantly better than a two-level model with time and allocation ($\chi^2_{(1)}$=1.189; P = 0.28). In supplemental table S2 we show the estimates of the linear mixed model for weight during the study (intention-to-treat). These results indicate that there is no allocation effect and also no allocation-time interaction. We found no interaction of sex with time and allocation (data not shown).

Table 2. Differences in outcome variables after two years of follow-up between the Cognitive Behavioral Group Therapy group (CBGT) and the control group (intention-to-treat)

Outcome variables*	Control	CBGT	Between-group difference
Primary outcomes			
Weight (kg)	101.4 [96.7, 106.1]	100.2 [95.8, 104.7]	-1.2 [-7.7, 5.3]
Weight regain# (kg)	4.7 [3.0, 6.3]	4.0 [2.3, 5.6]	-0.7 [-3.1, 1.6]
Secondary outcomes			
Waist circumference (cm)	116.0 [112.7, 119.2]	115.0 [111.9, 118.1]	-1.0 [-5.4, 3.5]
Systolic blood pressure (mmHg)	140.0 [135.4, 144.7]	139.2 [134.8, 143.7]	-0.8 [-7.3, 5.6]
HbA1c (%)	8.1 [7.7, 8.5]	8.0 [7.6, 8.4]	-0.1 [-0.6, 0.5]
HbA1c (mmol/mol)	64.9 [60.6, 69.1]	64.0 [59.8, 68.1]	-0.9 [-6.8, 5.0]
Insulin dose (IU)	43.5 [26.9, 60.1]	40.4 [24.3, 56.6]	-3.1 [-26.3, 20.2]
Total cholesterol (mmol/l)	4.20 [3.90, 4.50]	4.48 [4.19, 4.77]	0.29 [-0.13, 0.70]
LDL cholesterol (mmol/l)	2.34 [2.10, 2.58]	2.65 [2.42, 2.88]	0.31 [-0.03, 0.64]
HDL cholesterol (mmol/l)	1.24 [1.16, 1.32]	1.22 [1.14, 1.30]	-0.02 [-0.13, 0.10]
Triglycerides (mmol/l)	2.08 [1.50, 2.66]	2.29 [1.73, 2.84]	0.21 [-0.60, 1.01]
Depression (HADS)	5.3 [4.2, 6.3]	5.5 [4.5, 6.6]	0.3 [-1.2, 1.8]
Anxiety (HADS)	5.3 [4.1, 6.4]	6.1 [4.9, 7.2]	0.8 [-0.8, 2.4]
Self-esteem (RSE)	31.1 [29.1, 33.1]	29.9 [27.9, 31.9]	-1.2 [-4.0, 1.7]
Quality of life (EQ5D)	0.69 [0.62, 0.76]	0.69 [0.63, 0.76]	0.01 [-0.09, 0.10]
Fatigue (CIS)	31.2 [27.9, 34.5]	33.4 [30.2, 36.7]	2.2 [-2.4, 6.9]
Eating disorders (EDE-Q)	1.70 [1.39, 2.01]	2.11 [1.80, 2.41]	0.41 [-0.02, 0.84]
Physical activity (SQUASH)	4176 [2160, 6191]	5453 [3427, 7480]	1278 [-1580, 4136]

**Estimates after two years of follow-up and between group difference [95% CI] and #change from randomization to two years [95%CI] and between group difference [95% CI]; all analyzed via linear mixed model procedure. $HbA1_c$ = glycated hemoglobin; LDL = low-density lipoprotein; HDL = high-density lipoprotein*

Secondary outcomes

Change in weight from baseline to two years was not significantly different between the two groups (intention-to-treat: 0.1 [95% CI -2.5-2.7] kg (*P* = 0.951) Figure 2A; per-protocol: -0.8 [95% CI -3.7-2.2] kg, *P* = 0.613, Figure 2B). None of the other secondary outcomes was significantly different between the intervention and control group at two years (Table 2). Also, the change from baseline was not different between the two groups for any of the secondary outcome variables (data not shown). At two years of follow-up, both the CBGT and the control group had a significantly lower waist circumference, insulin dose, depression score and fatigue score than at baseline (*P*< 0.05). In addition, the EDE-Q subscale scores on weight concern and shape concern significantly improved during the two years of follow-up for both groups (*P*< 0.01).

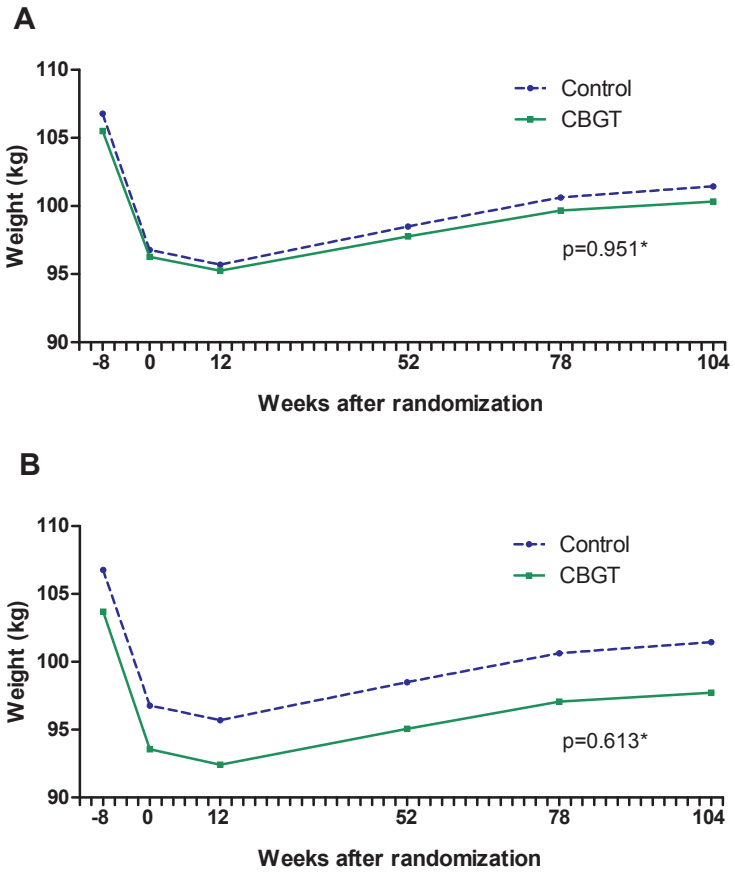

Figure 2. Estimates of weight from baseline to two years of follow-up in cognitive behavioral group therapy (CBGT) and control group: (A) intention-to-treat; (B) per-protocol.
**p-value of between-group difference in weight from baseline to two years of follow-up, analyzed by mixed modelling procedure*

CONCLUSIONS

In this randomized controlled trial, CBGT did not reduce the problem of regaining weight following a successful diet-induced weight reduction in overweight and obese adults with type 2 diabetes. Moreover, the secondary outcomes were not different between the intervention and control group, while the average waist circumference, insulin dose, depression score and fatigue score remained significantly lower during follow-up after the very-low calorie diet for both groups.

Weight regain usually occurs in the first year after weight loss (4, 28-30). In line, the participants of both groups showed a gradual regain of weight during the two years of follow-up. In a post-hoc analysis of the Look AHEAD trial, a sustained weight loss of ≥10% was associated with a 21% decrease in the incidence of cardiovascular disease, indicating that increasing the magnitude of long term weight loss potentially could lead to a positive effect on hard endpoints (5). In our trial, only 18% of the participants maintained a weight loss of ≥10% in both the CBGT and the control group. Clearly, CBGT did not improve the magnitude of the sustained weight loss. In the Look AHEAD trial (4), 17% of the participants in the control group and 27% of the participants in the intervention group maintained a weight loss of ≥10% after 8 years of follow-up. This long term preservation of weight loss in the intervention group was more impressive than in our study, probably because of the increase in physical activity. Physical activity has been shown to produce small but significant benefits to the maintenance of weight loss (31). In our study, physical activity did not differ between the groups during the 2-years of follow-up.

The rate of non-compliance with the CBGT intervention in our study was 40%, which is similar to 35-50% non-compliance reported in other CBT studies (32). Non-compliance may have diminished the effect of the CBGT. However, analyses restricted to the compliant group did not show an effect of CBGT on weight at 2 years nor at any intermediate time point. Notably, post-hoc power calculations showed that we included a sufficient number of participants for the intention-to-treat as well as the per-protocol analysis enabling detection of relatively small differences (Table 2 of reference (10)).

In obese individuals with type 2 diabetes, two observational studies have been conducted that showed favorable effects of combining CBGT with diet and/or exercise on long term weight loss (8, 9). Since CBGT was part of an intensive, combined intervention including diet and exercise in these studies, no conclusions can be drawn on the effectiveness of CBGT itself. Our randomized controlled trial does not support an effect of CBGT as suggested by the two observational studies.

In obese adults without type 2 diabetes, positive effects of CBGT on weight loss and weight loss maintenance have been described, and this treatment option has been incorporated in international obesity guidelines (6, 7, 11, 33). Our intervention was based on the

protocol of Werrij et. al. (11). They found that in obese non-diabetic individuals CBGT was superior to increasing physical activity in maintaining diet-induced weight loss. In addition to methodological considerations, our trial differs from these previous studies in a number of ways: the follow-up of our study was substantially longer and we restricted our study fully to participants with diabetes. Our results are in concordance with a randomized controlled trial that had a follow-up period of three years, in which CBGT did not improve weight loss maintenance in obese individuals without type 2 diabetes, despite improvements in cognition scores (34). We did not find an effect of CBGT on the cognition scores of concern about weight and shape, possibly indicating that the usual care in our tertiary referral center is already comprehensive and gives little window for CBGT for further improvement. Nevertheless, weight regain occurred in both groups, similarly to what has been shown by Cooper et al. in obese individuals without diabetes (34).

A recent meta-analysis showed that CB(G)T reduces depressive symptoms in persons with diabetes (35). We found no effect of CBGT on the depression scale that is part of the HADS. However, our CBGT was specifically designed for and aimed at maintenance of body weight loss and not at alleviating depression.

It could be argued that individual CBT is more effective than CBGT. Conversely, in obesity research one-to-one therapy has been shown equally (36) or even less effective (37) than group therapy in achieving weight loss and reducing attrition. Another potential weakness of our study could be that the contrast in treatment between our two study groups was diminished by psychological treatment outside the study. This is, however, unlikely as the self-reported psychological consultation outside the study was similar for both groups. Furthermore, it is also unlikely that the absence of an effect of CBGT could be attributed to the therapists, as they were both very experienced with CBGT, and we found no difference in results between them (data not shown).

Strengths of our study include the randomized, controlled design and the relatively long follow-up period. Participants were referred to a single tertiary center, therefore our findings may not be generalizable to the entire population of overweight and obese patients with type 2 diabetes. Obviously, our findings are exclusively applicable to patients, who are motivated and able to lose 5% or more of their body weight by dieting. Finally, our trial had a pragmatic design, not compensating for the increased attention received by the CBGT group. Despite greater attention, there was no difference in outcomes between both arms, thus strengthening our conclusions.

We conclude that in overweight and obese patients with type 2 diabetes, who were able to lose a clinically relevant amount of body weight on a very low-calorie diet, CBGT is not more effective in maintaining long term weight loss than usual care alone. Future research should elucidate whether CBGT is effective in subgroups of patients with type 2 diabetes and whether tailoring the CBGT program to individual needs improves its effectiveness in maintaining weight loss.

REFERENCES

1. Wing RR, Lang W, Wadden TA, Safford M, Knowler WC, Bertoni AG, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care. 2011;34(7):1481-6.
2. Norris SL, Zhang X, Avenell A, Gregg E, Brown TJ, Schmid CH, et al. Long-term non-pharmacologic weight loss interventions for adults with type 2 diabetes. Cochrane Database Syst Rev. 2005(2):CD004095.
3. Look Ahead Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med. 2013;369(2):145-54.
4. Look Ahead Research Group. Eight-year weight losses with an intensive lifestyle intervention: the look AHEAD study. Obesity (Silver Spring). 2014;22(1):5-13.
5. Gregg EW, Jakicic JM, Blackburn G, Bloomquist P, Bray GA, Clark JM, et al. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. Lancet Diabetes Endocrinol. 2016;4(11):913-21. doi: 10.1016/S2213-8587(16)30162-0. Epub 2016 Aug 30.
6. Shaw K, O'Rourke P, Del Mar C, Kenardy J. Psychological interventions for overweight or obesity. Cochrane Database Syst Rev. 2005(2):CD003818.
7. Van Dorsten B, Lindley EM. Cognitive and behavioral approaches in the treatment of obesity. Med Clin North Am. 2011;95(5):971-88.
8. Forlani G, Lorusso C, Moscatiello S, Ridolfi V, Melchionda N, Di Domizio S, et al. Are behavioural approaches feasible and effective in the treatment of type 2 diabetes? A propensity score analysis vs. prescriptive diet. Nutr Metab Cardiovasc Dis. 2009;19(5):313-20.
9. Mottalib A, Sakr M, Shehabeldin M, Hamdy O. Diabetes Remission after Nonsurgical Intensive Lifestyle Intervention in Obese Patients with Type 2 Diabetes. J Diabetes Res. 2015;2015:468704.
10. Berk KA, Buijks H, Ozcan B, Van't Spijker A, Busschbach JJ, Sijbrands EJ. The Prevention Of WEight Regain in diabetes type 2 (POWER) study: the effectiveness of adding a combined psychological intervention to a very low calorie diet, design and pilot data of a randomized controlled trial. BMC Public Health. 2012;12:1026.
11. Werrij MQ, Jansen A, Mulkens S, Elgersma HJ, Ament AJ, Hospers HJ. Adding cognitive therapy to dietetic treatment is associated with less relapse in obesity. J Psychosom Res. 2009;67(4):315-24.
12. Thoolen B, De Ridder D, Bensing J, Maas C, Griffin S, Gorter K, et al. Effectiveness of a self-management intervention in patients with screen-detected type 2 diabetes. Diabetes Care. 2007;30(11):2832-7.
13. D'Zurilla TJ, Goldfried MR. Problem solving and behavior modification. J Abnorm Psychol. 1971;78(1):107-26.
14. Perri MG, Nezu AM, McKelvey WF, Shermer RL, Renjilian DA, Viegener BJ. Relapse prevention training and problem-solving therapy in the long-term management of obesity. J Consult Clin Psychol. 2001;69(4):722-6.
15. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002;52(2):69-77.
16. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.

