Body Transformation in Life after Tumor: Long-term Consequences for Endocrinology, Metabolism and Bone

With a special focus on craniopharyngioma

S.S. van Santen

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Body Transformation in Life after Tumor: Long-term Consequences for Endocrinology, Metabolism and Bone

With a special focus on craniopharyngioma

Lichaamstransformatie in het leven na een tumor: langetermijnconsequenties voor endocrinologie, metabolisme en botgezondheid

met bijzondere aandacht voor het craniopharyngioom

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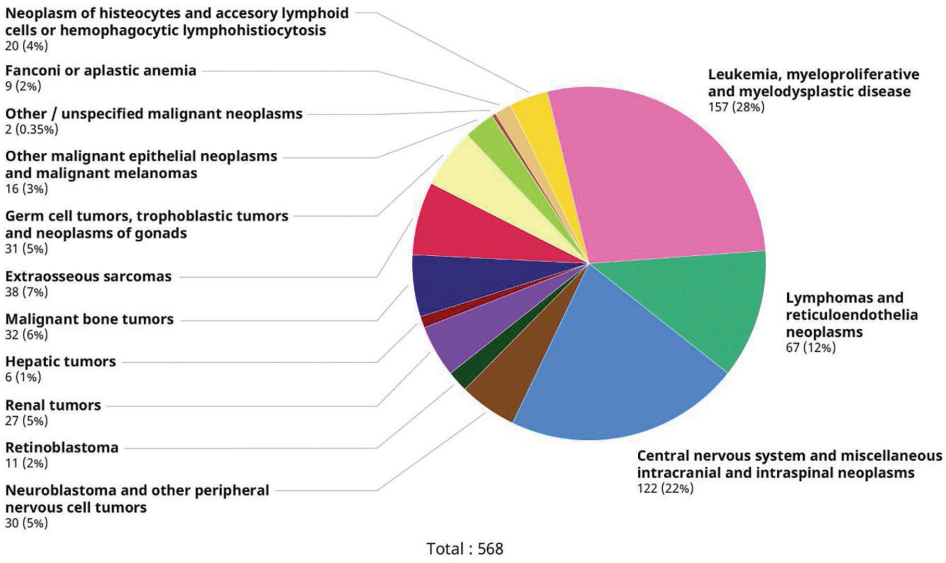
General Introduction

Cancer: an extensive health problem

Two out of five individuals develop cancer in their lives.[1] In the Netherlands, it is the leading cause of death in men and shares the first place with cardiovascular disease in women.[2] One out of three men and one out of four women die due to this devastating disease.[2] This impressive number underlines that cancer is a major burden and concern in modern society. The incidence of cancer has grown over the years: in 2016, 17.2 million cases of cancer were diagnosed worldwide, and 8.9 million people died of it.[3] It costed 213.2 million disability adjusted life years (DALYs) in only one year.[3] Although the average yearly incidence rates for cancer increased between 2006 and 2016 in most countries, the death rates relatively decreased.[3]

Cancer is not solely a disease of adults or elderly, but can occur in children as well. Cancer in children differs from cancer in adults in cancer type, causes of late death and survival rates. Although childhood cancer represents only a small part of all cancers (~1%),[4] it is still a very important cause of death in their age category, only exceeded by congenital anomalies and accidents.[5] Globally, estimates for the yearly incidence of cancer in the age group 0-14 years range from 163,284 to 184,856 individuals.[4] In the Netherlands, around 600 children are newly diagnosed with cancer yearly.[6] Childhood cancer is a very heterogeneous disease.[7] Common childhood cancer types are leukemias, lymphomas, and immature tumors, i.e. blastomas as well as soft tissue sarcomas, epithelial or germ cell tumors (Figure 1), whereas adults with cancer suffer mostly from more differentiated forms, such as carcinomas and chronic leukemias (Figure 2).[4,6,8] Current cancer treatment often combines multiple treatment modalities such as surgery, chemotherapy, stem cell transplantation, radiotherapy, and novel strategies such as immunotherapy.[9] Not all tumors (or 'neoplasms') are necessarily malignant or considered to be cancer, but benign tumors can cause problems as well.

Figure 1 Types of childhood cancer



Mean yearly incidence of different types of childhood cancer in the Netherlands according to the SKION basal registration.[6]

Survival after tumors

While the number of deaths due to a neoplasm has increased over time in adults, it decreased in children (Figure 3).[5] The 5-year survival rate in adults with cancer is approximately 54%,[10] while children have a much better prognosis with 80% survival.[1] Survival rates in children improved due to better care and the treatment modalities mentioned above.[7,9,11] This has led to a large group of between 300,000 and 500,000 living childhood cancer survivors in Europe alone.[11,12] However, childhood cancer survivors remain at increased risk of death their entire life, especially after intensive treatment.[13,14] Their late overall cumulative mortality is 13-30% at 30-40 years from diagnosis.[15-20] The main cause of late death after childhood cancer is recurrence of the original cancer, especially during the first 15 years post-diagnosis; other frequent causes are subsequent neoplasms, cardiac and pulmonary death.[16-18,20-27] Survivors of brain tumors seem even more at risk of premature death: the cumulative mortality of pediatric medulloblastoma survivors was 23% after only 15 years.[28,29] Benign neoplasms can be associated with

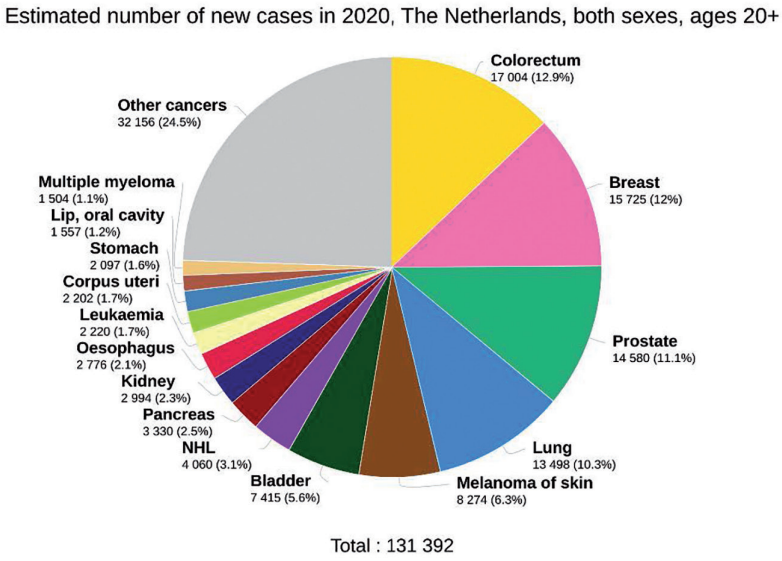
decreased survival rates as well. For instance, after craniopharyngioma, a benign brain tumor after which only 66-85% of the patients survive after 20 years.[30-32] Another example of benign brain tumors are pituitary adenomas, of which the 10-year survival rate is estimated at 69% in men and 76% in women.[33]

Chronic diseases

Next to survival, quality of life is an important consideration. In the whole world, one in three adults has multiple chronic conditions.[34] In high-income countries, the most important conditions leading to decrease in DALYs are non-communicable diseases, including ischemic heart disease, stroke, diabetes, lung cancer, and pain in the neck and back.[34,35] Chronic diseases form a serious challenge, as they are a burden on the individual as well the economy.[36] This underlines the importance of preventing of these diseases if possible, especially in high risk groups. Also, approximately 313 million of surgeries are performed worldwide each year, which can be accompanied with complications leading to death after surgery in 8% of the cases.[37-39] Postoperative complications are globally the third largest contributor to mortality.[39] Postoperative complications after major surgery in general is associated with lower survival.[40]

A group at high risk for chronic diseases are childhood cancer survivors; nearly all (95-99%) suffer from a chronic health condition at the age of 50.[41,42] The surgery, chemotherapeutics and radiotherapy that survivors owe their life to, have long-term consequences.[18,42-45] Any organ system may be impaired in childhood cancer survivors,[42,46] but endocrine conditions are one of the most common adverse health outcomes, and occur in 62% of survivors.[42] Not only childhood cancer survivors are affected by endocrine conditions; they are highly prevalent in patients with benign brain tumors, patients with a primary auto-immune deficiency, those with obesity and in women (with menopause being an endocrine condition that naturally occurs with advancing age).[47-53] Endocrine conditions can cause metabolic alterations.[54] This contributes to an increased risk of cardiovascular disease[9,55-62] and stroke[63-65] (Table 1).[42,46,49]

Figure 2 Types of adulthood cancer[8]

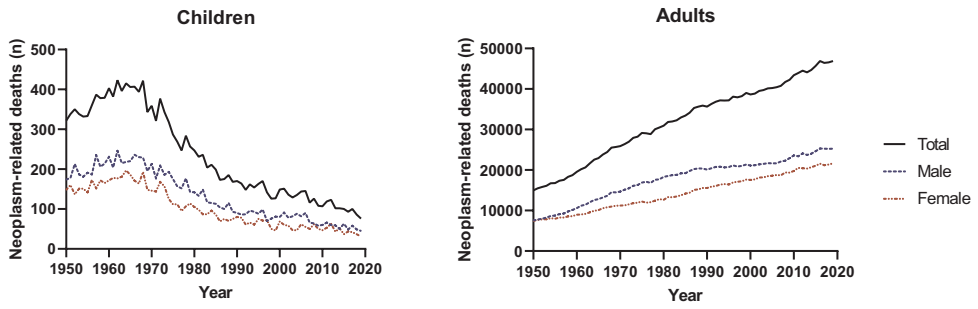


Endocrinology

Endocrinology is very important for homeostasis (or stable equilibrium in physiological processes) in the body. It is the study of hormones, which were classically defined as a chemical messenger that spreads from cell to cell along the bloodstream.[66] The first structures of hormones were discovered in 1849.[66] The masters of the endocrine system are the hypothalamus and pituitary gland. Figure 4 gives an illustration of a healthy pituitary gland, as imaged by magnetic resonance imaging (MRI), while Figure 5 illustrates the general anatomy. In general, the hypothalamus produces hormones that stimulate the pituitary, and the pituitary stimulates other endocrine glands such as the thyroid, reproductive organs, breasts, liver, kidney and adrenals, to produce hormones as well.[67] These hormones in turn provide negative feedback towards pituitary and hypothalamus.[67] Endocrine glands regulate a variety of functions like growth, bone health, metabolism and blood glucose control, and sexual and reproductive functions.[68-70] These glands make necessary changes to the internal environment in response to the external environment.[68-70] It is a system that continuously aims to maintain the balance. As the final hormone cleverly provides its

own negative feedback, the stimulus for producing this final hormone diminishes. Thereafter the negative feedback diminishes as well, leading to an increase of this hormone back again: a balance is established.

Figure 3 Neoplasm-related deaths in children and adults in the Netherlands (1950-2019)



Source: CBS.[5] Yearly cumulative neoplasm related deaths in children (0-20 years) and adults (20 years or older) in the Netherlands.

An example of a hormone system for which careful balancing is needed, is the regulation of the blood glucose. The pancreas produces the blood glucose-lowering hormone insulin, and the hormone glucagon, which in turn increases blood glucose levels. The most important endocrine organ for blood glucose regulation is the pancreas, which produces two key hormones: insulin (through the beta-cells in the pancreatic islets) and glucagon (through the alpha-cells).[71,72] Insulin decreases blood glucose levels after food intake, while glucagon increases glucose in the circulation by increasing take up of glucose stored in the form of glycogen in the liver (glycogenolysis), new-formed glucose from other components (gluconeogenesis) by the liver and possibly release of glycerol and fatty acids from triacylglycerol of white adipose tissue (lipolysis).[71,73,74]

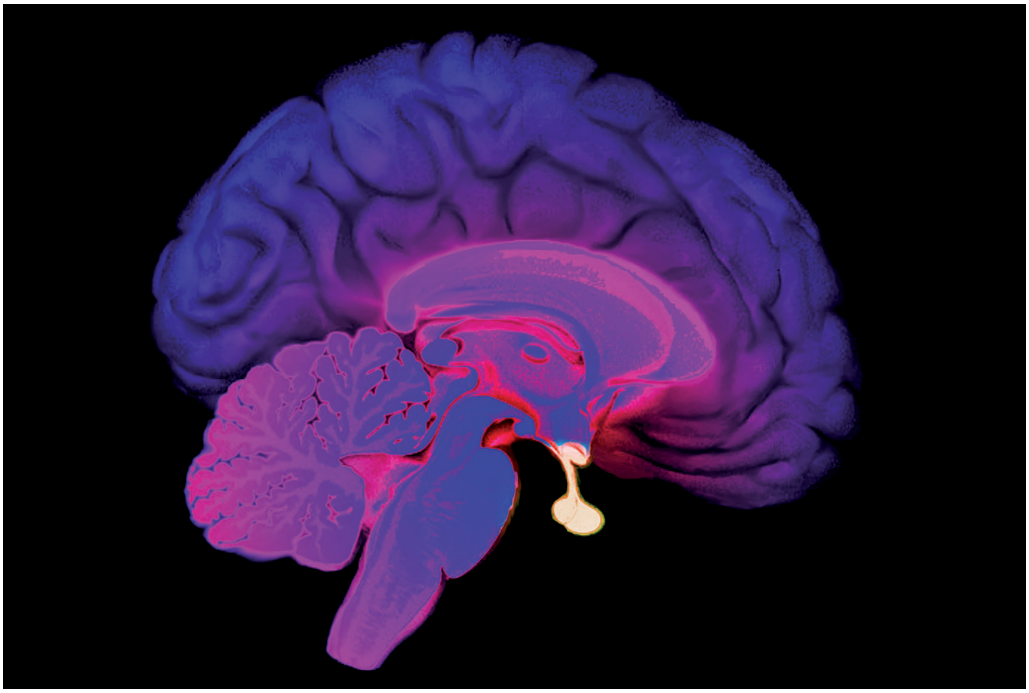
Table 1 Endocrine and metabolic late effects after childhood cancer[258,284-286]

Organ system	Potential complication	Risk factor
Hypothalamic-pituitary axis	Pituitary deficiencies	Total body irradiation Neurosurgery Cranial radiotherapy
	· Growth hormone	Immune checkpoint inhibitors
	· Follicle-stimulating hormone and luteinizing hormone	Immune checkpoint inhibitors
	· Adrenocorticoid stimulating hormone	Immune checkpoint inhibitors
	· Thyroid stimulating hormone	Immune checkpoint inhibitors
	· ADH	
	Delayed puberty	Pelvic radiotherapy, glucocorticoids
	Excess pituitary hormones Precocious puberty Hyperprolactinemia	Cranial radiotherapy
Hypothalamus	Hypothalamic obesity	Tumor in its surroundings Neurosurgery Cranial radiotherapy
	Underweight (diencephalic syndrome)	Damage to AgRP-expressing neurons
	Alterations in body temperature	Tumor in its surroundings Neurosurgery Cranial radiotherapy
Thyroid	Primary hyperthyroidism	Radiotherapy on the head, neck, cervical spine, whole spine or total body Iodine-131-metaiodobenzyl-guanidine (I-131-MIBG) Tyrosine kinase inhibitors Immune checkpoint inhibitors
	Primary hypothyroidism	Radiotherapy on the head, neck, cervical spine or whole spine Tyrosine kinase inhibitors Immune checkpoint inhibitors
	Benign and malignant thyroid nodules	I-131-MIBG

	Auto-immune thyroiditis	Hematopoietic stem cell transplantation Immune checkpoint inhibitors Interferon
Adrenals	Adrenal insufficiency	Direct insult due to tumor expansion or surgery Glucocorticoids (transient)
Gonads	♀ Gonadal dysfunction (premature ovarian insufficiency)	Alkylating agents Heavy metals Radiotherapy on the abdomen, pelvis, sacral or whole spine, or total body I-131-MIBG Bevacizumab
	♂ Leydig and germ cell dysfunction	Alkylating agents Radiotherapy to the pelvis or total body
Bone	Impaired final height/short stature	Growth hormone deficiency Glucocorticoids Radiotherapy on the spine, chest, abdomen or total body Retinoic acid Hedgehog pathway inhibitors
	Low bone mineral density/ Osteoporosis	Glucocorticoids Methotrexate
Metabolism	Obesity	Hypothalamic damage Hypopituitarism Cranial radiotherapy and total body irradiation Glucocorticoids Surgery
	Diabetes mellitus	Radiotherapy on the abdomen or total body Alkylating agents
	The metabolic syndrome	Radiotherapy to the head, abdomen and total body

Alkylating agents is a drug category containing busulfan, carmustine, chlorambucil, cyclophosphamide, dacarbazine, ifosfamide, lomustine, mechlorethamine, melphalan, procarbazine, temozolomide, thiotepa. Examples of applied heavy metals are carboplatin and cisplatin. Examples of tyrosine kinase inhibitors are imatinib, sorafenib and sunitinib. An immune checkpointinhibitor-anti-CTLA4 monoclonal antibody is ipilimumab.[30,231,285-293]

Figure 4 The Pituitary



3D MRI, midsagittal section, showing a normal brain, highlighting the pituitary gland and the pituitary stalk (yellow). By: medicalimages.com.

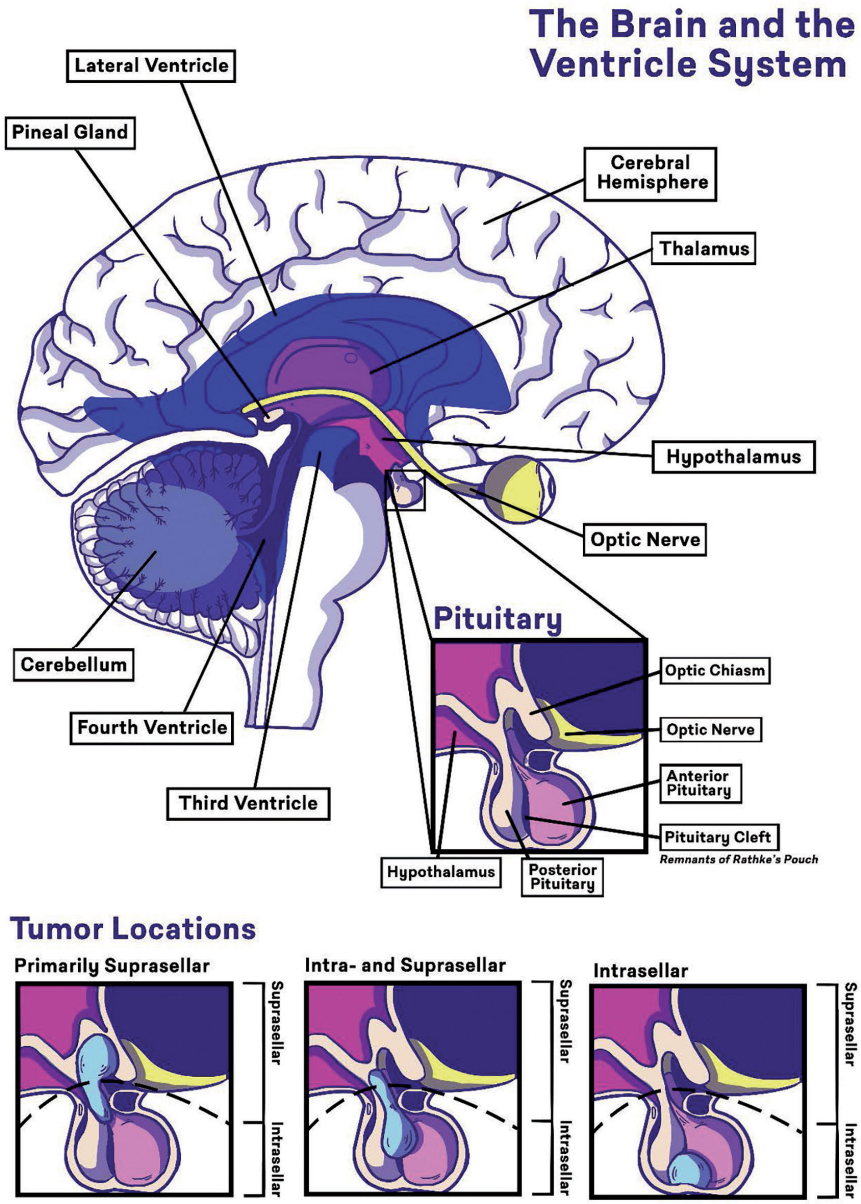
White adipose tissue is most known for its ability of energy storage, but is potentially the largest endocrine organ in humans as well.[75,76] White adipose produces the hormones leptin and adiponectin.[76] Leptin inhibits food intake by sending anorexigenic signals to the brain.[76] Adiponectin is important for insulin sensitivity and lipid metabolism, and has anti-atherogenic properties.[77] In case of excessive nutrition, fat accumulates excessively. This is called obesity; a disease in which adipose tissue dysfunctions and health may be impaired.[75] Obesity occurs quite regularly in the general population: in 2019, 13% of all Dutch citizens were obese.[78] People with a history of childhood cancer are at even higher risk of obesity; it is 3.8 times higher in survivors than in the general population.[60] Obesity is associated with diseases such as type 2 diabetes mellitus, non-alcoholic fatty liver disease, cancer and cerebro- and cardiovascular disease.[75,79,80] Endocrine alterations occur

frequently in case of obesity.[81,82] Obese subjects have high leptin levels while the exerted anorexigenic effect is lowered (leptin resistance).[76] On the other hand, adiponectin levels are decreased and therefore the impact on anti-atherogenicity and insulin sensitivity is lowered as well.[77] The combined presence of too much accumulated fat (adiposity), decreased insulin sensitivity (insulin resistance), abnormal serum lipid levels (dyslipidemia) and high blood pressure (hypertension) is called the metabolic syndrome.[79,83-99] The metabolic syndrome quintuples type 2 diabetes risk, and doubles the risk of cardio- and cerebrovascular disease.[79,83-99]

The embryonic development of the hypothalamus and pituitary

As mentioned, the hypothalamus and pituitary are the master glands of the endocrine system. The pituitary consists of an anterior and a posterior part, the adenohypophysis and neurohypophysis.[100] The anterior and posterior lobe have distinct functions and are derived from different tissues in embryonal development (Figure 6).[100,101] During embryogenesis, the neurohypophysis and endocrine hypothalamus are derived from neural ectoderm, while the adenohypophysis is derived from an invagination of oral ectoderm, called Rathke's pouch.[100,102,103] The neurohypophysis stores and secretes antidiuretic hormone and oxytocin, hormones which are produced in the hypothalamus.[100] The adenohypophysis, or anterior pituitary, has lactotropic, somatotropic, gonadotropic, corticotropic and thyrotropic cells which produce the hormones prolactin, growth hormone, luteinizing hormone (LH) and follicle stimulating hormone (FSH), adrenocorticotropic hormone (ACTH) and thyroid stimulating hormone (TSH), respectively.[100]

Figure 5 Normal anatomy of the brain, ventricle system and pituitary, and possible locations for pituitary tumors

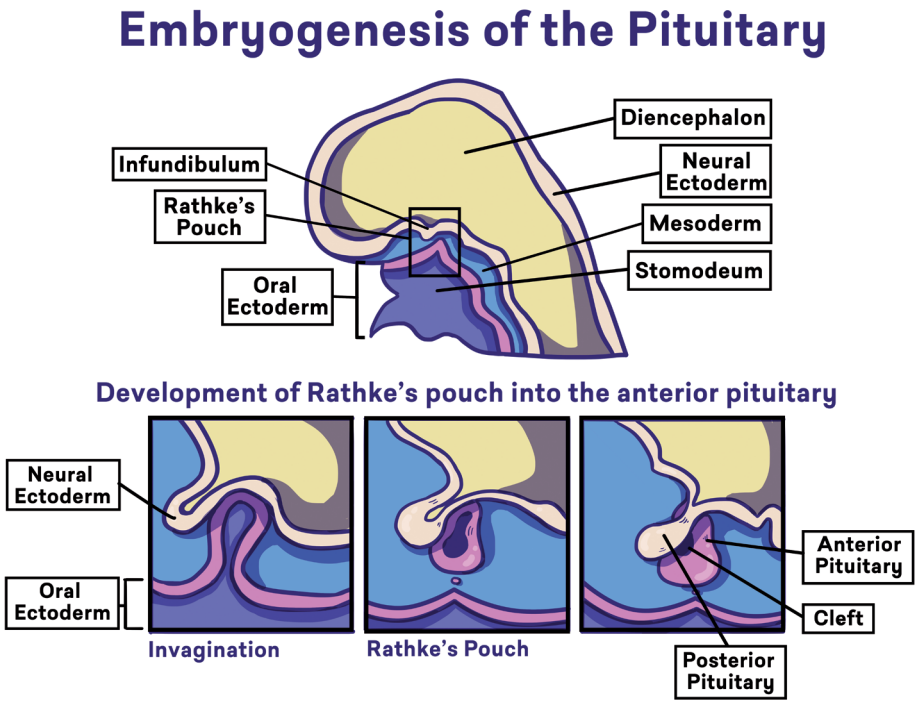


By: Ana G.G. de Lima.

Functions of the posterior pituitary

Antidiuretic hormone, or AVP is released after a stimulus by increasing osmolality and inhibits diuresis. This is established by stimulation of thirst, and acting on G-coupled V2 receptors in the kidneys leading to increased water reabsorption.[104] When oxytocin is released from the posterior pituitary, it stimulates the epididymal and uterine muscle contraction, and stimulates the nipples for breastfeeding.[105,106] Furthermore, oxytocin is important for social functioning, as it enhances sociality and influences behavior regarding sexual contact and aggressive attacks.[105,107]

Figure 6 Embryogenesis of the pituitary gland



The anterior pituitary is developed from neural ectoderm, and the posterior pituitary from oral ectoderm. By: Ana G.G. de Lima.

Functions of the anterior pituitary

The hypothalamo-prolactin axis

The hypothalamo-prolactin axis is predominantly inhibitory, as opposed to the other axis.[108] Dopaminergic neurons in the hypothalamus inhibit the lactotropic cells from producing prolactin, a hormone named after its main function, which is promoting lactation.[108] Prolactin increases dopamine secretion and therefore provides its own negative feedback.[108] During lactation, a physiological state of hyperprolactinemia occurs due to a loss of sensitivity of this feedback system, and suckling causes a further release of prolactin.[108,109] Prolactin has several other functions next to lactation in the maternal adaptation to pregnancy, which relate to maternal behavior, bone metabolism, lipid metabolism, neurogenesis, glucose homeostasis, appetite regulation, reproduction, stress responses and oxytocin secretion.[108,110-115]

Hypothalamo-pituitary-somatotropic axis

Growth hormone is mostly known for the properties of enhancing linear growth but is also essential for its metabolic properties and for increasing bone mass.[69,116,117] Growth hormone-releasing hormone (GHRH) from the hypothalamus stimulates the anterior pituitary to release growth hormone.[69,118,119] This in turn stimulates production of insulin-like growth factors (IGFs).[69,118,119] Negative feedback is provided from somatostatin produced in the hypothalamus, ghrelin (the 'hunger hormone') produced in the stomach, estrogens and androgens from the gonadal organs, and from growth hormone and IGF themselves.[69,118,119] Growth hormone is released in a pulsatile manner; factors that stimulate release are hypoglycemia and stress, while hyperglycemia suppresses its release.[69] The liver is stimulated to produce insulin-like growth factor 1 (IGF-1), but the relationship between levels of growth hormone and IGF-1 are not linear: many other factors influence IGF-1 concentrations, such as age, puberty status and BMI.[69,120] When aging, growth hormone and IGF-1 levels decline until the levels are very low at the age of 60 years and older.[121] IGF-1 and growth hormone have slightly different

metabolic abilities: growth hormone leads to elevated insulin and glucose levels and reduced insulin sensitivity, while IGF-1 reduces insulin and improves insulin sensitivity.[122] IGF-1 and growth hormone both enhance the energy expenditure and lower protein oxidation.[122] As the secretion of growth hormone is stimulated by exercise and inhibited by food intake, measuring a randomly taken growth hormone measurement is unreliable to evaluate either growth hormone deficiency or oversecretion.[69] Instead, growth hormone deficiencies are evaluated by tests which stimulate growth hormone production, such as the insulin tolerance test, GHRH or intravenous arginine infusion test.[69] When growth hormone is replaced after a deficiency, this causes an increase in lean body mass, potentially an increase in bone mineral density, and decrease in fat mass.[123-125] If excessive growth hormone secretion is expected (acromegaly), this can be evaluated with an oral glucose tolerance test.[126]

The hypothalamic-pituitary-gonadal axis

The hypothalamic-pituitary-gonadal axis has important reproductive functions and influences bone mineralization.[127] It relies on the gonadotrophs LH and FSH in the pituitary, which are stimulated by hypothalamic GnRH in a pulsatile way.

