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/m² 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.

Keywords:

Obesity; Type 2 Diabetes Mellitus; Diet; Weight loss; Soluble LR11; Cardiovascular disease risk factors

Abbreviations

ApoB: Apolipoprotein B

BAT: brown adipose tissue

BMI: Body Mass Index

CVD: cardiovascular disease

HbA1c: glycated hemoglobin

HDL: high density lipoprotein

GLP-1: Glucagon-like peptide-1

GLUT4: glucose transporter 4

LDL: low density lipoprotein

sLR11: soluble low density lipoprotein receptor-relative with 11 ligand-binding repeats

T2D: diabetes mellitus type 2

TGRL: triglyceride-rich lipoproteins

WAT: white adipose tissue

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^{o}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 μl 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).

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).

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

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

316 sLR11 has recently been identified as a negative regulator of brown adipose
317 tissue (BAT) activity (17). It is tempting to speculate that BAT activity increased, possibly
318 contributing to weight loss and improved metabolic profile, as a result of the decreased
319 sLR11 levels in our study population. The association of sLR11 levels with the glycemic
320 state of the participants, as reflected by HbA1c, has been reported previously for the
321 diabetic as well as the non-diabetic population (21, 23, 24). In mouse models, the
322 increased thermogenic activity in brown and white adipose tissue that is associated with
323 decreased sLR11 levels, has been shown to improve insulin sensitivity and the glycemic
324 state (17). Interestingly, in a recent study mice lacking LR11 expression showed
325 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.

Conflict of interest

The authors have no conflicts of interest to declare.

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Author contributions

K.B. participated in the design of the study, recruited all participants, collected data, analyzed data and wrote the manuscript. R.V. participated in the design of the study, contributed to the data analysis, contributed to the writing and edited the manuscript. M.J. and H.B. performed the plasma sLR11 measurement and reviewed/ edited the manuscript, W.S participated in the design of the study and reviewed/edited the manuscript. R.T. conducted the data analysis and contributed to the design of the study and the writing of the manuscript. A.V. participated in the design of the study,

reviewed/edited the manuscript, and contributed significantly to the discussion. E.S. and M.M. supervised the analyses, reviewed and edited the manuscript, and contributed significantly to the discussion. All authors approved the final version of the manuscript. The guarantor's of the manuscript are M.M. and E.S.

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Figures and tables

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.

497 **Table 1**

498 **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)*

Table 2

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

	B	95%CI	R^2	*p*
Univariate				
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
∆Weight	0.04	-0.01-0.09	0.05	0.076
∆Waist circumference	0.03	-0.02-0.09	0.02	0.243
∆HDL cholesterol	0.32	-1.03-1.66	0.00	0.639
∆non-HDL cholesterol	0.59	0.25-0.93	0.17	0.001
∆Triglyceride	0.01	-0.14-0.15	0.00	0.917
∆CRP	-0.02	-0.04-0.01	0.02	0.245
∆HbA1c	0.03	0.01-0.05	0.11	0.007
∆Fasting 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.

	B	95%CI	Partial R^2	*p*
Multivariate				
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	