17. Rosenberg M. Society and The Adolescent Self-Image. Princeton, NJ: Princeton University Press. 1965.
18. The EuroQol Group. EuroQol–a new facility for the measurement of health-related quality of life. . Health Policy. 1990;16(3):199-208.
19. Busschbach JJ, McDonnell J, Essink-Bot ML, van Hout BA. Estimating parametric relationships between health description and health valuation with an application to the EuroQol EQ-5D. J Health Econ. 1999;18(5):551-71.
20. Vercoulen J, Alberts M, Bleijenberg G. De Checklist Individual Strength (CIS). Gedragstherapie. 1999;32:131-6.
21. Bultmann U, de Vries M, Beurskens AJ, Bleijenberg G, Vercoulen JH, Kant I. Measurement of prolonged fatigue in the working population: determination of a cutoff point for the checklist individual strength. J Occup Health Psychol. 2000;5(4):411-6.
22. Wendel-Vos GC, Schuit AJ, Saris WH, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epidemiol. 2003;56(12):1163-9.
23. Fairburn CG, Beglin SJ. Assessment of eating disorders: interview or self-report questionnaire? Int J Eat Disord. 1994;16(4):363-70.
24. Aberson CL. Applied power analysis for the behavioral sciences. New York: Routledge; 2010.
25. Anderson JW, Kendall CW, Jenkins DJ. Importance of weight management in type 2 diabetes: review with meta-analysis of clinical studies. J Am Coll Nutr. 2003;22(5):331-9.
26. Little RJA, Rubin DB. Statistical analysis with missing data. New York: John Wiley and Sons; 1987.
27. Singer JD, Willett JB. Applied longitudinal data analysis. Oxford, UK: Oxford University Press; 2003.
28. Leibel RL, Seeley RJ, Darsow T, Berg EG, Smith SR, Ratner R. Biologic Responses to Weight Loss and Weight Regain: Report From an American Diabetes Association Research Symposium. Diabetes. 2015;64(7):2299-309.
29. Action for Health in Diabetes Study Group. Association of Weight Loss Maintenance and Weight Regain on 4-Year Changes in CVD Risk Factors: the Action for Health in Diabetes (Look AHEAD) Clinical Trial. Diabetes Care. 2016;39(8):1345-55.
30. Wing RR. Handbook of Obesity: Clinical Applications. Bray G, Bouchard C, editors. New York: Informa Health Care USA, Inc.; 2008, p. 227-248.
31. Dombrowski SU, Knittle K, Avenell A, Araujo-Soares V, Sniehotta FF. Long term maintenance of weight loss with non-surgical interventions in obese adults: systematic review and meta-analyses of randomised controlled trials. Bmj. 2014;348:g2646.
32. Bados A, Balaguer G, Saldana C. The efficacy of cognitive-behavioral therapy and the problem of drop-out. J Clin Psychol. 2007;63(6):585-92.
33. National Institute for Health and Care Excellence (NICE). Obesity: identification, assessment and management (Clinical guideline CG189) 2014 [updated november 2014. Available from: https://www.nice.org.uk/guidance/cg189?unlid=292261183201624213554].
34. Cooper Z, Doll HA, Hawker DM, Byrne S, Bonner G, Eeley E, et al. Testing a new cognitive behavioural treatment for obesity: A randomized controlled trial with three-year follow-up. Behav Res Ther. 2010;48(8):706-13.

35. Wang ZD, Xia YF, Zhao Y, Chen LM. Cognitive behavioral therapy on improving the depression symptoms in patients with diabetes: a meta-analysis of randomized control trials. Biosci Rep. 2017.
36. Minniti A, Bissoli L, Di Francesco V, Fantin F, Mandragona R, Olivieri M, et al. Individual versus group therapy for obesity: comparison of dropout rate and treatment outcome. Eat Weight Disord. 2007;12(4):161-7.
37. Paul-Ebhohimhen V, Avenell A. A systematic review of the effectiveness of group versus individual treatments for adult obesity. Obes Facts. 2009;2(1):17-24.

SUPPLEMENTAL TABLES

Supplemental table S1. Baseline characteristics excluded vs. included participants

Characteristic*	Excluded participants† (n=48)	Included participants (n=158)	p-value‡
Age (y, range)	50.6 (25-70)	53.7 (28-74)	0.141
Female (No. (%))	30 (62.5)	88 (55.7)	0.404
Caucasian (No. (%))	25 (52.1)	87 (55.1)	0.717
Low education (No. (%))	14 (29.2)	46 (29.1)	0.497
Years after diagnosis T2D	8.0 (2.5-13.0)	9.0 (3.0-15.0)	0.414
Weight (kg)	106.9±16.9	106.1±20.8	0.806
$HbA1_c$ (%)	8.5 (7.6-10.0)	7.6 (7.0-8.5)	0.001
$HbA1_c$ (mmol/mol)	69.5 (59.3-86.3)	60.0 (53.0-69.0)	0.001
Fasting glucose (mmol/l)	10.1 (8.3-13.0)	8.4 (6.8-10.6)	<0.001
LDL cholesterol (mmol/l)	2.6 (2.0-3.5)	2.6 (2.1-3.1)	0.706
Insulin users (No. (%))	25 (52.1)	101 (63.9)	0.456
Insulin dose among users (IU/day)	111.1±61.6	97.8±49.0	0.258
Depression score (HADS)	7.0 (4.0-11.0)	7.0 (4.0-9.0)	0.395
Anxiety score (HADS)	8.0 (4.0-11.0)	6.0 (3.0-9.0)	0.038
Quality of life (EQ5D score)	0.81 (0.69-0.84)	0.78 (0.65-0.84)	0.320
Eating disorder (EDE-Q score)	2.1±1.3	2.2±1.1	0.946
Physical activity (SQUASH score)	4200 (1440-8405)	2940 (1350-5775)	0.327

**Data are mean±SD, median (interquartile range) or number (%).†Participants were excluded when they lost <5% of body weight during the 8-week phase-in very low-calorie diet. ‡Between-group differences were analysed using a Pearson Chi-Square test, an independent samples t-test or a Mann-Whitney U test, depending on normality of the data.*

CBGT = cognitive behavioral group therapy group; T2D = type 2 diabetes; BMI = body mass index; $HbA1_c$ = glycated hemoglobin; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

Supplemental table S2. Linear mixed model of weight course from baseline to two years of follow-up and allocation to group (ITT)

Parameter	Estimate	95%CI	p-value
Intercept	106.769	102.327, 111.211	<0.001
Time	0.361	0.293, 0.429	<0.001
Quadratic time	-0.001	-0.002, -0.001	<0.001
Logarithmic time	-5.818	-6.400, -5.237	<0.001
Allocation	-1.274	-7.403, 4.855	0.682
Time*allocation	-0.033	-0.127, 0.061	0.491
Quadratic time*allocation	0.000	-0.001, 0.001	0.720
Logarithmic time*allocation	0.473	-0.331, 1.278	0.248

Chapter 8

General discussion

The primary aim of my thesis was to determine the effectiveness of cognitive behavioral group therapy (CBGT) in maintaining weight during 2 years of follow-up after weight loss via a very low-calorie diet (VLCD) in overweight and obese adults with type 2 diabetes (T2D). The secondary objectives were to establish which participants benefit most from a VLCD, and to evaluate the short-term effect of a VLCD on conventional and non-conventional cardiovascular risk factors.

In this chapter, the main findings of the current thesis are discussed in a broader perspective and some methodological issues are addressed. Further, the implications of our findings for clinical practice and views for future research are outlined.

Quick answers to the research questions

- Cognitive behavioral group therapy did not result in better 2-year weight maintenance after weight loss via a very low-calorie diet, compared to usual care only.
- Cognitive behavioral group therapy did not result in better 2-year outcomes on cardiovascular risk factors and psychological wellbeing, compared to usual care only.
- Short term diet-induced weight loss was predicted by the baseline variables fasting glucose, insulin dose, waist-to-hip ratio, anxiety and numb feeling in extremities (related to neuropathy).
- A short-term very low-calorie diet improved glycemic control, lipid profile, sLR11 level and levels of biomarkers of endothelial dysfunction and inflammation, while reducing the need for insulin.
- Diet-induced weight loss increased Lp(a) levels in overweight and obese adults with and without type 2 diabetes; an effect that was absent after weight loss via bariatric surgery in obese adults without type 2 diabetes.
- After 2 years of follow-up, despite weight regain, a very low-calorie diet still resulted in a clinically relevant decrease in weight, need for insulin, depression score and fatigue score.

OVERVIEW AND INTERPRETATION OF MAIN FINDINGS

Weight loss maintenance

What was already known on cognitive behavioral group therapy for weight loss maintenance?

- In non-diabetic obese adults, cognitive behavior group therapy is effective in achieving weight loss when combined with diet and/or exercise, and also in enhancing weight loss maintenance.
- In 2 observational studies in obese adults with type 2 diabetes, cognitive behavioral group therapy led to weight loss when combined with diet and/or exercise.

What knowledge is added by this thesis?

- In our randomized controlled trial, cognitive behavioral group therapy did not result in better weight loss maintenance after diet-induced weight loss in obese adults with type 2 diabetes.

Since being overweight or obese is particularly detrimental for individuals with type 2 diabetes (T2D), increasing morbidity and mortality, weight loss is a cornerstone of treatment (1-4). Diet-induced weight loss induces various beneficial effects in these persons, such as improved glycemic control, lipid profile and blood pressure (5). Unfortunately, from clinical care experience and past research it is known that weight regain after successful weight loss is a common problem in people with obesity (6-9). As described in the introduction of this thesis, both behavioral and physiological challenges should be tackled in order to succeed in maintaining weight loss.

Cognitive behavioral therapy for weight loss maintenance

In order to achieve weight loss maintenance, a sustained (long-term) change in behavior is needed. Behavioral modification techniques like goal setting, self-monitoring, stimulus control, portion control, changing the environment, problem solving and relapse prevention have been intensively studied and shown more or less effective in improving weight loss maintenance in the obese population (10). There is evidence suggesting that cognitive change precedes and produces behavior change, and that therefore cognitive skills like cognitive restructuring and problem-solving techniques should be incorporated in weight loss programs in order to achieve long-term weight loss maintenance (10, 11). Cognitive behavioral group therapy (CBGT) for non-diabetic obese individuals has been shown to facilitate weight loss as well as weight loss maintenance (10, 12-16). However, not all studies have shown positive results of CBGT. Cooper et al. (11, 17) were strong advocates of a more cognitive approach to weight loss management,

but showed negative results of a cognitive behavioral therapy (CBT) intervention (24 individually delivered sessions over 44 weeks, with 3 years of follow-up) for weight loss in obese individuals (18). Only two observational studies reported the effect of CBGT as part of dietary weight loss interventions in T2D: *i.*) in a prospective cohort study, a diet plus CBGT resulted in weight loss and improved metabolic control after four years of follow-up; *ii.*) in a retrospective cohort study, an intervention combining diet, exercise, intensive medication adjustments, group education and CBGT led to weight reduction and maintenance for one year (19, 20). Until now, the effect of CBGT on weight loss maintenance has not been studied in a randomized controlled manner in persons with T2D. In chapter 7, we showed in a randomized controlled trial in overweight and obese adults with T2D, that CGBT on top of usual care did not perform better than usual care only in preventing regain of weight during 2 years of follow-up, after participants lost ≥5% of weight via a VLCD (figure 1A). Moreover, we did not find any significant difference between the CBGT and the usual care group for the secondary outcome measures at any time point during the trial, despite the CBGT group receiving more attention as indicated by the higher number of visits to the outpatient clinic. Even in compliant participants, who actually followed most of the CBGT sessions (predefined in the protocol), no effect on weight during 2 years of follow-up was seen as compared to usual care (figure 1B).

Those new findings are in contrast with most of the literature on CBGT. The CBGT method we used was adapted from the method used by Werrij et al. (13). They found that CBGT performed significantly better than exercise on maintaining weight loss in obese persons without T2D after 1 year of follow-up (13). The CBGT group in our study improved in the cognition scores weight concern and shape concern, in concordance with the studies of Cooper et.al. and Werrij et.al.. These improvements did not result in better long term weight maintenance in our trial and in the study of Cooper et.al. in obese non-diabetic persons, but they did result in better weight loss maintenance in the study of Werrij et.al.. What could explain this difference in result between their and our trial? The dietary intervention we used as a phase-in period to achieve weight loss was a VLCD, while Werrij et. al. used a LCD. Then again, well-designed trials provide evidence that use of a VLCD or LCD does not differentially influence weight regain or maintenance (21, 22). Another difference was that our follow-up was twice as long. However, we did not find an effect of the CBGT at any intermediate time point. This leaves us with a very important difference between the two studies: the difference in study population. Could overweight T2D adults be metabolically different from non-diabetic overweight adults? Unfortunately, no literature exists comparing persons with and without diabetes in their ability to maintain weight loss or their metabolic response to weight loss dieting, so future studies are warranted focusing on these differences. In my study, the participants in the CBGT group tended to blame their antidiabetic medication and medical condition (diabetes complications) rather than their own behavior for their overweight and inability

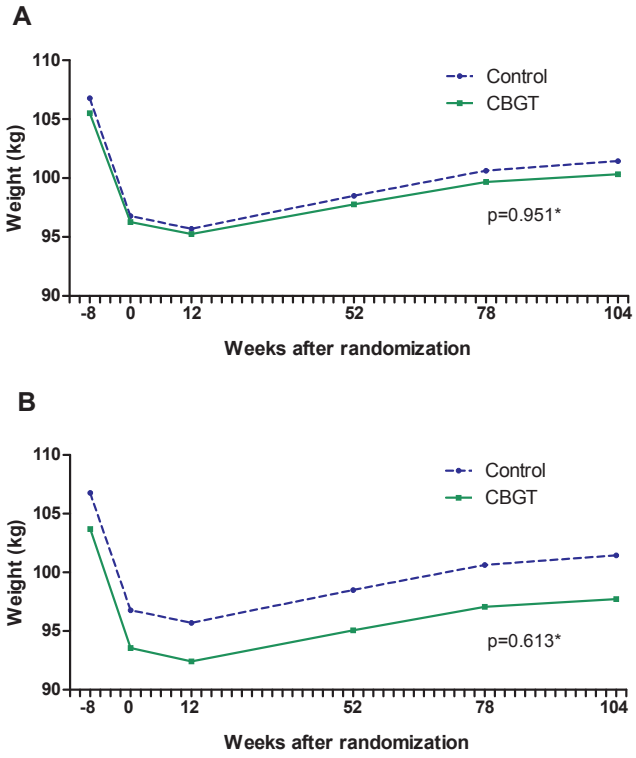

Figure 1. Estimates of weight from baseline to two years of follow-up in cognitive behavioural group therapy (CBGT) and control group: (A) intention-to-treat; (B) per-protocol.
**p-value of between-group difference in weight from baseline to two years of follow-up, analysed by mixed modelling procedure*

to maintain weight loss. These external factors could play a role in weight loss and weight loss maintenance. However, in the intervention (CBGT) group, the presence of diabetic complications was not correlated with long term weight loss. Also the baseline insulin dose or change in insulin dose was not correlated with long term weight loss. We found that older participants, male participants and participants who initially lost the most weight, were more likely to maintain their weight loss. Yet, these correlations were found for both the CBGT and the control group. Another explanation for the lack of effect of the CBGT could be the large heterogeneity in educational background of the participants in the CBGT group. In order to master all the techniques of CBT, a basic knowledge on behavior and a minimum intellectual capability may be needed. Nonetheless, we did not find a correlation between educational level and long-term weight loss in the CBGT group. So unfortunately, we did not find any clues to identify subgroups for which CBGT could be helpful in maintaining weight loss. Of course, the sample size may have limited subgroup analysis.

In weight maintenance research several limitations have been identified (23):

1. Few studies report the number of participants successful in maintaining a significantly lower body weight, a highly relevant outcome parameter.
2. Most studies lack a control group.
3. The rate of loss to follow-up is high, falsely inflating the reported mean weight loss.
4. Follow-up is generally short (i.e. <1 year)

In our trial, we tried to avoid abovementioned shortcomings by reporting the percentage of participants successful in maintaining weight: 39% of the participants achieved a (generally considered) clinically relevant weight loss of ≥5%, while 18% maintained a weight loss of ≥10% after 2 years of follow-up. Secondly, we chose for a pragmatic randomized controlled design, comparing CBGT plus usual care to usual care only. With this design, we were able to draw conclusions about the effectiveness of the intervention, relevant for the clinician. Thirdly, we experienced a rather low rate of loss to follow-up: 22 participants (14%) dropped out of the study during follow-up (at various time points), but were kept in the analyses as data with missing time points. Unlike statistical methods most often used in weight maintenance trials (Repeated Measures ANOVA), the method we used (linear mixed modeling) provides unbiased estimates of at random missing data points, and no cases will be 'lost' (24). The latter is also in line with the intention-to-treat principle. Fourthly, our follow-up period was 2 years, which is considered a medium length follow-up, where most regain in weight is believed to have taken place. Finally, previous studies often randomized prior to weight loss, focusing on long term weight loss, making it impossible to draw conclusions about weight regain after initial weight loss. In our trial, we have chosen for a design where participants were randomized after a period of weight loss in order to study weight regain, answering a to our opinion more important question.