In females of reproductive age, LH stimulates production of the pre-hormone androstenedione by the theca cells in the ovaries.[104,128] FSH stimulates ovarian follicular growth in the first place.[104,128] Furthermore, FSH stimulates the granulosa cells to generate progesterone, and estrogen derived from androstenedione through conversion with aromatase enzymes.[104,128] Estrogen has important functions. It is involved in multiple organ systems including reproduction and bone maturation, and it protects against bone mass loss and cardiovascular disease.[129-131] Estrogen levels may rise towards excessive levels in case of obesity, as androstenedione levels are increased 3 to 4-fold.[132] Consequently, the target organs such as breasts and ovaries are stimulated, which unfortunately gives a risk of developing neoplasias.[132] After the reproductive age, around the ages of 46-52 years, the

menopause occurs.[133,134] The natural course of life in women leads to this final menstrual period, which is a form of low gonadal hormones (hypogonadism) combined with high FSH levels.[135] The final menstrual period is defined as 12 months of amenorrhea and FSH levels being two standard deviations higher than the mean level of women of peak reproductive age.[134-136] The progressive decline of estrogen levels is accompanied with a decline in bone mass and increase in percentual fat mass, especially at the abdominal/visceral region.[134,137]

In males, LH stimulates release of testosterone by the Leydig cells in the testes, while FSH stimulates production of (androgen-binding) protein and initiation of spermatogenesis by the Sertoli cells in the testes.[104,138,139] In case of obesity, testosterone production does not change, but sex-hormone binding proteins are decreased, which leads to increased clearance rates and low levels of circulating testosterone.[132] Testosterone levels correlate with higher lean (muscle) mass and lower fat mass in men.[140]

The hypothalamic-pituitary-adrenal axis

The hypothalamic-pituitary-adrenal (HPA-) axis is important for stress-responses.[141] Corticostropin-releasing hormone (CRH) is synthesized in the hypothalamus and stimulates the anterior pituitary to produce ACTH in a pulsatile manner.[104,142,143] ACTH thereafter stimulates the zona fasciculata in the cortex of the adrenals to release the glucocorticoid cortisol, the 'stress hormone'.[104,142,143] Cortisol signals negative feedback towards the hypothalamus and pituitary.[142] Activation of the HPA-axis leads to decreased activity of the growth hormone and gonadal axis.[144-146]

Cortisol can affect almost all organ systems, such as the cardiovascular, immune and respiratory system, and induce an inflammatory and/or stress response.[147,148] In case of a continuous threat of internal or external stressors to the body, at first the sympathetic nervous system is activated, inducing the 'flight or flight' response with release of catecholamines (i.e. epinephrine) by the adrenals.[149]

If the stressor remains, the HPA-axis is activated, and cortisol induces catabolic mechanisms.[150,151] This especially aims to maintain energy substrates in the circulation at high enough levels to provide the body with energy in these flight-or-flight conditions, especially the brain.[151,152] These energy substrates can be fatty acids, amino acids and glucose.[152] Cortisol stimulates the liver's gluconeogenesis and glycogenolysis, and inhibits glycogen synthesis, inducing higher glucose levels.[151,153,154] Cortisol causes the muscles to decrease their glucose uptake due to insulin resistance, which further increases circulating glucose levels.[152,154,155] Furthermore, the muscles are stimulated by cortisol to liberate amino acids by increased breakdown of proteins (proteolysis). In fat tissue, lipolysis is enhanced, freeing fatty acids.[152,154] Cortisol increases the activity catecholamines and increases leptin concentrations.[152,154,156]

Cortisol release is characterized by a circadian rhythm, as the amplitude of ACTH and cortisol release is altered during the day: it is at the highest peak at 8 AM and low between 8 PM and 2 AM.[104,143,157] Physical or physiological stress may increase ACTH and cortisol production, while exogenous glucocorticoids decrease CRH release and therefore impair ACTH and cortisol release as well, as a negative feedback.[104,158] Low cortisol levels (hypocortisolism) can be caused by primary adrenal insufficiency, such as Addison's disease (due to an autoimmune response),[159] or secondary adrenal insufficiency, which is caused by low levels of ACTH.[154] Hypocortisolism can be life threatening and present with hypotension and shock.[154,159] Hypocortisolism can be tested with early morning cortisol, (low dose) ACTH test, insulin tolerance test or metapyrone test.[159,160] High cortisol levels (hypercortisolism or Cushing syndrome) can occur due to a tumor on the adrenal gland or in the pituitary.[152,161] Endogenous hypercortisolism can be diagnosed by determining late night salivary cortisol or urine free cortisol, and by the low-dose dexamethasone suppression test.[150,161] Chronic hypercortisolism causes an increased amount of visceral or abdominal adipose tissue and reduced bone mineral density.[152,156]

The hypothalamus-pituitary-thyroid axis

Thyroid hormones are highly important for metabolic pathways, and cause a general increase in basal energy expenditure.[162] Furthermore, thyroid hormones are important in brain and skeletal development in children, and bone maintenance in adults.[163,164] The hypothalamus-pituitary-thyroid axis starts with the release of thyrotropin-releasing hormone (TRH) in the hypothalamus, stimulating the pituitary to produce thyrotropin (TSH).[165] Further on the axis, TSH stimulates the thyroid to produce thyroxine (T4) and triiodothyronine (T3). T3 is a biologically active thyroid hormone, and the thyroid receptor's main ligand due a 10-fold higher affinity with T3 than T4.[166] T3 is predominantly produced in peripheral tissues, especially the liver and kidney, after conversion from T4; only <20% is produced by the thyroid itself.[166-168] T3 and T4 give a negative feedback impulse to the pituitary and hypothalamus.[165] Low thyroid hormone levels (hypothyroidism) are associated with gain in body weight, constipation, bradycardia, decreased gluconeogenesis, increased concentrations of atherogenic lipoproteins, hyperlipidemia and decreased bone turnover.[162-164,169] High levels (hyperthyroidism) on the other hand are associated with weight loss, reduced cholesterol levels, increased lipolysis, gluconeogenesis, diarrhea, muscle weakness and accelerated bone loss or fracture risk.[163,164,169]

The thyroid axis is clearly influenced by other pituitary axes. Start of growth hormone replacement therapy may unmask a disguised central hypothyroidism, as growth hormone gives an increase in serum free T3 and a decrease in T4, suggesting the rising IGF-1 levels stimulate the conversion from T4 to T3.[167] Dopamine (agonists) and glucocorticoids inhibit TSH secretion.[167] Gonadal hormones have a minor influence on the axis; estradiol treatment increases the number of TRH receptors, and testosterone analog fluoxymesterone shows a decreased response of the pituitary on THR in hypogonadal men.[167,170-172]

Endocrine alterations due to tumors – too high, too low

The pituitary axis may be altered by many factors, and tumors and related treatment is one of them. An increased hormone production can be directly caused by tumors in endocrine organs or ectopic tumors.[173]

Decreased pituitary hormones (hypopituitarism) are most often caused by tumors in the hypothalamo-pituitary region (in ~65% of the cases).[174] Radiotherapy for treatment of cancer is also an important risk factor for endocrine conditions.[42] When endocrine organs such as the hypothalamus, pituitary, thyroid and reproductive organs lie in the irradiation area, this may lead to a lowered hormone production.[46,175] Approximately 40% of patients irradiated for brain tumors which were not near the hypothalamus or pituitary, develop hypopituitarism as well.[174,176,177] Surgical removal of endocrine tissue can cause endocrine deficiencies too,[178] particularly after pituitary surgery.[179] Endocrine conditions are an important cause for need of hospitalization in childhood cancer survivors.[180]

Pituitary tumors

Tumors do not necessarily have to be malignant to cause major health problems in the short as well as the long term. A benign tumor at an unfortunate location can have serious adverse outcomes. Tumors in the pituitary region may lead to increased or decreased secretion of hormones, or oppress other structures in the brain and impair their function. The most common pituitary (and even intracranial) tumors are pituitary adenomas, which have a prevalence of 1 in 1000 persons.[181] The pituitary adenoma is indeed a benign tumor derived from proliferation of anterior pituitary cells, which can cause a hypersecretion of the hormones produced by the specific differentiated cell types (functioning pituitary adenoma) or have a mass effect.[182,183] Of the hormone-secreting adenomas, the lactotroph adenoma (prolactinoma) is most

common (25-41%), with thereafter the somatotroph adenoma (10-15%) and corticotroph adenoma (~10%), while thyrotroph adenomas and gonadotroph adenomas are more rare (<1%).[184] The treatment is dependent on the pattern of hormone secretion. Prolactinomas are primarily treated pharmaceutically with dopamine agonists.[185] Other pituitary adenomas are intervened with by surgical removal, and if necessary additional pharmaceutical treatment with somatostatin analogues, dopamine agonists, growth hormone receptor antagonist pegvisomant in somatotroph adenomas (acromegaly), and sometimes radiotherapy.[184] Other entities which are enlisted in the differential diagnosis of neoplasms occurring in the pituitary region, are hemangioblastomas, eosinophilic granulomas, dermoid/epidermoid or arachnoid cysts, optic nerve gliomas, lipomas, meningiomas, teratomas, germinomas, chordomas or chondrosarcomas, hamartomas, Rathke's cleft cysts and craniopharyngiomas.[186] The Rathke's cleft cyst, which is a diverticulum in Rathke's pouch,[52,187,188] is characterized by lower rates of visual impairment, hypothalamic damage and endocrine deficiencies compared to craniopharyngioma.[30] The craniopharyngioma is more rare than the pituitary adenoma, and has an incidence of 0.5-2.5 new cases per million persons per year.[30,189,190] This tumor is more often associated with serious adverse outcomes.[30] Craniopharyngiomas induce the highest mortality among all pituitary tumors.[191]

Craniopharyngioma – epidemiology, presentation and diagnosis

Craniopharyngiomas are brain tumors with a low histological malignancy (WHO grade I), which still show aggressive clinical behavior.[30,192] Although they are considered benign, they are closely situated to important neurovascular structures, such as the hypothalamus, pituitary, carotid arteries and optic nerves.[30,193] The function of these structures can be impaired, as the tumor does not respect its boundaries, and treatment may cause additional damage.[30] Craniopharyngioma can occur at any age, but the distribution is bimodal, with peak incidences between the ages 5-15 and 45-60 years (Figure 7).[30,190,194] Between 30-50% of the cases are diagnosed

during childhood or adolescence.[30,194,195] Craniopharyngiomas account for 5-11% of intracranial tumors in children and are therefore the most common non-neuroepithelial intracerebral neoplasm in this age category.[30,196-198] Children most frequently present with endocrine deficiencies leading to growth retardation and polyuria due to a declined release of ADH (central diabetes insipidus); another important feature is visual impairment.[30] In adults, central diabetes insipidus and visual impairment can manifest as well; other common signs and symptoms are headaches and other signs of high intracranial pressure, hypothalamic dysfunction (i.e. dysregulation in body temperature and body weight) and endocrine deficiencies.[30,199-201] The tumor can consist of a solid part with calcifications and/or a cystic part.[202] The location of a craniopharyngioma is most often described as either intrasellar or suprasellar.[30] For this designation, the sella turcica is used as a reference. The sella turcica is a depression in the sphenoid bone which contains the pituitary gland.[30] Most craniopharyngiomas (75%) originate suprasellarly and extend to the intrasellar region, while 20% remains fully suprasellar, and only a small number (5%) remains entirely intrasellar.[203] Approximately half of the tumors originate from the third ventricle floor[30] with high risk of damaging the hypothalamus.[204] The preferred imaging modalities to support the diagnosis and prepare for neurosurgery are magnetic resonance imaging with and without gadolinium contrast enhancement, and computed tomography for evaluation of calcifications.[205]

Adamantinomatous and papillary craniopharyngioma

There are two distinct histopathological or morphologic subtypes: the adamantinomatous (ACP) and papillary craniopharyngioma (PCP) (Table 2 and Figure 8).[206] The papillary subtype represents only a small proportion of all craniopharyngiomas (~10%).[30,207] ACP and PCP differ in their pathogenesis, genetic make-up and age distribution.[30] Both craniopharyngioma types develop from remnants of the embryological development of the hypothalamus and pituitary and can therefore occur along the hypothalamic-pituitary axis.[30] ACPs

are derived from remnants of Rathke's pouch, the craniopharyngeal duct epithelium.[30,193,208,209] PCPs develop from metaplasia of squamous epithelial cells which are remnants of the part of the stomodeum that contributed to the buccal mucosa.[209] The bimodal age distribution for craniopharyngioma[30,190] relates to these subtypes. The adamantinomatous subtype can occur in children and adults, while the papillary subtype almost exclusively occurs in adults.[30,210] Regarding genetic makeup: ACPs carry somatic *CTNNB1* clonal mutations in in 75-96% of the cases, a gene in exon 3 which regulates beta-catenin stability.[211-216] Nuclear beta-catenin accumulation is an important characteristic in adamantinomatous craniopharyngioma, and is absent in PCP and Rathke's cleft cysts.[217] PCPs are very frequently (in ~95% associated with somatic *BRAF*^{V600E} clonal mutations.[214,216] However, *BRAF* and *CTNNB1* mutations can occur simultaneously, too.[218]

Treatment of craniopharyngioma

Craniopharyngiomas are mainly treated with neurosurgery, frequently followed by radiotherapy in case of residual tumor tissue.[219,220] The goal of craniopharyngioma treatment is to achieve tumor control with as little neurovascular damage as possible, in order not to aggravate symptoms and keep tumor- and treatment related comorbidities to a minimum (described in a summary of Figure 9).[221] The treatment of choice is dependent on tumor- and patient characteristics, and on the experience and expertise of the treating center.[220]

Surgical treatment may have urgent indications such as raised intracranial pressure or vision loss.[30] Neurosurgery can be performed in the form of gross total resection or as limited surgery, such as partial resection.[30] The surgical approach depends on precise tumor location and size; predominantly intrasellar tumors can often be operated transsphenoidally.[30] Transcranial resection is performed by either pterional, subfrontal, transcallosal or transcortical-transventricular route (Figure 10).[220] Higher morbidity rates are observed in those who are initially treated with cyst aspiration or who need pterional surgery, and furthermore when patients become ill at a young age, or have

symptoms of intracranial hypertension, compared with patients without these characteristics.[193,199]

Table 2 Comparison of adamantinomatous and papillary craniopharyngioma

	Adamantinomatous subtype	**Papillary subtype**
Origin	Embryogenetic theory: Embryonic ectodermal epithelial remnants of the craniopharyngeal duct or Rathke's pouch. The duct and pouch are derived from the stomodeum	Metaplastic theory: Metaplasia of adenohypophyseal cells in the pars tuberalis of the adenohypophysis (remnants of the part of the stomadeum that contributed to the buccal mucosa), which results in formation of squamous cell nests
Age group	Presentation in children and adults: bimodal incidence peaks at 5-15 and 45-60 years	Presentation in adults: incidence peak between 40 and 55 years
Genetic aberrations	Somatic *CTNNB1* mutations Mostly point mutations within exon 3	Somatic *BRAF*^{V600E}mutations
Mutation rate	Low: ~15 non-synonymous mutations per megabase	Low: ~15 non-synonymous mutations per megabase
Pathway	Increase beta-catenin stability by overactivation WNT pathway	Mitogen-activated protein kinase (MAPK) signaling pathway activation in the basal cells surrounding the fibrovascular cores, which are structures containing blood vessels and stroma surrounded by well-defined lining epithelium that supports tumor growth. They also express high main effectors of MAPK (phosphorylated extracellular signal-regulated kinase 1 and 2) and SOX2

Important symptoms	Visual impairment Hypopituitarism Headache	Headache Hypothalamic dysfunction Psychiatric changes
MRI descriptions	Cauliflower-like shape ~90% calcifications ~90% cysts with cholesterol-rich oily fluid ~90% enhancement	"Fibrovascular cores lined by non-keratizing squamour epithelium"[30]
Pathological features	"Distinctive epithelium that forms stellate regiculum, wet keratin and basal palisades"[30]	"Fibrovascular cores lined by non-keratinizing squamous epithelium"[30]
Immunohistochemical features	Sporadic cells with nucleocytoplasmatic accumulation of beta-catenin in single cells throughout the tumor or in cell clusters; most tumor cells have normal membranous beta-catenin expression. Beta-catenin accumulating cells often located at the base of finger-like protrusions of tumor epithelium that invade surrounding tissues	No beta-catenin accumulating cells
Inflammatory mediators	High concentrations of cytokines IL-1β, IL-6, IL-8, CXCL1, IL-10, IL-18, TNF in cystic fluid, and high expression of receptors and coreceptors on the tumor: compatible with inflammasome activation. High expression of immunosuppressive factors IL-10, indoleamine-pyrrole 2,3-dioxygenase, galectin-1, programmed death ligand 1 and its receptor: promote escape of immune surveillance	Not investigated except for expression of PD-L1 in basal cells
Potential novel targeted therapies	Being developed; relate to IL-6, PD1/PD-L1, MEK, IDO-1, but not yet applied	*BRAF* inhibitors (dabrafenib, bemurafenib) combined with MEK inhibiters (i.e., trametinib), applied scarcely

Adapted from Müller et al. 2019 and Müller et al. 2014.[30,101,197,209,294,295]

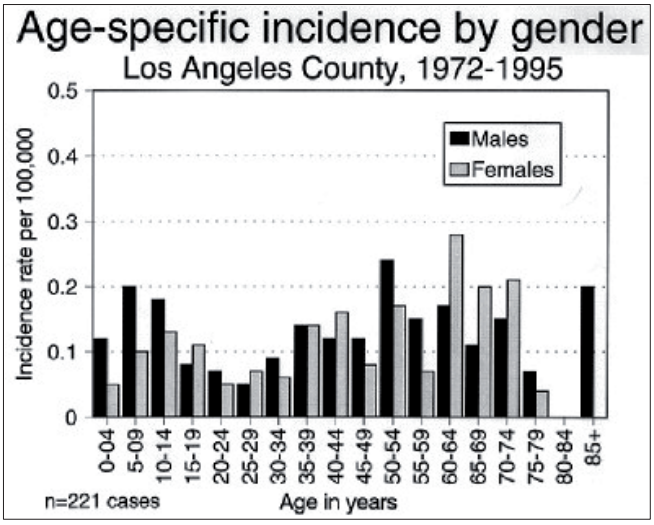
The choice for either gross total resection or subtotal resection remains a topic of discussion.[220] The severity of adherence to the hypothalamus and third ventricle (walls) must be evaluated preoperatively, to anticipate the surgical risk of hypothalamic injury and plan the degree of removal.[30,222,223] Craniopharyngiomas with hypothalamic adhesion generally have the worst outcomes.[30,222] The degree of tumor removal with the intent to achieve tumor control, is generally divided as either gross total resection or partial resection with often postoperative radiotherapy. The choice for limited surgery is made to alleviate or prevent symptoms and optimize dose delivery of postoperative radiotherapy.[30] Radiotherapy can be administered as stereotactic radiosurgery or intracystic application of ^{90}Yttrium, which emits beta energy.[219] Intracystic application of chemotherapeutics such as bleomycin or interferon-alpha are alternative treatment options.[219] If it is decided to apply postoperative radiotherapy, a total dose of 50-54 Gy in fractions of 1.8-2.0 Gy are normally applied.[224] Conventional radiotherapy sends X-ray in different directions towards the tumor to scatter unintended but unavoidable irradiation of non-target tissue, while proton beam therapy deposits a dose along a path that ends in the target.[30] Proton beam therapy therefore reduces the dose in non-target tissue significantly.[30]

Craniopharyngioma: survival, long-term sequelae and comorbidities

As the craniopharyngioma is considered benign, the oncological aggressiveness of the tumor is not the main factor in the prognosis of patients.[30] Moreover, the prognosis is dependent on the location of the tumor and involvement of neurovascular structures, and to treatment-related damage.[30] Overall survival rates are estimated at 54-96% after five years, and 66-85% after 20 years.[30-32] Long-term tumor control rates[30,225] and survival rates are similar between gross total resection and subtotal resection with radiotherapy (reported 5-year survival rates 82-100% versus 85-100% and 5-year recurrence-free survival rates 60-100 versus 72-82%, respectively).[32,226,227] If radiotherapy is not applied after subtotal resection, 5-year survival rates and especially

recurrence-free survival rates are generally lower (5-year overall survival 75-90%; recurrence-free survival 25-47%).[32,226,227] There are no known histopathological characteristics which predict survival in patients with childhood-onset disease.[228] In adulthood-onset patients, calcifications are related to higher recurrence rates and unfavorable outcome.[30,229]

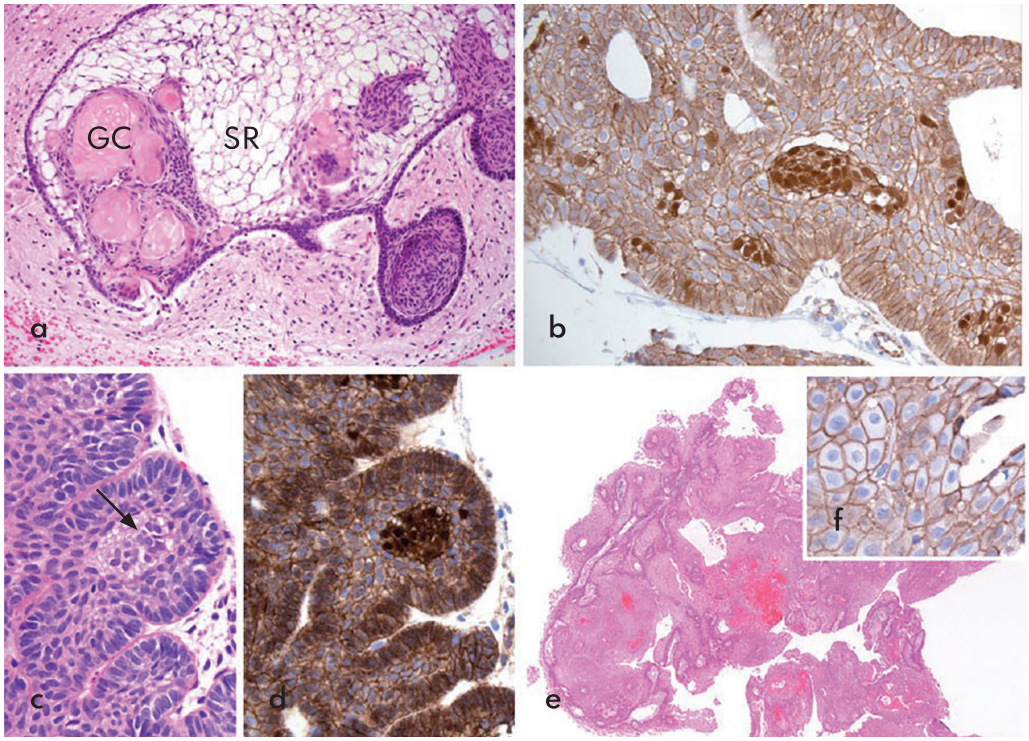
Figure 7 Epidemiology of craniopharyngioma



Graph showing the age-specific incidence of craniopharyngioma derived from the University of Southern California/Los Angeles county CSP data for the years 1972–1995. From: Bunin 1997 (with permission).[194]

Long-term health issues can be derived from either persistently presenting symptoms or occurrence after tumor treatment, and can impair quality of life.[30,201,230-235] The most frequent long-term health issues consist of pituitary hormone deficiencies, visual impairment and hypothalamic damage related obesity (Figure 11).[30]

Figure 8 Histopathology of craniopharyngioma



Adamantinomatous craniopharyngioma (a–d). a Classical appearance with peripheral palisading epithelium (arrow), loose 'stellate reticulum' (SR) and nodules of 'ghost cells' (GC). The tumor is invading brain. b Clusters and individual tumor cells show nuclear b-catenin translocation. Note that in most tumor cells b-catenin remains at the cell membrane. c, d Epithelial nodules (arrows) within the advancing front of the tumor commonly show nuclear b-catenin expression. A papillary craniopharyngioma is characterized by clefted (pseudo-) papillae lacking 'stellate reticulin' and 'ghost cells'. b-catenin remains at the cell membrane (f). See text for details. a, c, e haematoxylin and eosin, b, d, f b-catenin immunohistochemistry (brown reaction product). (a 9200, b, c, d 9400, e 9100, f 9600). From: Larkin et al. 2013 (with permission).[296]

Obesity in patients with craniopharyngioma

Hypothalamic obesity occurs in ~50% of the patients diagnosed with craniopharyngioma (Figure 11).[30,86,199,236,237] Visual impairment and hypothalamic damage are risk factors for the metabolic syndrome (components) in these patients.[86] The metabolic syndrome which occurred in 40% of Dutch craniopharyngioma patients versus 26% in controls.[86] This partially explains their increased risk to develop type 2 diabetes mellitus (standardized incidence ratio [SIR] 4.4) and cerebral infarction (SIR 4.9).[200]

Hypothalamic damage comes with a parasympathetic predominance, causing reduced heart rate and body temperature, and increased sleepiness during the day, resulting in a reduced energy expenditure.[238,239] This contributes the high risk of obesity and is associated with hyperinsulinemia, hypopituitarism, psychosocial disorders and hyperphagia as well.[231] There is currently very little evidence for the efficacy of pharmaceutics or lifestyle changes for the treatment of hypothalamic obesity.[231] In rare cases, hypothalamic damage can express itself at the opposite end of the spectrum, with the diencephalic syndrome (in ~4% of the patients from the German Childhood Craniopharyngioma Registry), which results in cachexia and severe weight loss.[30,240,241]

Body weight is mainly composed of fat mass, muscle mass and bone mass. The pituitary hormones influence body composition, particularly growth hormone.[60,242] As patients with craniopharyngioma have a high risk of pituitary deficiencies (~92%),[86] their body composition may be altered as well. Obesity is often evaluated using anthropomorphic measurements such as body mass index (BMI), which only accounts for total mass, and does not particularly check adiposity. Alternatively, body composition can be evaluated with the dual-energy X-ray absorptiometry (DXA)-scan; this is considered the gold standard for evaluating adiposity if the body composition is potentially altered.[243-245] In childhood cancer survivors, adiposity is underestimated using BMI if compared with DXA-scan derived body fat percentage.[243] In patients with craniopharyngioma, it has not yet been investigated whether obesity rates are correctly evaluated with BMI.

Figure 9 Summary of long-term sequelae of craniopharyngioma

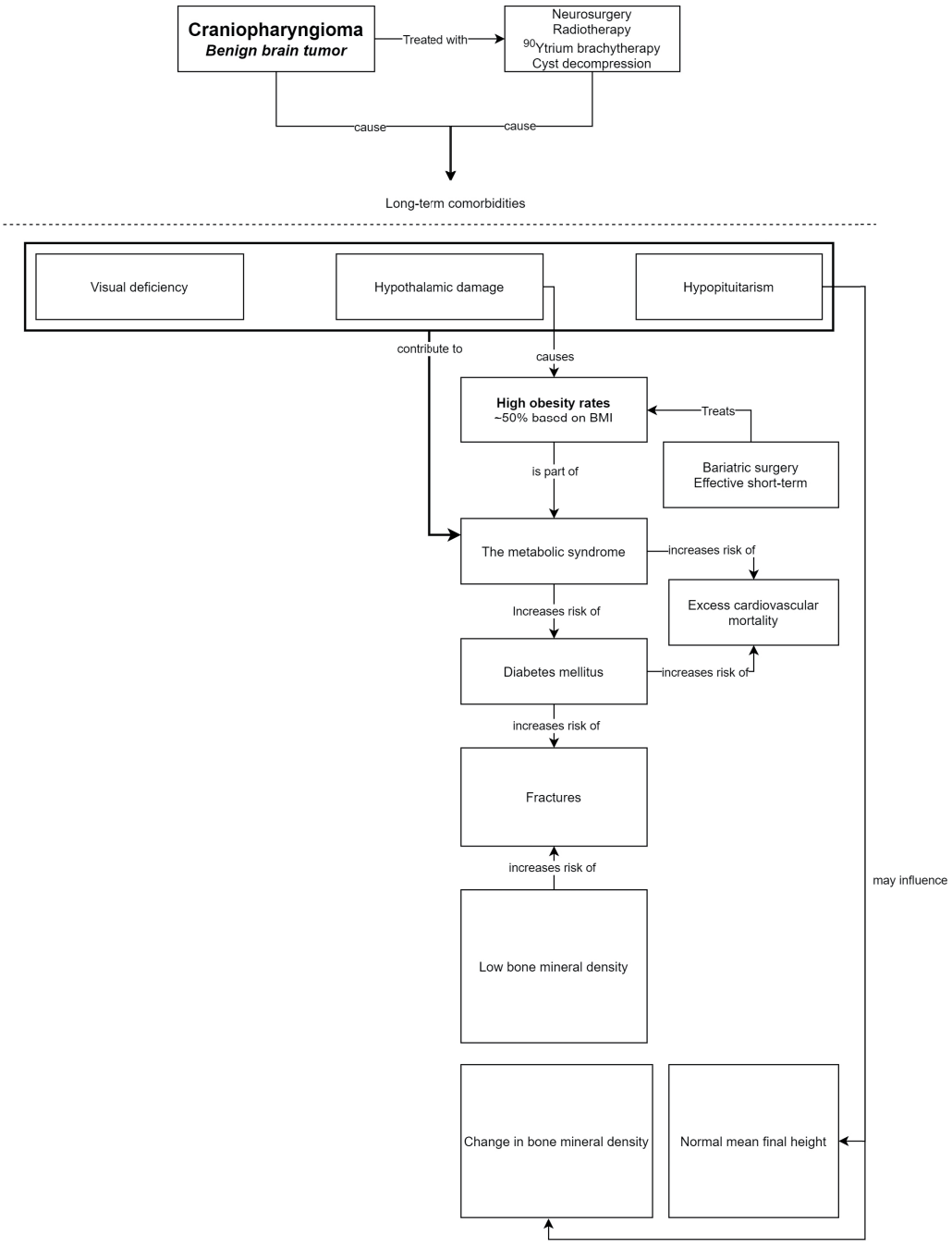
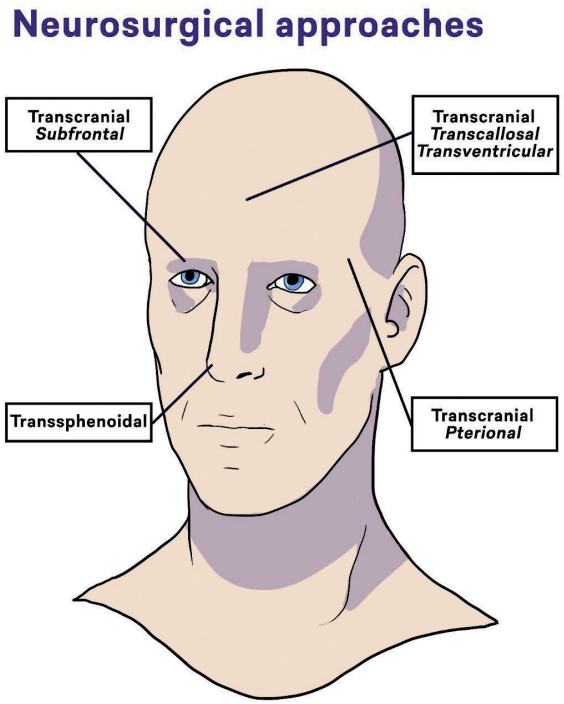


Figure 10 Neurosurgical approaches for treatment of craniopharyngioma



By: Ana G.G. de Lima.

In the general population, severe obesity can be treated with bariatric surgery.[231,246-249] Bariatric surgery appears an effective weight loss strategy in patients with craniopharyngioma as well, even regardless presence of hypothalamic damage, for up to two years past this intervention; longer follow-up data are not yet available.[250]

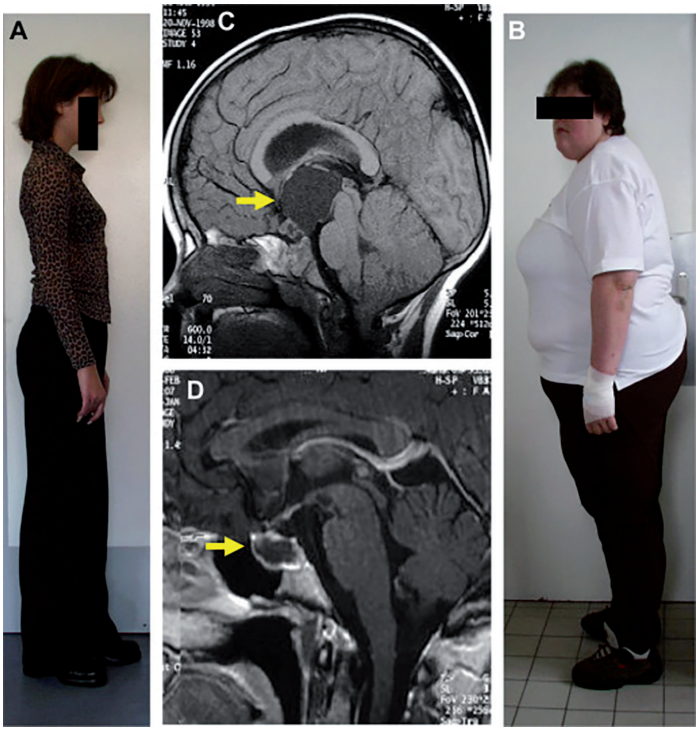
Bone health in patients with craniopharyngioma

The DXA-scan is also the gold standard for evaluation of bone mineral density, to evaluate the presence of osteoporosis.[251] In the general population, bone mass and density reach their peak at a young adult age (20-30 years old) and remain relatively constant until the age of 50, and then decline.[252-254] The bone density values measured by DXA-scan are compared to values of a reference population, expressed

as a T-score or Z-score.[252,253] When bone mass is very low (T-score ≤ -2.5), this is a sign of osteoporosis, which occurs in 0.6% of the general population.[252] Osteoporosis is defined as "a systemic skeletal disease characterized by a reduction in bone mass and qualitative skeletal changes (macro- and microarchitecture, material properties, geometry, and micro-damage) that cause an increase in bone fragility and higher fracture risk."[251] Fractures cause pain and at least temporary, or perhaps even permanent loss of function, may require hospitalization and give reduced DALYs.[255,256] Fragility fractures are mostly located at the vertebral column, proximal side of the humerus and femur, and distal side of the radius.[251] Application of the DXA-scan is already advised in childhood cancer survivors, who do often do not reach a normal peak bone mass, causing low bone mineral density in ~45-51% and increased risk of long-bone fractures.[255,257,258] Risk factors for pathological bone density and fractures in survivors were exposure to glucocorticoids and methotrexate, growth hormone and gonadal hormone deficiency, male sex, smoking status and cranial or abdominal irradiation, while height, weight and attained age were protective factors.[255,258,259] These factors are partially applicable to patients with craniopharyngioma. They could have a high fracture risk as well, due to a combined risk of low bone density and high risk of falling.[260-262] Low bone density is associated to hypopituitarism: growth hormone deficiency gives reduced bone remodeling activity, and both patients with isolated growth hormone deficiency and multiple pituitary deficiencies are at high risk of reduced bone mineral density.[30,260,261,263-266] The growth hormone deficiency can also add to the potential risk of falling, as it causes decreased muscle mass and muscle function,[263] leading to a higher fracture risk.[267] Other potential falling risk factors that occur frequently in patients with craniopharyngioma, are diabetes,[86,268] epilepsy,[32,199,269,270] visual deficiencies[271-273] and neurological conditions.[199,274,275] Some studies have indeed demonstrated a high risk of pathological bone density[276-278] of 53%.[277] Only a few studies investigated fracture rates in patients with craniopharyngioma; some studies[196,279] did indeed find a high fracture risk, but not all.[200] The above described risk factors for fractures and bone density (changes) have barely been investigated in patients with craniopharyngioma. In small cohorts of patients

with craniopharyngioma, risk factors for low bone density were as hypothalamic involvement, low levels of sex steroids or insufficient gonadal hormone replacement.[261,278] It is unknown what factors are important for the change in bone mineral density or fracture risk, what type of fractures occur in patients with a craniopharyngioma, and there are only limited studies performed that regard final height.[235,280-283]

Figure 11 Hypothalamic obesity



Degree of obesity with regard to location of childhood craniopharyngioma. In both patients, craniopharyngioma (as indicated by the arrows on MRI before surgery) could be completely resected. Both patients had complete hypopituitarism after surgery, requiring endocrine substitution of all hypothalamic-pituitary axes. The patient in (B) developed severe obesity because of hypothalamic lesions of suprasellar parts of craniopharyngioma (C). The patient in (A) presented with a small tumor confined to the sellar region (D). After complete resection she kept normal weight without any eating disorders (A). (From Müller HL, Kaatsch P, Warmuth-Metz M, et al. Kraniopharyngeom im Kindesund Jugendalter – Diagnostische und therapeutische Strategien. Monatsschr Kinderheilkd 2003; 151:1056-63;[297] with permission.)

Aims and outline of this thesis

The aim of this thesis is to examine long-term endocrine and metabolic alterations and related risk factors in who suffer(ed) from a tumor, with a special focus on patients with tumors near the pituitary (craniopharyngioma and macro-adenoma). In the current chapter (**Chapter 1**), an introduction is given of important characteristics of childhood cancer, craniopharyngioma and metabolic complications. **Chapter 2** describes a unique case illustrating the potential severity of pituitary disease and treatment issues of a very young boy with acrogigantism. **Chapter 3** reveals results on low bone density and fractures in patients with a craniopharyngioma, risk factors for fractures and achieved final height. In **Chapter 4**, we report the assessment of changes in body composition and bone mineral density over time, including factors influencing changes bone mineral density in patients with a craniopharyngioma. In **Chapter 5**, we show results of a study that aimed to evaluate the added value of applying a dual-energy X-ray absorptiometry scan for the diagnosis of obesity and the metabolic syndrome, and information of related risk factors of the metabolic syndrome in patients with a craniopharyngioma. **Chapter 6** reports as a systematic review on the value of diagnostic and prognostic value of novel biomarkers for metabolic syndrome in childhood cancer survivors. **Chapter 7** shows the comparison of efficacy of bariatric surgery for the treatment of obesity in patients with craniopharyngioma versus controls. **Chapter 8** provides a general discussion of this thesis.