To conclude, CBGT as performed in our study, did not solve the problem of weight regain after diet in overweight and obese T2D adults. How the long-term effectiveness of weight loss dieting can be enhanced in this patient group remains to be established. In the following paragraphs, we elaborate on other potentially effective strategies for weight loss maintenance.

Promising psychological interventions for weight loss maintenance

Some other promising psychological interventions for weight loss (maintenance) have been identified, for example cue exposure therapy. It has been shown that successful weight loss maintainers differ from obese people in their cognitive responses to high-calorie food cues (25). In cue exposure therapy, obese individuals are repeatedly exposed to cues associated with food, like the sight, smell, taste of palatable food or a situation in which overeating typically occurs. When these cues are not followed by the

actual eating, the responses on appetite associated with these cues can extinguish. An RCT is underway which aims to determine the effect of a cue exposure therapy on weight loss and short term weight maintenance (26). Another promising therapy is executive functioning training in obese individuals. Eating behavior and ability to lose and maintain weight has been associated with individual differences in executive functioning, like planning ability and inhibitory control. Internal disinhibition has been associated with poorer weight loss maintenance (27). In small short-term studies, executive functioning training has been shown to increase weight loss and weight loss maintenance (28-30). Future studies should focus on the effect of these psychological interventions on long term weight loss maintenance in overweight and obese adults with and without T2D.

Changing diet composition for weight loss maintenance

As described in the introduction of this thesis, weight loss triggers several physical adaptations in the body, promoting appetite and decreasing energy expenditure. Counteracting these responses via long-term changes in diet and exercise could assist in achieving weight loss maintenance. Johansson et. al. conducted a meta-analysis of randomized controlled trials focusing on strategies for weight loss maintenance after a (very) low-calorie diet. In figure 2, the results of this meta-analysis are shown. For illustrative purposes, I added the data of the POWER trial to the graph. The authors concluded that the prolonged use of meal replacements and high-protein diets were associated with improved weight loss maintenance (31). The largest trial on the effect of different dietary patterns on weight loss maintenance is the Diogenes study (32). A total of 773 obese participants, who lost at least 8% of their body weight via a VLCD, were randomized to one of the five ad libitum weight maintenance diets: a low-protein and low-glycemic-index diet, a low-protein and high-glycemic-index diet, a high-protein and low-glycemic-index diet, a high-protein and high-glycemic-index diet, or a control diet. After 26 weeks, the high-protein and low-glycemic-index diet resulted in the best weight loss maintenance. Moreover, the compliance with this diet intervention was highest. In concordance with these findings, different studies have shown that a weight loss maintenance diet with a minimum of 30% of energy intake derived from protein, limits the drop in resting and total energy expenditure normally seen after weight loss (33, 34). Apparently, the physical adaptations to weight loss can partly be antagonized by diet composition, although the effect size is only modest. Unfortunately, persons with T2D were underrepresented in these trials, so the results could and should not be generalized and future studies are required to analyze persons with T2D separately. In the weight maintenance phase of the POWER trial, we slowly reintroduced a diet which contained approximately 15 energy% of protein and 60 energy% of carbohydrates. We encouraged the use of unprocessed products high in fiber to reduce the glycemic-index. Nonetheless, we should consider the results of the Diogenes trial when implementing the POWER diet program into clinical

care in order to enhance weight loss maintenance. As mentioned, long-term effectiveness in individuals with T2D still needs to be studied. Alternatively, repeated VLCD may be an effective strategy for weight loss maintenance. There is some evidence that intermittent VLCD periods are beneficial for weight loss and weight loss maintenance. In patients with T2D, a regimen of 5 consecutive days of VLCD every 5 weeks improved weight loss and HbA1c compared to standard behavioral therapy (35). Also in a 50-week diet study, T2D patients lost more weight and had better glycemic control during an intermittent VLCD regimen than during a continuous LCD, although these benefits were largely due to the first 12-week VLCD period (36). Long term RCT's studying the effect of repeated VLCD periods on weight loss maintenance in T2D are warranted.

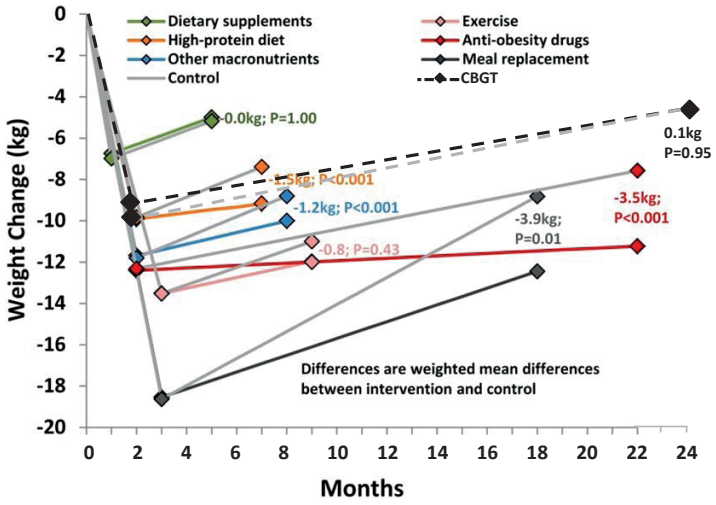

Figure 2. Overview of changes in body weight during the rapid weight-loss phase and the weight-loss maintenance period in 20 randomized controlled trials that evaluated different anti-obesity drug, diet, and exercise weight-loss maintenance strategies after an initial very-low-calorie diet or low-calorie diet (<1000 kcal/d). The dashed lines represent the POWER study (black is CBGT and gray is control), gray lines represent the control subjects in each subcategory weights and p-values reflect differences with the control subjects. (Adapted from: Johansson et al Am J Clin Nutr 2014 Jan;99(1):14-23).

Exercise for weight loss maintenance

One of the biological adaptions to weight loss is the decrease in energy expenditure, which has been shown to persist over time, predisposing to weight regain (37). Theoretically, increased physical activity is needed to counteract this adaptive decrease in energy expenditure and to prevent the loss in fat free mass (22). The effect of exercise on initial weight loss is only modest, but the importance of exercise in weight loss maintenance has been shown repeatedly (38). Relatively high doses of physical activity are needed in order to achieve long-term weight loss success. Individuals who engaged in regular physical activity of approximately 300 min/week were far more likely to

maintain 10% weight loss for more than 1 year (39, 40). In our POWER trial, we recommended 60 minutes of physical activity daily (420 min/week), in concordance with national recommendations for weight loss. In all study meetings, we promoted the engagement in regular physical activity and we encouraged personal goal setting. Despite our recommendations, no increase in physical activity was seen during the 2 years of follow-up. Perhaps this was related to the absence of an integrated exercise program. Indeed, some participants mentioned a wish for more support in achieving their exercise goals during the evaluation of the program. In children with obesity, the incorporation of active video gaming (for example Nintendo Wii) was more effective in increasing physical activity and reducing weight compared to following a weight loss program without active gaming (41). Whether active video gaming is also a suitable intervention for obese adults with T2D remains to be investigated. Nonetheless, in future weight maintenance programs, the possibility of a more structured exercise support in the weight maintenance phase should be explored.

Drug therapy for weight loss maintenance

In the earlier discussed meta-analysis of the effect of weight loss maintenance strategies after a V(LCD), the use of the anti-obesity drugs Orlistat and Sibutramine has been shown effective in maintaining weight (31) (figure 1). Sibutramine has been retracted from the European market due to cardiovascular side-effects. Another drug that facilitates weight loss is the glucagon-like peptide-1 receptor agonist (GLP-1 RA). In two randomized controlled trials, a GLP-1 RA has been shown to improve weight maintenance after diet-induced weight loss (42, 43). Moreover, a GLP-1 RA diminished the decrease in plasma leptin levels upon diet-induced weight loss, possibly leading to a decreased craving for food (43). Interestingly, there seems to be a ceiling on the weight loss effect of a GLP-1 RA, regardless whether it is used for weight loss or weight loss maintenance and the weight loss is maintained only during the prolonged use of a GLP-1 RA (44). Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a new class of oral antidiabetic drugs. Inhibiting SGLT2 decreases reabsorption of glucose and sodium in the kidney which results in increased diuresis and enhanced glucose (energy) loss with subsequent reduction in blood glucose and body weight (45). The effect of SGLT2 inhibitors on long term weight loss or weight loss maintenance has not yet been investigated.

New technologies for weight loss maintenance

In this era of rapid technological improvements, it is logical that numerous promising new devices have been developed to facilitate people in maintaining weight loss. Many technology-based weight loss interventions have been conducted in the last decade using for example e-mail, interactive websites, mobile phones or wearable devices. However, results were mixed and technology-based interventions did not perform better

than non-technology-based interventions in maintaining weight loss (46, 47). In a large RCT in overweight young adults, the addition of a wearable device (and accompanying web interface) to monitor diet and physical activity to a standard behavioral intervention, resulted in less weight loss over 24 months compared to usual care only. The authors concluded that devices that monitor and provide feedback on physical activity and diet may not offer an advantage over standard behavioral weight loss approaches (48). Also in another RCT, social and mobile technologies did not facilitate sustained reductions in weight among young adults (49). Again, these studies have been conducted in non-T2D populations, but technology-based interventions alone do not seem to hold promise for long-term weight management. Though, combining technology based interventions with traditional face-to-face care may provide additional benefit in weight loss and deserves further study.

A very low-calorie diet for weight loss

What was already known on VLCD induced weight loss?

- A very low-calorie diet is effective in producing short term weight loss in obese adults with and without type 2 diabetes.

What knowledge is added by this thesis?

- After 2 years of follow-up, a very low-calorie is still effective in producing a clinically relevant weight loss in obese adults with type 2 diabetes, which is accompanied by improvements in waist circumference, fatigue and depression score, and need for insulin.

In our Prevention Of Weight Regain (POWER) trial we used a very low-calorie diet (VLCD) to induce weight loss, as the phase-in to the randomized controlled trial. We intended to achieve a large initial weight loss in our participants, to create a big window for differences in weight regain to occur between the intervention and control group during follow-up. In previous research, VLCDs have been shown effective in producing short term weight loss in adults with T2D. In the meta-analysis of Tsai et. al., participants (with and without T2D) who were prescribed a VLCD for a mean of 12.7 weeks, lost 16.1 ± 1.6% of their bodyweight, while participants on a low-calorie diet (LCD) lost 9.7 ± 2.4% of bodyweight, in line with the difference in energy deficit (p=0.0001 for between group difference) (50). Recently, a meta-analysis has been conducted on the effectiveness of VLCDs in adults with T2D (51). The authors identified 9 studies and showed that VLCD's led to greater weight loss after 6 months compared to usual care (between-group difference -8.5 kg (95%CI -15.6 to -1.3; p=0.02) and also compared to an LCD (between-group difference -5.7 kg (95%CI -11.1 to -0.35; p=0.04).

In chapter 2 we presented the short term results on weight. The short-term weight loss achieved in the phase-in of our trial seems modest compared to literature, with 7.8±4.6 kg (95%CI 7.2-8.5; p<0.001), but this was after only 8 weeks of dieting, while the mean duration of the interventions in previous studies was 13 weeks. Moreover, we prescribed a VLCD of 750 kcal per day while others used 450-600 kcal per day. We chose for this less stringent regimen as it allowed our participants to use a low-fat, low-carbohydrate dinner along with their family. There is not much evidence on long term efficacy of VLCDs with regard to weight loss in adults with T2D. In 1 RCT, a 24-week VLCD resulted in a weight loss of 13.4±9.7% after 1-year follow-up, which decreased to 6.8±7.6% after a follow-up of 2 years (36). In line with these results, we showed that our participants maintained an average weight loss of 5.1±6.2% (95%CI 4.0-6.1) after 2 years of follow-up. However, our results are biased by the design of our long-term follow-up trial, since we only included participants with an initial weight loss of at least 5%. Nevertheless, this amount of weight loss was accompanied by a lower waist circumference, lower score on fatigue and depression, and an improved insulin sensitivity illustrated by a reduced need for insulin.

One argument against 'crash' diets like a VLCD is that it's believed to result in more weight regain thereafter. Is rapidly lost weight also more quickly regained? This research question was studied in two recent randomized controlled trials (21, 22). In the study of Purcell et al. (21), 200 obese participants were randomized to either rapid weight loss dieting during 12 weeks or gradual weight loss dieting during 36 weeks. 81% of the participants in the rapid weight loss group and 50% of the participants of the gradual weight loss group achieved 12.5% weight loss. The participants of both groups who lost at least 12.5% of weight were subsequently placed on the same weight maintenance diet. After 144 weeks, there was no difference between the two groups in weight regain: both groups regained around 70% of their lost weight. The study of Vink et al. (22) showed similar results, comparing a 5-week VLCD (rapid weight loss) with a 12-week low-calorie diet (LCD, slow weight loss). Both groups experienced the same amount of weight loss and regain of weight during the following 9 months. In addition, no difference in food cravings was reported in an RCT comparing a 20-week LCD with a 20-week VLCD. These findings do not support the common belief that restricting intake of certain foods leads to increased craving for these foods, or that the magnitude of weight loss is related to food cravings (52).

In conclusion, we and others have shown that VLCDs are effective in producing weight loss in overweight individuals with T2D. Secondly, weight regain following a short term VLCD is similar to that following a (more traditional) LCD.

Effect diet-induced weight loss on cardiovascular disease risk factors

What was already known on the effect of weight loss dieting on cardiovascular disease risk factors?

- In obese adults with type 2 diabetes, diet-induced weight loss results in improved classical cardiovascular disease risk factors, as well as in improved biomarkers for endothelial dysfunction and inflammation.

What knowledge is added by this thesis?

- The diet-induced improvements in biomarkers for endothelial dysfunction and inflammation was independent of cardioprotective medication and the duration of type 2 diabetes.
- Diet-induced weight loss decreased the new cardiovascular disease risk factor sLR11, and this reduction was associated with improvements in lipid profile and the glycemic state.
- Another emerging cardiovascular risk factor Lp(a) increased during short term weight loss via diet in obese adults with and without type 2 diabetes, while it was unaffected by weight loss via bariatric surgery.
- After 2 years of follow-up, this effect on Lp(a) had waned off.

In chapter 3, we showed that besides a favorable effect on weight, our VLCD intervention also led to significant improvements in glycemic control and lipid profile, and a large decrease in the need for insulin, which is in concordance with previous studies in individuals with T2D (53). We additionally showed that after 4 months of weight loss dieting, markers of endothelial dysfunction and inflammation were significantly lower than before start of the diet, which is in line with previous studies as well (54-57). These markers have been associated with vascular complications and mortality in individuals with T2D, suggesting that weight loss dieting has attenuated their risk of developing cardiovascular disease (58-63). Until now it was unknown whether diet-induced weight loss still has an effect on vascular function in T2D adults, who are on (maximum) cardioprotective medical treatment, and whether recently diagnosed patients benefit more compared to patients with a long history of T2D. It is possible that in a late stage of disease many pathological changes to the vasculature have become irreversible (64). Here, we added to the existing evidence by showing that the positive effects of weight loss dieting were not influenced by the use of cardioprotective drugs, nor by the duration of T2D. This findings suggests that individuals on intensive medical treatment or with a long history of T2D still benefit from a weight loss intervention similar to newly diagnosed patients. A limitation of these findings is that biomarkers were measured after only 4

months of dieting. After 2 years of follow-up, measurement of the biomarkers could have been repeated in a non-random subset of participants only, because participants who lost <5% of their weight after the first diet phase were excluded from further participation. Therefore, we do not have long-term data. Another limitation is our use of surrogate markers of endothelial dysfunction and inflammation to study CVD risk. The extent of the short-term reduction in the biomarkers, such as hs-CRP and sICAM-1, that we found is in line with previous observations (54-56). In two studies, this diet-induced reduction in CRP and sICAM-1 was accompanied by a significant improvement in flow-mediated dilatation, a functional test for endothelial dysfunction (55, 65). This indicates that the reduction we found in markers of endothelial dysfunction and inflammation may be clinically relevant to our participants.

Furthermore, we showed for the first time that VLCD-induced weight loss led to a decrease in soluble LDL receptor relative sLR11, which is a novel CVD risk factor in overweight and obese adults with T2D (chapter 4). This decrease was associated with a simultaneous improvement in lipid profile (non-HDL cholesterol) and glycemic control (HbA1c). High sLR11 levels have been associated with vascular complications in adults with type 2 diabetes (66-68). Whether the decrease in sLR11 we found leads to less diabetic complications still needs to be investigated.

In contrast to the diet-induced improvements of various cardiovascular risk factors we found that Lp(a), an independent risk factor for cardiovascular disease in T2D (69-74), increased with diet-induced weight loss (chapter 5). The Lp(a) levels increased significantly after 4 months of weight loss dieting in 3 independent cohorts of overweight individuals with and without T2D. This increase in Lp(a) could potentially reduce the positive effects of weight loss dieting on CVD risk. In a subset of our overweight T2D participants, we observed that the Lp(a) levels returned almost to baseline values 2 years after the diet intervention, suggesting that the initial increase in Lp(a) upon diet was an acute effect that waned off after a longer period of a normal diet. The long-term change in Lp(a) was not associated with weight loss or regain during follow-up, implying that other factors associated with the diet have been of influence. It has been shown previously that in healthy subjects, the dietary fat content affected the Lp(a) levels: diets high in total and saturated fat lowered Lp(a) levels, while diets high in unsaturated fatty acids increased Lp(a) levels (75-77). The VLCD we used in our trial was low in total fat content (33 gram/day) and relatively high in unsaturated fatty acids with 17 grams/day. Low-fat diets may increase Lp(a) levels via an altered metabolism of Lp(a) particles. However, more studies are needed to clarify this mechanism Hypothetically, a diet low in carbohydrates and high in fat could lead to a lowering of Lp(a) levels, while still producing weight loss and the accompanied benefits on CVD risk. This should be investigated in future clinical trials in overweight individuals with and without T2D. The effect of Lp(a) on CVD has only been studied in observational designs and via Mendelian randomisation (78). Evidence from

genetic studies support a causal relation between Lp(a) and CVD (79, 80), however, evidence from randomised controlled trials is currently lacking. Hence, clinical studies addressing the effect of Lp(a) change (upon diet) on hard clinical endpoints are needed. Recently, new Lp(a) lowering drugs became available. A pooled analysis of individual participant data taken from PCSK9 inhibitor trials has shown that both alirocumab and evolocumab could lead to a reduction of Lp(a) by up to 25–30% (81). Additionally, antisense oligonucleotides targeting apolipoprotein(a) might be promising as inhibitors of Lp(a) synthesis (82). Long-term follow-up studies are required to establish whether adding an Lp(a)-lowering agent to a dietary intervention will improve long-term CVD outcome in obese individuals with and without type 2 diabetes.

In summary, short term effects of weight loss dieting are quite positive with regard to improving classical CVD risk factors, sLR11 and markers of endothelial dysfunction and inflammation, with the possible exception of the short-term increase in Lp(a). Future studies are needed to establish the long-term effect of weight loss dieting on these biomarkers and their associations with cardiovascular end points, in order to show clinical relevance. Moreover, future studies should focus on elucidating the underlying mechanisms.

Predicting short term weight loss

What was already known on predicting weight loss?

- Many predictors of weight loss have been identified for obese adults without type 2 diabetes, but these predictors have not been studied in individuals with type 2 diabetes, and diabetes-specific variables have not been included in previous research in this field.

What knowledge is added by this thesis?

- Successful short term diet-induced weight loss was predicted by the baseline variables fasting glucose, insulin dose, waist-to-hip ratio, anxiety and numb feeling in extremities (related to neuropathy).
- 3 out of these 5 predictors are diabetes-related, suggesting that considering diabetes specific characteristics is of importance in achieving successful weight loss in type 2 diabetes.

An alternative approach to the problem of weight regain is focusing on (pre-treatment) predictors of weight loss success. Personalized medicine is the ultimate goal for the treatment of obesity. Ideally clinicians should have a screening tool to select individuals for an intervention based on simple measurable baseline variables, in order to offer the best and most cost-effective treatment to their patients with obesity and T2D. Another option

is to screen and evaluate the treatment response of individuals after a certain amount of time, to be able to direct them to alternative approaches when indicated.

In our POWER trial, the effect of a VLCD on weight showed a marked variability: the initial weight change during the 8-week phase-in diet ranged from -21.3% to +1.0%. In participants who initially achieved 5% weight loss, weight change at 2 years of follow-up varied even more: from -28.3% to +11.5%. Apparently, there are responders and non-responders as well as sustainers and non-sustainers (23). Also in literature this large heterogeneity in weight loss successes has been described (9). Since fairly all research in predicting weight loss has been carried out in obese persons without T2D, we developed a prediction model for short-term weight loss in persons with T2D. In chapter 2, we showed that successful short term VLCD-induced weight loss was predicted by the baseline variables fasting glucose, insulin dose, waist-to-hip ratio, anxiety and numb feeling in extremities (related to neuropathy). Interestingly, 3 out of those 5 predictors were diabetes related. The predictors previously identified in obese adults without diabetes were not associated with weight loss in our T2D group. This suggests that the diabetes status is of importance in the ability of achieving weight loss. Whether these predictors are specific for VLCD-induced weight loss or represent predictors of weight loss induced by any type of diet is unknown. Theoretically, the predictors we found are able to predict short-term weight loss for any diet with a large enough energy deficit in obese T2D patients, however, more studies are needed to prove this.

In our study, only 25% of the variance in short-term weight loss was explained by our model, which is comparable to previous research in the field of obesity (83). Apparently, the most important factors that explain the variance of weight loss are unknown. Many different factors contribute to weight loss success, each accounting only for a small proportion of the variance. Previous studies in the field of obesity reported obviously positive predictors of weight loss, like initial body weight, male gender, resting metabolic rate, self-efficacy, initial/early weight loss, social support, self-monitoring, physical activity, etc. (83). The main difficulty to predict success of weight loss strategies is heterogeneity of the treatments for weight control, the populations studied, and of the predicting variables. Another problem is that certain predictors (such as weight and coping strategies) change over time and can be pre-treatment predictors but also process predictors.

A common problem in prediction research is that underpowered studies generate false negatives (Type II error). On the other hand, tests that have many predictors and set the significance cut-off at the usual 5% may generate large series of false positive predictors (Type I errors). It has been shown that a minimum of 2 subjects per variable are required in order to adequately estimate the regression coefficients of the model (84). With approximately 10 subjects per variable, we have reduced the chance of overfitting the model. Additionally, we used statistical techniques (bootstrapping) to improve the

precision of our results. However, replication in another independent cohort is clearly necessary to further substantiate our findings.

Predicting long term weight loss

Predictors of short-term weight loss and weight loss maintenance may be different. Again, most work in this field has been done in the obese population without T2D (39, 85-88).

In our POWER trial, 61 of the 158 participants (39%) maintained a weight loss of 5% or more, while 28 participants (18%) maintained a weight loss of 10% or more for 2 years. This result is biased by the design of our long-term follow-up trial, since we only included participants with an initial weight loss of at least 5%. Nonetheless, this percentage of successful long term weight loss is consistent with previous research in obese adults with and without T2D (89). In a post-hoc analysis, we found that age and sex were predictors of weight loss after 2 years of follow-up compared to baseline ($r=-0.306$, $p<0.001$ and $r=0.237$, $p=0.007$): older, male participants achieved more weight loss. We also found that initial weight loss (after 8 weeks of VLCD) was strongly associated with long term weight loss ($r=0.453$, $p<0.001$). In a multivariate regression analysis, only initial weight loss remained associated with long-term weight loss ($\beta=0.324$, $p=0.023$), which is consistent with literature (88, 90). In the Look AHEAD trial with persons having T2D, age was a predictor of weight loss at 8 years of follow-up after an intensive lifestyle intervention: the oldest participants (65-76 years) lost more weight than the younger individuals (89). In line with our trial, big initial weight loss was a predictor of long-term weight loss in the Look AHEAD trial (90). Interestingly, participants with a high initial weight loss but full regain of weight during follow-up, still had better HbA1c values after 4 years than those with less or no initial weight loss. The authors suggest a positive legacy effect of having achieved a larger initial weight loss, even if it is (partially) regained, and conclude that a large initial weight loss should be encouraged in adults with T2D (90).

Using the long-term data of the POWER trial, I have developed a prediction model for 2-year weight loss success (defined as ≥3% of bodyweight). In previous research, cut-off values of 3% and 5% long term weight loss have been used to discriminate between responders and non-responders (23, 91, 92). In this prediction model, successful long term weight loss was predicted by initial (short term) weight loss, initial reduction in insulin need, age and presence of eye problems (0.78 (95%CI 0.69-0.87) post-test likelihood of predicting successful long term weight loss). Ideally, the combination of our prediction model for short-term (initial) weight loss should be combined with this model for long-term weight loss and tested prospectively on the prediction of long-term weight maintenance after diet in overweight and obese persons with T2D.

Future research should focus on identifying pre-treatment, in-treatment and process-predictors of weight loss and maintenance in adults with T2D, since virtually all research

has been done with non-diabetic persons with obesity. Moreover, research programs should be developed to reach the goal of matching treatments to the individuals' needs to improve success at weight loss maintenance instead of a 'one size fits all' approach. We also need to recognize that people may need different things at different points in their treatment cycle. What might help them in the weight loss phase may be quite different from what is helpful in the maintenance phase (83, 93).

CLINICAL IMPLICATIONS

My results indicate that there is no scientific justification to offer overweight and obese adults with T2D CBGT, as performed in my studies, on top of usual care in order to optimize the effect of weight loss dieting. Although CBGT can have positive effects on depressive symptoms and eating disorders in individuals with T2D (94-96), at this moment clinicians should not offer this expensive treatment to their T2D patients for weight loss maintenance. Future studies should focus on the possibility that certain T2D subgroups could benefit from CBGT or a modified CBGT for weight loss maintenance. Despite weight regain, the diet intervention used in our trial was quite successful: almost 40% of the participants initially lost 5% or more of their bodyweight and maintained this weight loss for 2 years. Moreover, the waist circumference, need of insulin, depression score and fatigue score was on average lower at 2 years compared to baseline. For this reason, I started an implementation project with the help of the Dutch Diabetes Research Foundation, to implement the study diet intervention into the usual care of the diabetes team of the Erasmus Medical Center (POWER 2.0). We found that the POWER 2.0 program was effective in reducing weight, improving glycemic control and reducing the need of insulin in 77 overweight and obese adults with T2D, after 1 year of follow-up. In figure 2, the effect of the POWER 2.0 program is shown on weight, HbA1c, and insulin dose. These results are comparable to the effects of the POWER trial. Moreover, the program was successfully integrated in the usual care of the diabetes team of the Erasmus MC. Subsequently, we conducted a pilot study to determine the effect and feasibility

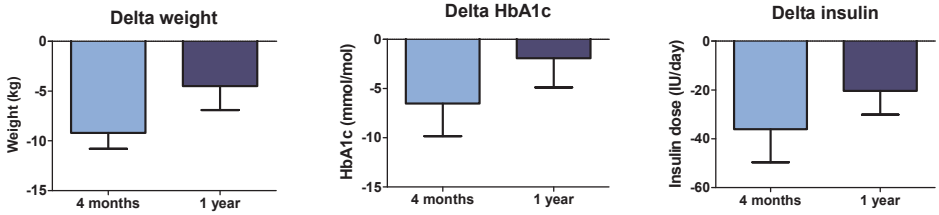

Figure 3. Results of the POWER 2.0 implementation trial
Shown are means with 95% confidence interval.

of implementing the diet intervention in a primary care setting ('Huisartsen Onder Een Dak' (HOED), Overschie). In this explorative pilot study in 10 participants, we found that the POWER 2.0 program was effective in reducing weight and can be successfully implemented in the primary setting as well. A second group of participants already started with the program, showing the intention of HOED Overschie to incorporate this treatment option into their usual diabetes care.

To further improve the long term effectiveness of weight loss dieting in overweight and obese adults with T2D, it is important to acknowledge that weight loss maintenance is influenced by many factors, like diet and exercise behavior, psychological factors, culture, environment, biological adaptions to weight loss, etc. Targeting to change only one factor (behavior) like we did in our trial appears to be insufficient. Perhaps different strategies must be combined to combat all the drivers behind weight regain, and preferably studied in pragmatic clinical trials in the future.

Stop the rise in obesity and type 2 diabetes: prevention

In this thesis, I studied the effect of diet and CBGT in a group of people with obesity and T2D. Worldwide, this group is steadily growing. From the Rotterdam Study we learned that nowadays 1 out of 3 adults aged 45 years will develop T2D. Moreover, having a higher BMI has been shown to increase this lifetime risk even more (97). Needless to say that this puts a heavy burden on our future healthcare system. One of the most important reasons for the obesity and obesity-related T2D pandemic is the present-day obesogenic environment, making it extremely difficult to choose for and maintain a healthy lifestyle. Obviously, people bear individual responsibility for their health, but environmental factors can encourage or undermine the ability of people to act in their own self-interest. Obesity has been called the "Cholera of the 21st century" (Tom Farley, 2001). The cholera epidemic was successfully combatted 150 years ago by environmental changes. In the same way, we have to fight the obesity epidemic via broad environmental modifications (98). Additionally, it is of great importance to educate people about nutrition, starting with our children. During their school career, primary school children only receive 7-8 hours of nutrition education. To create a generation with a positive mind set and sufficient knowledge on healthy lifestyle, we need to offer our children more and better 'lifestyle' education. Fortunately, the Dutch government has recently taken action on improving nutrition education and I have recently co-authored a book about healthy food for children (99). Hopefully, with these initiatives we can halt the rise in (childhood) obesity and obesity-related T2D in the near future.

CONCLUSION

With the research presented in this thesis I showed that a short term very low-calorie diet has sustainable effects on weight, insulin need and psychological wellbeing in persons with obesity-related T2D, although regain of weight occurred in the majority of people. To solve this problem of weight regain, a psychological intervention like cognitive behavioral group therapy is not sufficient. Now, we face the challenge of inventing new strategies, hypothetically combining dietary-, drug-, behavioral- and environmental interventions, to improve the long term effectiveness of weight loss dieting. With the ultimate goal of curing obesity-related T2D and preventing its complications in the near future.