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2

Complicated Clinical Course in Incipient Gigantism Due To A Treatment Resistant, *AIP*-mutated Pediatric Somatotropinoma

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Abbreviations: *AIP* = aryl hydrocarbon-receptor interacting protein; FSH = follicle stimulating hormone; fT4 = free T4/thyroxine; GH = growth hormone; IGF-1 = Insulin-like Growth Factor 1; LH = luteinizing hormone; PA = pituitary adenoma; standardized deviation score = SDS; SSA = somatostatin receptor analogue; somatostatin receptors = SSTRs; TSH = thyroid stimulating hormone.

Highlights:

- This 7-year-old male patient had accelerated growth, headaches and a high IGF-1
- Pituitary macro-adenoma occurred due to a novel truncating *AIP* mutation, p.Tyr202*
- Multiple treatment modalities were needed to achieve tumoral/biochemical control
- In vitro tissue response to SSA may better predict in vivo response than SSTR immunohistochemistry
- The patient will likely need radiotherapy due to continued tumor growth

Abstract

Objective: To describe the clinical course and treatment challenges in a patient with a pituitary adenoma due to a novel *aryl hydrocarbon-receptor interacting protein* (*AIP*) gene mutation.

Methods: A 7-year-old boy with headache, visual field defects and accelerated growth following failure to thrive.

Results: A growth hormone (GH)- and prolactin-secreting pituitary macroadenoma was identified by magnetic resonance imaging (MRI). The patient underwent three neurosurgical procedures, with every time apparent total resection of the lesion, but the tumor recurred. There were no pituitary insufficiencies, but GH levels remained elevated. A loss of somatostatin receptor 5 was observed between the second and third tumor resections. *In vitro*, no effect on tumoral GH release by pasireotide and pasireotide/cabergoline was seen. *In vivo*, hormonal/tumoral control could not be achieved with lanreotide or pasireotide, while IGF-1 levels could be reduced with the GH receptor blocker pegvisomant. Genetic analysis revealed a novel germline *AIP* mutation: p.Tyr202* (pathogenic; class 4).

Conclusions: A 7-year-old boy with incipient acrogigantism presented with a pathological *AIP* mutation. In this case, *in vitro* response of tumor tissue to somatostatin may better predict tumoral *in vivo* responses of somatostatin analogues than somatostatin receptor immunohistochemistry. The clinical course was complex, as the responses to surgeries and multiple systemic therapies to control hormone levels and tumor growth were unsatisfactory.

Keywords: acromegaly; gigantism; *AIP* mutation; pituitary adenoma; macroadenoma; somatotropinoma

Introduction

Pituitary adenomas (PAs) are among the most frequent intracranial tumors with a prevalence of 1 per 1000 clinically-relevant adenomas in adults.[1] PAs produce signs and symptoms due to abnormal hormonal secretion or mass effects of the tumor itself on local structures. Most cases occur sporadically, but 5% have a familial background,[1,2] the most common being familial isolated pituitary adenomas (FIPA). In FIPA, ~15-30% of cases are associated with pathological germline variants in the *aryl hydrocarbon receptor-interacting protein* (*AIP*) gene, a tumor suppressor gene located on chromosome 11q13.[2-6] Germline *AIP* mutations are particularly associated with growth hormone- (GH) and/or prolactin-secreting pituitary adenomas,[3-6] which occur at a younger age than non-mutated counterparts and comprise an important proportion of somatotropinomas in pediatric/adolescent populations.[7] Up to 21% of pediatric macroadenomas show *AIP* mutations.[2] Patients with *AIP* mutations are often male, have an aggressive clinical phenotype and have large invasive tumors.[2,5,7] *AIP* mutations are the most frequent genetic cause of pituitary gigantism (29%).[8] The median age at presentation in *AIP*-mutated pituitary adenomas is during mid-to-late adolescence up to early adulthood.[9] Herein, we report a case of a recurrent somatotropinoma in a young patient with a novel familial germline *AIP* mutation.

Case report

A 7-year-old boy was hospitalized for evaluation of multiple progressive complaints over the past two years, including frontal headache, fatigue, tics, leg pain, nocturnal sweating, constipation and poor food intake. He was born with a normal birthweight/height following an unremarkable pregnancy and his family history was normal. The growth curve showed normal growth until the age of three, followed by a marked decrease to about -2SDS at the age of six (Figure 1). Thereafter, his growth increased rapidly compared to Dutch national standards. His parents were of modest stature for Dutch standards (midparental height 1.74 m). A sellar tumor was discovered and was initially suspected to be

craniopharyngioma (Figure 2). However, the sella turcica was enlarged. Laboratory analysis showed no signs of pituitary insufficiencies (TSH 1.07 mU/l, fT4 20.2 pmol/l, afternoon cortisol 270 nmol/l). Prolactin level was slightly elevated (0.5 nmol/l). LH and FSH were undetectable, and there were no signs of precocious puberty. However, his IGF-I level was clearly elevated with 56.5 nmol/L (SDS +3.24). Hence, the tumor was diagnosed as a GH-secreting macroadenoma. Over time, growth rate further accelerated (Figure 1), in parallel to a rise in IGF-1 level (71.2 nmol/l; +4.25 SDS), with random GH level of 30.8 mcg/l. Prolactin reached a maximum level of 0.75 nmol/l and he complained of vomiting and loss of appetite. GH levels were not suppressed during an oral glucose tolerance test (lowest GH value of 26.7 mcg/l). Treatment with lanreotide 120 mg four-weekly was initiated, which did neither result in a biochemical response (IGF-I 76.5 nmol/l, GH 28.4 mcg/l), nor in inhibition of tumor growth after four months/injections. Lanreotide was switched to pasireotide LAR 60 mg four-weekly. One month after switching, the first transsphenoidal surgery was performed, because of symptomatic compression of the optic chiasma (onset of bitemporal field defects), and headaches unresponsive to somatostatin receptor analogues (SSAs). Two months postneurosurgery, treatment resulted in a modest effect with a decrease of IGF-I to 70.3 nmol/l, of GH to 23.4 mcg/l. After three months of pasireotide, it was replaced with a weekly dose of 40 mg (GH receptor antagonist) pegvisomant. IGF-I levels dropped to 34.1 nmol/L (0.87 SDS)(GH 48.6 mcg/l). Unfortunately, after one month of pegvisomant, severe headaches returned, and bitemporal hemianopsia reoccurred due to tumor progression (Figure 2). Pegvisomant was stopped and a second transsphenoidal resection followed (Figure 2). The histopathological-anatomical report revealed a pituitary adenoma staining positive for GH and negative for prolactin (Figure 3). One month after the second transsphenoidal surgery, IGF-I level declined to 29.3 (0.4 SDS), GH level to 2.7 mcg/L and prolactin from 0.60 to 0.38 nmol/l after surgery without systemic treatment. Five months after surgery, the headaches returned and an MRI one month thereafter showed a small remnant lateral of the right internal carotid artery (Figure 2). IGF-I level increased again to +2.7 SDS. A third transsphenoidal surgery was performed, leading to normalization of

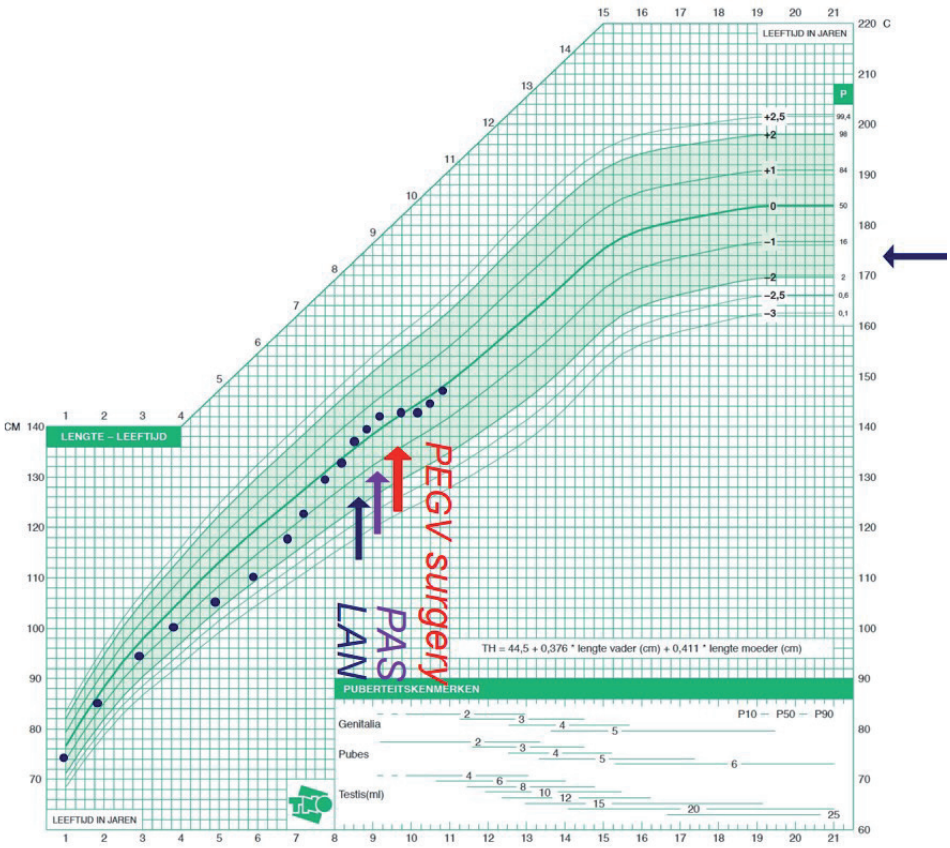
GH and IGF-I levels. Due to the presentation with a macroadenoma at a young age germline genetic testing for sequence variants and deletions in *AIP* and Multiple Endocrine Neoplasia type 1 was performed. A novel heterozygotic truncating variant in the *AIP* gene was discovered (p.Tyr202*) which was accompanied by a second missense variant (p.Pro232 Leu), both paternally inherited. Screening by MRI and hormone evaluation of his 37-year-old father was negative.

Histopathological analysis revealed a loss of SSTR5 expression between the second and third operations (Figure 3). In vitro characterization of the first surgery showed no significant response to coincubation with pasireotide or pasireotide with cabergoline (Figure 4). Other compounds could not be tested due to the limited amount of available tissue.

Discussion

This case report describes a complicated *AIP*-mutation-related somatotropinoma leading to accelerated longitudinal growth which presented at a young age of 7 years.[10] Acro-gigantism can occur with increased growth velocity in young children, even without extreme height compared to age- and sex-matched references. In our patient, the increased growth rate occurred after a period of a relatively decreased longitudinal growth, so that in this case the incipient gigantism was somewhat masked on the growth chart. He is an example of how the totality of growth characteristics is important when assessing children with aberrant growth. Patients with *AIP*-mutation-bearing somatotropinomas require multiple therapeutic modalities applied together than patients with non-*AIP* adenomas.[7] Somatotropinomas are primarily treated with (transsphenoidal) neurosurgery, SSAs, dopamine agonists or GH receptor antagonists.[11] In a large series, patients with *AIP* mutations required more frequently multiple surgeries than patients without *AIP* mutations (22 vs. 6%).[7] Disease control occurred in 27% of 96 *AIP* mutation-positive somatotropinoma patients, versus 81% in non-*AIP* acromegaly patients.[7] Overall, in acromegaly long-acting SSAs can achieve biochemical normalization of GH and IGF-I in 50-60% and often

Figure 1 Growth chart of the patient with incipient gigantism



The initially normal growth of the patient had been declining from three to six years of age, but then deflected markedly upwards. He was diagnosed at the age of 7 years. The blue arrow corresponds with treatment with lanreotide ("LAN"); the purple arrow corresponds with treatment of pasireotide ("PAS") and the red arrow ("PEGV surgery") with pegvisomant and surgery.

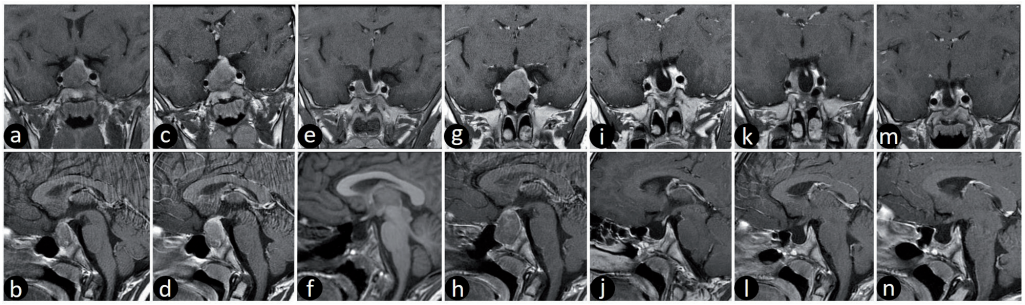
lead to tumor shrinkage.[11-14] Patients with *AIP* mutations had, however, significantly less tumor shrinkage and lower hormonal responses to first-generation SSAs.[7] Patients with *AIP*-mutation-bearing somatotropinomas require more therapeutic modalities than patients with non-mutated adenomas.[7] Somatotropinomas are primarily treated with (transsphenoidal) neurosurgery, SSAs, dopamine agonists or pegvisomant.[11] In a large series, patients with *AIP* mutations required

more frequent multiple surgeries (22 vs. 6%) than patients without *AIP* mutations.[7] Disease control occurred in 27% of 96 *AIP* mutation-positive somatotropinoma patients, versus 81% in non-*AIP* acromegaly patients.[7] Overall, in acromegaly long-acting SSAs can achieve biochemical normalization of GH and IGF-I in 50-60% and often lead to tumor shrinkage.[11-14] Patients with *AIP* mutations had, however, significantly less tumor shrinkage[7] and lower hormonal responses to first-generation SSAs.[7]

SSAs act via somatostatin receptors (SSTRs1-5).[6] The first-generation SSAs octreotide and lanreotide have the highest affinity for SSTR2, and have a low affinity to SSTR3 and SSTR5,[6] while the second-generation SSA pasireotide has the highest affinity for SSTR5, followed by SSTR2, SSTR3 and SSTR1.[15] As reported previously, pasireotide resistance is more related to SSTR2 expression than to SSTR5 in the general acromegalic population.[16,17] SSA resistance may occur if the tumor is lacking SSTR2.[6] Daly et al. recently reported two *AIP*-mutated acromegaly patients with resistance to first-generation SSA, in which pasireotide treatment led to marked tumor shrinkage and persistent hormonal control.[7] In one case, very low to absent SSTR2 levels were seen and the efficacy of pasireotide must have been through other SSTRs like SSTR5.[7]

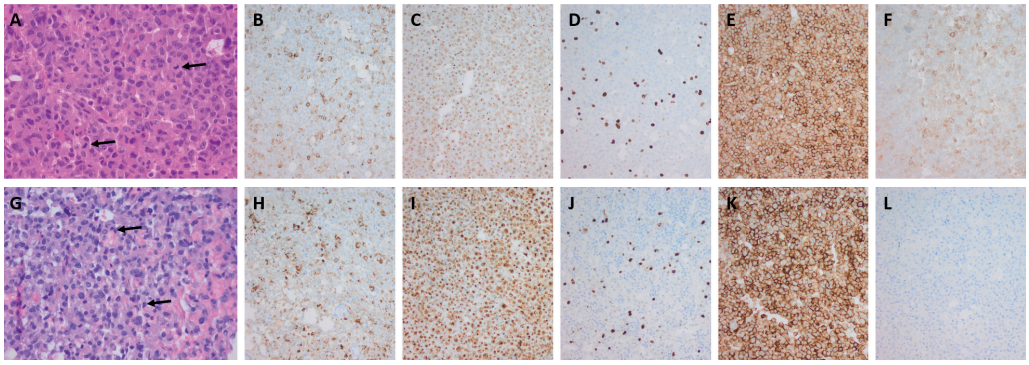
Our case illustrates that in *AIP* mutated somatotropinoma, resistance to first-generation SSAs is not always accompanied by pasireotide responsiveness as was observed previously.[18] The resistance probably relates (partially), to the low SSTR5 expression, since SSTR2 expression remained present. Nevertheless the signaling via SSTR2 may be affected while leaving receptor expression unaffected. Possible factors in this phenomenon include ZAC1 and miR-34a, which both influence SSTR2 signaling.[11,19] In these cases, it may be preferable to test in vitro response of tumor tissue assessed by decreases in GH secretion.[17] Given the lack of tumor size control with first and second generation SSAs and the unresectable remnant, our patient is facing radiotherapy at the age of ten, and will require intensive (endocrinological) follow-up, although no pituitary deficiencies have occurred to date. If needed, excessive GH actions can be controlled by pegvisomant as was shown before, albeit with high vigilance for tumor regrowth.

Figure 2 Sequential magnetic resonance imaging over the clinical course of the patient between 2018 and 2020



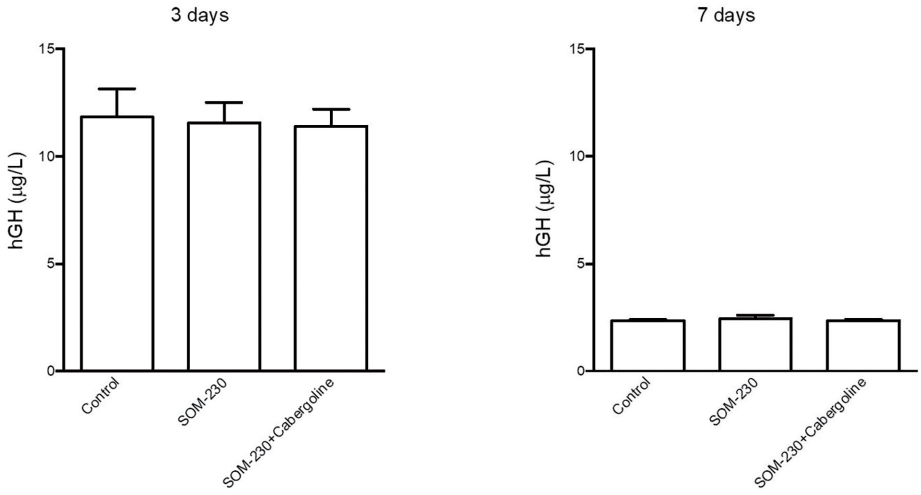
Contrast-enhanced T1-weighted sequences in coronal (**a, c, e, g, l, k, m**) and sagittal (**b, d, f, h, j, l, n**) planes were chosen and corrected for grey scale and magnification. At clinical presentation (**a, b**), before the first operation (**c,d**), delayed postoperatively after the first operation (**e, f**), before the second operation (**g, h**), delayed postoperatively after the second operation (**i, j**), before the third operation (**k, l**), delayed postoperatively after the third operation (**m, n**).

Figure 3 Histopathological features of the tumor at the second and third surgery



A-F: second surgery; **G-L:** third surgery.
A & G: H&E staining show a pituitary adenoma with interspersed mitoses in both surgeries (black arrows).
B & H: GH expression. **C & I:** PanCK immunohistochemistry shows only a few fibrous bodies in both specimens.
In both specimen there is increased proliferation activity (Ki67 staining in **D & J**). Tissue from both surgeries with homogeneous expression of SSTR2 (E & K), while SSTR5 is moderately expressed in the specimen of the first surgery (**F**) and absent in the tissue of the second surgery (**L**).

Figure 4 Experiment to determine *in vitro* sensitivity of tissue to pasireotide and cabergoline



Tumor tissue did not respond to pasireotide (SOM-230) or pasireotide with cabergoline in vitro: there was no significant change in growth hormone production after three days (A) or seven days (B) of exposure.

Conclusion

This unique case of an incipient gigantism in a 7-year old child with a novel *AIP* mutation, p.Tyr202*, was associated with a highly-resistant somatotropinoma. In general, typical features of *AIP* mutation-related PAs were his male sex, young age, macro-adenoma, excessive GH secretion and treatment resistance. This case shows the importance of closely monitoring growth velocity next to height SDS in children. Although previous literature suggests a favorable response to pasireotide in some patients with *AIP* mutations and acromegaly,[18] pasireotide had only limited effect in our patient, possibly related to decreasing SSTR5 expression of the tumor. *In vitro* compound-related GH suppression in cultured tumor tissue may predict *in vivo* treatment response better than assessing SSTR. This patient had tumor size increase despite three neurosurgeries and all available systemic medical therapies. Unfortunately, he would likely need radiotherapy soon before entering puberty, which will have significant impact on the development of his skull and brain. Genetic testing including aberrations of the entire *AIP* gene should be advocated in all patients with GH-secreting pituitary adenomas occurring in childhood and/or in patients with established or incipient pituitary gigantism.[20]

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3

Fractures, Bone Mineral Density, and Final Height in Craniopharyngioma Patients with A Follow-up of 16 Years

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Abbreviations: AO, adulthood onset; BMD, bone mineral density; BMI, body mass index; CO, childhood onset; CP, craniopharyngioma patient; DXA, dual-energy X-ray absorptiometry; GHD, growth hormone deficiency; GHRT, GH replacement therapy; OR, odds ratio; SDS, standardized deviation score.

Précis: Male craniopharyngioma patients are at higher risk of fractures than females, while they receive less often medication to increase BMD. A T-score ≤-2.5 or Z-score ≤-2.0 measured using DXA does not predict risk of fracture in patients with CP.

Abstract

Context: Pituitary hormonal deficiencies in patients with craniopharyngioma may impair their bone health.

Objective: To investigate bone health in patients with craniopharyngioma.

Design: Retrospective cross-sectional study.

Setting: Dutch and Swedish referral centers.

Patients: Patients with craniopharyngioma (n=177) with available data on bone health after a median follow-up of 16 years (range 1-62) were included [106 (60%) Dutch, 93 (53%) male, 84 (48%) childhood-onset disease].

Main outcome measures: Fractures, DXA-derived bone mineral density (BMD), and final height were evaluated. Low BMD was defined as T- or Z-score ≤-1, very low BMD as ≤-2.5 or ≤-2.0, respectively.

Results: Fractures occurred in 31 patients (18%) and were more frequent in men than in women (26% vs. 8%, $P = 0.002$). Mean BMD was normal [Z-score total body 0.1 (range -4.1- 3.5)] but T or Z-score ≤-1 occurred in 47 (50%) patients and T-score ≤-2.5 or Z-score ≤-2.0 in 22 (24%) patients. Men received less often treatment for low BMD than women (7% vs. 18%, $P = 0.02$). Female sex (OR 0.3, $P = 0.004$) and surgery (OR 0.2, $P = 0.01$) were both independent protective factors for fractures, while anti-epileptic medication was a risk factor (OR 3.6, $P = 0.03$); whereas T-score ≤-2.5 or Z-score ≤-2.0 was not (OR 2.1, $P = 0.21$). Mean final height was normal and did not differ between men and women, or adulthood and childhood-onset patients.

Conclusions: Men with craniopharyngioma are at higher risk than women for fractures. In patients with craniopharyngioma, a very low BMD (T-score ≤-2.5 or Z-score ≤-2.0) seems not to be a good predictor for fracture risk.

Keywords: craniopharyngioma, bone health, fractures, bone mineral density, final height

Introduction

Craniopharyngioma is a rare tumour in the pituitary region with peak incidences in the age categories 5-9 and 40-44 years.[1] Age of onset correlates highly with tumour histology: the adamantinomatous subtype occurs mainly in childhood, and in adulthood, while the papillary subtype almost exclusively occurs at adult age.[2] The pathogenesis of the two subtypes differs as well, as adamantinomatous craniopharyngioma is driven by somatic mutations in *CTNNB1*, while the papillary subtypes harbour *BRAF*^{V600E} mutations.[2] Craniopharyngioma patients (CP) require extensive long-term follow-up, since the survival rate is relatively high and the patients often suffer from multiple co-morbidities.[1,3] Several comorbidities could give CP an increased risk of fractures, osteoporosis and reduced growth: CP are at risk of pituitary insufficiency and/or possibly non-physiological replacement therapy,[3-9] visual deficiency,[10] late puberty induction, hypothalamic damage and limited physical activity.[11-14] In addition, chronic neurological disease is associated with clumsiness and high incidence of falls.[15,16] Moreover, anti-epileptic therapy may even contribute more to the lifetime fracture risk than the seizures themselves.[17] All these factors may influence bone health and could result in osteoporosis. Osteoporosis is a systemic disease characterized by three elements: loss of bone mass, deterioration of the microarchitecture of the bone, and an increased fracture risk.[18] Fractures may cause chronic pain, disability and need for rehabilitation.[18]

Despite the knowledge of these frequent occurring comorbidities, studies addressing fracture risk and osteoporosis or bone mineral density (BMD) in CP are scarce. Previously found frequencies of fractures were higher compared to matched populations and lie between 15 to 25%.[19-21] Olsson et al. described an increased risk of fractures with a standardized incidence rate (SIR) of 2.1 in a large cohort of Swedish CP.[1] No studies have yet extensively investigated risk factors for fractures in CP.

In foregoing research regarding BMD, very few adulthood onset (AO) patients were included: osteoporotic/osteopenic BMD values were found in 6 out of 10, and 5 out of 6 cases, respectively.[22,23] The

studies regarding childhood onset (CO) CP are slightly larger but led to different conclusions regarding the influence of gender on the risk of fracture;[11,24] Müller et al. found that men were at risk for lower volumetric BMD (n=61),[24] while Holmer et al. found a low BMD in women (n=39).[11]

Only a few studies have addressed final height, mainly in CO CP. In these studies, CO CP reach slightly below average or normal final height.[19,25-33]

In summary, information on bone health in CP is scarce and contradictory. Also, factors predicting increased risk of fractures in patients with CP have not yet been studied. In order to improve long-term care and increase knowledge of possible risk factors of impaired bone health in CP, we investigated bone fractures, BMD, and final height in a large CP cohort.

Design and methods

In this retrospective cross-sectional study, CO and AO CP treated at the Erasmus University Medical Center (Rotterdam, the Netherlands)/Sophia Children's Hospital (Rotterdam, the Netherlands) and Sahlgrenska University Hospital (Gothenburg, Sweden) were included. Data were collected as previously described.[10,34] Subjects were included if data were available on fractures, Dual-Energy X-ray Absorptiometry (DXA)-scan results for BMD, or on final height.

Data on fractures were acquired as described before;[10] data on fractures were included from 1987 until April 2019. Data regarding fractures from the Dutch patients concerns both inpatient as well as outpatient data; for the Swedish patients, data until 2014 concerns only inpatient data. If only the year of fracture was known, the first of January was used as date to calculate age at fracture. Medication to improve BMD was defined as current or past use of bisphosphonates, vitamin D or calcium. Gonadal axis replacement therapy or other hormonal replacement therapy was not included since the indication of treating

pituitary deficiencies was broader than only improving BMD and not solely for preservation of bone health. The definition of hypothalamic damage was described before: it concerns tumour- and/or treatment-related injury to the hypothalamus and/or third ventricle as visualized by neuroimaging.[34] The research proposal was accepted by the Ethical Review Board of the Erasmus MC and the Regional Ethical Review Board of the Gothenborg University; all patients gave informed consent.

All types of DXA-scanners were accepted in the analysis and include Lunar DPXL, Lunar iDXA and Lunar Prodigy. A list of accepted DXA-scanners is shown in Table 1.[35] For the current study, low BMD was defined as T- or Z-score below -1. Osteoporosis was defined as T-score below -2.5 or Z-score below -2. Osteopenia was defined as T- or Z-score between -1 and -2.5 or -2, respectively. If it is not specified in the text whether low BMD, osteopenia or osteoporosis are based on T- or Z-score, or on which site, it is found to exceed the limit of either T- or Z-score, and is measured at the location of femur neck, L2-L4, and/or total body.[36] If multiple DXA-scans were performed, the most recent was chosen. The decision to perform a DXA-scan was made clinically by the physician who was treating the patient.

Final height was defined as the highest measured value, after the age of 18 years. Standardized deviation scores (SDS) or final height for Dutch subjects were calculated based on requested data with references from the Dutch National Statistics ("Centraal Bureau voor Statistiek")[37] based on age, sex and year of measurement (available on request). If final height was measured before 1981 or after 2017, references of 1981 or 2017 respectively were used in Dutch subjects. Final height SDS of Swedish subjects was calculated with references of the same sex compared with young adults with birth year matched as closely as possible.[38-40]

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 24.0 and Graphpad Version 8.01. Data are presented as mean and standard deviation (SD) unless stated otherwise. Significance was accepted if $P \leq 0.05$. For normally distributed data, an unpaired T-test was used for group comparisons, while a Mann-Whitney U was used for nonnormally distributed data. Comparisons of proportions were conducted using either the $\chi 2$ test or the Fisher's exact test as indicated; in case of comparison of two related dichotomous variables, McNemar's test was applied. To identify influencing factors of low BMD at last DXA-scan and fractures, a univariable logistic regression model was primarily performed; only significant predictors ($P < 0.05$) were entered in the multiple logistic regression analysis thereafter. If the number of events allowed it, the multiple logistic regression model was refined by adding variables with *P*-values < 0.20. If more variables were significant in univariable analysis than could be entered in multivariable model due to the size of the cohort, the most significant variables were selected in multivariable analysis. If the options were comparable, the variable contributing to the best discrimination and highest Nagelkerke's R^2 was chosen. The dependent variables were studied with forced entry. For fractures, a Cox Regression model was established with the apparent main predictors from the logistic regression model. The assumption of proportional hazards was verified by a goodness of fit test with Shoenfeld residuals and time and checking significance of time-dependent covariates. The Wilcoxon rank sum test was used to compare nonnormally distributed variables and the Student's t-test was used for normally distributed variables. A two-way ANOVA was applied for comparisons of multiple groups. The incidence rate was calculated as total incidence of fractures divided by the cumulative follow-up years and multiplied by 1000 to calculate the fracture rate per 1000 person-years.

Table 1 Included Dual-Energy X-ray Absorptiometry scanners that were used in this craniopharyngioma cohort

	First DXA-scan (n=117)	Last DXA-scan (n=95)
Unknown/other	10 (9)	8 (8)
Idexa Gothenborg University Hospital	0 (0)	19 (20)
DPXL total	61 (52)	14 (15)
DPXL Erasmus MC	35 (30)	12 (13)
DPXL Gothenborg University Hospital	26 (22)	2 (2)
Prodigy total	46 (39)	54 (57)
Prodigy (1) Erasmus MC	6 (5)	9 (10)
Prodigy (2) Erasmus MC	6 (5)	6 (6)
Prodigy Gothenborg University Hospital	34 (29)	39 (41)

DXA-scanners included in the article. Data is given as N (%). Prodigy (1) is used at the dept. of Nuclear Medicine in the Erasmus MC; Prodigy (2) at the dept. of Internal Medicine. Total includes all scanners of the same type in both centers.

Results

Baseline characteristics

Baseline characteristics of the 177 CP are depicted in Table 2 and Table 3.[41] Data were available on DXA-scan results for 117 patients and on final height for 171 patients. Patients with a DXA-scan available had a higher percentage of diabetes insipidus (68% vs. 51%, $P = 0.03$), of growth hormone deficiency (GHD) (93% vs. 72%, $P < 0.001$) and of TSH deficiency (95% vs. 86%, $P = 0.06$) than patients with no DXA-scan, and less often epilepsy (13% vs. 27%, $P = 0.03$) or a hydrocephalus (23% vs. 40%, $P = 0.03$). There was no difference in fractures (18% vs.

18%, $P = 0.95$). The cohort consisted of 93 AO CP (53%). There were 106 Dutch (60%) and 71 Swedish (40%) patients included; 93 patients were men (53%) and 15 patients (8%) used medication for epilepsy. The median age at last follow-up was 45 years (range 15-92). Median follow-up time was 16 years (range 1-62). Mean body mass index (BMI) was 31 ± 7 kg/m^2 (range 17 – 60) in all patients at last DXA-scan (or, if DXA-scans at adult age were unavailable, last available BMI) and was higher in women than in men (30 ± 6 vs. 33 ± 8 kg/m^2, $P = 0.02$). CO CP had more often received radiotherapy as tumour treatment (66% vs. 38%, $P < 0.001$), had a higher occurrence of hydrocephalus (38% vs. 17%, $P = 0.002$) and epilepsy (26% vs. 12%, $P = 0.01$) than AO CP. In addition, CO CP had more often a GHD (92% vs. 79%, $P = 0.02$) and had higher occurrence of diabetes insipidus (77% vs. 52%, $P < 0.001$). Sex hormone replacement therapy was used in (125 patients) 94% of women aged 50 years or younger and men with gonadal axis failure. In two patients, presence of GHD was unknown. In the GHD group, CO CP were more often using growth hormone replacement therapy (GHRT) than AO CP (87% vs. 74%, $P = 0.04$). Five patients (3%) underwent bariatric surgery (1 gastric sleeve, 4 gastric bypass); all of them were female. Of the 10 patients who were not treated with surgery, five had Yttrium, one was initially treated with RT, one had cyst aspiration, and the others were closely followed with imaging. The non-surgery group had significant lower frequency of DI (10% vs. 67% in the entire cohort, $P < 0.001$), TSH deficiency (50% vs. 95%, $P < 0.001$) and trend towards lower visual deficiencies (50% vs. 78%, $P = 0.09$). Furthermore, BMI was not significantly different ($P = 0.34$). The tumour was described as stable during follow-up of these patients.