REFERENCES

1. Tanaka S, Tanaka S, Iimuro S, Ishibashi S, Yamashita H, Moriya T, et al. Maximum BMI and microvascular complications in a cohort of Japanese patients with type 2 diabetes: the Japan Diabetes Complications Study. J Diabetes Complications. 2016;30(5):790-7.
2. Tanaka S, Tanaka S, Iimuro S, Yamashita H, Katayama S, Akanuma Y, et al. Predicting macro- and microvascular complications in type 2 diabetes: the Japan Diabetes Complications Study/the Japanese Elderly Diabetes Intervention Trial risk engine. Diabetes Care. 2013;36(5):1193-9.
3. Tobias DK, Pan A, Jackson CL, O'Reilly EJ, Ding EL, Willett WC, et al. Body-mass index and mortality among adults with incident type 2 diabetes. N Engl J Med. 2014;370(3):233-44.
4. Maggio CA, Pi-Sunyer FX. Obesity and type 2 diabetes. Endocrinol Metab Clin North Am. 2003;32(4):805-22, viii.
5. Look Ahead Research Group, Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Bright R, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes Care. 2007;30(6):1374-83.
6. Dombrowski SU, Knittle K, Avenell A, Araujo-Soares V, Sniehotta FF. Long term maintenance of weight loss with non-surgical interventions in obese adults: systematic review and meta-analyses of randomised controlled trials. Bmj. 2014;348:g2646.
7. Greenway FL. Physiological adaptations to weight loss and factors favouring weight regain. Int J Obes (Lond). 2015;39(8):1188-96.
8. Maclean PS, Bergouignan A, Cornier MA, Jackman MR. Biology's response to dieting: the impetus for weight regain. Am J Physiol Regul Integr Comp Physiol. 2011;301(3):R581-600.
9. MacLean PS, Wing RR, Davidson T, Epstein L, Goodpaster B, Hall KD, et al. NIH working group report: Innovative research to improve maintenance of weight loss. Obesity (Silver Spring). 2015;23(1):7-15.
10. Van Dorsten B, Lindley EM. Cognitive and behavioral approaches in the treatment of obesity. Med Clin North Am. 2011;95(5):971-88.
11. Fabricatore AN. Behavior therapy and cognitive-behavioral therapy of obesity: is there a difference? J Am Diet Assoc. 2007;107(1):92-9.
12. Shaw K, O'Rourke P, Del Mar C, Kenardy J. Psychological interventions for overweight or obesity. Cochrane Database Syst Rev. 2005(2):CD003818.
13. Werrij MQ, Jansen A, Mulkens S, Elgersma HJ, Ament AJ, Hospers HJ. Adding cognitive therapy to dietetic treatment is associated with less relapse in obesity. J Psychosom Res. 2009;67(4):315-24.
14. Stahre L, Hallstrom T. A short-term cognitive group treatment program gives substantial weight reduction up to 18 months from the end of treatment. A randomized controlled trial. Eat Weight Disord. 2005;10(1):51-8.
15. Stahre L, Tarnell B, Hakanson CE, Hallstrom T. A randomized controlled trial of two weight-reducing short-term group treatment programs for obesity with an 18-month follow-up. Int J Behav Med. 2007;14(1):48-55.
16. Painot D, Jotterand S, Kammer A, Fossati M, Golay A. Simultaneous nutritional cognitive–behavioural therapy in obese patients. Patient Educ Couns. 2001;42(1):47-52.
17. Cooper Z, Fairburn CG. A new cognitive behavioural approach to the treatment of obesity. Behav Res Ther. 2001;39(5):499-511.

18. Cooper Z, Doll HA, Hawker DM, Byrne S, Bonner G, Eeley E, et al. Testing a new cognitive behavioural treatment for obesity: A randomized controlled trial with three-year follow-up. Behav Res Ther. 2010;48(8):706-13.
19. Forlani G, Lorusso C, Moscatiello S, Ridolfi V, Melchionda N, Di Domizio S, et al. Are behavioural approaches feasible and effective in the treatment of type 2 diabetes? A propensity score analysis vs. prescriptive diet. Nutr Metab Cardiovasc Dis. 2009;19(5):313-20.
20. Mottalib A, Sakr M, Shehabeldin M, Hamdy O. Diabetes Remission after Nonsurgical Intensive Lifestyle Intervention in Obese Patients with Type 2 Diabetes. J Diabetes Res. 2015;2015:468704.
21. Purcell K, Sumithran P, Prendergast LA, Bouniu CJ, Delbridge E, Proietto J. The effect of rate of weight loss on long-term weight management: a randomised controlled trial. Lancet Diabetes Endocrinol. 2014;2(12):954-62.
22. Vink RG, Roumans NJ, Arkenbosch LA, Mariman EC, van Baak MA. The effect of rate of weight loss on long-term weight regain in adults with overweight and obesity. Obesity (Silver Spring). 2016;24(2):321-7.
23. Langeveld M, DeVries JH. The long-term effect of energy restricted diets for treating obesity. Obesity (Silver Spring). 2015;23(8):1529-38. doi: 10.002/oby.21146. Epub 2015 Jul 14.
24. Little RJA, Rubin DB. Statistical analysis with missing data. New York: John Wiley and Sons; 1987.
25. Phelan S, Hassenstab J, McCaffery JM, Sweet L, Raynor HA, Cohen RA, et al. Cognitive interference from food cues in weight loss maintainers, normal weight, and obese individuals. Obesity (Silver Spring). 2011;19(1):69-73. doi: 10.1038/oby.2010.138. Epub Jun 10.
26. van den Akker K, Schyns G, Jansen A. Enhancing inhibitory learning to reduce overeating: Design and rationale of a cue exposure therapy trial in overweight and obese women. Contemp Clin Trials. 2016;49:85-91.(doi):10.1016/j.cct.2016.06.008. Epub Jun 21.
27. Niemeier HM, Phelan S, Fava JL, Wing RR. Internal disinhibition predicts weight regain following weight loss and weight loss maintenance. Obesity (Silver Spring). 2007;15(10):2485-94.
28. Gettens KM, Gorin AA. Executive function in weight loss and weight loss maintenance: a conceptual review and novel neuropsychological model of weight control. J Behav Med. 2017;3(10):017-9831.
29. Verbeken S, Braet C, Goossens L, van der Oord S. Executive function training with game elements for obese children: a novel treatment to enhance self-regulatory abilities for weight-control. Behav Res Ther. 2013;51(6):290-9. doi: 10.1016/j.brat.2013.02.006. Epub Mar 4.
30. Wyckoff EP, Evans BC, Manasse SM, Butryn ML, Forman EM. Executive functioning and dietary intake: Neurocognitive correlates of fruit, vegetable, and saturated fat intake in adults with obesity. Appetite. 2017;111:79-85.(doi):10.1016/j.appet.2016.12.039. Epub Dec 29.
31. Johansson K, Neovius M, Hemmingsson E. Effects of anti-obesity drugs, diet, and exercise on weight-loss maintenance after a very-low-calorie diet or low-calorie diet: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr. 2014;99(1):14-23.
32. Larsen TM, Dalskov SM, van Baak M, Jebb SA, Papadaki A, Pfeiffer AF, et al. Diets with high or low protein content and glycemic index for weight-loss maintenance. N Engl J Med. 2010;363(22):2102-13.
33. Ebbeling CB, Swain JF, Feldman HA, Wong WW, Hachey DL, Garcia-Lago E, et al. Effects of dietary composition on energy expenditure during weight-loss maintenance. Jama. 2012;307(24):2627-34.
34. Soenen S, Martens EA, Hochstenbach-Waelen A, Lemmens SG, Westerterp-Plantenga MS. Normal protein intake is required for body weight loss and weight maintenance, and elevated

protein intake for additional preservation of resting energy expenditure and fat free mass. J Nutr. 2013;143(5):591-6.

35. Williams KV, Mullen ML, Kelley DE, Wing RR. The effect of short periods of caloric restriction on weight loss and glycemic control in type 2 diabetes. Diabetes Care. 1998;21(1):2-8.
36. Wing RR, Blair E, Marcus M, Epstein LH, Harvey J. Year-long weight loss treatment for obese patients with type II diabetes: does including an intermittent very-low-calorie diet improve outcome? Am J Med. 1994;97(4):354-62.
37. Rosenbaum M, Hirsch J, Gallagher DA, Leibel RL. Long-term persistence of adaptive thermogenesis in subjects who have maintained a reduced body weight. Am J Clin Nutr. 2008;88(4):906-12.
38. Jakicic JM. The effect of physical activity on body weight. Obesity (Silver Spring). 2009;17 Suppl 3:S34-8.
39. Wing RR, Hill JO. Successful weight loss maintenance. Annu Rev Nutr. 2001;21:323-41.
40. Jakicic JM, Marcus BH, Lang W, Janney C. Effect of exercise on 24-month weight loss maintenance in overweight women. Arch Intern Med. 2008;168(14):1550-9; discussion 9-60.
41. Trost SG, Sundal D, Foster GD, Lent MR, Vojta D. Effects of a pediatric weight management program with and without active video games a randomized trial. JAMA Pediatr. 2014;168(5):407-13.
42. Wadden TA, Hollander P, Klein S, Niswender K, Woo V, Hale PM, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. Int J Obes (Lond). 2013;37(11):1443-51.
43. Iepsen EW, Lundgren J, Dirksen C, Jensen JE, Pedersen O, Hansen T, et al. Treatment with a GLP-1 receptor agonist diminishes the decrease in free plasma leptin during maintenance of weight loss. Int J Obes (Lond). 2015;39(5):834-41.
44. Bunck MC, Corner A, Eliasson B, Heine RJ, Shaginian RM, Taskinen MR, et al. Effects of exenatide on measures of beta-cell function after 3 years in metformin-treated patients with type 2 diabetes. Diabetes Care. 2011;34(9):2041-7. doi: 10.337/dc11-0291.
45. Solini A. Role of SGLT2 inhibitors in the treatment of type 2 diabetes mellitus. Acta Diabetol. 2016;53(6):863-70.
46. Lee S, Lindquist R. A review of technology-based interventions to maintain weight loss. Telemed J E Health. 2015;21(3):217-32.
47. Okorodudu DE, Bosworth HB, Corsino L. Innovative interventions to promote behavioral change in overweight or obese individuals: A review of the literature. Ann Med. 2015;47(3):179-85.
48. Jakicic JM, Davis KK, Rogers RJ, King WC, Marcus MD, Helsel D, et al. Effect of Wearable Technology Combined With a Lifestyle Intervention on Long-term Weight Loss: The IDEA Randomized Clinical Trial. Jama. 2016;316(11):1161-71.
49. Godino JG, Merchant G, Norman GJ, Donohue MC, Marshall SJ, Fowler JH, et al. Using social and mobile tools for weight loss in overweight and obese young adults (Project SMART): a 2 year, parallel-group, randomised, controlled trial. Lancet Diabetes Endocrinol. 2016;4(9):747-55.
50. Tsai AG, Wadden TA. The evolution of very-low-calorie diets: an update and meta-analysis. Obesity (Silver Spring). 2006;14(8):1283-93.
51. Rehackova L, Arnott B, Araujo-Soares V, Adamson AA, Taylor R, Sniehotta FF. Efficacy and acceptability of very low energy diets in overweight and obese people with Type 2 diabetes mellitus: a systematic review with meta-analyses. Diabet Med. 2016;33(5):580-91.
52. Harvey J, Wing RR, Mullen M. Effects on food cravings of a very low calorie diet or a balanced, low calorie diet. Appetite. 1993;21(2):105-15.

53. Baker S, Jerums G, Proietto J. Effects and clinical potential of very-low-calorie diets (VLCDs) in type 2 diabetes. Diabetes Res Clin Pract. 2009;85(3):235-42.

54. Belalcazar LM, Haffner SM, Lang W, Hoogeveen RC, Rushing J, Schwenke DC, et al. Lifestyle intervention and/or statins for the reduction of C-reactive protein in type 2 diabetes: from the look AHEAD study. Obesity (Silver Spring). 2013;21(5):944-50.

55. Hamdy O, Ledbury S, Mullooly C, Jarema C, Porter S, Ovalle K, et al. Lifestyle modification improves endothelial function in obese subjects with the insulin resistance syndrome. Diabetes Care. 2003;26(7):2119-25.

56. Thompson D, Walhin JP, Batterham AM, Stokes KA, Cooper AR, Andrews RC. Effect of diet or diet plus physical activity versus usual care on inflammatory markers in patients with newly diagnosed type 2 diabetes: the Early ACTivity In Diabetes (ACTID) randomized, controlled trial. J Am Heart Assoc. 2014;3(3):e000828.

57. Lips MA, van Klinken JB, Pijl H, Janssen I, Willems van Dijk K, Koning F, et al. Weight loss induced by very low calorie diet is associated with a more beneficial systemic inflammatory profile than by Roux-en-Y gastric bypass. Metabolism. 2016;65(11):1614-20. doi: 10.016/j.metabol.2016.07.013. Epub Aug 16.

58. Tousoulis D, Papageorgiou N, Androulakis E, Siasos G, Latsios G, Tentolouris K, et al. Diabetes mellitus-associated vascular impairment: novel circulating biomarkers and therapeutic approaches. J Am Coll Cardiol. 2013;62(8):667-76.

59. Stehouwer CD, Gall MA, Twisk JW, Knudsen E, Emeis JJ, Parving HH. Increased urinary albumin excretion, endothelial dysfunction, and chronic low-grade inflammation in type 2 diabetes: progressive, interrelated, and independently associated with risk of death. Diabetes. 2002;51(4):1157-65.

60. Kanai A, Kawamura T, Umemura T, Nagashima M, Nakamura N, Nakayama M, et al. Association between future events of brain infarction and soluble levels of intercellular adhesion molecule-1 and C-reactive protein in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract. 2008;82(2):157-64.

61. Frankel DS, Meigs JB, Massaro JM, Wilson PW, O'Donnell CJ, D'Agostino RB, et al. Von Willebrand factor, type 2 diabetes mellitus, and risk of cardiovascular disease: the framingham offspring study. Circulation. 2008;118(24):2533-9.

62. Schillinger M, Exner M, Amighi J, Mlekusch W, Sabeti S, Rumpold H, et al. Joint effects of C-reactive protein and glycated hemoglobin in predicting future cardiovascular events of patients with advanced atherosclerosis. Circulation. 2003;108(19):2323-8.

63. Schulze MB, Rimm EB, Li T, Rifai N, Stampfer MJ, Hu FB. C-reactive protein and incident cardiovascular events among men with diabetes. Diabetes Care. 2004;27(4):889-94.

64. Johansen OE. Interpretation of cardiovascular outcome trials in type 2 diabetes needs a multiaxial approach. World J Diabetes. 2015;6(9):1092-6.

65. Raitakari M, Ilvonen T, Ahotupa M, Lehtimaki T, Harmoinen A, Suominen P, et al. Weight reduction with very-low-caloric diet and endothelial function in overweight adults: role of plasma glucose. Arterioscler Thromb Vasc Biol. 2004;24(1):124-8.

66. Takahashi M, Bujo H, Shiba T, Jiang M, Maeno T, Shirai K. Enhanced circulating soluble LR11 in patients with diabetic retinopathy. Am J Ophthalmol. 2012;154(1):187-92.

67. Shiba T, Bujo H, Takahashi M, Sato Y, Jiang MZ, Hori Y, et al. Vitreous fluid and circulating levels of soluble lr11, a novel marker for progression of diabetic retinopathy. Graef Arch Clin Exp. 2013;251(12):2689-95.

68. Ogita M, Miyauchi K, Dohi T, Tsuboi S, Miyazaki T, Yokoyama T, et al. Increased circulating soluble LR11 in patients with acute coronary syndrome. Clin Chim Acta. 2013;415:191-4.

69. Bennet A, Di Angelantonio E, Erqou S, Eiriksdottir G, Sigurdsson G, Woodward M, et al. Lipoprotein(a) levels and risk of future coronary heart disease: large-scale prospective data. Arch Intern Med. 2008;168(6):598-608.

70. Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. Circulation. 2008;117(2):176-84.

71. Emerging Risk Factors C, Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. Jama. 2009;302(4):412-23.

72. Hiraga T, Kobayashi T, Okubo M, Nakanishi K, Sugimoto T, Ohashi Y, et al. Prospective study of lipoprotein(a) as a risk factor for atherosclerotic cardiovascular disease in patients with diabetes. Diabetes Care. 1995;18(2):241-4.

73. James RW, Boemi M, Sirolla C, Amadio L, Fumelli P, Pometta D. Lipoprotein (a) and vascular disease in diabetic patients. Diabetologia. 1995;38(6):711-4.

74. Waldeyer C, Makarova N, Zeller T, Schnabel RB, Brunner FJ. Lipoprotein(a) and the Risk of Cardiovascular Disease in the European Population – Results from the BiomarCaRE Consortium. European Heart Journal. 2017;Apr 24. doi: 10.1093/eurheartj/ehx166.

75. Berglund L, Lefevre M, Ginsberg HN, Kris-Etherton PM, Elmer PJ, Stewart PW, et al. Comparison of monounsaturated fat with carbohydrates as a replacement for saturated fat in subjects with a high metabolic risk profile: studies in the fasting and postprandial states. Am J Clin Nutr. 2007;86(6):1611-20.

76. Clevidence BA, Judd JT, Schaefer EJ, Jenner JL, Lichtenstein AH, Muesing RA, et al. Plasma lipoprotein (a) levels in men and women consuming diets enriched in saturated, cis-, or trans-monounsaturated fatty acids. Arterioscler Thromb Vasc Biol. 1997;17(9):1657-61.

77. Faghihnia N, Tsimikas S, Miller ER, Witztum JL, Krauss RM. Changes in lipoprotein(a), oxidized phospholipids, and LDL subclasses with a low-fat high-carbohydrate diet. J Lipid Res. 2010;51(11):3324-30.

78. PR K. - Lipoprotein(a) and ischemic heart disease–a causal association? A review. Atherosclerosis. 2010;211(1):15-23.

79. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. Jama. 2009;301(22):2331-9.

80. Saleheen D, Haycock PC, Zhao W, Rasheed A, Taleb A, Imran A, et al. Apolipoprotein(a) isoform size, lipoprotein(a) concentration, and coronary artery disease: a mendelian randomisation analysis. Lancet Diabetes Endocrinol. 2017;5(7):524-33. doi: 10.1016/S2213-8587(17)30088-8. Epub 2017 Apr 10.

81. Raal FJ, Giugliano RP, Sabatine MS, Koren MJ, Blom D, Seidah NG, et al. PCSK9 inhibition-mediated reduction in Lp(a) with evolocumab: an analysis of 10 clinical trials and the LDL receptor's role. J Lipid Res. 2016;57(6):1086-96.

82. Viney NJ, van Capelleveen JC, Geary RS, Xia S, Tami JA, Yu RZ, et al. Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials. Lancet. 2016;388(10057):2239-53.

83. Stubbs J, Whybrow S, Teixeira P, Blundell J, Lawton C, Westenhoefer J, et al. Problems in identifying predictors and correlates of weight loss and maintenance: implications for weight control therapies based on behaviour change. Obes Rev. 2011;12(9):688-708.

84. Austin PC, Steyerberg EW. The number of subjects per variable required in linear regression analyses. J Clin Epidemiol. 2015;68(6):627-36. doi: 10.1016/j.jclinepi.2014.12.014. Epub 5 Jan 22.

85. Butryn ML, Phelan S, Hill JO, Wing RR. Consistent self-monitoring of weight: a key component of successful weight loss maintenance. Obesity (Silver Spring). 2007;15(12):3091-6.

86. Ogden LG, Stroebele N, Wyatt HR, Catenacci VA, Peters JC, Stuht J, et al. Cluster analysis of the national weight control registry to identify distinct subgroups maintaining successful weight loss. Obesity (Silver Spring). 2012;20(10):2039-47.

87. Phelan S, Wyatt HR, Hill JO, Wing RR. Are the eating and exercise habits of successful weight losers changing? Obesity (Silver Spring). 2006;14(4):710-6.

88. Thomas JG, Bond DS, Phelan S, Hill JO, Wing RR. Weight-loss maintenance for 10 years in the National Weight Control Registry. Am J Prev Med. 2014;46(1):17-23.

89. Look Ahead Research Group. Eight-year weight losses with an intensive lifestyle intervention: the look AHEAD study. Obesity (Silver Spring). 2014;22(1):5-13.

90. Look Ahead Research Group. Association of Weight Loss Maintenance and Weight Regain on 4-Year Changes in CVD Risk Factors: the Action for Health in Diabetes (Look AHEAD) Clinical Trial. Diabetes Care. 2016;39(8):1345-55.

91. Espeland MA, Glick HA, Bertoni A, Brancati FL, Bray GA, Clark JM, et al. Impact of an intensive lifestyle intervention on use and cost of medical services among overweight and obese adults with type 2 diabetes: the action for health in diabetes. Diabetes Care. 2014;37(9):2548-56.

92. Klein S, Burke LE, Bray GA, Blair S, Allison DB, Pi-Sunyer X, et al. Clinical implications of obesity with specific focus on cardiovascular disease: a statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. Circulation. 2004;110(18):2952-67.

93. Teixeira PJ, Going SB, Sardinha LB, Lohman TG. A review of psychosocial pre-treatment predictors of weight control. Obes Rev. 2005;6(1):43-65.

94. Safren SA, Gonzalez JS, Wexler DJ, Psaros C, Delahanty LM, Blashill AJ, et al. A randomized controlled trial of cognitive behavioral therapy for adherence and depression (CBT-AD) in patients with uncontrolled type 2 diabetes. Diabetes Care. 2014;37(3):625-33.

95. Hermanns N, Schmitt A, Gahr A, Herder C, Nowotny B, Roden M, et al. The effect of a Diabetes-Specific Cognitive Behavioral Treatment Program (DIAMOS) for patients with diabetes and subclinical depression: results of a randomized controlled trial. Diabetes Care. 2015;38(4):551-60.

96. Tovote KA, Fleer J, Snippe E, Peeters AC, Emmelkamp PM, Sanderman R, et al. Individual mindfulness-based cognitive therapy and cognitive behavior therapy for treating depressive symptoms in patients with diabetes: results of a randomized controlled trial. Diabetes Care. 2014;37(9):2427-34.

97. Ligthart S, van Herpt TT, Leening MJ, Kavousi M, Hofman A, Stricker BH, et al. Lifetime risk of developing impaired glucose metabolism and eventual progression from prediabetes to type 2 diabetes: a prospective cohort study. Lancet Diabetes Endocrinol. 2016;4(1):44-51. doi: 10.1016/S2213-8587(15)00362-9. Epub 2015 Nov 11.

98. Roberto CA, Swinburn B, Hawkes C, Huang TT, Costa SA, Ashe M, et al. Patchy progress on obesity prevention: emerging examples, entrenched barriers, and new thinking. Lancet. 2015;385(9985):2400-9. doi: 10.1016/S0140-6736(14)61744-X. Epub 2015 Feb 19.

99. Berk KA, Houweling B, Kleefstra N. Etenstijd; ISBN 9789082491418: Uitgeverij Langerhans; 2016.

Appendix

SUMMARY

Over the past decades, both the prevalence of obesity and type 2 diabetes (T2D) have been increasing dramatically, with devastating consequences for the health related quality of life of the affected individuals and for society. Overweight and obesity increase cardiovascular morbidity and mortality in patients with T2D. Weight loss improves several cardiovascular disease risk factors and is therefore a cornerstone in the treatment of obesity related T2D. However, the effect of weight loss dieting is highly variable between individuals and subsequent weight regain is a substantial problem in the dietary treatment of obese adults with or without T2D.

A prediction model of weight loss may assist in selecting those individuals that would respond best to a weight loss diet, hereby improving cost-effectiveness of the treatment and preventing patient distress upon failure. In Chapter 2, we examined which physiological and psychological variables predict weight loss induced by a short-term very low-calorie diet (VLCD). In 192 overweight or obese adults with T2D, who underwent an eight-week VLCD, we found that successful weight loss (i.e. ≥5%) was predicted fairly well by five baseline parameters, which were predominantly diabetes related. These data enabled us to develop a prediction model of diet-induced weight loss in T2D. I propose to test this prediction model in future prospective diet intervention studies in patients with T2D.

When obese persons with T2D lose weight, several conventional cardiovascular disease risk factors, like hyperlipidemia and hyperglycemia, improve dramatically. In chapter 3, I showed that diet-induced weight loss also led to a reduction in biomarkers of endothelial dysfunction and inflammation within four months of dieting. This positive effect was independent of medication frequently prescribed to T2D patients, such as statins, ACE inhibitors and metformin, and also independent of T2D history. The conclusion is that even on intensive medical drug treatment as well as after a long history of T2D, vascular health of these patients may still benefit from diet-induced weight reduction.

New candidate biomarkers for cardiovascular disease risk have recently emerged, such as increased plasma levels of soluble low density lipoprotein receptor-relative with 11 ligand-binding repeats (sLR11) and lipoprotein(a) [Lp(a)]. In the research reported in chapter 4, we determined the effect of diet-induced weight loss on plasma sLR11 levels in overweight and obese individuals with T2D. Weight loss dieting resulted in a reduction in plasma sLR11 levels that was associated with improvements in lipid profile and the glycemic state. In chapter 5, I examined the effect of weight loss via diet and bariatric surgery on lipoprotein(a) [Lp(a)] levels in overweight and obese individuals with and without T2D. In three independent cohorts of overweight and obese subjects with or without T2D, weight loss upon four months of dieting was accompanied by an increase in Lp(a) levels, while conventional cardiovascular disease risk factors improved.

This increase in Lp(a) levels may potentially antagonize the beneficial cardio-metabolic effects of diet-induced weight reduction. This increase in Lp(a) after weight loss was not observed upon bariatric surgery-induced weight loss. In a subset of the participants with T2D, the Lp(a) levels had returned almost to baseline levels two years after the diet intervention, suggesting that the initial increase in Lp(a) upon diet was an acute effect that waned off after a longer period of a normal diet.

Weight regain after successful weight loss dieting is a universal problem, also for patients with T2D. This may well lead to loss of the potential benefits on cardiovascular disease risk achieved by short-term weight loss. In obese individuals without T2D, cognitive behavioral group therapy (CBGT) has been shown effective in weight loss maintenance. Therefore, I hypothesized that CBGT would prevent weight regain after diet-induced weight loss in obese individuals with T2D. To test this, we performed the Prevention Of Weight Regain (POWER) trial, a single center, parallel-group, randomized controlled trial (chapter 6). The results of this trial are reported in chapter 7. Contrary to my expectations, CBGT after VLCD-induced weight loss did not prevent weight regain when given on top of usual care during 2 years of follow-up. Moreover, CBGT had no effect on cardiovascular disease risk factors and psychological wellbeing compared to usual care exclusively. Two years after finishing the VLCD, participants still had a better diabetes control than before, illustrated by a reduced need for insulin. However, this proved to be true for both the CBGT and the control group. Our results indicate that there is no scientific justification to offer CBGT on top of the usual care, provided in a tertiary referral center, to obese patients with T2D for weight loss maintenance after dieting.

In chapter 8, we reviewed our findings in a broader perspective and elaborated on the methodological aspects and potential clinical implications. Since CBGT did not solve the problem of weight regain after successful weight loss, we discussed other strategies to improve the effect of weight loss dieting and maintenance in T2D. Additionally we discussed the use of prediction models for short-term weight loss as well as for weight loss maintenance, to select those individuals that will benefit most of a diet intervention. In this chapter, I also described the implementation in our usual care of the very low-calorie diet intervention used in the POWER trial. I found that the POWER 2.0 program was effective in reducing weight, improving glycemic control and reducing the need of insulin in 77 overweight and obese adults with T2D, after 1 year of follow-up. Moreover, the POWER 2.0 program was successfully implemented in a primary care setting in a small pilot study and shown effective in reducing weight. Finally, I discuss directions for future research to identify pre-treatment and in-process predictors of weight loss and maintenance, and on new strategies for long term weight loss maintenance in obese patients with T2D.

To conclude, with the research presented in my thesis, I showed that a short term VLCD has sustainable effects on weight and diabetes control in persons with obesity-related T2D, although regain of weight occurred in the majority of people. To solve this problem

of weight regain, a psychological intervention like CBGT appeared not effective. Now, we face the challenge of designing new strategies to improve the long term effectiveness of weight loss dieting, with the ultimate goal of reversing obesity-related T2D and prevent its complications.

SAMENVATTING

Het aantal mensen met obesitas en type 2 diabetes (T2D) is de afgelopen decennia sterk toegenomen. Dit heeft negatieve gevolgen voor zowel het individu als voor onze maatschappij. Mensen met T2D die overgewicht of obesitas hebben, overlijden eerder aan cardiovasculaire ziekten in vergelijking met mensen die een gezond gewicht hebben. Gewichtsverlies leidt tot verbetering van het cardiovasculaire risico profiel en is daarom een belangrijk onderdeel van de behandeling van mensen met aan obesitas-gerelateerde T2D. Helaas verschilt het effect van een energiebeperkt dieet op het gewicht sterk tussen individuen. Bovendien neemt het gewicht vaak snel weer toe na een aanvankelijk succesvolle dieetbehandeling: het zogenoemde 'jojo-effect'.

Idealiter zouden zorgverleners vooraf mensen willen selecteren met de grootste kans om succesvol af te vallen. Hiermee zou namelijk de kosteneffectiviteit van de dieetbehandeling vergroot kunnen worden én zou de patiënt de negatieve gevoelens, die gepaard gaan met falen van het dieet, bespaard blijven. In hoofdstuk 2 hebben wij onderzocht welke fysiologische en psychologische variabelen voorspellend zijn voor succesvol gewichtsverlies (≥5 %) bij mensen met obesitas en T2D. Bij 192 mensen die gedurende acht weken een zeer laag calorisch dieet (very low-calorie diet, VLCD) volgden, werd succesvol gewichtsverlies redelijk goed voorspeld door vijf variabelen, die voornamelijk gerelateerd zijn aan diabetes. Met deze gegevens hebben wij een predictiemodel ontwikkeld. Dit predictiemodel zou in toekomstige prospectieve dieet interventie studies verder uitgetest moeten worden bij mensen met T2D.

Gewichtsverlies leidt bij mensen met obesitas en T2D tot verbetering van conventionele cardiovasculaire risico factoren, zoals hyperlipidemie en hyperglycemie. In hoofdstuk 3 hebben wij laten zien dat een gewichtsreducerend dieet gedurende vier maanden ook leidt tot verlaging van biomarkers voor endothele dysfunctie (schade aan de vaatwand) en systemische inflammatie (ontsteking). Dit positieve effect was onafhankelijk van het gebruik van cardioprotectieve medicatie, zoals statines, ACE inhibitoren en metformine. Ook was dit effect onafhankelijk van hoe lang mensen al T2D hadden. Onze conclusie is dat de gezondheid van de vaten van obese mensen met T2D verbetert door gewichtsreductie, ook al gebruiken zij daarvoor al medicatie en hebben zij al vele jaren T2D.