Fractures

Fractures occurred in 31 CP (18%). The fracture rate was 5.8 fractures per 1000 person years. Mean age at last follow-up of patients who had fractures was 52.0 ± 14.5 vs. 45.5 ± 18.5 years in patients who had no fractures ($P = 0.05$). Mean follow-up time was 16.8 ± 10.0 years of patients who had fractures vs. 18.6 ± 13.7 of patients who had no fractures ($P = 0.60$, n=135). Seven of the patients with fractures had

osteopenia (70%); four had osteoporosis (40%) (at last DXA-scan). Eight patients suffered from multiple fractures (26%). The mean number of fractures per patient were 1.5 ± 1.1 (range 1-6). The fracture types are described in Table 4.

Fractures occurred more often in men than women (26% vs. 8%, $P = 0.002$) and men were less often treated with medication to improve BMD (7% vs. 18%, $P = 0.02$). A trend was seen towards a higher proportion of fractures in AO CP than in CO CP (23% vs. 12%, $P = 0.06$). There was no difference in percentage of patients with fractures between Dutch and Swedish patients (18% vs. 17%, $P = 0.86$).

Table 2 Baseline characteristics of the included CP survivors

		All survivors (n=177)	Males (n=93)	Females (n=84)	*P*-value
Age at last follow-up (years)[a]		45 (15-92)	45 (16-92)	45 (15-82)	0.83
Age at presentation (years)[a]		23 (0-79)	26 (0-79)	22 (4-73)	0.92
(Female/corresponding) gender (n [%])		84 (48%)	93 (53%)	84 (47%)	0.50
Childhood onset disease (n [%])		84 (48%)	44 (46%)	40 (48%)	0.97
Tumor location at presentation (n [%])	Intrasellar	6 (4%)	5 (5%)	1 (1%)	0.22
	Suprasellar	69 (41%)	35 (52%)	34 (44%)	0.57
	Intra-/ suprasellar	95 (56%)	52 (57%)	43 (55%)	0.86
Craniopharyngioma treatment	Surgery only	77 (44%)	42 (46%)	35 (42%)	0.55
	Radiation only	2 (1%)	1 (1%)	1 (1%)	1.00
	Surgery and radiation	88 (50%)	44 (48%)	44 (52%)	0.59
	^{90}Yttrium brachytherapy	23 (13%)	8 (9%)	15 (18%)	0.09
Pituitary deficiencies	GH deficiency[b]	149 (85%)/ 120 (81%)	78 (86%)	71 (85%)	0.83

	TSH deficiency[b]	162 (92%)/ 161 (99%)	88 (95%)	74 (88%)	0.12
	Hypogonadism[b]	155 (88%)/ 125 (94%)	84 (90%)	71 (85%)	0.24
	Corticotrophic deficiency[b]	146 (83%)/ 142(99%)	81 (87%)	65 (77%)	0.09
	ADH deficiency[b]	113 (64%)/ 111 (98%)	61 (66%)	52 (61%)	0.61
Medical history	Recurrence/ progression	67 (39%)	33 (36%)	34 (41%)	0.53
	Hypothalamic damage	63 (40%)	35 (42%)	28 (38%)	0.67
	Hydrocephalus ever	47 (27%)	22 (24%)	25 (30%)	0.38
	Visual impairment	125 (77%)	67 (41%)	58 (36%)	0.50
	Epilepsy	33 (19%)	18 (19%)	15 (18%)	0.80
	Diabetes mellitus	26 (15%)	11 (12%)	15 (18%)	0.26
	BMD medication	21 (12%)	6 (7%)	15 (18%)	**0.02**

In 7 patients, tumor location at presentation was unknown. Bold values represent significant differences between males and females ($P \leq 0.05$). [a]Median (range). [b]All/using replacement therapy. Abbreviations: ADH, antidiuretic hormone; BMD medication, bone mineral density-increasing medication.

Table 3 Baseline characteristics of the included CP survivors: adulthood onset vs. childhood onset

	Childhood onset CP (n=84)	**Adulthood onset CP (n=93)**	***P*-value**
Age at last follow-up (years)[a]	32 (15-74)	57 (25-92)	**<0.001**
Age at presentation (years)[a]	10 (0-17)	41 (18-79)	**<0.001**
Female gender (n [%])	40 (48%)	44 (47%)	0.97
Tumor location at presentation (n [%])			
Intrasellar	4 (5%)	2 (2%)	0.42
Suprasellar	29 (36%)	40 (44%)	0.28
Intra-/suprasellar	47 (59%)	48 (53%)	0.48
Craniopharyngioma treatment			
Surgery	79 (96%)	86 (93%)	0.34
Radiation	55 (66%)	35 (38%)	**<0.001**
^{90}Yttrium brachytherapy	12 (15%)	10 (11%)	0.42
Pituitary hormonal deficiencies			
GH deficiency	77 (92%)	72 (79%)	**0.02**
TSH deficiency	78 (92%)	84 (90%)	0.55
Hypogonadotrophic hypogonadism	71 (85%)	84 (90%)	0.24
Corticotrophic deficiency	68 (81%)	78 (84%)	0.61
ADH deficiency	65 (77%)	48 (52%)	**<0.001**

Medical history			
Recurrence/progression	34 (42%)	33 (36%)	0.45
Hypothalamic damage	33 (45%)	30 (36%)	0.23
Hydrocephalus ever	31 (38%)	16 (17%)	**0.002**
Visual impairment	60 (78%)	65 (76%)	0.72
Epilepsy*	22 (26%)	11 (12%)	**0.01**
Diabetes mellitus	9 (11%)	17 (18%)	0.16
BMD medication	12 (15%)	9 (10%)	0.31
Myocardial infarction	1 (1%)	10 (11%)	**0.01**

[a]Median (range). ADH = antidiuretic hormone; BMD medication = bone mineral density increasing medication; CP = craniopharyngioma; GH = growth hormone; N = number; TSH = thyroid stimulating hormone. *Anti-epileptic medication was comparable (8 (10%) vs. 7 (8%), *P* = 0.60).

Using a univariable logistic regression model investigating fractures, female sex (OR 0.3, *P* = 0.004) and previous surgery (OR 0.2, *P* = 0.01) were protective factors, while medication for epilepsy was identified as a risk factor (OR 3.6, *P* = 0.03) (Table 5). Osteoporosis was not a significant independent factor (OR 2.1, *P* = 0.21); for osteopenia, a trend was shown (OR 2.6, *P* = 0.09). There were 10 patients who never underwent surgery, of which 5 had a fracture; 26 out of 165 patients who did have surgery had a fracture. A trend was shown for radiotherapy as well, being protective to fractures (OR 0.5, *P* = 0.06). When these independent variables were applied in the multivariable Cox regression model, the following hazard ratio's were obtained: for sex 0.4 (95% CI 0.2-0.8, *P* = 0.02), for surgery 0.3 (0.1-0.8, *P* = 0.02) and for anti-epileptic medication use 2.7 (1.1-6.7, *P* = 0.03) (-2LL Chi^2 <0.001, Omnibus Chi^2 0.001). Fracture free survival curves are depicted in Figure 1.

Low BMD values based on either T- or Z-scores was found in 11 patients (65%) with fractures as opposed to 32 patients (42%) without fractures in

their history (P = 0.08) (Table 6).[41] Patients who had never been treated with surgery (n=10) suffered from more fractures than patients who had been operated (50% vs. 16%, P = 0.006). A trend for more fractures was seen in patients who had never received radiotherapy compared to patients treated with radiotherapy (23% vs. 12%, P = 0.06).

Table 4 Frequencies and site of fractures

Location	Male (all)	Male (Dutch/ Swedish)	Female (all)	Female (Dutch/ Swedish)	All subjects	Dutch/ Swedish
Unknown*	**2 (5%)**	**1 (5%) / 1 (6%)**	**0 (0%)**	**0 (0%) / 0 (0%)**	**2 (4%)**	**1 (4%) / 1 (5%)**
Femur	2 (5%)	1 (5%) / 1 (6%)	0 (0%)	0 (0%) / 0 (0%)	2 (4%)	1 (4%) / 1 (5%)
Radius	1 (3%)	0 (0%) / 1 (6%)	1 (11%)	0 (0%) / 1 (33%)	2 (4%)	0 (0%) / 2 (10%)
Tibia	2 (5%)	1 (5%) / 1 (6%)	1 (11%)	0 (0%) / 1 (33%)	3 (7%)	1 (4%) / 1 (5%)
Fibula	2 (5%)	0 (0%) / 2 (12%)	1 (11%)	1 (17%) / 0 (0%)	3 (7%)	1 (%) / 2 (10%)
Lower leg (unspecified)	2 (5%)	2 (10%) / 0 (0%)	0 (0%)	0 (0%) / 0 (0%)	2 (4%)	2 (8%) / 0 (0%)
Humerus	1 (3%)	0 (0%) / 1 (6%)	2 (22%)	1 (17%) / 1 (33%)	3 (7%)	1 (4%) / 2 (10%)
Ulna	1 (3%)	1 (5%) / 0 (0%)	1 (11%)	1 (17%) / 0 (0%)	2 (4%)	2 (8%) / 0 (0%)
Clavicle	2 (5%)	1 (5%) / 1 (6%)	0 (0%)	0 (0%) / 0 (0%)	2 (4%)	1 (4%) / 1 (5%)
Cervical vertebrae	3 (8%)	0 (0%) / 3 (18%)	0 (0%)	0 (0%) / 0 (0%)	3 (7%)	0 (0%) / 3 (15%)
Lumbar vertebrae	1 (3%)	1 (5%) / 0 (0%)	1 (11%)	1 (17%) / 0 (0%)	2 (4%)	2 (8%) / 0 (0%)
Long pipebones/ vertebrae	**17 (46%)**	**7 (35%) / 10 (59%)**	**7 (78%)**	**4 (67%) / 3 (100%)**	**24 (52%)**	**11 (42%) / 13 (65%)**
Rib	3 (8%)	2 (10%) / 1 (6%)	0 (0%)	0 (0%) / 0 (0%)	3 (7%)	2 (8%) / 1 (5%)
Pelvis	1 (3%)	0 (0%) / 1 (6%)	0 (0%)	0 (0%) / 0 (0%)	1 (2%)	0 (0%) / 1 (5%)

Facial bones/ nose	4 (11%)	3 (15%) / 1 (6%)	0 (0%)	0 (0%) / 0 (0%)	4 (9%)	3 (12%) / 1 (5%)
Hand	5 (14%)	4 (20%) / 1 (6%)	1 (11%)	1 (17%) / 0 (0%)	6 (13%)	5 (19%) / 1 (5%)
Foot (calcaneus/ toe/ unspecified)	5 (14%)	3 (15%) / 2 (12%)	1 (11%)	1 (17%) / 0 (0%)	6 (13%)	4 (15%) / 2 (10%)
Other	**18 (49%)**	**12 (60%) / 6 (%)**	**2 (22%)**	**2 (33%) / 0 (0%)**	**20 (43%)**	**14 (52%) / 6 (30%)**
Total	**37 (100%)**	**20 (54%) / 17 (46%)**	**9 (100%)**	**6 (67%) / 3 (33%)**	**46 (100%)**	**26 (100%) / 20 (100%)**

Fracture locations of all fractures and its frequencies. Data is presented as n (% of all fractures in this category); 80% of all fractures occurred in males and 57% in the Dutch cohort. Percentages of categories unknown, long pipebones/vertebrae and other fractures may not add up to 100% because of rounding issues. *Data was lost during transition of electronic patient files.

Bone mineral density

Information on BMD is shown in Table 7. Mean age at last DXA-scan is 44.8 ± 18.4 years. Overall mean BMD T- and Z-scores at last DXA-scan were in the normal range: for example, for total body, femur neck and L2-L4 the Z-scores were 0.1 ± 1.5 (range -4.1 – 3.5), -0.1 ± 1.3 (range -2.7 – 4.7) and 0.0 ± 2.0 (range -3.5 – 6.8), respectively (Table 7). However, low BMD in any of these sites was reported in 47 patients (50%) (while an SDS of -1 should correspond to a percentage of 16%). Scatter plots of BMD T- and Z-scores are shown in Figure 2, showing a wide spread of SDS values, also in patients with fractures. Osteoporosis occurred in 22 patients (24%) (Table 7). AO CP had a lower BMD of the femur (neck) than CO CP (0.92 ± 0.15 vs. 1.09 ± 0.28, $P = 0.01$) (Table 7) and a lower mean T-score of the femur (neck) (-0.8 ± 1.2 vs. 0.2 ± 2.1, $P = 0.03$), but comparable Z-scores. A trend was found for lower Z-score of the femur neck in males than in females (-0.4 ± 1.2 vs. 0.2 ± 1.4, $P = 0.08$). Of the patients with osteoporosis, 19% has hypothalamic damage, as opposed to 36% of patients without osteoporosis ($P = 0.15$).

First, a univariable analysis for very low BMD/osteoporosis was established: (borderline) significant contributors were age at DXA-scan (OR 1.032 (1.004-1.063), *P* = 0.03), obstructive sleep apnoea syndrome (OR 2.9 (1.0-8.3), *P* = 0.05), and hydrocortisone dose (OR 1.1 (1.0-1.2), *P* = 0.06. After establishing a multivariable analysis, age (OR 1.03 (95% CI 1.00-1.06, *P* = 0.03) was identified as a contributing independent prognostic factor (Table 8).[41] Hypothalamic damage did not contribute significantly to osteoporosis, nor did it contribute in a multivariable model for osteopenia when adjusted for age, medication to improve BMD and GHRT (Table 8: OR 1.6, *P* = 0.49, model not significant).

Final height

CP had a final height SDS within the normal range (Table 7). There were no differences in final height SDS between males and females (-0.3 ± 1.2 vs. -0.3 ± 1.2, *P* = 0.82) or between CO and AO CP (-0.3 ± 1.4 vs. -0.3 ± 1.0, *P* = 0.90).

Table 5 Univariable and multivariable logistic regression analysis for determinants of fractures in CP survivors

	Univariable analysis		Multivariable analysis (Nagelkerke R^2 =0.18)	
Variables	OR (95% CI)	*P*	OR (95% CI)	*P*
Age at presentation	1.0 (0.99-1.0)	0.17		
Female sex	**0.3 (0.1-0.6)**	**0.004**	**0.3 (0.1-0.7)**	**0.004**
Adulthood onset disease	0.2 (1.0-4.9)	0.07		
Swedish cohort	0.9 (0.4-2.1)	0.86		
Surgery	**0.2 (0.1-0.7)**	**0.01**	**0.1 (0.0-0.6)**	**0.009**
Radiotherapy	0.5 (0.2-1.0)	0.06		
Hypothalamic damage	0.9 (0.4-2.0)	0.79		
Visual impairment	1.9 (0.6-5.9)	0.26		
Medication for epilepsy	**3.6 (1.2-11.0)**	**0.03**	3.0 (0.9-10.0)	0.07
Growth hormone deficiency	2.9 (0.6-13.0)	0.16		
GHRT	1.7 (0.7-4.3)	0.25		
Adrenal axis deficiency	0.9 (0.3-2.3)	0.77		
Hydrocortisone dose	1.0 (0.9-1.1)	0.95		
Gonadal axis deficiency*	2.3 (0.5-10.4)	0.28		
TSH deficiency	1.4 (0.3-6.6)	0.66		
Diabetes insipidus	1.2 (0.5-2.8)	0.62		
BMI	0.9 (0.9-1.0)	0.07		
Osteopenia	2.6 (0.9-7.7)	0.09		
Osteoporosis	2.1 (0.7-6.4)	0.21		
BMD increasing medication	2.1 (0.7-5.8)	0.17		

Age at last follow-up not included (violation of assumption of linearity of logit). Bold values represent significant variables ($P \leq 0.05$). *Replacement therapy OR 1.6 (95%CI 0.7-4.0, $P = 0.28$) / after exclusion of postmenopausal females OR 1.3 (95%CI 0.4-4.2, $P = 0.62$). Hosmer Lemeshow $P = 0.81$, Omnibus $Chi^2 < 0.001$. No subjects were excluded. Receiver operating characteristic area under the curve 0.72. Abbreviations: BMD, bone mineral density; BMI, body mass index; GHRT, GH replacement therapy.

Table 6 Characteristics of survivors with and without fractures

		Fracture in history (n=31)	No fracture in history (n=146)	*P*-value
Baseline characteristics				
Age (years) at last FU		52.0 (14.5)	45.5 (18.5)	0.05
Female sex		7 (23%)	77 (53%)	**0.002**
Childhood onset disease		10 (12%)	74 (51%)	0.06
Tumor treatment				
Surgery		26 (84%)	139 (97%)	**0.02**
Radiotherapy		11 (36%)	79 (54%)	0.06
Yttrium brachytherapy		3 (10%)	19 (14%)	0.77
Comorbidities				
Recurrence or progression		10 (33%)	57 (40%)	0.52
Visual impairment		23 (85%)	102 (75%)	0.25
Epilepsy		9 (29%)	24 (16%)	0.10
Hydrocephalus		6 (19%)	41 (29%)	0.29
Hypothalamic damage		11 (38%)	52 (41%)	0.79
Bariatric surgery		0 (0%)	5 (3%)	0.29
Diabetes mellitus		4 (13%)	22 (15%	1.00
Growth hormone deficiency		29 (94%)	120 (83%)	0.18
TSH deficiency		29 (94%)	133 (91%)	1.00
LH/FSH deficiency		29 (94%)	126 (86%)	0.38
ACTH deficiency		25 (81%)	121 (83%)	0.77
Diabetes insipidus		21 (68%)	92 (63%)	0.62
Medication				
Hydrocortisone dose		21.0 (4.9)	21.1 (6.4)	0.57
Ever BMD increasing medication		8 (26%)	25 (17%)	0.28
Gonadal axis replacement		24 (77%)	99 (68%)	0.29
Anti-epileptic treatment		6 (19%)	9 (6%)	**0.03**

DXA-scan results			
Age (years)	48.0 (15.6)	44.1 (19.0)	0.39
Height (cm)	171.8 (11.7)	171.6 (19.0)	0.60
Weight (kg)	93.6 (21.2)	91.9 (19.5)	0.80
BMI (kg/m^2)	31.5 (5.2)	31.3 (5.8)	0.65
Total body T-score	0.30 (1.5)	0.12 (1.7)	0.72
Total body Z-score	-0.2 (1.4)	0.1 (1.5)	0.46
Femur T-score	-0.2 (1.4)	-0.1 (1.6)	0.81
Femur Z-score	-0.3 (1.4)	-0.2 (1.4)	0.70
Femur neck T-score	-0.7 (1.1)	-0.3 (1.7)	0.85
Femur neck Z-score	-0.4 (1.0)	0.0 (1.4)	0.53
Lumbar spine (L2-L4) T-score	0.1 (2.5)	0.1 (1.9)	0.68
Lumbar spine (L2-L4) Z-score	0.0 (2.6)	0.0 (1.8)	0.93
Bone health			
Low BMD (T-score)	9 (53%)	30 (42%)	0.40
Low BMD (Z-score)	9 (53%)	32 (42%)	0.42
Low BMD (T/Z-score)	11 (65%)	37 (48%)	0.21
Osteopenia (T-score)	6 (35%)	22 (31%)	0.73
Osteopenia (Z-score)	9 (53%)	26 (34%)	0.15
Osteopenia (T/Z-score)	11 (65%)	32 (42%)	0.08
Osteoporosis (T-score)	5 (29%)	13 (19%)	0.32
Osteoporosis (Z-score)	3 (18%)	12 (16%)	0.85
Osteoporosis (T/Z-score)	6 (35%)	16 (21%)	0.20
Final height	173.1 (11.0)	172.1 (9.9)	0.41
Final height SDS	-0.6 (1.3)	-0.3 (1.1)	0.13

Abbreviations: BMD = Bone Mineral Density; BMI = Body Mass Index; DXA = Dual-Energy X-ray Absorptiometry; FU = follow-up; SDS = standardized deviations scores. Data are presented as mean (SD) or n (%). BMI is measured at last DXA-scan or at last follow-up. BMD results are of the last DXA-scan. Bone health corresponds with grouped variables of low BMD/osteopenia/osteoporosis at measured at femur neck, L2-L4 or total body. N in the first row represents the total number of patients of which data is available on this topic. Not all data is available in all cases. Pituitary deficiencies are evaluated at last follow-up.

Table 7 Bone mineral density and final height of the included CP survivors

		All		Male		Female		
		Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	*P*-value
Age at last DXA[a]		44.8 (18.4)	95	47.1 (19.2)	47	42.6 (17.4)	48	0.26
BMI at last DXA		31.3 (5.3)	84	30.9 (4.8)	43	31.8 (5.8)	41	0.41
BMD	Total body	1.20 (0.16)	78	1.25 (0.15)	43	1.14 (0.15)	35	**0.002**
	Femur	1.04 (0.22)	65	1.00 (0.20)	32	1.07 (0.23)	33	0.26
	Femur neck	0.99 (0.22)	34	0.95 (0.20)	31	1.03 (0.24)	33	0.12
	L2-L4	1.24 (0.25)	76	1.32 (0.27)	37	1.17 (0.21)	39	**0.01**
T-score	Total body	0.5 (1.7)	79	0.5 (1.8)	44	0.5 (1.6)	35	0.85
	Femur	-0.1 (1.5)	63	-0.4 (1.5)	30	0.1 (1.6)	33	0.22
	Femur neck	-0.4 (1.6)	64	-0.8 (1.5)	31	-0.1 (1.6)	33	0.09
	L2-L4	0.1 (2.0)	73	0.5 (2.1)	36	-0.2 (1.8)	37	0.10
Z-score	Total body	0.1 (1.5)	84	0.0 (1.6)	45	0.2 (1.3)	39	0.57
	Femur	0.0 (1.4)	65	-0.3 (1.3)	32	0.2 (1.4)	33	0.17
	Femur neck	-0.1 (1.3)	64	-0.4 (1.2)	31	0.2 (1.4)	33	0.08
	L2-L4	0.0 (2.0)	75	0.3 (2.2)	36	-0.3 (1.7)	39	0.18
Final height		172.3 (10.1)	171	178.1 (8.0)	91	165.6 (8.0)	80	**<0.001**
Final height SDS		-0.3 (1.2)	171	-0.3 (1.2)	91	-0.3 (1.2)	80	0.82
Low BMD		47 (50%)	94	25 (53%)	47	22 (47%)	47	0.54
Osteoporosis		22 (23%)	94	13 (28%)	47	9 (19%)	47	0.33
Osteopenia		43 (46%)	94	21 (45%)	47	22 (47%)	47	0.84

Age is given in years. BMD (T- and Z-scores) are given of the first DXA scan. For the raw BMD and BMI values, children were excluded. The minimum age at first DXA scan is 6 years. Data are given as mean (SD); proportions are given as n (%). Low BMD is a T- or Z-score below -1.Osteoporosis is a T-score below -2.5 or a Z-score below -2. Osteopenia is a T-score

		CO CP		AO CP		
		Mean (SD)	n	Mean (SD)	n	*P*-value
Age at last DXA[a]		32.9 (14.3)	45	55.6 (14.7)	50	**<0.001**
BMI at last DXA		31.1 (5.1)	37	31.6 (5.5)	47	0.69
BMD	Total body	1.19 (0.17)	37	1.21 (0.15)	47	0.72
	Femur	1.11 (0.26)	27	0.98 (0.16)	38	**0.03**
	Femur neck	1.09 (0.28)	25	0.92 (0.15)	39	**0.01**
	L2-L4	1.22 (0.21)	34	1.26 (0.28)	42	0.53
T-score	Total body	0.4 (1.7)	37	0.5 (1.7)	42	0.87
	Femur	0.4 (1.9)	24	-0.4 (1.2)	39	0.05
	Femur neck	0.2 (2.1)	24	-0.8 (1.2)	40	**0.03**
	L2-L4	-0.1 (1.6)	31	0.3 (2.3)	42	0.46
Z-score	Total body	-0.1 (1.6)	41	0.2 (1.4)	43	0.39
	Femur	0.2 (1.7)	26	-0.2 (1.1)	39	0.29
	Femur neck	0.2 (1.8)	24	-0.3 (1.0)	40	0.20
	L2-L4	-0.4 (1.6)	33	0.3 (2.2)	42	0.10
Final height		172.9 (11.2)	80	171.7 (9.0)	91	0.41
Final height SDS		-0.3 (1.4)	80	-0.3 (1.0)	91	0.90
Low BMD		21 (49%)	43	26 (51%)	51	0.84
Osteoporosis		8 (19%)	43	14 (28%)	51	0.31
Osteopenia		18 (42%)	43	25 (49%)	51	0.49

between -1 and -2.5 or a Z-score between -1 and -2. This is evaluated at 3 locations: L2-L4, femur neck, and total body. Patients were also included if data were available at less than 3 locations. Bold values represent significant differences between groups ($P \leq 0.05$). Abbreviations: AO, adulthood onset; BF%, body fat percentage; BMD, bone mineral density (in g/cm^2); CO, childhood onset; CP, craniopharyngioma patient; DXA = dual-energy X-ray absorptiometry scan; L2-L4 = located at lumbar vertebral body 2–4; SDS = standardized deviation scores. [a]n = 95.

Table 8 Univariable and multivariable logistic regression analysis for determinants of bone health in CP survivors

	T- or Z-score ≤-1			
	Univariable analysis		Multivariable analysis	
Variables	OR (95% CI)	*P*	OR (95% CI)	*P*
Age at DXA-scan	**1.04 (1.0-1.1)**	**0.005**	1.0 (1.0-1.1)	0.08
BMI	0.98 (0.9-1.1)	0.60		
Weight	1.0 (1.0-1.0)	0.37		
Diabetes mellitus	0.8 (0.2-2.7)	0.69		
Hydrocortisone dose	1.0 (1.0-1.1)	0.43		
Childhood onset disease	1.2 (0.5-2.7)	0.69		
Female sex	0.8 (0.4-1.9)	0.68		
Hydrocephalus	1.05 (0.5-2.4)	0.92		
Hypothalamic damage	**0.4 (0.2-1.0)**	**0.04**	1.6 (0.4-5.5)	0.49
Medication for epilepsy	1.3 (0.3-6.2)	0.74		
Growth hormone deficiency**	0.2 (0.0-2.3)	0.22		
GHRT	0.4 (0.11-1.3)	0.11	10.4 (0.9-125.8)	0.07
Adrenal axis deficiency	1.2 (0.4-3.7)	0.71		
Gonadal axis deficiency	1.7 (0.4-6.3)	0.46		
TSH deficiency	1.0 (0.1-7.7)	0.97		

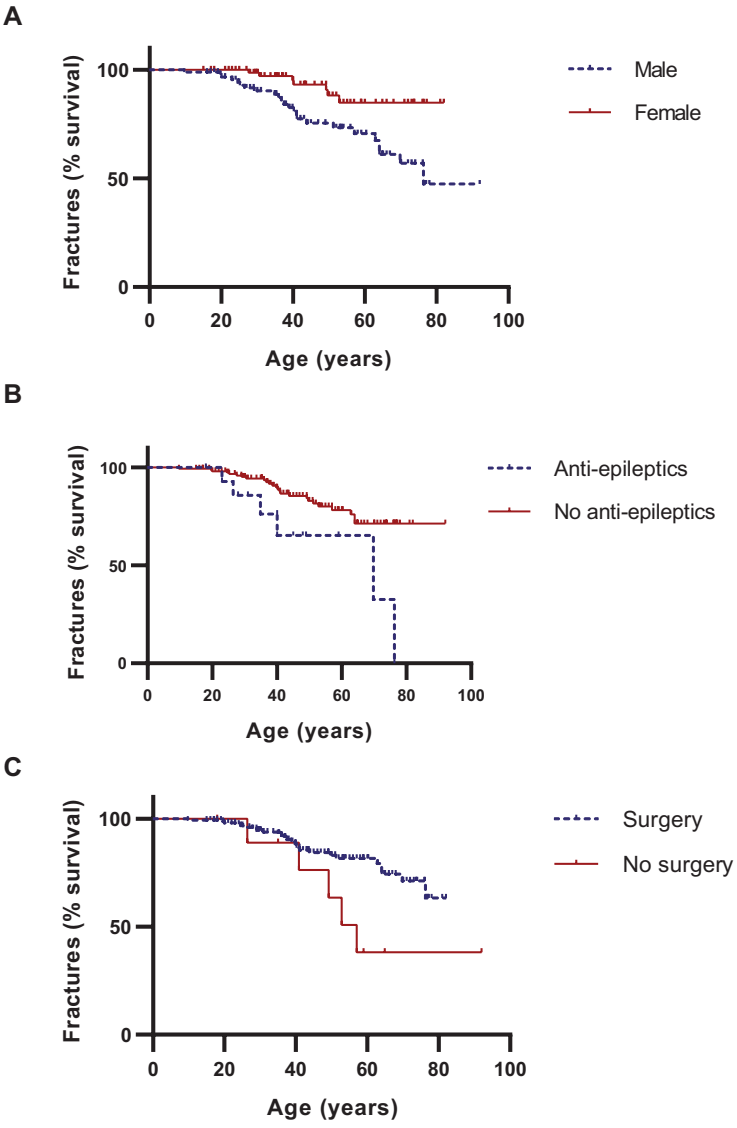
Sex steroid replacement therapy	0.7 (0.3-1.7)	0.41		
Diabetes insipidus	1.4 (0.6-3.4)	0.42		
Visual impairment	1.1 (0.4-2.9)	0.91		
BMD increasing medication	2.4 (0.7-8.3)	0.18	5.8 (1.1-29.7)	0.03
Scannertype: iDXA	1.6 (0.5-5.2)	0.44		
Scannertype: Prodigy	0.3 (0.0-1.8)	0.19		
Scannertype: DPXL	0.7 (0.1-4.0)	0.67		

	T-score ≤-2.5 or Z-score ≤-2			
	Univariable analysis		Multivariable analysis	
Variables	OR (95% CI)	*P*	OR (95% CI)	*P*
Age at DXA-scan	**1.03 (1.004-1.1)**	**0.03**	1.032 (1.003-1.1)	**0.03**
BMI	0.9 (0.9-1.0)	0.28		
Weight	1.0 (1.0-1.0)	0.49		
Diabetes mellitus	1.3 (0.3-5.2)	0.75		
Hydrocortisone dose	1.1 (1.0-1.2)	0.06		
Childhood onset disease	1.7 (0.5-4.4)	0.32		
Female sex	0.6 (0.2-1.6)	0.33		
Hydrocephalus	1.4 (0.6-3.4)	0.44		
Hypothalamic damage	0.4 (0.1-1.4)	0.16		
Medication for epilepsy	1.3 (0.2-7.4)	0.74		
Growth hormone deficiency**	0.2 (0.03-1.2)	0.07	0.2 (0.03-1.4)	0.10

GHRT	0.5 (0.1-1.6)	0.25		
Adrenal axis deficiency	1.3 (0.3-5.0)	0.74		
Gonadal axis deficiency	0.7 (0.2-2.9)	0.60		
TSH deficiency	NA*	NA*		
Sex steroid replacement therapy	0.7 (0.23-1.9)	0.44		
Diabetes insipidus	1.9 (0.64-5.8)	0.25		
Visual impairment	3.4 (0.7-15.8	0.13		
BMD increasing medication	2.4 (0.7-8.3)	0.18		
Scannertype: iDXA	0.7 (0.2-2.8)	0.64		
Scannertype: Prodigy	0.3 (0.0-3.2	0.33		
Scannertype: DPXL	0.9 (0.1-6.6)	0.93		

Abbreviations: BMD = bone mineral density; BMI = Body Mass Index; DXA = Dual-Energy X-ray Absorptiometry; GHRT = Growth Hormone Replacement Therapy; ROC = Receiver Operating Characteristic; TSH = Thyroid Stimulating Hormone. Univariable and multivariable model for low bone mineral density (BMD) (T- or Z-score at last DXA-scan ≤-1) and osteoporosis (T-score ≤-2.5 or Z-score ≤-2 at last DXA-scan). Height at last DXA-scan violates assumption of linearity of logit and is thus not included. No significant multivariable model for low BMD could be established. The best available model is shown. Several outliers were identified but not excluded from analysis. Omnibus Chi^2 $P = 0.09$, Nagelkerke $R^2=0.14$, Hosmer and Lemeshow $P = 0.50$. *NA: there were no cases of patients with osteoporosis and no TSH deficiency, bariatric surgery, surgery as tumor treatment, or Yttrium treatment. Multivariable logistic regression model osteoporosis: Omnibus Chi^2 $P = 0.02$, Nagelkerke $R^2=0.13$, Hosmer and Lemeshow $P = 0.11$. ROC-curve 0.65. **Small sample size for non-growth hormone deficiency: only 5 patients do not have a growth hormone deficiency and have DXA-scan results available.

Figure 1 Fracture free survival curves in craniopharyngioma survivors



Fracture free survival (Kaplan Meier) curves. Multivariable Cox regression model hazard ratios: (A) sex 0.4 (95%CI 0.2-0.83, *P* = 0.02), (B) for surgery 0.32 (0.12-0.84, *P* = 0.02) and (C) for anti-epileptics use 2.68 (1.08-6.69, *P* = 0.03) (-2LL Chi^2 <0.001, Omnibus Chi^2 0.001).

Discussion

Eighteen percent of the CP had suffered from at least one fracture during a median follow-up of 16 years. Fractures occurred more often in males than females and males were less often treated with medication intended to improve BMD, which could indicate that males were undertreated. DXA revealed overall mean BMD values in the normal range in our cohort and no differences in low BMD or T- or Z-scores between patients with and without fractures. However, the spread was wide: 46% had osteopenia and 24% had osteoporotic BMD T- or Z-scores.