Verhoogde plasmaconcentraties van 'soluble low density lipoprotein receptor-relative with 11 ligand-binding repeats' (sLR11) en lipoproteine(a) [Lp(a)] zijn recentelijk geïdentificeerd als onafhankelijke biomarkers voor het cardiovasculair risico. In het onderzoek dat beschreven wordt in hoofdstuk 4 hebben wij het effect onderzocht van gewichtsverlies door dieet op de hoeveelheid sLR11 in het bloed bij mensen met obesitas en T2D. Het gewichtsreducerende dieet leidde tot verlaging van sLR11. De mate waarmee sLR11 verminderde was geassocieerd met verbeteringen van het lipiden profiel en de diabetes regulatie. Het gunstige effect van het dieet werkt dus deels via verlaging van het sLR11.

In het onderzoek gepresenteerd in Hoofdstuk 5 is het effect van gewichtsverlies op de hoeveelheid Lp(a) in het bloed bestudeerd bij obese mensen met en zonder T2D. In drie onafhankelijke onderzoeksgroepen resulteerde een gewichtsreducerend dieet in een onverwachte stijging van Lp(a), terwijl de klassieke cardiovasculaire risicofactoren juist verbeterden. Deze stijging in het Lp(a) niveau zou potentieel het gunstige cardio-metabole effect van een gewichtsreducerend dieet kunnen verminderen. Bij mensen die gewicht verloren door middel van bariatrische chirurgie werd geen Lp(a) stijging waargenomen. In een subgroep van mensen met T2D heb ik het Lp(a) niveau ook twee jaar na het dieet kunnen meten: toen was de Lp(a) spiegel weer vrijwel gelijk aan het niveau van vóór het dieet. Dit suggereert dat de Lp(a) stijging een acute reactie is op het dieet, die weer verdwijnt gedurende een periode met normale voeding.

Weer zwaarder worden na succesvol afvallen is een universeel probleem, ook voor mensen met T2D. Hierdoor worden potentiele voordelen van gewichtsverlies op de lange termijn teniet gedaan. Uit studies bij mensen met obesitas, zonder T2D, is gebleken dat cognitieve groeps-gedragstherapie ('cognitive behavioral group therapy', CBGT) effectief is in het bereiken en behouden van gewichtsverlies. Mijn hypothese was dat CBGT ook bij obese mensen met T2D terugval in gewicht na succesvol gewichtsverlies kan voorkómen. Om deze hypothese te testen heb ik de 'Prevention Of Weight Regain (POWER) trial' opgezet: een gerandomiseerde, gecontroleerde studie met parallelle groepen, uitgevoerd in één onderzoekscentrum (hoofdstuk 6). De resultaten van dit onderzoek zijn beschreven in hoofdstuk 7. Anders dan verwacht, voegde CBGT niets toe aan de gebruikelijke behandeling om de terugval in gewicht na een VLCD te voorkomen. Ook vonden wij geen extra effect van CBGT op risicofactoren voor hart- en vaatziekten of psychisch welbevinden bovenop dat van de gebruikelijke zorg. Twee jaar na het VLCD hadden de deelnemers in zowel de CBGT als de controle groep nog steeds minder insuline nodig en hadden zij minder last van depressieve gevoelens en vermoeidheid. Ik concludeer daarom dat er wetenschappelijk gezien geen reden is obese mensen met T2D voor behoud van hun gewichtsverlies CBGT aan te bieden, bovenop de gebruikelijke derdelijnszorg.

In hoofdstuk 8 bediscussieer ik mijn bevindingen en plaats deze in een breder perspectief. Daarnaast ga ik in op methodologische aspecten van de in dit proefschrift beschreven studies en van soortgelijke studies, en bespreek ik potentiele klinische implicaties. Aangezien CBGT het probleem van terugval in gewicht niet heeft opgelost, zijn duidelijk andere strategieën nodig om het langetermijneffect van gewichtreducerende diëten verbeteren. Daarnaast wordt het gebruik van predictiemodellen voor gewichtsverlies en gewichtsbehoud besproken. Verder beschrijf ik in dit hoofdstuk dat implementatie van het VLCD dieetprogramma (POWER 2.0) als onderdeel van de behandeling door het diabetesteam van het Erasmus MC, vergelijkbare gunstige effecten heeft als in onze klinische studie. Ook hebben we in een pilotstudie het POWER 2.0 dieetprogramma

in de eerstelijnszorg geïmplementeerd, met goed effect op gewicht. Tot slot bespreek ik welke richting toekomstig onderzoek op zou moeten gaan met betrekking tot het identificeren van voorspellers van gewichtsverlies en het behoud daarvan, en het ontwikkelen van nieuwe strategieën voor het behoud van gewichtsverlies op de lange termijn voor mensen met obesitas en T2D.

Concluderend blijkt uit het in mijn proefschrift gepresenteerde onderzoek, dat een kort durend 'very low-calorie diet' blijvend gunstige effecten heeft op gewicht en insuline behoefte bij mensen met obesitas en T2D, alhoewel bij het merendeel van de mensen het gewicht weer toenam. Met een cognitieve groepstherapie gericht op gedragsverandering wordt de terugval in gewicht niet voorkomen. Er zullen dus nieuwe strategieën ontwikkeld moeten worden om het lange termijn effect van gewichtsreducerende diëten te verbeteren. Het ultieme doel is om daarmee de diabetes controle bij obesitas-gerelateerde T2D te verbeteren en complicaties te voorkomen of te verminderen.

PHD PORTFOLIO

Summary of PhD training and teaching activities

Name:	Kirsten A.C. Berk
Erasmus MC Department:	Internal Medicine
Research School:	COEUR
PhD period:	2010 – 2017
Promotor(s):	Prof.dr. E.J.G. Sijbrands and Prof.dr. J.J. van Busschbach
Supervisor(s):	dr. A.J.M. Verhoeven and dr. M.T. Mulder

1. PhD training		
	Year	**Workload (hours/ECTS)**
General academic skills		
- Biomedical English Writing and Communication	2012	4
- Research Integrity	2012	1
- BROK course + recertification	2012 + 2016	1.5
Research skills		
- Principles of Research in medicine and Epidemiology	2008	0.7
- Introduction to Public Health	2008	0.7
- Methods of clinical research	2010	0.7
- Clinical trials	2010	0.7
- Courses for the quantitative researcher	2010	1.4
- Biostatistics for clinicians	2012	1.0
- Regression analyses for clinicians	2012	1.9
- Repeated measurements in clinical studies	2012	1.9
- Quality of life measurements	2012	0.9
In-depth courses (e.g. Research school, Medical Training)		
- Seminar: glucose metabolism and vascular disease (prof dr E. Sijbrands)	2012	0.4
- Coeur lecture: HDL's Protein Cargo: Friend or Foe in Cardioprotection? (prof dr J.W. Heijnecke)	2013	0.1
- Coeur seminar: gender differences in cardiovascular disease' (prof J. Roos)	2013	0.4
- Coeur debate: 'cardiovascular controversies'	2014	0.4
- Coeur lecture: 'Science update on tea and cardiovascular health' (dr R. Draijer)	2015	0.1
Total ECTS courses:		*17.8 ECTS*

	Year	Workload (hours/ECTS)
Oral presentations and chairmanship		
- National Diabetes Day: 'modedieten bij diabetes'	2010	0.3
- Diabetes and Nutrition Organization jubilee symposium, chair and organisation	2010	0.3
- Researchmeeting Internal Medicine Antwerp (3x poster presentation, 1x oral presentation)	2010,2014, 2015,2016	1.2
- Vascular Rounds: 'diet as a cure for diabetes type 2'	2011	0.3
- NESPEN:'cognitive behavioural therapy in DM2 and overweight'	2011	0.3
- National Insulin Congress: 'VLCD bij insuline afhankelijke diabetes'	2011	0.3
- Annual Dutch Diabetes Research Meeting 2013: 'effect VLCD induced weight loss on sLR11 levels in diabetes'	2013	0.3
- Big 5 congress: 'Gewichtsbeheersing in de praktijk'	2013	0.3
- Research meeting Antwerp: oral presentation 'effect VLCD induced weight loss on sLR11 levels in diabetes'	2014	0.3
- National Diabetes Day: 'resultaten POWER-onderzoek'	2014	0.3
- Annual Dutch Diabetes Research Meeting 2014: 'effect VLCD induced weight loss on endothelial markers and inflammation in T2D'	2014	0.3
- Langerhans diabetes congress: 'diabetesdiëtist anno 2015'	2015	0.3
- National diabetes congress: 'goede voeding bij diabetes type 2'	2015	0.3
- Annual Dutch Diabetes Research Meeting 2015: 'No effect of cognitive behavioral therapy on weight maintenance in T2D: results of the POWER-trial'	2015	0.3
- Internal Medicine Research meeting: 'Effect of weight loss via diet and bariatric surgery on Lp(a) levels'	2016	0.3
- Annual Dutch Diabetes Research Meeting 2016: 'Effect of weight loss on Lp(a) levels in obese subjects with and without T2D'	2016	0.3
- 'Voeding Nederland 2016' congress: chair session 'metabolomics in nutrition'	2016	0.3
- 'Studiedag diabetes voor diëtisten': chair	2017	0.3
International conferences		
- EASD Vienna	2009	1
- ISA Amsterdam	2015	1
- EASD Lissabon	2017	1
Total ECTS congresses and presentations:		*9.3 ECTS*
Seminars and workshops		
- PRISMA course VUMC	2009	0.8
- Coeur PhD day (organisation)	2012-2014	0.9
- PhD retreat: life after PhD	2012	0.8

	Year	Workload (hours/ECTS)
Didactic skills		
- Teach the Teacher I (Desiderius school)	2014	0.8
- Workshop 'tentamen vragen maken' (Desiderius school)	2014	0.2
- Workshop 'individuele begeleiding' (Desiderius school)	2014	0.2
- Workshop 'omgaan met groepen' (Desiderius school)	2014	0.2
- Workshop 'feedback geven' (Desiderius school)	2014	0.2
- University Teaching Qualification (portfolio)	2016	0.6
Total ECTS seminars and workshops		*4.7 ECTS*

2. Teaching activities		
	Year	**Workload (Hours/ECTS)**
Lecturing		
- Ba1C1 ZO 'behandeling en preventie van overgewicht en obesitas'	2010 t/m 2017	2.1
- Minor department of medical psychology week 9 'diabetes'	2010 t/m 2015	1.5
- Post HBO dietetiek 'Voeding en diabetes' HAN, 4 times per year	2013 t/m 2017	3.0
- Post HBO POH 'Diet in Chronic vascular risk management'	2013, 2014	0.6
- Keuzevak Ba3 'Effectieve bestanddelen van psychotherapie in het ziekenhuis'	2014, 2015	0.6
- Education of AIO's: 'Voeding bij diabetes'	2014	0.3
Supervising Master's theses		
- Fabiana Kopra, master student psychology, university of Tilburg: 'non-compliance with cognitive behavioural therapy in patient with diabetes type 2 and overweight' oct 2013-May 2014	2013	1
- Thonke Oudshoorn, master student geneeskunde, university of Utrecht: 'Effect of weight loss on endothelial function in overweight type 2 diabetic patients' feb 2014-jun 2014	2014	0.6
- Edith van der Kraan, bachelor student Voeding&dietetiek, HvA: 'evaluation of the implementation of a very low calorie diet in the usual care of patients with type 2 diabetes and overweight' sept 2015-feb 2016	2015	1
- Supervising AIO (Mardin Licona) in research project: 'the effect of monomeric and oligomeric flavanols in the dietary treatment of patients with diabetes type 2 and microalbuminuria'	2014 t/m 2017	1.2
Total ECTS teaching		*11.9 ECTS*

	Year	Workload (hours/ECTS)
Other		
- Chair Diabetes and Nutrition Organization – member NDF	2009 t/m 2012	600 hours
- Member of PhD committee Coeur research school – organization Coeur day may 2013 + may 2014	2012 t/m 2014	1.2
- Program committee 'nationale diabetesdag 2014' Nederlandse Diabetes federatie	2014	0.3
- Wetenschapsdagen organization committee	2015-2017	0.9
- Member NIV guideline committee:'richtlijn behandeling diabetes mellitus type 2'	2015-2017	0.9
Total ECTS other:		*3.3 ECTS + 600 hours*
Total:		*48.2 ECTS*

LIST OF PEER REVIEWED PUBLICATIONS

Berk KA, Yahya R, Verhoeven AJM, Touw J, Leijten FP, van Rossum EFC, Wester VL, Lips M, Pijl H, Timman R, Erhart G, Kronenberg F, Roeters van Lennep JE, Sijbrands EJG, Mulder MT. Effect of diet-induced weight loss on Lipoprotein(a) levels in obese individuals with and without type 2 diabetes. Diabetologia, 2017; 60(6), 989-997. doi: 10.1007/s00125-017-4246-y

Berk KA, Oudshoorn TP, Verhoeven AJM, Mulder MT, Roks AJM, Dik WA, Timman R, Sijbrands EJG. Effect van gewichtsverlies door het volgen van een dieet op markers van endotheel dysfunctioneren en inflammatie bij behandelde diabetes type 2 patiënten. Voeding &Visie Clinical Nutrition Nespen, Jaargang 29; winter 2016: pp. 8-13.

Berk KA, Oudshoorn TP, Verhoeven AJM, Mulder MT, Roks AJM, Dik WA, Timman R, Sijbrands EJG. Diet-induced weight loss and markers of endothelial dysfunction and inflammation in treated patients with type 2 diabetes. Clinical Nutrition ESPEN 15 (2016), pp. 101-106. doi: 10.1016/j.clnesp.2016.06.011

Berk KA, Vongpromek R, Jiang M, Bujo H, Schneider W, Verhoeven AJM, Sijbrands EJG, Mulder MT. Reduced plasma soluble LR11 levels after diet-induced weight loss in overweight patients with type 2 diabetes. Atherosclerosis. 2016 Nov;254:67-72. doi:10.1016

Berk KA, Mulder MT, Verhoeven AJ, van Wietmarschen H, Boessen R, Pellis LP, van 't Spijker A, Timman R, Ozcan B, Sijbrands EJ. Predictors of Diet-Induced Weight Loss in Overweight Adults with Type 2 Diabetes. PLoS One. 2016 Aug 5;11(8):e0160774. doi: 10.1371/journal.pone.0160774.

Berk KA, Buijks H, Ozcan B, van t Spijker A, Busschbach JJ, Sijbrands EJG. The Prevention Of WEight Regain in diabetes type 2 (POWER) study: the effectiveness of adding a combined psychological intervention to a very low calorie diet, design and pilot data of a randomized controlled trial. BMC Public Health 2012, Nov 23;12:1026. doi: 10.1186/1471-2458-12-1026.

Melis GC, **Berk KA**, Van der Steen JCM, Strack van Schijndel RJM The nutritional gap between ICU and general hospital ward. Clinical Nutrition 22 (april 2003), Suppl 1, S98

Berk KAC, van der Steen JCM. Voedingsbeleid IC-patienten bij overplaatsing naar verpleegafdeling. NTvD 59(7) 166-169.

CURRICULUM VITAE

Kirsten Berk was born on the 7th of April 1981 in Aalsmeer, The Netherlands. She graduated cum laude from secondary school (Alkwin Kollege, Uithoorn) in 1999. She then started studying Nutrition and Dietetics at the Amsterdam University of applied sciences (HvA), and graduated cum laude in 2003. From 2003 she worked as a registered dietitian at the department of Internal Medicine, Leiden University Medical Center, where she specialized in the field of nutrition and diabetes. From 2006 onwards she worked as a registered dietitian at the diabetes team of the department of Internal Medicine of the Erasmus Medical Center. From 2009 to 2012 she was chairwoman of the Diabetes and Nutrition Organization (member of the Dutch Diabetes Federation), an organization of dietitians specialized in diabetes. In 2010 she received a research grant of the Erasmus MC program 'Zorgonderzoek' and started working part-time on the research presented in this thesis (supervised by Prof.dr. Eric Sijbrands and Prof.dr. Jan van Busschbach); in the meantime she continued working as a dietitian in the diabetes team. In 2014 she obtained the Diabetes Research Foundation grant 'Innovatieonderzoek', to study the implementation of the very low-calorie diet intervention into daily practice of the Erasmus MC. In the same year she received sponsorship for the FLAVA trial, aimed to study the effect of monomeric and oligomeric flavanols on microalbuminuria in patients with type 2 diabetes. She currently supervises the researcher appointed to this project. She was member of the PhD committee of the research school COEUR for three years, and in that capacity helped organizing the yearly Coeur Research Day. During her whole professional career, she was involved in teaching both health care professionals and students, and has been invited as a guest speaker for many national congresses in the field of nutrition and diabetes. In 2016 she obtained her University Basic Teaching Qualification at the Erasmus Desiderius school. From 2016 onwards she is member of the 'Nederlandse Internisten Vereniging' committee for the development of the clinical guideline for the glucose lowering treatment of patients with T2D. Moreover, she writes opinion papers and blogs for national nutrition platforms. In 2016, she co-authored a children's book about healthy nutrition and lifestyle (www.boeketenstijd.nl). She also has an active family life: she is married and has two daughters. She will continue working as a dietitian at the diabetes team and start as a post doc researcher at the department of Internal Medicine, in the field of nutrition and diabetes.

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Promoveren is als een onervaren kok een driesterren maaltijd bereiden voor de koningin, onder tijdsdruk uiteraard. Gaandeweg het koken krijg je er wat meer handigheid in en zowaar plezier, maar op sommige momenten heb je de neiging om je misbaksels de prullenbak in te gooien… Het voordeel van een promotie traject boven een deelname aan Masterchef, is de enorme hoeveelheid hulp en steun die ik gehad heb van iedereen die erbij betrokken was. Graag voer ik u langs alle gangen van mijn 'driesterren maaltijd', onderwijl mijn dank uitsprekend aan een ieder die zijn of haar bijdrage heeft geleverd.

Voorgerecht

Waarom ben ik hier aan begonnen? Zo'n 14 jaar geleden is mijn interesse in de wetenschap aangewakkerd door mijn toenmalige afstudeerbegeleiders Peter Weijs en Gerdien Melis, tijdens een onderzoeksstage op de intensive care van het VUMC. Toch nog 7 jaar later zat ik met een onderzoek idee aan tafel bij Aart Bootsma en Adriaan van 't Spijker. Wat wilde ik met dit idee, wilde ik misschien promoveren? Ik beantwoordde positief, zonder enige voorkennis over wat een dergelijk traject zou inhouden. Aart en Adriaan, heel erg bedankt voor het geven van vertrouwen, en het planten van het idee dat ik ooit een onderzoeker zou kunnen worden. Wat volgde was het schrijven van een onderzoeksvoorstel, het aanschrijven van subsidieverstrekkers en het indienen van het protocol bij de medisch ethische commissie, zoveel werk voordat er ook maar 1 metaforische hap gegeten kon worden…

Eric Sijbrands nam al snel de pollepel over van Aart, toen het diabetesteam onder zijn hoede kwam. Eric, je was co-promotor en promotor in één. Letterlijk, doordat je na je inauguratie het promotorschap overnam van Ernst Kuipers. Maar ook figuurlijk doordat je zowel de dagelijkse zorg als de eind verantwoordelijkheid van mijn onderzoekswerk op je nam. Daarnaast heb je, ook niet geheel onbelangrijk, zorg gedragen voor het ontwikkelen van mijn smaak op het gebied van Rotterdamse (Italiaanse) traiteurs. Eric, je bent een visionair die het grote geheel blijft zien. Je kon me op belangrijke momenten stimuleren door wat peper op bepaalde plaatsen te stoppen, maar ook door me te complimenteren als een tussengerecht redelijk te eten was. Het was een gouden greep om mij op een bepaald moment op het lab te planten, ver buiten mij comfort zone. Adrie Verhoeven en Monique Mulder hebben me er thuis laten voelen. Monique, ik heb bewondering voor de rust die je uitstraalt en je gave om allerlei dwarsverbanden te leggen. Ik heb daarvan geprofiteerd door te mogen samenwerken met binnenlandse en buitenlandse onderzoekers uit jouw netwerk. Een metafoor voor jouw manier van werken zijn de vele etentjes bij jou thuis aan de grote keukentafel, met een mengelmoes aan culturen en smaken. Adrie, jij was en bent mijn wetenschappelijke geweten. Niets 'quick and dirty', jij hebt vrijwel ieder woord in dit proefschrift opgepakt, tegen het licht

gehouden en met de nodige droge humor van commentaar voorzien. Blijkbaar kun je als man van god toch een advocaat van de duivel zijn… Je bent een geboren educator en ik heb dan ook veel en graag van je geleerd: experimenteren met nieuwe ingrediënten waar ik nog nooit van had gehoord, creatief met hypotheses en samenhang. Achter dit team staat natuurlijk Edith Padberg, als een rots in de branding. Jij laat je, zoals je zelf zegt, niet zo gauw gek maken door alle dynamiek van de sectie vasculaire geneeskunde. Al met al een team waar menig sterren kok zijn vingers bij aflikt!

Hoofdgerecht

De belangrijkste gang is uiteraard het daadwerkelijk uitvoeren van het onderzoek zelf. Het allerleukste aan dit onderzoek was voor mij het begeleiden en motiveren van de deelnemers. Aan iedereen die deel heeft genomen: heel erg bedankt voor uw hulp aan de wetenschap. Alle gezelligheid en waardering hebben me altijd goed gedaan!

Natuurlijk kon het hoofdgerecht niet worden geserveerd zonder alle hulp en steun vanuit mijn eigen team: het diabetesteam. Ik ben trots op ons gezellige, multiculti team waarin de zorg voor onze patiënten altijd centraal staat! Mijn lieve dietetiek collega's Maaike en Holger: jullie hebben mij altijd gesteund in mijn onderzoek ambities. Onze wandelingetjes in het park samen met Bo hebben me regelmatig geholpen om weer even te 'aarden'. En bij de Starbucks hebben ze gelukkig niet alleen overgewaardeerde koffie, maar ook thee en koekjes! Bedankt alle diabetesverpleegkundigen (Bo, Elvia, Marianne, Zuzana, Jelena, Sofia, Anelida, Elly, Sijda, Liesbeth, Xiomara, Majorie) voor het beoordelen van al die duizenden bloedglucose dagcurves van mijn 'POWER-patiënten' en voor jullie collegialiteit. Bedankt dames van de balie en de prikpost Inwendige Geneeskunde (o.a. Linda, Simone, Patricia, Eveline, Trudy, Marjolein, Sita, Ursula), voor het beantwoorden van alle vragen en het oplossen van problemen (alweer het labformulier vergeten??). Joy, heel erg bedankt voor het met zoveel passie en enthousiasme includeren van deelnemers, wie kan er nu nee zeggen tegen jou? Bedankt Behiye, Mandy, Jeanine, Annet en alle arts-assistenten, voor jullie betrokkenheid bij mijn onderzoek en het doorsturen van mogelijke deelnemers. Bedankt Elina (praktijk EetZo) en mensen van HOED Overschie, voor jullie tijd, energie en enthousiasme bij het uitvoeren en evalueren van de pilot studie. Bedankt Joke, Mieke en Arjen, voor jullie altijd oprechte belangstelling en het creëren van de randvoorwaarden om dit project te kunnen uitvoeren (en het geven van het laatste zetje).

Lange tijd was de afdeling medische psychologie mijn tweede 'keuken', mede dankzij Adriaan. Adriaan, bedankt voor de tijd en energie die je in de begeleiding van 'mijn' patiënten hebt gestoken. In de flex-kamer van de afdeling medische psychologie, met steeds wisselend maar altijd interessant gezelschap, was het vaak een dolle boel. Ik heb goede herinneringen aan de afdelingsuitjes en het Sinterklaas-ruil-spel waarin iedereen ineens die foeilelijke theepot moest hebben… En dat alles onder bezielende leiding

van Jan Passchier en later Jan van Busschbach. 'Tweede' Jan, je bent wat later in mijn 'onderzoeksteam' gestapt als mede-promotor, maar hebt altijd een glimlach op mijn gezicht gebracht met je relativerende breedsprakigheid. Je gevleugelde uitspraak; 'het is af wanneer het af is' heeft menig gestreste PhD student doen kalmeren, mijzelf incluis. Bedankt voor alle, soms bijna filosofische, gesprekken. En dan mijn paranimf Hanneke Buijks, in de loop van de jaren ben je naast een collega ook een lieve vriendin geworden, waar ik alles bij kwijt kon en kan. De combinatie van je talent om de menselijke geest te analyseren en je inlevingsvermogen en bevlogenheid maakt je een goede psycholoog, fijne vriendin en een prachtig mens! Een andere reden waardoor ik nog steeds vaak en graag naar het Na-gebouw loop zijn mijn afspraken met Reinier: ik heb zoveel geleerd van het samen met jou perfectioneren van syntaxen, als ware het recepten voor culinaire hoogstandjes. En Hetty, altijd vol energie en gezelligheid, bedankt dat ik gebruik mocht maken van jouw grote organisatietalent! Daarnaast wil ik alle studenten (o.a. Sara, Jolien, Eva, Thonke, Marloes, Willian, Albert, Edith) bedanken die zich belangeloos hebben ingezet voor mijn onderzoek.

Halverwege het koken van keuken switchen lijkt het recept voor een catastrofe, maar niets is minder waar: toen ik verhuisde naar het lab van vasculaire geneeskunde voelde ik me meteen op mijn plek. Ik ben geen echte 'labrat' geworden (alleen bloed afdraaien telt niet echt mee natuurlijk), maar ben blij dat ik een klein steentje bij heb mogen dragen aan het goede werk van onder andere Leonie, Jeanette en Frank. Hier ook weer veel lol&lekker eten. Van moeders' dolma's (met omkeer-ritueel!) en zelfgebrouwen limoncello tot borrelen met een bijpassende taart bij het vieren van een artikel of posterprijs. And remember: no alcohol in the tiramisu! Bedankt promovendames: Reyhana, Mardin, Sandra en Roosmarijn, jullie hebben mijn PhD tijd gekruid met gezelligheid en soms gedeelde smart. En wie drinkt er nou champagne in Blijdorp?? Ik niet natuurlijk. Bedankt Anton, alleen al praten over wijn gaf ontspanning, en ik ben nog steeds van de omgekeerde smileys zoals je ziet (-;. Reyhana, fijn dat jij mijn andere paranimf wilde zijn! Je bent nu alweer bezig met een nieuw leven: een baan als huisarts in Nijmegen in verband met je opleiding, een kindje en een nieuw huis. Ook jij bent een echte vriendin geworden: ik mis nu al onze gezellige gesprekken over werk, kinderen, mode en natuurlijk eten. We hebben samen lekker gesleuteld aan artikelen, syntaxen en figuren (ok, soms werden we gillend gek), maar met een fantastisch eindresultaat, dat uiteraard gevierd werd op de enige goede manier: shoppen en eten!

To all my co-authors: it has been a privilege to work together with experts from within the Erasmus MC and from all around the world: Leiden, Zeist, Innsbruck, Vienna, Sakura. Special thanks to Wim Dik of the department of Immunology, Herman van Wietmarschen, Ruud Boessen and Linette Pellis of TNO Zeist, Hanno Pijl and Mirjam Lips of the Leiden University Medical Center, Hideaki Bujo and Meizi Jiang of the Toho University, Sakura Medical Center, Wolfgang Schneider of the Medical University of Vienna and Florian

Kronenberg and Gertraud Erhart of the Medical University of Innsbruck. Thank you so much for all your time, effort and knowledge! Together we conducted some very nice research, and I hope we will continue our collaboration.

En dan ligt daar het proefschrift, klaar om opgediend te worden. Een moment waarop lang is gewacht. Een goed moment om ook even aandacht te besteden aan het schilderij dat gebruikt is voor de cover. Het is gemaakt door Jasper, een kunstenaar van galerie de Brugspin in mijn woonplaats Ter Aar; een plek waar mensen met een verstandelijke beperking enorm mooie dingen maken. De kubistische voorstelling is een 'remake' van het werk 'still life with almonds' van Maurice de Vlaminck (1907). Met de toegevoegde insulinepen symboliseert het de continue aandacht die iemand met diabetes moet hebben voor de afstemming tussen voeding en medicatie. Diabetes lijkt soms een 'milde' ziekte, maar de energie die het kost om de bloedglucose waarde iedere dag, bij iedere hap en stap, goed te reguleren moet niet onderschat worden.

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Toetje

Het lekkerste heb ik voor het laatst bewaard. Wie mij wat beter kent weet: hoe zoeter hoe beter… Lieve familie en vrienden, heel erg bedankt voor het meelezen, meeleven en soms lekker meezeuren. Petra, Monique, Maike en José, jullie zijn al heel lang mijn meest dierbare vriendinnen en ik ben blij dat ik zulke mooie mensen om me heen heb! Lieve papa en mama, voor jullie is het denk ik niet altijd makkelijk geweest om me te zien stressen over zaken waar jullie me niet mee konden helpen. Maar de sterke basis en de positieve instelling (het komt altijd weer goed, op welke manier dan ook) die jullie me hebben meegegeven, helpen me in alles wat ik doe. Mama, vroeger bij de triatlon wedstrijden stond je altijd als meest trouwe supporter aan de kant, vaak met appeltaart. Hoe de wedstrijd ook ging, dat maakte voor jou niet uit! Nu sporten we gezellig samen en sta je nog steeds altijd voor mij en ons klaar, vaak met appeltaart… (-; Bedankt voor het vertrouwen en de emmers liefde die je geeft. Papa, van jou heb ik mijn perfectionistische aard en gedisciplineerdheid geërfd, wat soms een last is, maar ook zorgt dat we geen uitdagingen uit de weg gaan en dat heeft me wel gebracht waar ik nu ben. Van

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Lieve Frits, Liv, Wende en Tjes: wat een genot om na een dag hard werken thuis te komen bij mijn eigen lieverds. Om dan tijdens de (uiteraard gezonde, zelf gekookte) maaltijd weer met beide voeten op de grond gezet te worden door opmerkingen als: 'dat lust ik niet hoor, dat ziet er echt te vies uit om te eten!' Jullie zorgden er voor dat ik altijd wist waar mijn prioriteit lag. Woensdagmiddag en het weekend is voor ons gezin en dan wordt er niet gewerkt! Een regel waar ik me toch (bijna) altijd aan heb kunnen houden… Lieve Frits, bedankt voor je liefde en geduld, en gelukkig was er badminton… Als ik een voedingsmetafoor (wees gerust, bijna de laatste) zou moeten toepassen op jullie dan is dat: chocola, meer heb je niet nodig! Ik hoop dat we elkaar nog heel veel jaren gelukkig mogen maken, ik houd van jullie!

En nu is het klaar. Klaar om op te dienen. Aangezien menigeen direct doorbladert naar het dankwoord zou ik eenieder toch willen aansporen om hier en daar iets te proeven. Eet smakelijk!

Kirsten, 2017