In our study, osteoporosis was not a predictor of fracture risk. Obviously, there are more factors than only BMD that contribute to fracture risk. In the literature, prior and current exposure to glucocorticoids was associated with an increased fracture risk of substantial importance beyond explanations by BMD.[42] Using our logistic regression model for fractures, we did not find any role for pituitary hormonal deficiencies in the increased fracture rates. This is probably due to adequate replacement therapy, as illustrated by replacement rates of 94% for hypogonadotropic hypogonadism. As expected, epilepsy medication accelerated fracture risk, while previous treatment with surgery and female sex were protective. Anti-epileptic drugs can induce poor balance or clumsiness; certain antiepileptic drugs are associated with an increased rate of bone loss,[17] and some may cause hyponatremia, which correlates with fractures and low BMD.[43]

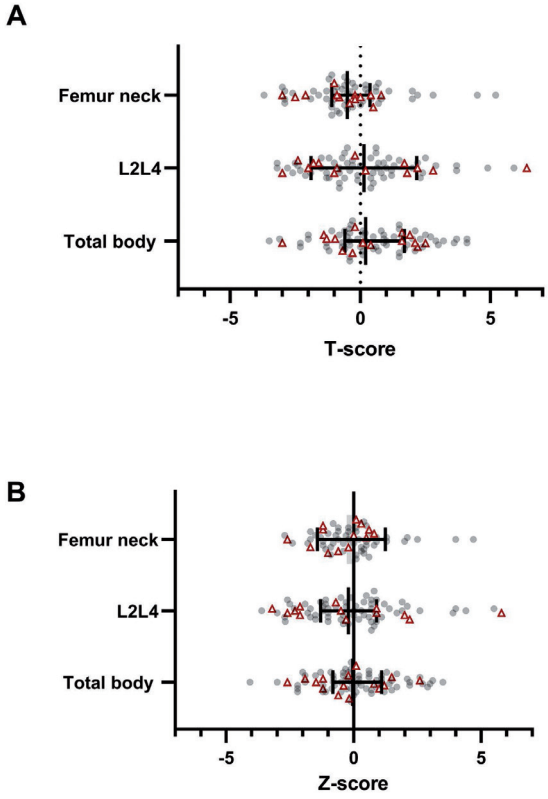
The observation that surgery as previous tumour treatment was identified as 'protective' factor, was surprising. Only a few patients were not treated with surgery; perhaps these are patients severely affect by comorbidities where surgery could not safely be performed, thereby having an increased risk for fractures as well. Patients with a fracture in their history had a higher mean age, were more often male, and had less often surgery. Female sex was observed to be a protective factor, which corresponds with the findings of Müller et al.[24] This might be related to the relatively young age of our study population, and to a higher BMI in women. In the premenopausal general population, higher

frequencies of fractures and lower osteoporosis preventive medication have been described in men, while in the postmenopausal general population, female sex is a risk factor for fractures.[44-46] A trend was shown for radiotherapy being protective for fractures. The general aim of the surgeons in treatment of CP have shifted from attempting gross total resection towards aiming at a more limited resection today, which may leave more tumour mass behind and cause the need to additional treatment with radiotherapy. Presumably, the lower risk for fractures observed in our study is therefore explained by a less damaging treatment strategy.

We found a high percentage of fractures in our study, since the cumulative fracture incidence in a European population was reported to be 7.8% in men and 9.5% in women.[19] In our previous study, no higher risk was found for fractures in our CP cohort.[10] This may partly be related to a lack of reliable Dutch reference data, which prompted Wijnen et al. to compare fracture incidence in Dutch patients with Swedish reference data. Fracture rate may differ between populations: it has been reported that Scandinavian countries have higher fracture rates than western Europe.[47] Olsson et al. previously showed an increased fracture risk.[1]

In a GHD population from the KIMS study (Pfizer International Metabolic Database), fracture rates were reported to be even higher compared to our study (27% in males and 29% in females); no significant differences of fracture prevalence between patients with or without (multiple) other hormonal pituitary deficiencies were found.[21] This suggests that GHD itself is an important factor in fracture risk, freestanding from other hormonal pituitary deficiencies. Given the high prevalence of GHD patients in our study, one might expect an even higher a frequency of fractures. Again, a demographic factor could play a role for a higher frequency of fractures, or a registration bias, or compensation of BMD by the protective factor of obesity in CP.[48] Obesity occurred in up to 75% of our patients[34] and a trend was shown for BMI as protective factor for fractures in our univariate logistic regression analysis. Gonadal axis hormonal deficiency does not seem to be a major contributor for a higher frequency of fractures, as demonstrated by our results; probably because 94% of premenopausal women and men received hormonal replacement therapy.

Figure 2 Scatterplot of T- and Z-scores of bone mineral density in survivors of craniopharyngioma with and without fractures



Scatterplot of T- (A) and Z-scores (B) of bone mineral density of the femur neck, L2-L4 and total body in survivors of craniopharyngioma. The error bars express median and quartiles. Every circle or triangle represents a measurement at last Dual-Energy X-ray Absorptiometry scan. The red triangles represent patients who had fractures in the past; the grey circles are patients who did not have fractures. A wide spread is shown in both patients with and without fractures in the past.

The mean BMD at last DXA-scan was normal in the total cohort, but low BMD occurred in 50% and osteoporosis in 24% (Table 7). The dispersion was rather large, and similar in patients with and without fractures as showed in Figure 1. BMD T- and Z-scores were similar between genders except for Z-score of the femur neck, which was lower in males (-0.4 ± 1.2 vs. 0.2 ± 1.4, $P = 0.08$). Sex or GHD were not a contributing factor in our logistic regression model for osteoporosis.

Final height in our patients was not impaired: the mean SDS score was -0.3 ± 1.2. It was also similar between AO CP and CO CP, and between genders. Apparently, GHRT had been sufficiently administered to these children. Indeed, 87% of patients with CO CP and GHD received GHRT. This is different from the findings of Kendall-Taylor et al., who did find for AO CP a significant difference in height (although it was on average only 3 cm or 0.6 SDS).[19] Perhaps the large size of their European cohort made it possible to find smaller differences, or there may be regional differences in treatment of CP, particularly the age at which GHRT is started.

Due to the retrospective cross-sectional design, there are some limitations of our study. Factors that may have contributed to a possible selection bias are the size and weight limitations of DXA-scanners,[49] DXA-scans were performed based on individual care plan decided by the insight of the clinicians. All types of DXA-scanners were included, while measurements by different DXA-scanners have shown intra-individual variability.[50] However, agreement between all DXA-devices is high.[51] By using age- and sex-matched SDS and applying generally used cut-offs to identify osteopenic or osteoporotic BMD values, we tried to limited the impact on our data. In our logistic regression model for osteoporosis, scanner type was not a contributing factor. Due to the retrospective design, relevant data on duration of GHRT, smoking, alcohol use, dietary intake, fractures of parents, physical activity and level of 25-hydroxyvitamin D were lacking. The percentage of fractures could be underestimated due to a reporting bias. Still, since studies on bone health in CP are so limitedly available, our study provides more insight and should create awareness for the importance of attention to bone health in CP.

This is the first study to date that investigated contributory factors for fractures in CP, and that describes bone health in a cohort existing of both CO and AO long-term survivors, with a large sample size. With this study, we hope to raise more awareness for the evaluation of bone health. The decision to either or not perform a DXA-scan is important in this respect, although DXA-scans alone do not evaluate the quality of the bone or fracture risk sufficiently. Fracture rate could also

be compromised by for example neurological defects. Nevertheless, clinicians should consider treatments that increase bone health, especially in males.

In conclusion, our cohort of CP showed a high frequency of fractures. Although men had a higher frequency of fractures, they received BMD increasing treatments less frequently. Pituitary hormone replacement therapy in our cohort overall seemed adequately managed, since pituitary hormonal deficiencies did not contribute significantly to fracture risk in our logistic regression model. Also of interest was our finding that osteoporotic BMD values did not predict the fracture risk. Our study suggests the importance of regularly evaluating fracture risk in every CP. We advise to take other risk factors than BMD into account, and suggest earlier evaluation of bone health increasing medication, especially in men.

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4

Body Composition and Bone Mineral Density in Craniopharyngioma Patients: A Longitudinal Study Over 10 Years

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Abbreviations: AO, adulthood onset; BF%, body fat percentage; BMD, bone mineral density; BMI, body mass index; CO, childhood onset; CP, craniopharyngioma; DI, diabetes insipidus; DXA, dual energy X-ray absorptiometry; FMI, fat mass index; FFMI, fat free mass index; GHRT, growth hormone replacement therapy.

Abstract

Context: Patients with craniopharyngioma suffer from obesity and impaired bone health. Little is known about longitudinal changes in body composition and bone mineral density (BMD).

Objective: To describe body composition and BMD (change).

Design: Retrospective longitudinal study.

Setting: Two Dutch/Swedish referral centers.

Patients: Patients with craniopharyngioma (n = 112) with a dual-energy X-ray absorptiometry (DXA) scan available (2 DXA scans, n = 86; median Δtime 10.0 years; range 0.4-23.3) at age ≥ 18 years (58 [52%] male, 50 [45%] childhood onset).

Main outcome measures: Longitudinal changes of body composition and BMD, and associated factors of ΔZ-score (sex and age standardized).

Results: BMI (from 28.8 ± 4.9 to 31.2 ± 5.2 kg/m^2, $P < 0.001$), fat mass index (FMI) (from 10.5 ± 3.6 to 11.9 ± 3.8 kg/m^2, $P = 0.001$) and fat free mass index (FFMI) (from 18.3 ± 3.2 to 19.1 ± 3.2 kg/m^2, $P < 0.001$) were high at baseline and increased. Fat percentage and Z-scores of body composition did not increase, except for FFMI Z-scores (from 0.26 ± 1.62 to 1.06 ± 2.22, $P < 0.001$). Z-scores of total body, L2-L4, femur neck increased (mean difference 0.61 ± 1.12, $P < 0.001$; 0.74 ± 1.73, $P < 0.001$; 0.51 ± 1.85, $P = 0.02$). Linear regression models for ΔZ-score were positively associated with growth hormone replacement therapy (GHRT) [femur neck: beta 1.45 (95% CI 0.51–2.39)]; and negatively with radiotherapy [femur neck: beta -0.79 (-1.49--0.09)], glucocorticoid dose [total body: beta -0.06 (-0.09--0.02)] and medication to improve BMD [L2-L4: beta -1.06 (-1.84--0.28)].

Conclusions: Z-scores of BMI, fat percentage, and FMI remained stable in patients with craniopharyngioma over time, while Z-scores of FFMI and BMD increased. Higher glucocorticoid dose and radiotherapy were associated with BMD loss and GHRT with increase.

Keywords: craniopharyngioma, DXA, body composition, sarcopenia, bone mineral density, longitudinal study

Introduction

Patients with craniopharyngioma (CP) suffer from a tumor that may affect the pituitary, optic nerve and hypothalamus, causing damage and impaired function of these important structures.[1] The age at presentation of the disease has a bimodal distribution, with incidence peaks observed in children aged 5-14 [childhood onset (CO) patients with CP] and in adults aged 50-74 years [adulthood onset (AO) patients with CP].[2,3] Patients with CP have excess mortality,[1,3,4] especially due to obesity-related disorders (standardized mortality ratio 3.2- 19).[3-7] Neurological or endocrinological dysfunction may increase fracture risk[8] and obesity. Obesity was reported in up to 75% of the patients.[9] Several factors may contribute to obesity in patients with CP, such as endocrine aberrations related to hypopituitarism, visual and neurological sequelae with decreased sympathetic nerve activity, sleep disturbances and daytime somnolence.[10] The simplest way to investigate obesity is to calculate body mass index (BMI): it is non-invasive and inexpensive. Unfortunately, it does not well differentiate body fat from fat free mass.[11] Dual-Energy X-ray absorptiometry (or DXA-scan) is considered a reliable method to determining body composition in case of suspected discordance of BMI and adiposity,[9,12] and can be used to measure bone mineral density (BMD).[13] Only a couple of small studies have published cross-sectional data on DXA-scan derived body composition measures in patients with CP.[14-17] In a study including 11 patients with CP, it was found that resting energy rate was significantly reduced in obese subjects, even after controlling for fat free mass.[16] In another study with 185 CO patients with CP, obesity was found to be associated with higher BMI at diagnosis, higher maternal BMI, presence of ventriculoperitoneal shunts and hypothalamic tumor involvement.[18]

Studies in patients with CP investigating the longitudinal changes in BMI[18-21] or body composition[15] are scarce. Weight gain in patients with CP was observed mostly before[19] or in the first year after treatment/ diagnosis.[18,19,22,23] The only study investigating changes in body fat percentage (BF%) in 19 patients with CP receiving growth hormone replacement treatment (GHRT) reported no change in BF% after 60 months of follow-up.[15] To the best of our knowledge, no longitudinal

studies in patients with CP on sarcopenia or BMD change and influencing factors for BMD change have been performed to date.[1,24-28] Therefore, the aim of the present study was to describe the course of body composition and BMD in patients with CP, during follow-up, and to identify potential influencing factors for BMD changes.

Materials and Methods

This longitudinal retrospective study included patients who were treated for craniopharyngioma either at the Erasmus MC (Rotterdam, the Netherlands), or Sahlgrenska University Hospital (Gothenborg, Sweden). Only DXA-scans from patients over 18 years of age were included in the study. The research proposal was approved by the Ethical Review Board of the Erasmus MC and the Regional Ethical Review Board of the Gothenborg University; all patients gave their informed consent.

Data collection and patient identification methods have previously been described.[4, 8, 24] Data were collected from the first and most recent DXA scan regardless of scanner type. DXA scan data included pooled data of Lunar DPXL, Lunar iDXA, Lunar Prodigy. The study evaluated the Lunar DPXL and Lunar Prodigy data separately, since different scanner types might generate different results.[8] We did not do this for the Lunar iDXA because there was only a limited number of results from this scanner type. Gathered data existed of body composition measures (such as BF%, fat mass index [FMI] and fat free mass index [FFMI]), BMI, and BMD values and corresponding sex-specific T-scores and sex- and age-specific Z-scores as described in DXA scanner reports. The mean of the differences between first and last DXA scan was calculated. Furthermore, sex- and age-specific Z-scores were computed;[29-38] for body composition measures, Swedish references were used if Dutch references were unavailable.[9, 34]

All definitions were previously described.[8] Hypothalamic damage was defined as tumor- and/or treatment-related injury to the hypothalamus and/or third ventricle as visualized by neuroimaging.[9,24] In our analysis we evaluated patients who had radiotherapy and

hypothalamic damage together as 1 group, as we assumed that they had hypothalamic dysfunction. Medication to improve BMD was defined as current or past use of bisphosphonates, vitamin D, or calcium (gonadal axis replacement therapy or other hormonal replacement therapy were excluded for this definition). Patients were categorized as using high or low glucocorticoid dose, where patients with mean or higher glucocorticoid dose (17.7 mg of hydrocortisone equivalent dose) were considered to have a high dose. FFMI was calculated as lean mass and mineral bone mass (kg) per square height (meters); FMI as body fat mass (kg) per square height (meters); and BMI as total body weight per square height (meters).

Cut-offs of categories for BMD (osteopenia and osteoporosis)[39] and for high or low body composition measures are shown in Table 1 and Supplementary Table 1AB.[40] BMD categories may be specified through single or multiple sites (at either of femur neck, L2-L4, and/or total body). Patients were considered as obese based on BMI Z-scores >2.0.

Table 1 Definitions of cutoffs for body composition and BMD measures

	Male	Female
Body composition		
High BMI	≥ 30 kg/m^2 or Z-score ≥2	≥ 30 kg/m^2 or Z-score ≥2
High BF%	≥26% if aged 20-39 years old or ≥29% if aged 40-59 years old, or Z-score ≥2[38]	≥39% if aged 20-39 years old; ≥41% if aged 40-59 years old, or Z-score ≥2
High FMI	≥ 9 or Z-score ≥2[37]	≥ 13 or Z-score ≥2
Low FFMI	Z-score ≤-2	Z-score ≤-2
BMD		
Osteopenia	T-score -1 - -2.5 or Z-score -1 - -2	
Osteoporosis	T-score ≤-2.5 or Z-score ≤-2	

Abbreviations: BF% = body fat percentage; BMD = bone mineral density; BMI = body mass index; FMI = fat mass index; FFMI = fat free mass index.

Statistical analysis

Statistical analysis was performed using Version 25.0 of IBM SPSS Statistics for Windows, and Graphpad Version 8.01. Data are presented as mean and standard deviation (SD) unless stated otherwise. *P*-values of < 0.05 were considered significant. Comparisons of proportions were performed by using either the $\chi 2$ test, the Fisher's exact test or McNemar's test as appropriate. For normally distributed data, T-test was used for group comparisons, while nonparametric equivalents were used in case of violation of the normality assumption. Univariable and multivariable linear regression models were estimated to investigate determinants of changes in BMD Z-scores; baseline Z-scores and age at first DXA-scan were incorporated in each model. The model with the biggest R^2 and most significant variables was ultimately chosen. A diagnostic check was performed on model fitting, homoscedasticity, multicollinearity, influential cases and outliers.

Results

Baseline characteristics of subjects

Baseline characteristics of 112 included patients with CP are shown in Table 2. Most of the included patients originate from a previously reported cohort.[4, 24] Patients were previously treated with surgery (n = 108; in 64 patients a transsphenoidal approach and in 29 patients a transcranial approach), radiotherapy (n = 61), and yttrium (n = 13). The median number of surgical procedures was 1 (mean 1.3 ± 0.9, range 0-5). The median age at first presentation of CP was 25 years (range 0-73). Mean follow-up time was 19 ± 11 years (range 1-62). At last follow-up, 15 patients (13%) had died. Men received less often medication to improve BMD (4 [7%] vs. 12 [22%], *P* = 0.02) than women (as previously reported)[8]. Gonadal deficiencies were not different between men and women (95% vs. 85%, *P* = 0.15). Gonadal axis replacement therapy was more often administered to men than women (91% vs. 57% *P* < 0.0001) but not different if postmenopausal women (defined as >51 years) were excluded (91% vs. 94%, *P* = 1.00). Of 105 growth hormone deficient patients, 93 were using GHRT (89%). Patients

diagnosed before the year 2000 or from 2000 and onwards did not show any differences in body composition or BMD, except for total body BMD Z-score (−0.22 ± 1.48 vs. 0.51 ± 1.24, $P = 0.04$).[40]

Table 2 Baseline characteristics of craniopharyngioma patients

	All patients with CP (n=112)	Males	Females	*P*-value
Age at last follow-up (years)[a]	49 (16-82)	52 (16-78)	46 (18-82)	0.36
Age at presentation (years)[a]	25 (0-73)	27 (0-62)	23 (6-73)	0.93
(Female/ corresponding) gender (n [%])	54 (48%)	58 (100%)	55 (100%)	0.78
Childhood onset disease (n [%])	50 (45%)	24 (41%)	26 (48%)	0.47
Tumor location at last follow-up (n [%])				
Intrasellar	2 (2%)	1 (2%)	1 (2%)	1.0
Suprasellar	45 (40%)	22 (38%)	23 (43%)	0.50
Intra-/suprasellar	63 (56%)	35 (60%)	28 (52%)	0.49
CP treatment				
Surgery	108 (96%)	58 (100%)	50 (93%)	0.05
Radiation	62 (55%)	31 (53%)	31 (57%)	0.76
Pituitary deficiencies				
GH deficiency[c]	105 (94%) / 93 (83%)	53 (91%) / 48 (83%)	52 (96%) / 45 (83%)	0.44
TSH deficiency[c]	107 (96%) / 107 (96%)	58 (100%) / 58 (100%)	49 (91%) / 49 (91%)	**0.02**

Hypogonadism[bc]	102 (91%) / 84 (75%)	55 (95%) / 53 (91%)	47 (87%) / 31 (57%)	0.19
Corticotropic deficiency[c]	95 (85%) / 92 (84%)	53 (91%) / 50 (89%)	42 (78%) / 42 (78%)	0.045
ADH deficiency[c]	76 (68%) / 75 (67%)	40 (69%) / 40 (69%)	36 (67%) / 35 (65%)	0.80
Medical history				
Recurrence/ progression	40 (36%)	19 (33%)	21 (39%)	0.54
Hypothalamic damage	38 (36%)	21 (38%)	17 (35%)	0.77
Hydrocephalus ever	26 (23%)	11 (19%)	15 (28%)	0.29
Visual impairment	81 (76%)	42 (76%)	39 (75%)	0.99
Epilepsy	14 (13%)	5 (9%)	9 (17%)	0.20
Diabetes mellitus	13 (12%)	7 (12%)	6 (11%)	0.85
Fracture in history	21 (19%)	16 (28%)	5 (9%)	**0.01**
BMD medication	16 (14%)	4 (7%)	12 (22%)	**0.02**

The bold values indicate that they are statistically significant ($P < 0.05$). Tumor location and recurrence or progression were unknown in 2 and 1 patient(s), respectively. Abbreviations: ADH, antidiuretic hormone; BMD medication, bone mineral density increasing medication; CP, Craniopharyngioma; GH, growth hormone; N, number; TSH, thyroid stimulating hormone. [a]Median (range). [b]In females aged 50 years or younger and men, 83/90 subjects (92%) used gonadal hormone replacement therapy. [c]All/using replacement therapy.

Baseline values and longitudinal change in body composition

Median age at first DXA scan was 36 years (range 18-79) and age at last follow-up was 49 years (range 16-82). The median time since first tumor related treatment at first DXA scan was 9.9 years (range –9.2 to 47.0) and the median time between the first and last DXA scan was 10.0 years (range 0.41-23.3). The proportion of patients with obesity increased when defined by BMI Z-scores (from 28 [41%] to 38 [55%], $P = 0.02$) and FMI Z-scores (from 28 [48%] to 36 [61%], $P = 0.04$); other definitions of obesity did not change during follow-up (Table 3). Unstandardized values of BMI (from 28.8 ± 4.9 to 31.2 ± 5.2 kg/m^2, $P < 0.001$), FMI (from 10.5 ± 3.6 to 11.9 ± 3.8 kg/m^2, $P = 0.001$) and FFMI (from 18.3 ± 3.2 to 19.1 ± 3.2 kg/m^2, $P < 0.001$) were high at baseline and increased significantly (Table 4, Figure 1, and Supplementary Tables[40]). However, if standardized, only FFMI Z-scores increased (from 0.26 ± 1.62 to 1.06 ± 2.22, $P < 0.001$) (Figure 2). BF% (Z-scores) did not change (Table 4). There was no difference in change of body composition measures or body composition Z-scores between men and women over time (Figures 1 and 2). Patients treated for CP before 2000 had longer time difference from first to last DXA scan (12.4 ± 6.5 vs. 6.3 ± 4.2, $P < 0.001$) but no differences in BMI or body composition values at first DXA scan, last DXA scan or change over time (data not shown).

Subgroups: childhood onset vs. adulthood onset patients

The follow-up time since first presentation was significantly longer in CO patients than AO patients (22.7 ± 12.4 vs. 16.3 ± 9.0 years, $P = 0.03$). At baseline, CO patients had a higher proportion of subjects with normal BMI than AO patients (30% vs. 10%, $P = 0.02$) and had higher BF% (39.5 ± 13.2 vs. 34.2 ± 9.2, $P = 0.048$), but lower FFMI (16.6 ± 2.8 vs. 19.7 ± 3.0, $P < 0.001$) and FFMI Z-score values (–0.8 ± 1.4 vs. 0.7 ± 1.4, $P < 0.001$) than AO patients. During follow-up, CO patients increased more in BMI than AO patients (mean difference 2.8 ± 3.9 vs. 1.3 ± 2.9, $P = 0.008$) and increased in BF% Z-scores while AO patients decreased (mean difference 0.2 ± 0.9 vs. –0.3 ± 0.6, $P = 0.04$).

Subgroups: patients with vs. without radiotherapy/ hypothalamic damage

This group consisted of 34 patients who had radiotherapy only, 16 patients who had hypothalamic damage only, and of 22 patients who had both. At baseline, patients with radiotherapy or hypothalamic damage had a significant higher BMI (29.6 ± 5.1 vs. 27.2 ± 4.3, *P* = 0.02), higher BMI Z-scores (1.7 ± 1.9 vs. 0.7 ± 1.7, *P* = 0.004), and higher FMI Z-scores (1.6 ± 1.5 vs. 1.0 ± 1.2, *P* = 0.06). As a group, they had an increase in BF% Z-scores instead of a decrease in patients without radiotherapy or hypothalamic damage (mean change 0.1 ± 0.7 vs. −0.3 ± 0.8, *P* = 0.02) and increased more in FMI (mean change 1.3 ± 2.6 vs. 0.2 ± 2.1, *P* = 0.03). At last DXA scan, patients with radiotherapy or hypothalamic damage had not only a higher total body mass and fat-related body composition measures (BMI 32.3 ± 5.6 vs. 29.2 ± 3.5, *P* = 0.01; BMI Z-scores 1.8 ± 1.7 vs. 1.0 ± 1.2, *P* = 0.01; BF% Z-scores 1.8 ± 0.8 vs. 1.3 ± 1.1, *P* = 0.03; FMI Z-scores 2.5 ± 1.6 vs. 1.4 ± 1.3, *P* = 0.007), but also higher muscle mass-related measures (FFMI Z-scores 1.5 ± 2.6 vs. 0.3 ± 1.4, *P* = 0.03) than patients without radiotherapy or hypothalamic damage.

Table 3 Baseline DXA-scan and changes of BMD and body composition categories

	All CP		
	First DXA-scan	**Last DXA-scan**	***P***
Age (years)	37 ± 15	48 ± 16	**<0.001**
Osteoporosis (T/Z-score)	19/79 (24%)	20/79 (24%)	1.00
Osteoporosis (T-score)	13/75 (17%)	18/75 (24%)	0.38
Osteoporosis (Z-score)	19/77 (25%)	13/77 (17%)	0.24
Osteopenia (T/Z-score)	47/78 (60%)	42/79 (49%)	0.41
Osteopenia (T-score)	38/75 (51%)	27/75 (36%)	**0.04**
Osteopenia (Z-score)	39/77 (51%)	34/77 (44%)	0.46
BMI	28.8 ± 4.9	31.2 ± 5.1	**<0.001**
BMI Z-score	1.4 ± 1.9	1.5 ± 1.6	0.38
Low BMI	2/69 (3%)	1/69 (1%)	1.00

Normal BMI	12/69 (18%)	5/69 (7%)	**0.04**
Overweight	27/69 (40%)	25/69 (37%)	0.83
Obese	28/69 (41%)	38/69 (55%)	**0.02**
FMI			
Low FMI	0/59 (0%)	0/59 (0%)	NA
Normal FMI	10/59 (17%)	6/59 (10%)	0.29
Excess fat FMI	21/59 (36%)	17/59 (29%)	0.48
Obese FMI	28/59 (48%)	36/59 (61%)	**0.04**
FFMI			
Low FFMI	5/41 (12%)	2/41 (5%)	0.25
Normal FFMI	29/41 (71%)	29/41 (71%)	1.00
High FFMI	7/41 (17%)	10/41 (24%)	0.25
BF%			
Low BF%	0/48 (0%)	0/48 (0%)	NA
Normal BF%	16/48 (33%)	12/49 (25%)	0.34
High BF%	31/48 (65%)	36/48 (75%)	0.18

Baseline first DXA-scan and changes during follow-up (Δ). Data are presented as mean ± SD or n (%) as applicable. The bold values indicate that they are statistically significant ($P < 0.05$). For applied cutoffs, see Table 1 and Supplementary Table 1.[40] There are no significant differences between male and females at first or last DXA-scan. Abbreviations: BF% = Body Fat Percentage; BMI = Body Mass Index; DXA = Dual-Energy X-ray Absorptiometry Scan; FFMI = Fat Free Mass Index; FMI = Fat Mass Index; NA = Not Applicable (empty groups); *P* = *P*-value.

Subgroups: patients with vs. without certain pituitary hormone deficiencies

Patients with gonadal axis deficiency increased in BMI Z-scores (mean difference 0.2 ± 1.4 vs. −0.7 ± 1.0, $P = 0.03$) and increased more in higher FFMI at last DXA scan than patients without gonadal axis deficiency (mean change 1.4 ± 1.9 vs. −0.2 ± 1.2, $P = 0.009$). Patients with adrenocorticotropin deficiency increased during follow-up in BMI Z-scores (mean difference 0.2 ± 1.5 vs. −0.6 ± 1.0, $P = 0.03$) and FMI Z-scores (mean difference 0.1 ± 0.7 vs. −0.4 ± 1.5, $P = 0.03$). If patients

with diabetes insipidus (DI) were compared with patients without DI, they increased more in BMI (mean difference 2.6 ± 3.6 vs. 0.8 ± 2.6, *P* = 0.02), FMI Z-scores (mean difference 0.2 ± 0.7 vs. −0.2 ± 1.1, *P* = 0.006), and FFMI Z-scores from first to last DXA scan (mean difference 1.4 ± 1.4 vs. 0.1 ± 1.1, *P* = 0.005). Patients with high glucocorticoid dose had no significant differences from patients with low glucocorticoid dose except for higher unstandardized FFMI at first DXA scan (19.0 ± 3.2 vs. 16.9 ± 2.6, *P* = 0.003) and at last DXA scan (19.6 ± 3.3 vs. 18.1 ± 2.7, *P* = 0.04).

Table 4 DXA-results of any DXA-scanner type – Bone Mineral Density and Body Composition in all patients with craniopharyngioma

	First DXA-scan	Last DXA-scan	Δ	*P*-value
Age (years)	37.0 ± 14.9	48.0 ± 16.5	11.0 ± 6.5	**<0.001**
Bone				
Bone mineral density				
Total body	1.17 ± 0.13	1.19 ± 0.16	0.04 ± 0.10	**0.001**
L2-L4	1.13 ± 0.19	1.22 ± 0.26	0.11 ± 0.17	**<0.001**
Femur neck	0.96 ± 0.18	0.99 ± 0.22	0.04 ± 0.26	0.29
Femur	1.03 ± 0.21	1.04 ± 0.21	0.03 ± 0.32	0.70
T-score				
Total body	-0.10 ± 1.49	0.43 ± 1.68	0.66 ± 1.07	**<0.001**
L2-L4	-0.70 ± 1.57	0.14 ± 2.03	0.78 ± 1.63	**<0.001**
Femur neck	-0.64 ± 1.48	-0.40 ± 1.60	0.23 ± 1.95	0.44
Femur	-0.27 ± 1.61	-0.10 ± 1.52	0.26 ± 2.19	0.53
Z-score				
Total body	-0.49 ± 1.37	-0.05 ± 1.44	0.61 ± 1.12	**<0.001**
L2-L4	-0.77 ± 1.59	-0.03 ± 1.97	0.74 ± 1.73	**<0.001**
Femur neck	-0.62 ± 1.32	-0.09 ± 1.33	0.51 ± 1.85	**0.02**
Femur	-0.32 ± 1.44	-0.01 ± 1.35	0.29 ± 2.11	0.55
Body composition				
BMI	28.8 ± 4.9	31.2 ± 5.1	2.01 ± 3.36	**0.001**
BMI SDS	1.39 ± 1.92	1.52 ± 1.55	0.09 ± 1.41	0.38

FMI	10.5 ± 3.6	11.9 ± 3.8	0.97 ± 2.43	**0.001**
FMI SDS	1.37 ± 1.41	2.14 ± 1.46	0.10 ± 0.90	0.43
FFMI	18.3 ± 3.2	19.1 ± 3.2	1.13 ± 1.87	**<0.001**
FFMI SDS	0.26 ± 1.62	1.06 ± 2.22	0.91 ± 1.39	**<0.001**
BF%	36.4 ± 11.6	37.5 ± 8.4	0.28 ± 9.37	0.15
BF% SDS	1.41 ± 1.06	1.62 ± 0.96	-0.02 ± 0.73	0.61

Data are expressed as mean ± SD. The **bold** values indicate that they are statistically significant ($P < 0.05$). Δ = mean difference; BF% = Body Fat Percentage; BMD = Bone Mineral Density; BMI = Body Mass Index; DXA = Dual-Energy X-ray Absorptiometry; FFMI = Fat Free Mass Index; FMI = Fat Mass Index; N= number.

Longitudinal change in BMD

BMD, and corresponding T- and Z-scores were slightly below average at baseline, but increased for total body and L2-L4, and the Z-score for femur neck as well (mean difference Z-scores 0.61 ± 1.12, $P < 0.001$; 0.74 ± 1.73, $P < 0.001$; 0.51 ± 1.85, $P = 0.02$, respectively) (Table 4 and Figure 3). There was no significant difference in (change in) Z-scores between patients with or without radiotherapy, with or without hypothalamic damage, with or without tumor progression, or CO or AO patients (Figure 3). There was a decrease in osteopenia rates from first to last DXA scan in the entire group if it defined by low T-score (38 [51%] vs. 27 [36%], $P = 0.04$) but no difference in proportion of osteoporosis at first (19 [24%]) or last (20 [24%]) DXA scan ($P = 1.00$) (Table 3). Patients treated for CP before 2000 had lower total body Z-scores at first (–0.77 ± 1.30 vs. 0.11 ± 1.36, $P = 0.02$) and last (–0.22 ± 1.48 vs. 0.51 ± 1.24, $P = 0.04$) DXA scan than patients treated from 2000 and onwards. Other BMD-related values did not differ (data not shown).

Prodigy and DPXL

Using the Lunar Prodigy, almost all body composition results increased significantly, but not using DPXL.[40] The BMD results follow a similar pattern, except for femur neck: femur neck BMD, T-scores, and Z-scores significantly improved if measured using Lunar DPXL, in contrast to Lunar Prodigy.

Effect of prognostic factors for change in BMD Z-scores

Univariable and multivariable linear regression models were estimated to identify possible predictors of changes in total body Z-score, L2-L4 Z-score, and femur neck Z-score (Table 5).

In a univariable model, time from first to last DXA scan (beta 0.04 [0.003-0.08]), hydrocortisone equivalent dose (beta −0.06 [−0.10 to −0.02]) and medication to improve BMD (beta −0.95 [1.83 to −0.08]) were associated with change in total body Z-score. In the multivariable analysis, time from first to last DXA scan was not associated with change in total body Z-score (beta 0.03 [−0.005 to 0.07]) while hydrocortisone equivalent dose was (beta −0.06 [−0.09 to −0.02]). In a univariable model, medication to improve BMD and progression were not associated with change in L2-L4 Z-score (beta −1.30 [−2.78 to 0.18] and beta 0.86 [0.02-1.73], respectively). In multivariable analysis, medication to improve BMD was associated with change in L2-L4 Z-score (beta −1.06 [−1.84 to −0.28]), while tumor progression was not (beta 0.04 [−0.45 to 0.52]). In the univariable model for change in femur neck Z-score, GHRT (beta 1.45 [0.51-2.39]) and previous radiotherapy (beta −0.79 [−1.49 to −0.09]) were significant explanatory variables. In multivariable analysis, GHRT and radiotherapy were however not identified as significant prognostic factors (with corresponding estimated regression coefficients of beta −0.37 [−1.27 to 0.53]) and −0.05 [−0.67 to 0.57]).

Table 5 Linear regression model: univariable model and multivariable models of change in Z-scores of BMD

	Univariable linear regression model					
	Δ Total body Z-score		Δ L2-L4 Z-score		Δ Femur neck Z-score	
	Beta	95%CI	Beta	95%CI	Beta	95%CI
Time from first to last DXA	0.04	0.003 – 0.08	0.02	-0.04 – 0.09	-0.02	-0.08 – 0.04
Time since first treatment at last DXA	0.01	-0.01 – 0.03	-0.01	-0.04 – 0.03	0.001	-0.03 – 0.03
Female sex	-0.06	-0.57 – 0.44	0.05	-0.85 – 0.95	0.47	-0.26 – 1.19
BMI at last DXA	0.03	-0.03 – 0.08	-0.002	-0.09 – 0.08	0.05	-0.03 – 0.12
BMD medication	-0.95	-1.83 – -0.08	-1.30	-2.78 – 0.18	-0.67	-2.08 – 0.74
Adulthood onset	0.35	-0.38 – 1.08	0.93	-0.36 – 2.22	-0.30	-1.32 – 0.73
Hypothalamic damage	0.27	-0.31 – 0.85	-0.06	-1.06 – 0.95	-0.18	-1.04 – 0.68
Growth hormone replacement therapy	0.40	-0.48 – 1.27	1.03	-0.31 – 2.38	1.45	0.51 – 2.39
Gonadal replacement therapy	0.49	-0.13 – 1.10	0.64	-0.38 – 1.66	-0.17	-1.01 – 0.68
Hydrocortisone equivalent dose	-0.06	-0.10 – -0.02	-0.03	-0.10 – 0.05	0.05	-0.03 – 0.12
Epilepsy medication	0.78	-0.01 – 1.57	0.15	-1.24 – 1.53	-0.14	-1.24 – 0.96
Ever hydrocephalus	-0.16	-0.75 – 0.44	0.06	-1.01 – 1.12	0.18	-0.73 – 1.09
Progression	0.31	-0.21 – 0.83	0.86	-0.02 – 1.73	-0.16	-0.89 – 0.59
Surgery	-0.29	-2.34 – 1.76	0.71	-2.77 – 4.18	1.11	-1.58 – 3.79
Radiotherapy	-0.11	-0.61 – 0.39	0.14	-0.72 – 1.01	-0.79	-1.49 – -0.09
Yttrium	-0.32	-1.19 – 0.55	-0.05	-1.85 – 1.76	-0.22	-1.62 – 1.18

	Multivariable linear regression model					
	Δ Total body Z-score R^2=0.23		Δ L2-L4 Z-score R^2=0.15		Δ Femur neck Z-score R^2=0.65	
	Beta	95%CI	Beta	95%CI	Beta	95%CI
Time from first to last DXA	0.03	-0.005 – 0.07				
Time since first treatment at last DXA						
Female sex						
BMI at last DXA						
BMD medication			-1.06	-1.84 – -0.28		
Adulthood onset						
Hypothalamic damage						
Growth hormone replacement therapy					-0.37	-1.27 – 0.53
Gonadal replacement therapy						
Hydrocortisone equivalent dose	-0.06	-0.09 – -0.02				
Epilepsy medication						
Ever hydrocephalus						
Progression			0.04	-0.45 – 0.52		
Surgery						
Radiotherapy					-0.05	-0.67 – 0.57
Yttrium						

All models are corrected for baseline Z-score and age at first DXA-scan. Hydrocortisone dose is a hydrocortisone equivalent dose (mg). Abbreviations: BMD medication = medication to improve bone mineral density; CI = Confidence Interval; DXA = Dual-Energy X-ray Absorptiometry scan; BMI = Body Mass Index; *P* = *P*-value.

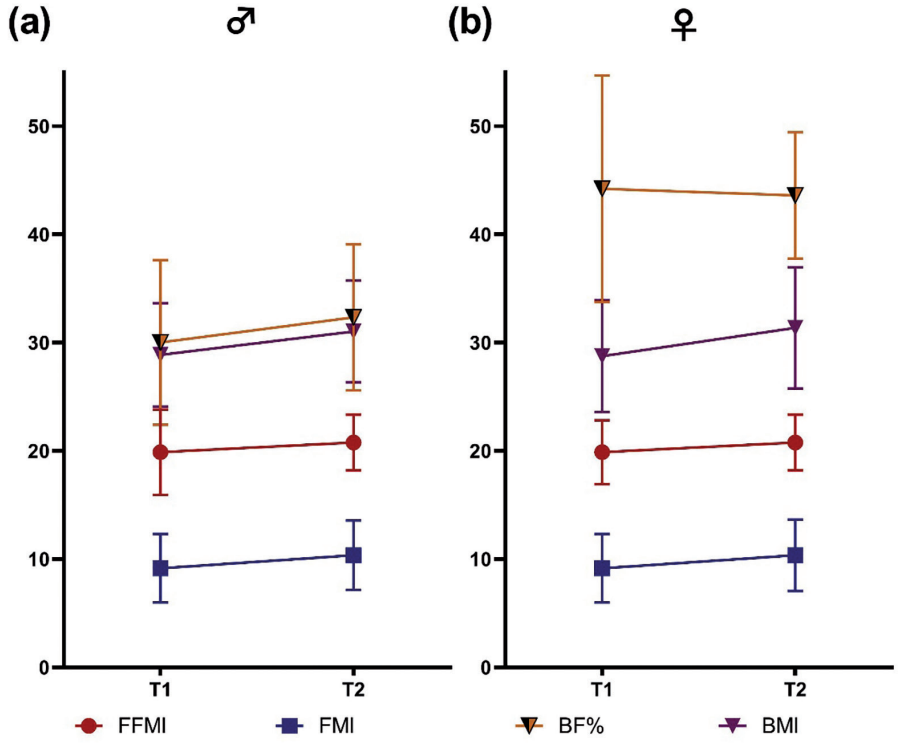
Discussion

This is the first study assessing longitudinally changes in 86 patients with CP, comparing anthropometric and BMD data, with a follow-up of 10 years. In addition, we investigated prognostic factors for BMD change.

Body composition improved in patients with CP during follow-up: FFMI increased and was relatively high, implying an improvement in muscle mass and bone mass, and suggesting that there was hardly any sign of sarcopenic obesity. This increase in age-standardized FFMI was peculiar, since in the general population FFMI usually decreases with advancing age.[41, 42] One may suggest that this increase in muscle and bone mass might be related to physical functioning. However, it is unclear whether gain in muscle mass was a reflection of improved physical performance or sufficient hormonal replacement therapy. In the elderly general population, impaired physical activity performance was associated with FMI rather than with FFMI,[43] and in the male general population, FFMI had a U-shaped relationship with mortality.[44] It is unknown whether the increase in FFMI in our study population affected the mortality in any way. We observed an increase in unstandardized values of body mass and fat-related measures, but not in the age- and sex-specific scores, suggesting that patients did gain fat and total weight with aging, similarly as the general population does. Loss of fat mass is a desired goal of treatment, as obesity and the metabolic syndrome occur very frequently in patients with CP, making improvement of their cardiovascular risk profile an enormous challenge.[9] Both physical activity level and basal metabolic rate are usually low in patients with CP, regardless of fat free mass.[16, 23] Patients may already gain weight in the first year after onset and even before diagnosis.[19] This underlines the difficulty of developing an effective strategy in patients with CP to prevent the development of obesity. Thus, anti-obesity treatment should ideally be started as soon as possible and preferably directly after confirmation of the CP diagnosis.

Interestingly, bone density of the total body, femur neck and L2-L4 improved during follow-up. Independent risk factors for a decrease in bone density scores were glucocorticoids, previous radiotherapy, and,

Figure 1 Body composition measures men and women with craniopharyngioma



Unstandardized mean and SD of fat free mass index (FFMI; red circles), fat mass index (FMI; blue squares), body fat percentage (BF%; black/orange triangles) and body mass index (BMI; purple triangles) are shown at the first Dual-Energy X-ray Absorptiometry (DXA-) scan (T1) and last DXA-scan (T2) in male (A) and female (B) patients with craniopharyngioma. As expected, men had significantly lower FMI values than women at T1 and T2 ($P \leq 0.001$), lower BF% ($P < 0.001$), and higher FFMI ($P < 0.001$); there was no difference in BMI or in changes from T1 to T2. There was a significant increase from T1 to T2 in all patients in BMI ($P < 0.001$), FMI ($P < 0.001$) and FFMI ($P < 0.001$), but not BF% ($P = 0.15$).

remarkably, medication given to improve BMD. It is well known that excessive glucocorticoids can reduce bone mass.[13] Cranial radiotherapy is not only an important risk for pituitary deficiencies and hypothalamic dysfunction, but also for obesity.[45] The authors hypothesized that the improvement in BMD in our cohort was explained by the high obesity rates in patients with CP, as obesity can induce an increase in bone mass and is generally considered to be a protective factor for osteoporosis.[43]

Factors involved in this increase of bone mass in obesity are augmented leptin levels and an increased peripheral conversions of androgens to estrogens.[21] However, in our study, BMI was not associated with bone density change. This is in line with new findings on obesity, if implicated with low-grade inflammation, does not necessarily concur with benefits on bone mass.[43] Obesity may cause a state of leptin resistance.[43] Central leptin resistance or insensitivity due to hypothalamic damage could mediate negative effects of obesity on bone metabolism.[43]

The unexpected finding that medication administered to improve BMD was associated with a decrease in BMD in our study might be due to bias by indication: this medication was likely to be given to patients who already had developed a poor bone health. Administration of GHRT was found to be associated with an increase in bone density. This is consistent with previous literature which describes that discontinuation of GHRT in CO patients before establishing peak bone mass in the first 3 decades of life may be associated with a high prevalence of pathological bone densities.[21]

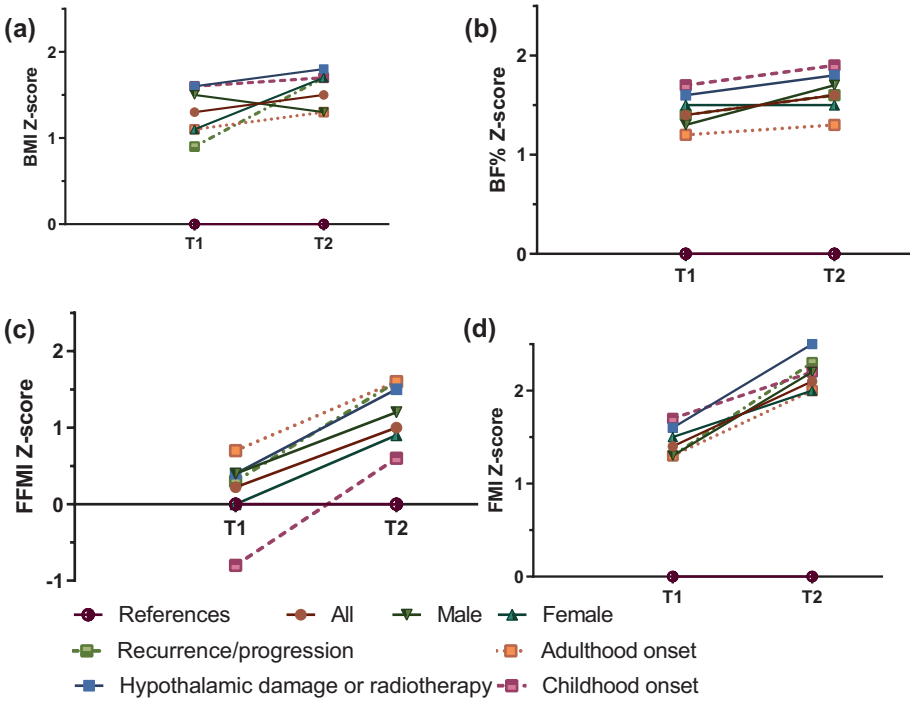
CO patients and patients with previous radiotherapy or hypothalamic damage seemed to be at higher risk for a less favorable body composition than their counter-subgroup. CO patients showed more increase in body mass, fat mass, and fat percentage, and less muscle mass at baseline than AO patients. This may have contributed to their previously found excess risk of diabetes mellitus type 2, cerebral infarction and total mortality,[4] and of morbid obesity, and be related to the higher risk of hypothalamic involvement and panhypopituitarism of CO patients.[24] In addition, the increase in FFMI Z-scores may be, at least partly, related to GHRT.[28, 46, 47] Treatment of CP has changed from gross total resection to more conservative surgery,[24] which could affect body composition and BMD. However, patients treated before and from 2000 onwards almost did not differ, except for total body Z-score, follow-up time, and cohort size.

There are some limitations in this research due to the retrospective design. As discussed before,[8,9] differences in observation can be perceived from different types of DXA-scanners; in 15 out of 198 scan-

results, the scanner type was unknown due to a time period where both DPXL and Prodigy were used. We coped with this aspect by also analyzing data separately per DXA-scanner for the most often used scanner types, and using Z-scores. This study is unique in reporting factors on BMD change in patients with CP, and it is one among few studies reporting longitudinal change in body composition, and represents a large cohort with an extensive follow-up.

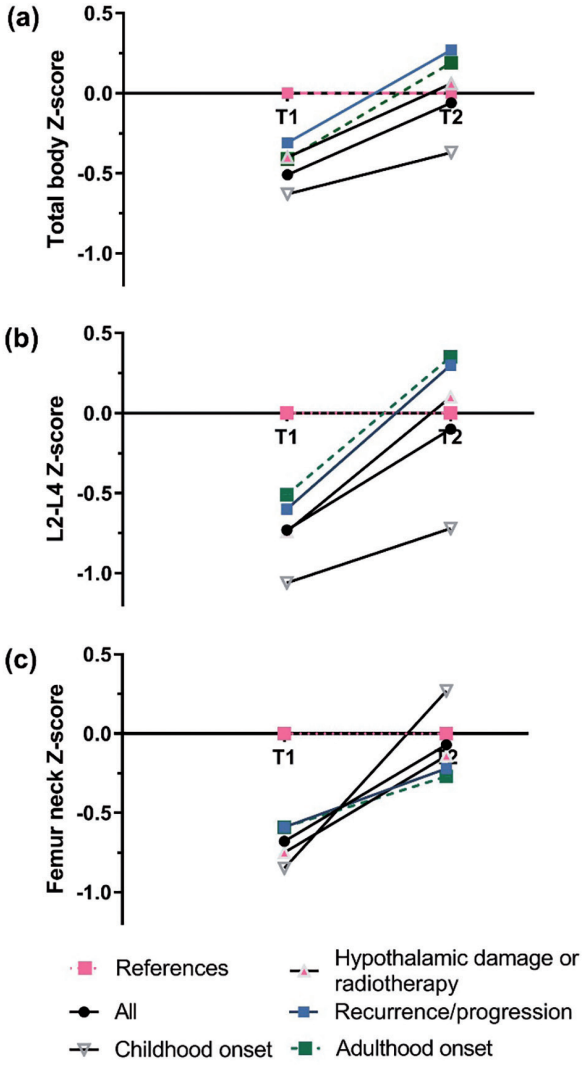
Summarizing, patients with CP remained as stable in body composition as the general population over time, and even showed an increase in bone and muscle mass. Higher glucocorticoid dose and central nervous system irradiation negatively influenced this increase of BMD, while GHRT shows the opposite and it is associated with an increase in bone density. Even though these results are beneficial at glance, there still remains considerable need for improvement, as cardiovascular risk and fracture rates remain unacceptably high in patients with CP.[4,8] In addition, subgroups of CP patients like those with CO disease and hypothalamic damage remain at high risk for adverse anthropometric effects. Future studies among patients with CP should therefore focus on development of methods for early prevention of obesity, interventions to influence body composition and improvement of bone quality in affected individuals, already from the diagnostic phase.

Figure 2 BMI Z-scores at first and last DXA-scan



Sex- and age standardized Z-scores are presented of (A) body mass index (BMI), (B) body fat percentage (BF%), (C) fat free mass index (FFMI) and (D) fat mass index, at first (T1) and last (T2) Dual-Energy X-ray Absorptiometry (DXA-) scan. Data are given as mean ± standard deviation. Male and female patients did not differ in body composition Z-scores. Patients with recurrence or progression of disease increased in BMI Z-scores while patients without recurrence or progression decreased (mean change 0.7 ± 1.3 vs. -0.3 ± 1.4, $P = 0.04$). Patients with hypothalamic damage or radiotherapy had higher BMI Z-scores at T1 (1.7 ± 1.9 vs. 0.7 ± 1.7, $P = 0.004$), T2 (1.8 ± 1.7 vs. 1.0 ± 1.2, $P = 0.01$), higher BF% Z-scores at T1 (1.6 ± 1.0 vs. 1.1 ± 1.2, $P = 0.03$), T2 (1.8 ± 0.8 vs. 1.3 ± 1.1, $P = 0.03$) and differed in change of BF% Z-scores from T1 to T2 (0.1 ± 0.7 vs. -0.3 ± 0.8, $P = 0.02$). They also had a higher FMI Z-scores at T1 (1.6 ± 1.5 vs. 1.0 ± 1.2, $P = 0.06$) and T2 (2.5 ± 1.4 vs. 1.4 ± 1.3, $P = 0.007$), and FFMI Z-scores at T2 (1.5 ± 2.6 vs. 0.3 ± 1.4, $P = 0.03$). Childhood onset patients had higher BF% Z-scores at T2 (1.9 ± 0.8 vs. 1.3 ± 1.0, $P = 0.02$) than adulthood onset patients and increased instead of decreased in BF% Z-scores from T1 to T2 (mean difference 0.2 ± 0.8 vs. -0.3 ± 0.6, $P = 0.04$). They also had lower FFMI Z-scores at T1 (-0.8 ± 1.4 vs. 0.7 ± 1.4, $P < 0.001$) and borderline lower FFMI Zscores at T2 (0.6 ± 2.4 vs. 1.6 ± 2.0, $P = 0.07$).

Figure 3 Total body, L2-L4 and femur neck Z-scores of the first and last DXA-scan



Z-scores at first (T1) and last (T2) Dual-Energy X-ray Absorptiometry (DXA-) scan in all craniopharyngioma patients of (A) total body, (B) L2-L4 and (C) femur neck. Data is given as mean ± standard deviation. Z-scores improved significantly in all patients from T1 to T2 of total body (from -0.49 ± 1.37 to -0.05 ± 1.44, $P < 0.001$), L2-L4 (from -0.77 ± 1.59 to -0.03 ± 1.97, $P < 0.001$) and femur neck (from -0.62 ± 1.32 to -0.09 ± 1.33, $P = 0.02$). There was no significant difference in Z-scores between patients with or without radiotherapy/recurrence or progression/hypothalamic damage or patients with childhood- or adulthood onset disease, at T1, T2 or change from T1 to T2.

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Supplementary Tables

Supplementary Table 1A BMI and FFMI cutoffs

	Low	Normal	High/excess fat	Obese
BMI	<20 kg/m^2	20-24,99 kg/m^2	25-29,99 kg/m^2 (overweight)	≥ 30 kg/m^2 or ≥ 2 SDS
FFMI	≤ -2 SDS	-2 – 2 SDS	≥ 2 SDS	
FMI (M / F)	<3 / <5	3 – 6 / 5 – 9	>6 – 9 / >9 – 13	>9 / >13

Abbreviations: BMI = body mass index; FFMI = fat free mass index; FMI = fat mass index; M / F = Male / Female references; SDS = standardized deviation score. High BMI can be interpreted as an overweight individual. FMI is expressed as fat mass per squared height (kg/m^2).

Supplementary Table 1B BF% cutoffs

	Age 20-39 years		Age 40-59 years	
Sex	**Men**	**Women**	**Men**	**Women**
BF% category				
Low	≤8% or SDS-score ≤-2	≤21% or SDS-score ≤-2	≤11% or SDS-score ≤-2	≤23% or SDS-score ≤-2
Normal	8-26%	21-39%	11-29%	23-41%
High	≥26% or SDS ≥2	≥39% or SDS ≥2	≥29% or SDS ≥2	≥41% or SDS ≥2

Cutoff-values for low, normal and BF%.[1] Abbreviations: BF% = body fat percentage; SDS = standardized deviation scores.

Supplementary Table 2 Patients with craniopharyngioma diagnosed before and after 2000

	Diagnosis before 2000 (n=78)	Diagnosis after 2000 (n=32)	*P*-value
Female sex	38 (49%)	14 (44%)	0.64
Median age at first treatment (range)	20.0 (4 – 62)	9 (6 – 74)	0.08
Childhood onset disease	40 (51%)	10 (31%)	0.06
Surgery	77 (99%)	31 (97%)	1.00
Radiotherapy	43 (55%)	19 (59%)	0.68
Yttrium brachytherapy	11 (14%)	2 (7%)	0.31
Visual deficiencies	56 (77%)	25 (78%)	0.87
Recurrence/progression	28 (36%)	12 (38%)	0.91
Hypothalamic damage	22 (29%)	14 (48%)	0.08
Hydrocephalus	16 (21%)	10 (31%)	0.20
GH deficiency	73 (94%)	31 (97%)	0.49
TSH deficiency	75 (96%)	32 (100%)	0.63
Hypogonadism	71 (91%)	30 (94%)	0.93
Corticotropic deficiency	68 (87%)	27 (84%)	0.93
ADH deficiency	53 (68%)	23 (72%)	0.69
Fracture in history	14 (18%)	7 (22%)	0.63
BMD medication	14 (18%)	2 (6%)	0.20
Median time (years) since first presentation at first DXA	9.8 (0.8 – 57)	3.3 (-0.9 – 12.73)	**0.004**
Median age (years) at first DXA-scan (range)	35 (18-77)	32 (18 – 79)	0.57
Time difference from first to last DXA-scan (years)	12.4 ± 6.5	6.3 ± 4.2	**<0.001**
BMI at first DXA-scan	28.4 ± 4.7	30.0 ± 5.3	0.11
BMI at last DXA-scan	30.9 ± 4.6	32.2 ± 6.5	0.41
Change in BMI	2.3 ± 3.3	1.2 ± 3.4	0.20
BMI Z-score at first DXA-scan	1.2 ± 1.8	1.9 ± 2.1	0.05
BMI Z-score at last DXA-scan	1.4 ± 1.4	2.0 ± 1.89	0.10
Change in BMI Z-score	0.1 ± 1.4	0.0 ± 1.5	0.43

FMI at first DXA-scan	10.3 ± 3.3	11.1 ± 4.2	0.25
FMI at last DXA-scan	11.8 ± 3.7	12.4 ± 4.0	0.57
Change in FMI	1.2 ± 2.4	0.3 ± 2.4	0.24
FMI Z-score at first DXA-scan	1.3 ± 1.3	1.6 ± 1.6	0.21
FMI Z-score at last DXA-scan	2.1 ± 1.4	2.3 ± 1.6	0.60
Change in FMI Z-score	0.1 ± 1.0	0.2 ± 0.8	0.61
FFMI at first DXA-scan	18.1 ± 3.2	18.7 ± 3.2	0.46
FFMI at last DXA-scan	19.0 ± 3.0	19.5 ± 3.6	0.74
FFMI change	1.2 ± 1.9	0.9 ± 1.9	0.33
FFMI Z-score at first DXA-scan	0.1 ± 1.6	0.6 ± 1.7	0.37
FFMI Z-score at last DXA-scan	0.9 ± 2.2	1.4 ± 2.4	0.43
FFMI Z-score change	1.0 ± 1.4	0.6 ± 1.4	0.33
BF% at first DXA-scan	36.5 ± 12.0	36.3 ± 10.7	0.63
BF% at last DXA-scan	37.2 ± 8.5	38.5 ± 8.4	0.63
BF% change	0.2 ± 10.3	0.2 ± 5.6	0.47
BF% Z-score at first DXA-scan	1.3 ± 1.1	1.7 ± 0.7	0.06
BF% Z-score at last DXA-scan	1.6 ± 1.0	1.7 ± 0.8	0.71
BF% Z-score change	0.0 ± 0.8	-0.12 ± 0.57	0.62
Total body BMD at first DXA-scan	1.15 ± 0.12	1.21 ± 0.15	0.06
Total body BMD at last DXA-scan	1.18 ± 0.16	1.23 ± 0.14	0.31
Total body BMD change	0.05 ± 0.11	0.01 ± 0.08	0.23
Total body BMD T-score at first DXA-scan	-0.31 ± 1.45	0.50 ± 1.50	0.07
Total body BMD T-score at last DXA-scan	0.28 ± 1.71	1.00 ± 1.51	0.11
Total body BMD T-score change	0.76 ± 1.12	0.43 ± 0.99	0.38
Total body BMD Z-score at first DXA-scan	-0.77 ± 1.30	0.11 ± 1.36	**0.02**
Total body BMD Z-score at last DXA-scan	-0.22 ± 1.48	0.51 ± 1.24	**0.04**
Total body BMD Z-score change	0.71 ± 1.05	0.49 ± 0.91	0.94

L2-L4 BMD at first DXA-scan	1.13 ± 0.18	1.14 ± 0.22	0.73
L2-L4 BMD at last DXA-scan	1.21 ± 0.27	1.27 ± 0.21	0.19
L2-L4 BMD change	0.11 ± 0.17	0.13 ± 0.15	0.63
L2-L4 BMD T-score at first DXA-scan	-0.64 ±1.61	-0.85 ± 1.53	0.53
L2-L4 BMD T-score at last DXA-scan	-0.05 ± 2.21	0.43 ± 1.69	0.21
L2-L4 BMD T-score change	0.75 ± 1.70	1.04 ± 1.23	0.48
L2-L4 BMD Z-score at first DXA-scan	-0.65 ± 1.56	-0.91 ± 1.52	0.67
L2-L4 BMD Z-score at last DXA-scan	-0.19 ± 2.16	0.20 ± 1.58	0.23
L2-L4 BMD Z-score change	0.50 ± 1.91	1.21 ± 1.09	0.11
Femur neck BMD at first DXA-scan	0.95 ± 0.18	0.99 ± 0.20	0.21
Femur neck BMD at last DXA-scan	0.98 ± 0.23	1.03 ± 0.19	0.26
Femur neck BMD change	0.06 ± 0.27	0.00 ± 0.29	0.58
Femur neck BMD T-score at first DXA-scan	-0.69 ± 1.48	-0.46 ± 1.56	0.50
Femur neck BMD T-score at last DXA-scan	-0.44 ± 1.72	-0.26 ± 1.10	0.37
Femur neck BMD T-score change	0.42 ± 1.97	-0.25 ± 1.82	0.52
Femur neck BMD Z-score at first DXA-scan	-0.67 ±1.31	-0.47 ± 1.40	0.71
Femur neck BMD Z-score at last DXA-scan	-0.10 ± 1.41	-0.06 ± 1.02	0.81
Femur neck BMD Z-score change	0.69 ± 1.83	-0.06 ± 1.88	0.34

Data are given as number and percentage, or mean + SD unless stated otherwise. BF% = body fat percentage; BMD = bone mineral density; BMI = body mass index; DXA-scan = Dual-Energy X-ray Absorptiometry Scan; FFMI = fat free mass index; FMI = fat mass index.

Supplementary Table 3A DXA-results of any DXA-scanner type – Bone mineral Density and Body Composition in male craniopharyngioma patients

	First DXA-scan	Last DXA-scan	Δ	*P*-value
Age (years)	38.2 ± 14.6	49.5 ± 18.2	10.8 ± 6.7	**<0.001**
Bone				
Bone mineral density				
Total body	1.21 ± 0.14	1.24 ± 0.15	0.05 ± 0.09	**0.002**
L2-L4	1.16 ± 0.20	1.31 ± 0.27	0.14 ± 0.20	**<0.001**
Femur neck	0.97 ± 0.21	0.96 ± 0.20	-0.03 ± 0.29	0.41
Femur	1.05 ± 0.23	1.02 ± 0.20	-0.05 ± 0.32	0.28
T-score				
Total body	-0.06 ± 1.74	0.48 ± 1.74	0.72 ± 1.03	**<0.001**
L2-L4	0.60 ± 1.61	0.55 ± 2.21	0.91 ± 2.00	**0.003**
Femur neck	-0.80 ± 1.71	-0.68 ± 1.49	0.02 ± 2.20	0.71
Femur	-0.30 ± 1.80	-0.28 ± 1.46	0.02 ± 2.42	0.91
Z-score				
Total body	-0.54 ± 1.54	-0.02 ± 1.59	0.56 ± 1.30	**<0.001**
L2-L4	-0.52 ± 1.65	0.33 ± 2.23	0.60 ± 2.32	**0.03**
Femur neck	-0.69 ± 1.51	-0.31 ± 1.21	0.25 ± 2.09	0.48
Femur	-0.33 ± 1.66	-0.19 ± 1.31	0.03 ± 2.25	0.81
Body composition				
BMI	28.9 ± 4.7	31.0 ± 4.6	1.58 ± 2.50	**0.001**
BMI SDS	1.63 ± 2.28	1.36 ± 1.51	-0.26 ± 1.38	0.73
FMI	9.1 ± 3.2	10.4 ± 3.2	0.83 ± 2.33	**0.03**
FMI SDS	1.25 ± 1.50	2.24 ± 1.44	0.25 ± 0.92	0.25
FFMI	19.9 ± 2.9	20.8 ± 2.5	0.99 ± 1.93	**0.002**
FFMI SDS	0.45 ± 1.53	1.20 ± 1.79	0.81 ± 1.22	**0.009**
BF%	29.9 ± 7.8	32.4 ± 6.7	1.31 ± 6.42	0.29
BF% SDS	1.34 ± 1.15	1.72 ± 0.90	0.06 ± 0.89	0.91

Δ = mean difference; BF% = Body Fat Percentage; BMD = Bone Mineral Density; BMI = Body Mass Index; DXA = Dual-Energy X-ray Absorptiometry; FFMI = Fat Free Mass Index; FMI = Fat Mass Index; SDS = Standardized Deviation Scores. Data are expressed as mean ± SD.

Supplementary Table 3B DXA-results of any DXA-scanner type – Bone mineral Density and Body Composition in female craniopharyngioma patients

	First DXA-scan	Last DXA-scan	Δ	*P*-value
Age (years)	35.3 ± 15.2	46.4 ± 14.6	11.3 ± 6.4	**<0.001**
Bone				
Bone mineral density				
Total body	1.12 ± 0.09	1.13 ± 0.15	0.02 ± 0.11	0.24
L2-L4	1.10 ± 0.18	1.15 ± 0.22	0.08 ± 0.13	**0.003**
Femur neck	0.94 ± 0.14	1.02 ± 0.24	0.11 ± 0.23	**0.02**
Femur	0.98 ± 0.17	1.05 ± 0.23	0.16 ± 0.27	0.07
T-score				
Total body	-0.15 ± 1.16	0.38 ± 1.63	0.59 ± 1.13	**0.01**
L2-L4	-0.83 ± 1.52	-0.37 ± 1.89	0.65 ± 1.11	**0.01**
Femur neck	-0.43 ± 1.12	-0.16 ± 1.67	0.46 ± 1.63	0.15
Femur	-0.22 ± 1.26	0.06 ± 1.58	0.63 ± 1.84	0.21
Z-score				
Total body	-0.44 ± 1.13	-0.07 ± 1.26	0.66 ± 0.89	**0.001**
L2-L4	-0.95 ± 1.38	-0.47 ± 1.77	0.76 ± 0.97	**<0.001**
Femur neck	-0.52 ± 1.06	0.10 ± 1.41	0.80 ± 1.55	**0.007**
Femur	-0.29 ± 0.95	0.15 ± 1.38	0.74 ± 1.84	0.17
Body composition				
BMI	28.8 ± 5.2	31.4 ± 5.6	2.43 ± 4.03	**0.001**
BMI SDS	1.12 ± 1.39	1.67 ± 1.60	0.44 ± 1.38	0.11
FMI	12.3 ± 3.3	13.7 ± 3.6	1.14 ± 2.59	**0.01**
FMI SDS	1.52 ± 1.30	2.05 ± 1.50	-0.03 ± 0.87	0.96
FFMI	16.0 ± 1.8	17.2 ± 2.7	1.31 ± 1.81	**0.001**
FFMI SDS	0.05 ± 1.72	0.92 ± 2.58	1.00 ± 1.56	**0.006**
BF%	44.2 ± 10.5	43.6 ± 5.8	-0.97 ± 12.04	0.20
BF% SDS	1.50 ± 1.95	1.52 ± 1.02	-0.11 ± 0.53	0.37

Δ = mean difference; BF% = Body Fat Percentage; BMD = Bone Mineral Density; BMI = Body Mass Index; DXA = Dual-Energy X-ray Absorptiometry; FFMI = Fat Free Mass Index; FMI = Fat Mass Index; SDS = Standardized Deviation Scores. Data are expressed as mean ± SD.

Supplementary Table 4 DXA-results of the Prodigy – Body composition and bone mineral density in all craniopharyngioma patients

	First DXA-scan	Last DXA-scan	Δ	*P*-value
Body composition				
BMI	29.3 ± 5.5	31.2 ± 5.3	1.7 ± 3.1	**<0.001**
BMI SDS	1.9 ± 4.0	1.4 ± 1.6	0.2 ± 1.4	0.41
FMI	11.3 ± 3.6	12.3 ± 3.7	1.2 ± 2.2	**0.001**
FMI SDS	1.8 ± 1.4	2.2 ± 1.4	0.3 ± 0.8	**0.04**
FFMI	17.8 ± 2.8	18.8 ± 3.4	1.3 ± 1.7	**<0.001**
FFMI SDS	0.1 ± 1.7	1.3 ± 2.6	1.1 ± 1.3	**<0.001**
BF%	37.9 ± 8.1	39.7 ± 8.3	1.9 ± 4.8	**0.005**
BF% SDS	1.8 ± 1.2	1.9 ± 0.9	0.3 ± 0.7	**0.03**
Bone mineral density				
Total body	1.17 ± 0.14	1.21 ± 0.15	0.04 ± 0.08	**0.002**
L2-L4	1.16 ± 0.20	1.26 ± 0.25	0.08 ± 0.17	**0.004**
Femur neck	0.99 ± 0.18	1.01 ± 0.22	0.02 ± 0.24	0.79
Femur	1.03 ± 0.18	1.06 ± 0.21	0.03 ± 0.26	0.63
T-score				
Total body	0.00 ± 1.41	0.71 ± 1.63	0.56 ± 0.95	**<0.001**
L2-L4	-0.42 ± 1.65	0.27 ± 2.04	0.51 ± 1.65	0.02
Femur neck	-0.39 ± 1.45	-0.34 ± 1.64	0.05 ± 1.78	0.71
Femur	-0.21 ± 1.38	-0.02 ± 1.54	0.23 ± 1.85	0.72
Z-score				
Total body	-0.40 ± 1.30	0.13 ± 1.47	0.54 ± 0.85	**<0.001**
L2-L4	-0.48 ± 1.68	-0.03 ± 2.05	0.34 ± 1.78	0.08
Femur neck	-0.30 ± 1.27	0.00 ± 1.39	0.25 ± 1.74	0.26
Femur	-0.21 ± 1.30	0.11 ± 1.36	0.32 ± 1.80	0.32

Δ = mean difference; BF% = Body Fat Percentage; BMD = Bone Mineral Density; BMI = Body Mass Index; DXA = Dual-Energy X-ray Absorptiometry; FFMI = Fat Free Mass Index; FMI = Fat Mass Index; SDS = Standardized Deviation Scores.
Data are expressed as mean ± SD.

Supplementary Table 5 DXA-results of the DPXL – Body composition and bone mineral density in all craniopharyngioma patients

	First DXA-scan	Last DXA-scan	Δ	*P*-value
Body composition				
BMI	28.4 ± 5.1	28.7 ± 4.1	1.0 ± 2.5	0.06
BMI SDS	1.0 ± 1.3	1.0 ± 1.2	0.1 ± 1.1	0.22
FMI	10.7 ± 4.1	9.8 ± 3.6	-1.0 ± 3.9	0.21
FMI SDS	1.2 ± 1.3	1.2 ± 1.3	-0.2 ± 0.9	0.19
FFMI	18.0 ± 3.3	17.4 ± 4.4	-0.4 ± 3.4	0.61
FFMI SDS	0.3 ± 1.9	-0.1 ± 1.7	0.1 ± 0.8	0.77
BF%	35.5 ± 10.0	33.3 ± 9.9	-2.1 ± 5.0	**0.04**
BF% SDS	1.3 ± 1.3	1.2 ± 1.3	-0.4 ± 0.6	**0.001**
Bone mineral density				
Total body	1.14 ± 0.11	1.16 ± 0.11	0.03 ± 0.07	**0.005**
L2-L4	1.13 ± 0.16	1.23 ± 0.21	0.10 ± 0.09	**<0.001**
Femur neck	0.90 ± 0.13	0.97 ± 0.14	0.06 ± 0.08	**0.005**
T-score				
Total body	-0.29 ± 1.38	-0.14 ± 1.19	0.27 ± 0.87	0.07
L2-L4	-0.68 ± 1.39	0.14 ± 1.74	0.85 ± 0.77	**<0.001**
Femur neck	-1.04 ± 1.16	-0.46 ± 1.20	0.51 ± 0.96	**0.01**
Z-score				
Total body	-0.76 ± 1.16	-0.44 ± 1.26	0.45 ± 0.56	**0.001**
L2-L4	-0.72 ± 1.25	-0.12 ± 1.58	0.60 ± 0.88	**0.006**
Femur neck	-0.97 ± 1.08	-0.36 ± 0.98	0.60 ± 0.84	**0.002**

Δ = mean difference; BF% = Body Fat Percentage; BMD = Bone Mineral Density; BMI = Body Mass Index; DXA = Dual-Energy X-ray Absorptiometry; FFMI = Fat Free Mass Index; FMI = Fat Mass Index; SDS = Standardized Deviation Scores. Data are expressed as mean ± SD.

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Diagnosing Metabolic Syndrome in Craniopharyngioma Patients: Body Composition Versus BMI

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Abstract

Objective: Craniopharyngioma patients often have poor metabolic profiles due to hypothalamic–pituitary damage. Previously, using BMI as obesity marker, the occurrence of the metabolic syndrome in these patients was estimated at 46%. Our aim was to determine if dual-energy X-ray absorptiometry (DXA) scan in evaluation of obesity and metabolic syndrome would be superior.

Design: Retrospective study of craniopharyngioma patients for whom DXA scan results were available.

Methods: BMI, fat percentage and fat mass index were used to evaluate obesity and as components for obesity in metabolic syndrome.

Results: Ninety-five craniopharyngioma patients were included (51% female, 49% childhood-onset disease). Metabolic syndrome occurred in 34-53 (45-51%) subjects (depending on the definition of obesity, although all definitions occurred in higher frequency than in the general population). Metabolic syndrome frequency was higher if obesity was defined by fat percentage (52% vs. 42%) or fat mass index (51% vs. 43%) compared to BMI. Misclassification appeared in 9% (fat percentage vs. BMI) and 7% (fat mass index vs. BMI) for metabolic syndrome and 29% and 13% for obesity itself, respectively. For metabolic syndrome, almost perfect agreement was found for BMI compared with fat percentage or fat mass index. For obesity, agreement was fair to moderate (BMI vs. fat percentage).

Conclusion: Using BMI to evaluate obesity underestimates the true prevalence of metabolic syndrome in patients with craniopharyngioma. Furthermore, fat percentage contributes to a better evaluation of obesity than BMI. The contribution of DXA scan might be limited for identification of the metabolic syndrome.

Keywords: body composition, craniopharyngioma, metabolic syndrome, DXA-scan.

Introduction

Craniopharyngiomas (CPs) are tumors in the (supra)sellar region that occur both in children and adults, with peak incidences between ages 5–9 and 40–44 years.[1, 2] These tumors are rare with an the estimated incidence rate of 1.7 per million person years[1, 2] and relatively high 10-year survival rates at between 77 and 93%.[2, 3] Still, the burden to patients, their families[2, 4] and to the community is substantial, particularly because of the increased risk of long-term morbidity[2, 5, 6] and mortality compared to the general population.[2, 3, 5, 7] The standardized mortality ratio from cardio- and cerebrovascular disease has been reported to be between 3.2 and 19.4.[2, 6, 8]

Although histologically benign, CP can physically disturb important neurovascular structures,[9] particularly the hypothalamus, pituitary and optic nerves.[3, 9] The hypothalamus plays a major role in integrating hormonal, metabolic and neural signals for energy homeostasis.[7] Failure of the hypothalamo–pituitary axis is strongly linked with the development of obesity, metabolic syndrome[3, 7, 10, 11, 12] and subsequent cardiovascular disease.[8, 13] Visual impairment (i.e. due to tumor growth near the optic nerve) occurs in approximately 75% of the patients[3] and is a barrier to engage in physical activity.

Up to two-thirds of the patients are found to be overweight or obese,[3, 14] and in a study of 224 Dutch and Swedish patients, 9% has been diagnosed with type II diabetes mellitus (T2D).[5] Obesity and T2D are both associated with cardiovascular disease and cerebral infarction;[15, 16] the latter has been shown to be an important cause of mortality.[5] Severe weight gain is especially seen in the first year after the operation.[17] Both levels of physical activity and basal metabolic rate are low in patients with CP.[7, 18]

Obesity is an important contributor to the metabolic syndrome (MetS) in CP survivors.[6] Many definitions of MetS have been formulated, but all include obesity, dyslipidemia, hypertension and altered glucose metabolism as components.[6] MetS and T2D are two important risk factors for cardiovascular disease, giving a two-fold and five-fold

elevated risk respectively.[19] MetS is associated with an increase in all-risk mortality.[20] The prevalence of MetS has been estimated to be 46% in a previous study of CP survivors.[6] This is very high compared to the general population (15% in the Swedish and the 26% in Dutch populations of that age).[6] Obesity rates in the previous study were estimated based on BMI. BMI is the most accessible method for estimating obesity in a clinical setting, but does not take into account an altered body composition. Dual-Energy X-ray absorptiometry (DXA scan) is considered the gold standard for determining body composition where there is suspected discordance between BMI and adiposity.[21] Furthermore, compared with measurement of body fat percentage (BF%) by DXA scan, BMI has been found to underestimate obesity in adult, non-CP childhood cancer survivors.[22] Therefore, considering the relatively substantial contribution of adiposity to MetS in CP survivors, we hypothesized that the occurrence of MetS defined using BMI is underestimated in our cohort of CP patients due to their altered body composition.

Our aim was to investigate the value of DXA scan in cardiovascular risk assessment in CP patients. Our main objective was to compare the relative effectiveness of BMI and DXA scan-derived body composition measures such as BF% and fat mass index (FMI) in the evaluation of MetS. Our secondary objective was also to determine influencing factors of obesity and MetS in CP survivors. Our approach was to determine the agreement between methods and to perform logistic regression models.

Subjects and methods

Patients and study design

The study had a cross-sectional and retrospective design. Patients treated for CP at the Erasmus University Medical Center (Erasmus MC, Rotterdam, the Netherlands) and Sahlgrenska University Hospital (Gothenburg, Sweden) were included as described before.[6] Only patients with at least one DXA scan available were included in the study (included, n = 95; excluded, n = 61, description shown in Supplementary Table 1, see section on supplementary data given at the end of this

article). The decision to perform a DXA scan was made by the physicians in the context of general care. Although it was not possible to retrieve much information on why the decision was made, it may be assumed this was done to evaluate bone mineral density (BMD). If BMD was not of interest, bio-electrical impedance analysis measurements were an option in the Erasmus MC, which are less costly, easier to plan and do not involve any radiation. The most frequently used DXA scanners were Lunar DPXL, Lunar Prodigy and Lunar iDXA (see Supplementary Table 2). The study was approved by the Ethical Review Board of Erasmus MC and the Regional Ethical Review Board, Gothenburg University. All patients gave their informed consent.

Table 1 Definition of the metabolic syndrome: adjustments to the Joint Interim Statement[6]

At least three of the following five criteria:
Obesity defined by high body mass index (BMI), or defined by high body fat percentage (BF%), or defined by high fat mass index (FMI)
Fasting glucose ≥5.6 mmol/L (or corresponding HbA1c of ≥5.2% or 33.3 mmol/mol) or drug treatment for increased glucose
Triglycerides ≥1.7 mmol/L or drug treatment for elevated triglycerides
HDL cholesterol <1.0 mmol/L in males and <1.3 mmol/L in females or drug treatment for reduced HDL cholesterol
Blood pressure ≥130/85 mmHg or drug treatment for hypertension

HDL= High-density lipoprotein.
BMI was calculated by dividing the weight (kg) per squared height (meters). FMI was calculated by total fat mass (kg) per square height (meters).
Obesity (high BMI): defined by BMI >30, or by ≥2 SDS-score.
Obesity (high BF%): defined by high BF% with limits defined according to sex and age (for females as a BF% ≥39% if aged 20-39 years old or ≥41% between 40-59 years old, and for males ≥26% if 20-39 years old or ≥29% in the age category of 40-59), or by SDS-score ≥2).
Obesity (high FMI): defined by high FMI with limits defined according to sex and age (for adult females ≥ 13; for males ≥ 9).

Data collection

The methods and definitions for data collection were described previously.[6] Hypothalamic damage is defined as tumor- and/or treatment-related injury to the hypothalamus and/or third ventricle as visualized by neuroimaging.[6] If patients were treated for ACTH deficiency with cortisone acetate, the dose was converted to a hydrocortisone equivalent dose (described previously[23]). For the current study, the presence of MetS criteria was evaluated as close as possible (±3 years) to the last DXA scan. The results of DXA scan, including BMI, FMI and BF% were gathered. If patients had more than one scan, data from the first and last DXA scan were gathered.

The criteria used in the definition for MetS were according to the joint interim statement as described previously[6] with modification of the criterion of obesity and matching HbA1c values for high glucose (Table 1). MetS includes components of obesity, low high-density lipoprotein (HDL) cholesterol and high triglycerides, fasting glucose/HbA1c and blood pressure or pharmaceutical treatment (see below and Table 1). Three different definitions of obesity were used as criterion for MetS: based on high BMI, high BF% and high FMI. High BMI was defined as >30 kg/m^2 or SDS >2.[24, 25] High BF% was defined through total body fat percentage as measured by DXA; for females as a BF% ≥39% if aged 20–39 years old or ≥41% if aged 40–59 years old. For males, this was ≥26% if aged 20–39 years old or ≥29% if aged 40–59 years old, or by SDS-score ≥2.[21] High FMI (kg fat mass/m^2, measured by DXA scan) was defined for adult females as ≥13, for adult males ≥9[26] (Table 1). The MetS definitions are referred to as MetS (BMI), MetS (BF%) and MetS (FMI), since the obesity component is the only component varying. The cutoff value for BMI of >30 kg/m^2 was chosen, because this conforms with our previous research[6] and is an alternative for waist circumference according to the International Diabetes Federation (IDF) consensus[27] and World Health Organization (WHO) definition.[28]

Standardized deviation scores (SDS) of BMI, FMI and BF% were calculated with the corresponding reference groups.[29-40] For BF% in adults and FMI, data from a Swedish reference group was used.[29] If

the patient was of a different ethnic background from the majority, a reference group from the country of origin was used instead, if available. DXA data from any type of scanner were accepted. When the age of our subjects at the moment of DXA scan conformed to the reference population (30–70 for the Dutch and 45–69 years for the Swedish population), a comparison of occurrence of MetS at last DXA scan was made and a weighted mean was calculated based on the sex and country of origin.[30, 41] The same was done for the components of MetS; a comparison with the general population was made with two definitions for low HDL cholesterol and hypertension since the study (the NL de Maat study) used to compare the Dutch figures had different cutoff values and did not regard medication.[30]

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0 and Graphpad version 7.04. Unless stated otherwise, data are presented as mean and standard deviation (s.d.). Statistical significance was accepted at a $P \leq 0.05$. For normally distributed data, an unpaired T-test was used for group comparisons; Mann–Whitney U tests were used for non-normally distributed data. Comparisons of proportions were conducted using the Fisher's exact test or the $\chi 2$ test as indicated. McNemar's test was performed in the case of two related dichotomous variables. The Kruskal–Wallis test was used to compare multiple groups and non-normally distributed outcomes. To identify risk factors for MetS and its components, a univariable logistic regression model was performed first; only significant predictors ($P < 0.05$) were entered in the multiple logistic regression analysis thereafter. Refinement was performed by adding variables with P values < 0.20 if the number of events allowed it (with rule of thumb ~10 events per variable). The most significant contributor was left in the model if more candidates were present than number of variables to fill; when equal options were available, the highest Nagelkerke R^2 and best discrimination was chosen. The dependent variables were studied with forced entry. The Student's T-test was used to compare normally distributed variables, and the Wilcoxon rank-sum test was

used to compare non-normally distributed variables. The one sample binomial T-test was used to compare our data with the reference population Bonferroni adjustments were used if applicable to correct for multiple testing. Cohen's kappa and the Altman–Bland method (with the difference of the mean of two methods) were used to check for agreement between methods of measuring MetS and obesity to compare the definitions.

Results

Baseline characteristics

The baseline characteristics of the 95 CP patients included are shown in Table 2. Childhood onset (CO) of the disease was observed in 46 patients (49%) and 51% of all patients were female. The median follow-up time was 19 years (range 1–62). The median age at last follow-up was 45 years (range 16–78), mean age at first DXA scan was 35 years (range 11–79) and the mean time from first to last DXA scan was 10.4 years (range 0.1–23.3). The mean time from first treatment to first DXA scan was 8.9 years (s.d. 9.8, range −8.7 to 47.0). Patient characteristics did not differ significantly between males and females, except for pituitary deficiencies which were more prevalent in males (Table 2). In males, there was a trend for higher frequency of TSH deficiency (47 (100%) vs. 43 (90%), $P = 0.06$) and for higher ACTH deficiency (43 (92%) vs. 36 (77%), $P = 0.05$). Sex hormone replacement therapy was used by 74 patients with hypogonadotropic hypogonadism (79% of males and premenopausal females). Use of sex hormone replacement therapy was significantly higher in males than females (94 vs. 65%, $P = 0.001$), also after postmenopausal women were excluded (96 vs. 78%, $P = 0.012$). Patients with CO craniopharyngioma (CO CP) had a longer follow-up (median 22 vs. 16 years, $P < 0.05$), higher frequency of radiotherapy in the past (65 vs. 42%, $P = 0.02$) and greater occurrence of epilepsy (22 vs. 6%, $P = 0.03$) compared with patients with adulthood-onset (AO) CP. A comparison of the included and excluded patients from the original cohort[6] is presented in Supplementary Table 1. Of 95 patients, 93 had two or more DXA scans available; at first and last

DXA scan, respectively 66 and 74 patients had enough data available to evaluate MetS (BMI), 66 and 69 to evaluate MetS (BF%), and 61 and 67 patients to evaluate MetS (FMI).

Table 2 Characteristics of our cohort of 95 Dutch and Swedish craniopharyngioma patients

	All cranio-pharyngiomas (n=95)	Females (n=48)	Males (n=47)
Baseline characteristics			
Age at presentation (years)[a]	22 (3-62)	22 (4-62)	16 (3-62)
Childhood-onset (n [%])	47 (50)	24 (50)	23 (49)
Adult-onset (n [%])	48 (51)	24 (50)	24 (51)
Follow-up since presentation (years)[a]	19 (1-62)	20 (3-62)	17 (1-39)
Age at last follow-up (years)[a]	45 (16-78)	45 (17-77)	53 (16-78)
Tumor characteristics			
Location (n [%]) at presentation			
Intrasellar	2 (2)	1 (2)	1 (2)
Suprasellar	47 (50)	25 (52)	22 (47)
Intra-/suprasellar	39 (41)	21 (44)	18 (38)
No information available	7 (7)	1 (2)	6 (13)
Hydrocephalus (n [%])	20 (21)	12 (26)	8 (19)
Hypothalamic damage (n [%])	31 (34)	16 (34)	15 (34)

Craniopharyngioma treatment			
Neurosurgery (n [%])	93 (98)	46 (96)	47 (100)
Radiotherapy (n [%])	51 (54)	25 (52)	26 (55)
^{90}Yttrium brachytherapy (n [%])	9 (10)	7 (15)	2 (4)
Recurrence (n [%])	33 (35)	18 (38)	14 (31)
Long-term health outcome			
Pituitary hormone deficiencies (n [%])			
GH	89 (95)[b]	45 (96)	44 (94)
FSH/LH	85 (90)[c]	41 (85)	44 (94)
TSH	90 (95)[d]	43 (90)	47 (100)*
ACTH	79 (84)[d]	36 (77)	43 (92)**
AVP	65 (69)[d]	34 (71)	31 (67)
Visual impairment (n [%])	72 (78)[e]	37 (80)	35 (76)
Treatment for epilepsy (n [%])	6 (6)	3 (6)	4 (9)
Treatment for psychiatric illness (n [%])	12 (13)	6 (13)	6 (13)

[a]Median (range). [b]Replacement therapy was used by 80 patients with growth hormone deficiency (91%). [c]Replacement therapy was used by 74 patients with hypogonadotropic hypogonadism (79 % of males and premenopausal females); it was significantly higher in males than females (94% vs. 65%, $P = 0.001$), also after exclusion of postmenopausal women (96% vs. 78%, $P = 0.012$). [d]All patients were substituted with replacement therapy except for one patient, who was diagnosed with ACTH deficiency by metyraponetest but did not receive treatment later. [e]Missing data for 3 subjects; 76% of the entire cohort. ACTH = Adrenocorticotropic hormone; AVP = arginine vasopressin or antidiuretic hormone; FSH/LH = Follicle stimulating hormone/luteinizing hormone; GH = Growth hormone; n = Number; TSH = Thyroid stimulating hormone. *$P = 0.06$. **$P = 0.05$. Mean hydrocortisone dose or equivalent was 20.9 ± 6.2 mg, range 5-50 (data available for n=76).

The MetS and its components

Information on MetS (components) is presented in Tables 3 and 4. In 64 cases (78%), MetS components were evaluated within ±1 year of the last DXA scan. In Supplementary Table 3, a comparison is made for patients where evaluation of MetS criteria was performed within 1 year or more than 1 year before or after DEXA scan. Patients evaluated within 1 year of DXA scan had a lower rate of obesity based on BF% at last DXA scan (46 vs. 80%, $P = 0.03$).

At last DXA scan, MetS defined by BMI, BF% and FMI occurred in 33 (45%), 35 (51%), and 34 (51%) subjects, respectively (Table 3). The frequency of MetS was comparable to our previous study of CP patients in which DXA scans were not used (*P* values for BMI, BF% and FMI respectively $P = 0.45$, $P = 0.25$, and $P = 0.26$)[6], and were at all rates higher than those in the general population ($P < 0.001$). At last DXA scan, MetS is estimated to be (borderline) higher if defined by BF% or FMI vs. BMI ($P = 0.03$, $P = 0.06$) in the current cohort. Subjects had an increased occurrence of obesity compared to the general population (range: 53–67% vs. 30–31% depending on the definition, $P < 0.05$) (Table 3). The occurrence of hypertension and low HDL cholesterol was higher than the general population, with frequencies of 40 ($P < 0.001$) and 62% ($P < 0.001$), respectively. Here MetS criteria took into account medication use. MetS was significantly more prevalent in obese compared to non-obese subjects if obesity was defined with BMI (62 vs. 21%, $P = 0.001$), BF% (55 vs. 15%, $P = 0.01$) and FMI (63 vs. 25%, $P < 0.01$). Visual deficits were also more prevalent in obese compared with non-obese patients with CP (if defined by increased BF% at first DXA scan 85 vs. 59%, $P = 0.01$; if defined by increased FMI at first DXA scan 90 vs. 79%, $P < 0.05$; if defined by high FMI at last DXA scan 90 vs. 69%, $P = 0.03$). Unexpectedly, there was no significant difference in hypothalamic damage between obese and non-obese subjects, but a trend was shown for some definitions (based on BMI at first DXA scan 41 vs. 25%, $P = 0.14$; at last DXA scan 44 vs. 25%, $P = 0.07$, based on BF% at first DXA scan 40 vs. 29%, $P = 0.31$; at last DXA scan 46 vs. 32%, $P = 0.23$, based on FMI at first DXA scan 43 vs. 24%, $P = 0.06$; at last DXA scan 46 vs. 27%, $P = 0.09$).

CO CP patients had a higher occurrence of obesity defined by BF% at last DXA scan (87 vs. 59%, $P = 0.03$) and a lower occurrence of the MetS component hypertension (31 vs. 60%, $P < 0.01$) than AO CP. The presence or absence of growth hormone replacement treatment in patients had no effect on MetS components.

Longitudinal change of metabolic parameters

The following numbers include only patients that have MetS (components) evaluated at both first and last DXA scan to evaluate possible longitudinal changes. There was no significant change in frequency of MetS of any definition during follow-up for MetS based on BMI from 31 (49%) to 25 (40%), $P = 0.31$; for MetS based on BF% from 31 (53%) to 27 (47%), $P = 0.52$; for MetS based on FMI from 32 (56%) to 27 (47%), $P = 0.41$). Obesity frequencies defined by BMI showed a trend to increase between first and last visit (34 (44%) vs. 43 (56%), $P = 0.06$), but obesity rates defined by BF% and FMI did not change (respectively from 42 (66%) to 44 (69%), $P = 0.82$; from 27 (47%) to 32 (56%), $P = 0.27$. Importantly, the number of patients with hypertension increased significantly (19 (26%) vs. 34 (46%), $P = 0.008$). However, the MetS component low HDL cholesterol did not change significantly (from 38 (54%) to 27 (39%), $P = 0.09$). Neither was there a change in the components of high glucose (from 42 (62%) at first to 44 (65%) at last DXA scan, $P = 0.84$) or low HDL cholesterol (from 38 (54%) to 27 (39%), $P = 0.09$). The component high triglycerides decreased from 35 (51%) to 19 (28%) ($P = 0.01$).

Table 3 Metabolic syndrome and its components in patients with craniopharyngioma

	All CP	Ref. CP	Norm. data	*P*
MetS				
BMI	33 (45%)	20 (57%)	19%	**<0.001**
BF%	35 (51%)	20 (67%)	19%	**<0.001**
FMI	34 (51%)	19 (63%)	17%	**<0.001**

Metabolic components				
Obesity (FD)				
BMI	35 (43%)	16 (53%)	31%	**<0.05**
BF%	53 (64%)	21 (66%)	31%	**<0.05**
FMI	30 (47%)	17 (57%)	30%	**<0.05**
Obesity (LD)				
BMI	49 (57%)	29 (58%)	31%	**<0.05**
BF%	48 (75%)	18 (62%)	31%	**<0.05**
FMI	41 (59%)	22 (67%)	31%	**<0.05**
High glucose	52 (67%)	NA	NA	NA
High triglycerides	22 (29%)	NA	NA	NA
Low HDL	32 (41%)	4 (7%)*	7%	0.50
High blood pressure	37 (46%)	12 (22%)**	32%	0.07

	Dutch (n=35) vs. Sweden (n=60)	***P***	**♀ (n=48) vs. ♂ (n=47)**	***P***
MetS				
BMI	73% vs. 37%	**0.01**	43% vs. 46%	0.82
BF%	65% vs. 46%	0.18	54% vs. 46%	0.91
FMI	78% vs. 47%	0.15	52% vs. 50%	0.90
Metabolic components				
Obesity (FD)				
BMI	38% vs. 45%	0.58	40% vs. 46%	0.57
BF%	44% vs. 72%	**0.01**	59% vs. 69%	0.32
FMI	33% vs. 49%	0.48	40% vs. 53%	0.30
Obesity (LD)				
BMI	63% vs. 54%	0.45	52% vs. 61%	0.40
BF%	63% vs. 80%	0.21	69% vs. 81%	0.25
FMI	50% vs. 60%	0.54	55% vs. 62%	0.57
High glucose	75% vs. 64%	0.36	53% vs. 80%	**0.01**
High triglycerides	63% vs. 20%	**0.004**	42% vs. 18%	**0.02**

Low HDL	58% vs. 36%	0.09	51% vs. 31%	0.07
High blood pressure	38% vs. 48%	0.42	41% vs. 50%	0.42

Abbreviations: BF% = body fat percentage; BMI = body mass index; CP = craniopharyngioma; FD = first DXA-scan (Dual-Energy X-ray Absorptiometry scan); FMI = fat mass index; HDL = High-density lipoprotein cholesterol; LD = Last DXA-scan; Norm. = Normative; MetS = metabolic syndrome; n = number; NA = Not Available; *P* = *P*-value; Ref. CP = referenced CP (all CP in the same age group as reference population); ♀ = Female; ♂ = Male. Baseline differences between Dutch and Swedish patients were age at presentation (median 16 vs. 30 years; *P* = 0.021), growth hormone replacement therapy (74% vs. 92%, *P* = 0.018), hypothalamic damage (59% vs. 22%; *P* = 0.01). MetS (component) definitions: see Table 1. MetS (components) are components evaluated at LD, except obesity (FD and LD). *For all adult patients HDL ≤ 0.9 mmol/l regardless sex/ medication to compare with reference data. If defined as in Table 1, low HDL occurs in 15 patients (40%) (higher than the normative data (*P*<0.001)). **Defined as blood pressure >140/90 mmHg, regardless use of medication. If defined as in Table 1, it occurs in 24 patients (62%) (higher than normative data (*P*<0.001)). Respectively 74, 69 and 67 patients had enough data available to evaluate MetS (BMI), MetS (BF%), MetS (FMI). The data set was not complete in all patients.

Agreement between anthropometric measurements and DXA scan for MetS and obesity

A Cohen's kappa measurement of agreement was performed with MetS and obesity (Supplementary Table 4). Almost perfect agreements were found between MetS evaluated by BMI and either MetS evaluated by BF% (Kappa 0.82, *P* < 0.001) or MetS evaluated by FMI (Kappa 0.85, *P* < 0.001). MetS was evaluated incorrectly by BMI compared to BF% in six patients (9%) and FMI in five patients (7%) (Table 5). At last DXA scan, the estimated occurrence of MetS was lower when evaluated by BMI as compared to BF% and FMI (respectively 42 vs. 52% (*P* = 0.03), 43 vs. 51% (*P* = 0.06)). This was not the case for the first DXA scan (respectively 49 vs. 54%, *P* = 0.38; 48 vs. 53%, *P* = 0.25), suggesting the difference in estimation of MetS becomes less accurate as patients become older. In Figure 1, BMI was set out vs. BF% and FMI to illustrate discordances in the evaluation of obesity. The occurrence of obesity was lower if assessed by BMI when compared with obesity assessed by BF% (43 vs. 65%, *P* < 0.001 at first DXA scan, 58 vs. 74%, *P* = 0.03 at last DXA scan) but not when compared to FMI (41% vs. 47%, *P* = 0.22

at first DXA scan; 57 vs. 58%, $P = 1.00$ at last DXA scan). At last DXA scan, obesity estimations are discordant if BMI is compared to BF% (18 patients (29%)) and FMI (9 patients (13%)) at last DXA scan (see Table 6 for concordance of obesity measures). A Bland–Altman plot and analysis[42] was performed for BMI SDS with BF% and FMI SDS (Figure 2 and Supplementary Table 5). An upward trend is seen in the difference of the average for BMI/BF% SDS at first and last DXA scan (Figure 2). Differences outside the 95% agreement interval are observed, especially at the lower and higher averages, suggesting discrepancies occur mostly in the upper and lower end of the ranges. This effect was not observed for FMI.

Table 4 Occurrence of the criteria for metabolic syndrome in craniopharyngioma patients at last DXA-scan

MetS	MetS (BMI) (n, (%))	MetS (BF%) (n, (%))	MetS (FMI) (n, (%))
No criterion	6 (8%)	4 (6%)	5 (7%)
One criterion	13 (18%)	9 (13%)	11 (16%)
Two criteria	19 (26%)	16 (23%)	16 (24%)
Three criteria	15 (20%)	15 (22%)	18 (27%)
Four criteria	10 (14%)	5 (7%)	5 (8%)
Five criteria	4 (5%)	1 (1%)	4 (6%)
NA	7 (9%)	19 (28%)	8 (12%)

MetS = Metabolic Syndrome; MetS (BMI) = component of obesity defined with high body mass index (BMI >30) or increased standardized deviation score (SDS); MetS (BF%) = component of obesity defined with high fat percentage with limits defined according to sex and age, or by high SDS; MetS (FMI) = component of obesity defined with increased FMI with limits defined according to sex and age or SDS; n = number; NA = not available (not all criteria are known). The data set was not complete in all patients.

Table 5 Concordance in metabolic syndrome and obesity of BMI, BF% and FMI

MetS			**First DXA-scan**		**Last DXA-scan**	
			BMI		BMI	
			Non-MetS (n, %)	MetS (n, %)	Non-MetS (n, %)	MetS (n, %)
	BF%	Non-MetS (n, %)	28 (44%)	**1 (2%)**	32 (49%)	**0 (0%)**
		MetS (n, %)	**4 (6%)**	30 (49%)	**6 (9%)**	28 (42%)
	FMI	Non-MetS (n, %)	29 (48%)	**0 (0%)**	33 (49%)	**0 (0%)**
		MetS (n, %)	**3 (5%)**	29 (48%)	**5 (7%)**	29 (43%)
Obesity			**Non-obese (n, %)**	**Obese (n, %)**	**Non-obese (n, %)**	**Obese (n, %)**
	BF%	Non-obese (n, %)	26 (34%)	**1 (1%)**	12 (19%)	**4 (7%)**
		Obese (n, %)	**18 (23%)**	32 (42%)	**14 (23%)**	32 (52%)
	FMI	Non-obese (n, %)	33 (52%)	**1 (2%)**	25 (36%)	**4 (6%)**
		Obese (n, %)	**5 (8%)**	25 (39%)	**5 (7%)**	35 (51%)

Concordance of metabolic syndrome of for definitions of the criterion obesity and obesity itself with body mass index (BMI), body fat percentage (BF%) and fat mass index (FMI) at first and last DXA-scan in craniopharyngioma patients. N = number. Non-MetS represent subjects without presence of metabolic syndrome, MetS with presence of metabolic syndrome. The bold numbers and percentages are discordances of the different definitions. Metabolic syndrome is underestimated in 9% for BF% and 8% for FMI compared to BMI. At last DXA-scan, obesity is underestimated in 23% of the cases if defined by BF% in comparison to BMI; for FMI this percentage is much lower. The numbers may not add up to 100% due to rounding issues. The data set was not complete in all patients.

Determinants for occurrence of obesity and MetS and its components in patients with craniopharyngioma

Results of the univariable and multivariable logistic regression analyses on explanatory factors for MetS and its components at last DXA scan are shown in Supplementary Table 6. Explanatory factors in univariable models for MetS (BMI, BF% and FMI) were age at last DXA scan, recurrence or progression, hydrocephalus and visual impairment. These factors remained significant in multivariable analysis in one of the models with the exception of visual impairment. The explanation of the models was limited (Nagelkerke's R^2 0.15–0.29). The dose of glucocorticoid replacement was not a significant contributor (data not shown).

Figure 1 BMI versus body fat percentage and FMI in obesity

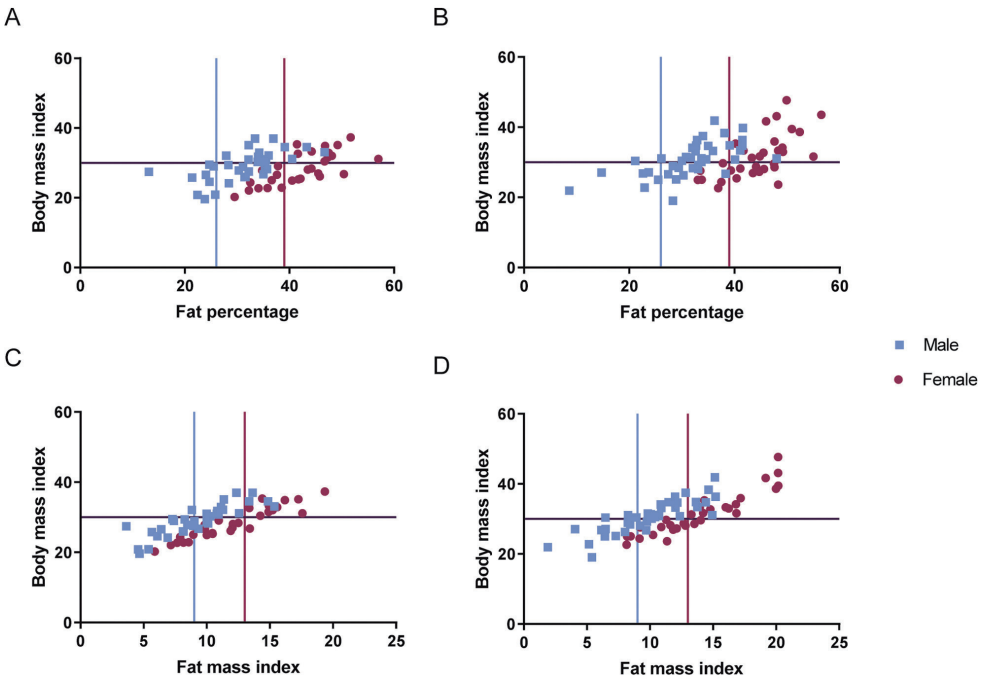

Figure 1: Body mass index (BMI) vs. body fat percentage (BF%) and fat mass index (FMI) at first (AC) and last (BD) DXA-scan in craniopharyngioma patients. Obesity based on BF% or FMI are bordered by the blue vertical line for males and by the red vertical line for females on the X-axis. The purple horizontal line borders obesity based on BMI. Female and male patients in the right lower quadrant are considered obese by fat percentage/ FMI, but not by BMI.

Type II diabetes mellitus and cardio- and cerebrovascular morbidity

Eleven patients with CP (12%) had diabetes mellitus of which one had type I diabetes mellitus. The frequency of T2D was higher in patients with CP compared with normative data (14% in subjects with the same age category as the normative data, vs. 6% in normative data; $P < 0.05$), but there was no difference in incidence between obese and non-obese CP patients. Myocardial infarctions occurred in four patients with CP (4%) with a median onset at 58 years of age (range 39–75). Nine subjects (10%) had experienced cerebrovascular accidents with a median age of onset of 41 years (range 16–66) and with a median of 8 years since first presentation of CP (range 0–25).

Discussion

This is the first study to assess the value of body composition measured by DXA scan in evaluating MetS in CP survivors. A discordancy in evaluation of MetS occurs in 9% of the cases if BMI is used as opposed to BF%. Moreover, the occurrence of obesity was estimated 22% higher if measured by BF% compared to BMI. Since obesity itself is a predictor of cardiovascular disease,[43] this suggests that DXA scan can be of great value in certain cases. In the Rotterdam/Gothenborg cohort, a standardized incidence ratio of 4.9 for cerebrovascular accidents was observed.[5] The risk of T2D was approximately doubled in CP patients compared to the general population. The long-term care of patients with CP should include cardiovascular risk management. Figure 2 suggests that discrepancy is most evident in the extremes, the very thin and very fat CP patients. Despite these results, the agreement between methods for MetS is good, as evaluated by Cohen's kappa. In clinical practice, confirmation by DXA scan will not be of added value if obesity is obviously apparent from BMI. Although discordance is not as impressive as found in childhood cancer patients,[22] obesity evaluation is discordant in one out of five patients and MetS evaluation is discordant in one out of ten if BMI is used instead of BF%. Therefore, our recommendation is to decide on a case-by-case basis if a DXA scan should be performed.

The risk of a decreased BMD should also be taken into account when deciding if a DXA scan should be included in the patients' management.

There was a striking sex-dependent difference in MetS components: while men had an increased risk of having the high glucose component, women were more likely to have high triglycerides (Table 3). This disparity may be explained by the higher risk for men to develop T2D,[44] and estrogen replacement therapy raising triglycerides in women.[45] Still, this effect should be limited: premenopausal females seem to be undertreated with gonadal replacement therapy, as they receive significantly less frequently replacement treatment compared with men. Being female has been shown to positively correlate with MetS,[46] but in our cohort, the MetS rate was equal between genders. Female sex was a protective factor for high glucose and a risk factor for high triglycerides and low HDL.

To determine factors that influence MetS and obesity, a logistic regression model was established. Age is a main predictor for all definitions of MetS (based on BMI, BF% and FMI; Supplementary Table as the prevalence of MetS increases with age.[47] Another important predictor for MetS (BF%) is visual impairment, which is in line with the findings of the previous study of Wijnen et al.,[6] who studied a larger cohort. To our knowledge, the only other study investigating MetS (components) in CP patients, is Tosta et al.,[46] who found that BMI SDS at diagnosis positively influenced the presence of the MetS posttreatment. Radiation was expected to be a factor involved, as this is a risk factor in developing the MetS and obesity in cancer survivors,[48] but it was not found to be so in our study. Although hypothalamic damage was expected to be a significant contributor, it was only borderline significant for two definitions of MetS (MetS (BMI) and MetS (BF%); Supplementary Table 6). Our cohort may have been underpowered to define hypothalamic damage and radiation therapy as a significant predictors. Although the hypothalamus plays a major role in weight maintenance, it has been shown that patients develop morbid obesity under hypothalamus-sparing operative strategies,[49] suggesting that obesity is multifactorial. Hydrocephalus[50] is associated with obesity, so

finding this as a significant contributor for MetS was not unexpected.

Predictors of poor outcomes are visual deterioration,[51] hydrocephalus and multiple operations due to tumor recurrence.[5,52] Recurrence or progression was a key predictor in all definitions. All predictors could be a sign of advanced brain disease and may be interrelated. On the other hand, no interaction was found while establishing the model. Advanced brain disease is likely to influence aspects of lifestyle such as physical activity.

Figure 2 Bland Altman Plot for BMI SDS and BF%/FMI SDS at first and last DXA-scan

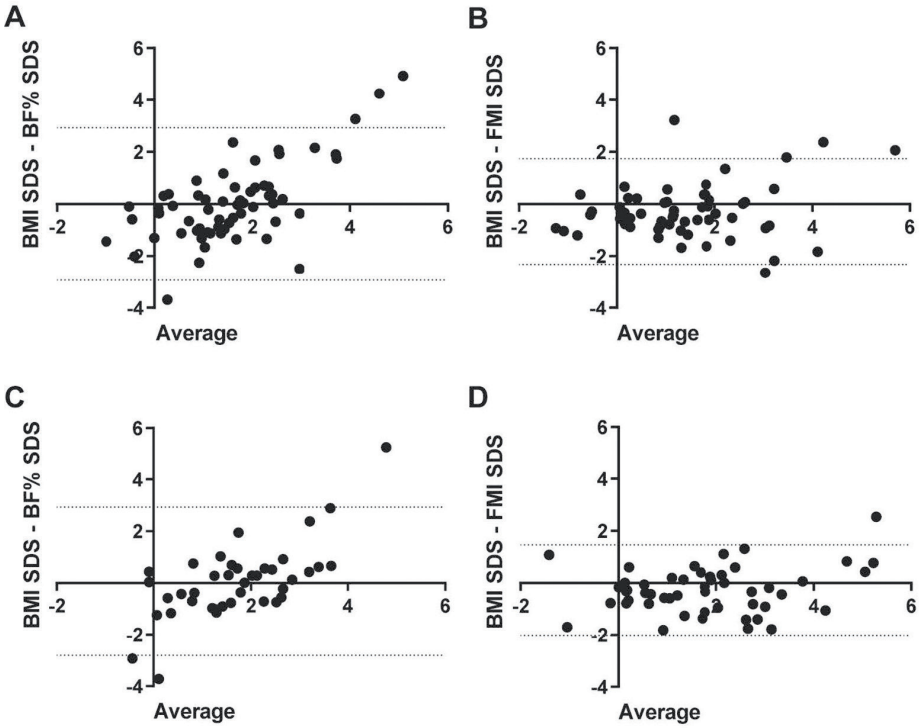

Figure 2: Bland Altman Plots. Plot A and B present data on the first DXA-scan; plot C and D of the last DXA-scan. Respectively, on the X-axis the average, and on the Y-axis the difference is expressed of body mass index standardized deviation scores (SDS) and body fat percentage SDS (AC) or fat mass index SDS (BD). An upward trend is seen in the difference of the average for BF% at first and last DXA-scan (AC). The difference in SDS of BMI and BF% seems larger at the end of the ranges, since the differences are observed outside the 95% agreement interval. These suggested discrepancies appear mostly in the upper and lower end of the ranges. For the difference of the average for FMI, the upward trend is not obviously shown.

There are some limitations in this study. Several factors contribute to a possible selection bias: there are size and weight limitations of DXA scanners,[53] the study was performed in referral centers, and the decision to perform a DXA scan was made by clinical judgment of the physicians, which is why only a subset of our previously studied cohort was assessed.[6] MetS criteria were evaluated within a window spanning 3 years either side of the last DXA scan. This period was chosen since earlier studies have shown that BMI change is central to other correlated features in the MetS[54] and BMI was stable for 3 years in a group of childhood cancer survivors.[22] Also, in a group of over 5000 French subjects, MetS was found to be stable over a period of 3 years.[55] Furthermore, any DXA scanner was accepted, even though it is known that the DXA scan has a considerable intraindividual variability[56] and results may differ between machines; it would have been ideal to cross-calibrate all scanners.[57] To cope with this, we used age- and sexmatched s.d. scores. The DXA scan is still considered to be the method of preference when BMI and adiposity are considered discordant.[21, 25] For evaluation of obesity by BMI, a cutoff of ≥30 kg/m^2 for reasons of conformity with our earlier study[6] and by the WHO guidelines,[58] as well as to avoid overdiagnosis. However, we realize that cutoffs used for the waist circumference according to the International Diabetes Federation (IDF) values were closer to matching a BMI of 25 kg/m^2 in males. The IDF definition notes that, if BMI >30 kg/m^2, central obesity can be assumed and waist circumference does not need to be measured.[27] This remains however a topic of discussion. Since we were unable to retrieve information on waist circumference and to avoid overdiagnosing as well as to be able to make comparisons with our previous research, we decided to use a cutoff level of >30 kg/m^2 for BMI.

Since the availability of literature is extremely limited on the topic, the data we present here are still highly important for clinicians in considering the use of DXA scans in long-term follow-up, despite its limitations. It is the only study in patients with CP that compares body composition measures vs. BMI for evaluation of obesity and the MetS as well as contains longitudinal follow-up.

In conclusion, patients with CP are at high risk of obesity and MetS. Obesity and MetS are underestimated if measured by BMI. Moreover, age, visual impairment and recurrence or progression are predictors of MetS or its components. This study is single in its existence providing evidence that DXA scan measured BF% is a better alternative for evaluation of obesity and MetS in certain patients with CP, especially those in the upper and lower range of BMI or BF%. The cost-effectiveness of performing DXA-scans remains to be determined before general clinical use in CP survivors can be recommended.

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Supplementary Tables

Supplementary Table 1 Comparison of craniopharyngioma patients with and without DXA-scan

		Patients with DXA scan (n=95)	Patients without DXA-scan (n=61)	*P*-value
Baseline characteristics	Age at presentation (years)[a]	22 (3-62)	22 (0-79)	0.43
	Childhood-onset (n [%])	46 (49)	28 (46)	0.66
	Follow-up since presentation (years [range])[a]	19 (1-62)	14 (3-33)	0.09
	Age at last follow-up (years [range])[a]	45 (16-78)	43 (18-92)	0.65
	Female sex (n [%])	48 (51)	26 (43)	0.38
	Swedish cohort (n [%])	69 (63)	10 (16)	**<0.001**
Tumor characteristics	Location (n [%]) at last imaging			
	Intrasellar	1 (1)	3 (5)	0.34
	Suprasellar	43 (51)	15 (26)	**0.005**
	Intra-/suprasellar	41 (48)	39 (68)	**0.02**
	Hydrocephalus (n [%])	20 (21)	18 (30)	0.28
	Hypothalamic damage (n [%])	31 (34)	25 (46)	0.17
Craniopharyn-gioma treatment	Neurosurgery (n [%])	93 (98)	55 (90)	0.06
	Radiotherapy (n [%])	51 (54)	28 (46)	0.34
	^{90}Yttrium brachytherapy (n [%])	9 (10)	13 (21)	**0.05**
	Recurrence (n [%])	33 (35)	26 (43)	0.31
Long-term health outcome	Pituitary hormone deficiencies (n [%])			
	GH	89 (95)	48 (80)	**0.005**
	FSH/LH	85 (90)	49 (82)	0.17
	TSH	90 (95)	56 (92)	0.47
	ACTH	79 (84)	49 (80)	0.55
	ADH	65 (69)	34 (56)	0.09
	Visual impairment (n [%])	72 (78)	42 (78)	0.95

	Treatment for epilepsy (n [%])	6 (6)	6 (10)	0.64
	Treatment for psychiatric illness (n [%])	12 (13)	7 (12)	0.84
	Bariatric surgery (n [%])	4 (4)	1 (2)	0.65
	OSAS (n [%])	21 (23)	6 (10)	0.04
	Diabetes mellitus (n [%])	11 (12)	14 (23)	0.08
	Cerebrovascular disease (n [%])	9 (10)	7 (12)	0.74
	Myocardial infarction (n [%])	4 (4)	5 (8)	0.31
	BMI (mean [range])	31.4 (19-47.7)	31.7 (16.9-59.5)	0.87
	MetS component obesity (based on BMI) (n [%])	54 (57)	30 (53)	0.613
	MetS component insulin resistance (n [%])	56 (74)	20 (26)	**0.006**
	MetS component low HDL cholesterol (n [%])	41 (46)	25 (38)	0.736
	MetS component high blood pressure (n [%])	48 (51)	31 (51)	0.976
	MetS component high triglycerides (n [%])	31 (34)	30 (54)	**0.017**
	Presence of MetS (n [%])	43 (47)	27 (44)	0.763
	Dead (n [%])	13 (14)	12 (20)	0.320

Comparison of 156 craniopharyngioma patients with (n=95) and without (n=61) DXA-scan. Data are given as mean and standard deviation (SD) unless stated otherwise [a]Median (range). ACTH = Adrenocorticotropic hormone; ADH = Antidiuretic hormone; FSH/LH = Follicle stimulating hormone/luteinizing hormone; GH = Growth hormone; n = Number; OSAS = obstructive sleep apnea syndrome; TSH = Thyroid stimulating hormone. Patients were only included for the measurement of BMI if they reached the age of 18 years at the moment of measurement; the measurement was at last DXA-scan or, if unavailable, at last follow-up. A lower occurrence of intra- and suprasellar location, Yttrium brachytherapy and MetS component of high triglycerides, and higher percentage of suprasellar location, GHD, obstructive sleep apnea syndrome and proportion of inclusion of Swedes appeared in the current cohort.

Supplementary Table 2 Included Dual X-ray Absorptiometry scanners

	First DXA-scan (n=95)	Last DXA-scan (n=93)
Unknown/other	1 (1%)	8 (9%)
Lunar iDXA Gothenborg University Hospital	0 (0%)	19 (20%)
Lunar DPXL total	58 (61%)	14 (15%)
DPXL Erasmus MC	32 (34%)	12 (13%)
DPXL Gothenborg University Hospital	26 (27%)	2 (2%)
Lunar Prodigy total	36 (38%)	52 (56%)
Prodigy (1) Erasmus MC	0 (0%)	9 (10%)
Prodigy (2) Erasmus MC	2 (2%)	4 (4%)
Prodigy Gothenborg University Hospital	34 (36%)	39 (42%)

DXA-scanners included in the research. Data is given as N (%). Prodigy (1) is used at the dept. of Nuclear Medicine in the Erasmus MC; Prodigy (2) at the dept. of Internal Medicine. Total includes all scanners of the same type in both centers.

Supplementary Table 3 Metabolic syndrome and its components in patients with craniopharyngioma

	CP <1yr	CP>1yr	*P*-value
MetS			
BMI	27 (44%)	6 (50%)	0.68
BF%	29 (50%)	6 (54%)	0.78
FMI	30 (52%)	4 (44%)	0.68
Metabolic components*			
Obesity (FD)			
BMI	26 (43%)	5 (39%)	0.68
BF%	42 (71%)	5 (39%)	0.05
FMI	27 (49%)	2 (29%)	0.43
Obesity (LD)			
BMI	34 (56%)	8 (50%)	0.68
BF%	37 (80%	6 (46%)	**0.03**
FMI	34 (61%)	5 (50%)	0.73
High glucose	39 (63%)	13 (81%)	0.17
High triglycerides	18 (29%)	4 (31%)	1.00
Low HDL	25 (39%)	7 (50%)	0.45
High blood pressure	31 (48%)	5 (31%)	0.21

Data are presented as n (%). CP <1yr or CP >1yr means that the patients have MetS components evaluated in within one year, or more than one year before or after DEXA-scan. Abbreviations: BF% = body fat percentage; BMI = body mass index; CP = craniopharyngioma; FD = first DXA-scan (Dual-Energy X-ray Absorptiometry scan); FMI = fat mass index; HDL = High-density lipoprotein cholesterol; LD = Last DXA-scan; Norm. = Normative; MetS = metabolic syndrome; n = number; NA = Not Available; *P* = *P*-value; ♀ = Female; ♂ = Male. MetS (components) are components evaluated at LD, except obesity (FD and LD). *MetS components are as defined in Table 1.

Supplementary Table 4 Bland-Altman bias of BMI SDS and BF%/FMI SDS scores at first and last DXA-scan

	Metabolic syndrome at last DXA scan	**Obesity**	
		First DXA-scan	Last DXA-scan
	Obesity defined with BMI	Defined with BMI	Defined with BMI
	Cut-off point (kappa; SE, (P))	Cut-off point (kappa; SE, (P))	Cut-off point (kappa; SE, (P))
Obesity (BF%)	0.82; 0.07 (<0.001)	0.53; 0.09 (<0.001)	0.37; 0.12 (0.002)
Obesity (FMI)	0.85; 0.06 (<0.001)	0.81; 0.07 (<0.001)	0.73; 0.08 (<0.001)

Agreement of anthropomorphic measurements and DXA-scan for evaluation of obesity and metabolic syndrome. For metabolic syndrome, the component of obesity is either defined with high body mass index (BMI), high body fat percentage (BF%), or high fat mass index (FMI). For obesity: defined on high body mass index (BMI >30) or increased standardized deviation score (SDS); high body fat percentage with limits defined according to sex and age, or by increased SDS; of with high fat mass index with limits defined according to sex and age or SDS; n=number. A Cohen's kappa measurement of agreement was set out with metabolic syndrome and obesity. For metabolic syndrome, an almost perfect agreement is found. For obesity, agreement is only fair to moderate.

Supplementary Table 5 Agreement of anthropomorphic measurements and DXA-scan for evaluation of obesity and metabolic syndrome

			BF% SDS	FMI SDS
First DXA-scan	Body mass index SDS	Bland- Altman bias	<0,001	-0,290
		SD of bias	1,496	-0,290
		LLA	-2,932	-2,319
		ULA	2,933	1,738
Last DXA-scan	Body mass index SDS	Bland- Altman bias	0,063	-0,273
		SD of bias	1,462	0,887
		LLA	-2,802	-2,012
		ULA	2,929	1,466

Bland-Altman bias of BMI SDS and BF%/FMI SDS scores in craniopharyngioma patients. BF% = body fat percentage; FMI = fat mass index; SD = standard deviation; SDS = standardized deviation scores; LLA = lower limit of 95% agreement interval; ULA = upper limit of 95% agreement interval. A Bland-Altman bias was performed of the mean difference of body mass index SDS and body fat percentage SDS/fat mass index SDS. The bias is only small. This table is complementary to Figure 1. Almost perfect agreement is found. For obesity, agreement is only fair to moderate.

Supplementary Table 6 Risk factors for the metabolic syndrome in patients with craniopharyngioma

	Univariable analysis					
	MetS (BMI)		MetS (BF%)		MetS (FMI)	
Variables	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age at DXA-scan	**1.03 (1.00-1.06)**	**0.03**	**1.04 (1.00-1.07)**	**0.03**	**1.04 (1.01-1.07)**	**0.02**
Age at presentation	1.03 (0.99-1.06)	0.15	1.02 (0.98-1.05)	0.37	1.03 (0.99-1.07)	0.10
Female sex	0.90 (0.36-2.24)	0.82	1.06 (0.41-2.72)	0.91	1.07 (0.41-2.79)	0.90
Recurrence or progression	**4.03 (1.46-11.11)**	**<0.01**	**2.89 (1.02-8.17)**	**<0.05**	2.22 (0.80-6.21)	0.13
Hydrocephalus	**3.88 (1.24-12.22)**	**0.02**	2.60 (0.85-7.90)	0.094	2.61 (0.85-7.99)	0.09
Hypothalamic damage	2.38 (0.92-6.21)	0.08	2.10 (0.79-5.56)	0.14	1.63 (0.64-4.19)	0.31
Medication for epilepsy	4.44 (0.49-40.98)	0.18	5.86 (0.64-53.09)	0.12	0.59 (0.65-53.47)	0.12
Medication for psychiatric disease	1.24 (0.32-4.83)	0.75	2.29 (0.52-9.99)	0.27	1.25 (0.31-5.13)	0.76
Growth hormone deficiency	2.52 (0.25-25.49)	0.43	1.03 (0.06-17.16)	0.98	1.03 (0.14-7.80)	0.98
GHRT	1.71 (0.39-7.45)	0.47	1.03 (0.24-4.51)	0.97	1.03 (0.24-4.53)	0.96
Adrenal axis deficiency	2.34 (0.66-8.29)	0.19	1.25 (0.37-4.20)	0.72	0.69 (0.20-2.437)	0.56
Gonadal axis deficiency	3.76 (0.74-19.09)	0.11	1.34 (0.33-5.50)	0.69	1.67 (0.42-6.55)	0.46
Sex steroid replacement therapy	2.31 (0.56-9.63)	0.25	1.04 (0.27-4.01)	0.96	1.2 (0.33-4.43)	0.78
Diabetes insipidus	2.14 (0.75-6.12)	0.15	2.09 (0.73-5.60)	0.17	1.21 (0.42-3.50)	0.73
Radiotherapy	1.43 (0.57-3.59)	0.45	1.34 (0.52-3.44)	0.55	1.19 (0.45-3.13)	0.72
^{90}Yttrium brachytherapy	5.59 (0.59-51.97)	0.14	2.07 (0.35-12.09)	0.42	4.27 (0.45-40.37)	0.21
Visual impairment	2.80 (0.89-8.86)	0.08	**3.31 (1.01-10.84)**	**<0.05**	2.10 (0.62-7.13)	0.23

	Multivariable analysis[a]					
	MetS (BMI)		MetS (BF%)		MetS (FMI)	
Variables	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age at DXA-scan	1.04 (1.00-1.08)	0.03	1.04 (1.00-1.07)	0.04	1.05 (1.01-1.08)	0.01
Age at presentation						
Female sex						
Recurrence or progression	3.17 (1.06-9.47)	0.04	2.04 (0.67-6.25)	0.21		
Hydrocephalus	5.64 (1.40-22.80)	0.02			4.07 (1.02-16.19)	<0.05
Hypothalamic damage						
Medication for epilepsy						
Medication for psychiatric disease						
Growth hormone deficiency						
GHRT						
Adrenal axis deficiency						
Gonadal axis deficiency						
Sex steroid replacement therapy						
Diabetes insipidus						
Radiotherapy						
^{90}Yttrium brachytherapy						
Visual impairment			2.64 (0.74-9.48)	0.14		

Univariable and multivariable logistic regression analysis. Abbreviations: CI = Confidence interval; GHRT = Growth hormone replacement therapy; MetS = Metabolic Syndrome; NA = not applicable; OR = Odds Ratio; O $\chi 2$ = Omnibus $\chi 2$; R^2 = Nagelkerke's R^2; SE = standard error. Hypothalamic damage at diagnosis. MetS is defined in Table 1. Age is

given in years. Hosmer Lemeshow test was non-significant in all models.

MetS (BMI): R^2 =0.29; O $\chi 2$ <0.001. MetS (BF%): R^2 =0.20; O $\chi 2$ =0.01. MetS (FMI): R^2 =0.18; O $\chi 2$ =0.008.

Explanatory (borderline) significant factors MetS components:

High glucose (univariable): female sex (OR 0.3, 95% CI 0.1-0.8, *P* = 0.01).

High blood pressure (univariable): age at DXA-scan (OR 1.1, 95% CI 1.0-1.1, *P* < 0.001), age of onset (OR 1.1, 95% CI 1.0-1.1, *P* = 0.001).

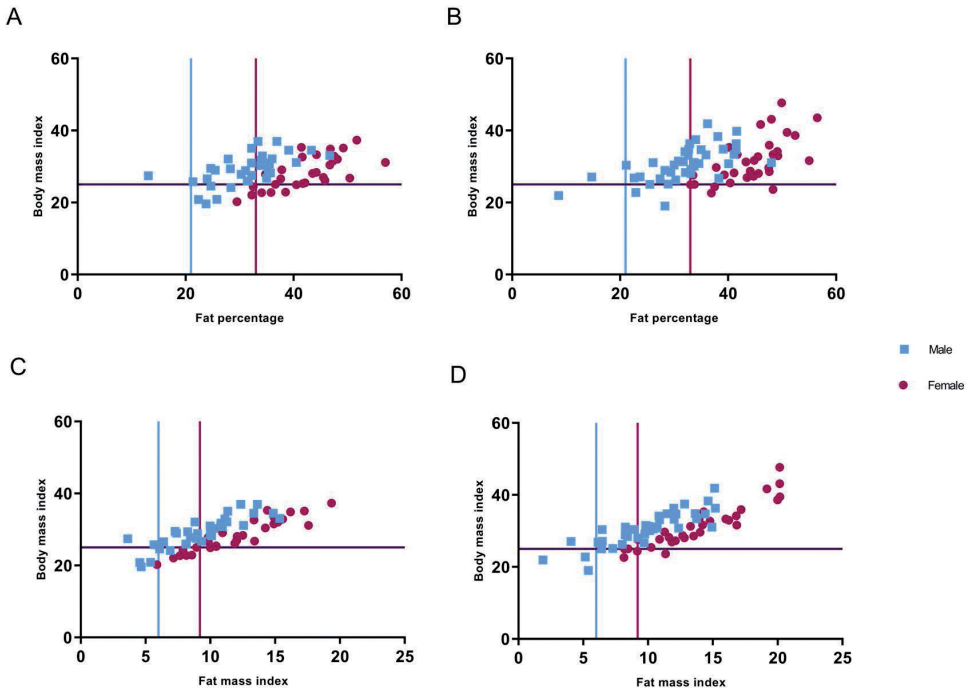
Low HDL (uni-/multivariable): female sex (OR 2.4, 95% CI 0.9-6.0, *P* = 0.07/ OR 3.9, 95% CI 1.1-13.1, *P* = 0.03), visual deficiency (OR 3.4, 95% CI 1.0-11.4, *P* = 0.05/ OR 5.0, 95% CI 0.9-29.1, *P* = 0.08), recurrence or progression (OR 5.8, 95% CI 2.1-15.8, *P* = 0.001/ OR 5.9, 95% CI 1.7-19.8, *P* = 0.004) and hypothalamic damage (OR 3.0, 95% CI 1.1-8.1, *P* = 0.03/ OR 3.9, 95% CI 1.0-16.1, *P* = 0.06). R^2 0.42, O $\chi 2$ (*P* < 0.001).

High triglycerides (uni-/multivariable): female sex (OR 3.3, 95% CI 1.1-9.4, *P* = 0.03/ OR 3.9, 95% CI 1.2-12.1, *P* = 0.02), recurrence or progression (OR 3.7, 95% CI 1.2-10.7, *P* = 0.02/ OR 3.8, 95% CI 1.2-11.4, *P* = 0.02), Yttrium brachytherapy (OR 15.3, 95% CI 1.7-140.2, *P* = 0.02/ NA), and borderline significant visual deficiency (OR 4.5, 95% CI 0.9-21.5, *P* = 0.06/ NA). R^2 0.21, O $\chi 2$ *P* = 0.003.

Obesity (BMI) (univariable): gonadal axis deficiency (OR 4.2, 95% CI 1.0-17.2, *P* = 0.04).

Obesity (FMI) (univariable): visual deficiency (OR 4.0 95% CI 1.1-14.8, *P* = 0.04).

Supplementary Figure 1 BMI versus body fat percentage and FMI in overweight subjects



Body mass index (BMI) vs. body fat percentage (BF%) and fat mass index (FMI) at first (AC) and last (BD) DXA-scan in craniopharyngioma patients. Overweight based on BF% or FMI are bordered by the blue vertical line for males and by the red vertical line for females on the X-axis. The purple horizontal line borders overweight based on BMI. Female and male patients in the right lower quadrant are considered overweight by fat percentage/ FMI, but not by BMI.[26,59]

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Can Biomarkers Be Used To Improve Diagnosis and Prediction of Metabolic Syndrome in Childhood Cancer Survivors? A Systematic Review

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Running title: Novel metabolic syndrome biomarkers in CCS

Abbreviations: CVD = cardiovascular disease; T2DM = type 2 diabetes mellitus; MetS = metabolic syndrome; CCS = childhood cancer survivors; DXA = Dual-energy X-ray Absorptiometry; hsCRP = high sensitivity C-reactive protein; TNF-alpha = Tumor Necrosis Factor alpha; IL-1 = interleukin 1; IL-6 = interleukin 6; apoB = apolipoprotein B; Lp(a) = lipoprotein(a); AUC = area under the curve; ROC = receiver operating characteristic; OR = odds ratio; HR = hazard ratio; GRADE = Grading of Recommendations Assessment Development and Evaluation; BMI = body mass index; ALL = acute lymphoblastic leukemia; apoA1 = apolipoprotein A1; LDL = low density lipoproteins; HOMA-IR = Homeostatic Model Assessment of Insulin Resistance; HDL = high density lipoproteins.

Abstract

Background: Childhood cancer survivors (CCS) are at increased risk to develop metabolic syndrome (MetS), diabetes and cardiovascular disease. Common criteria underestimate adiposity and possibly underdiagnose MetS, particularly after abdominal radiotherapy.

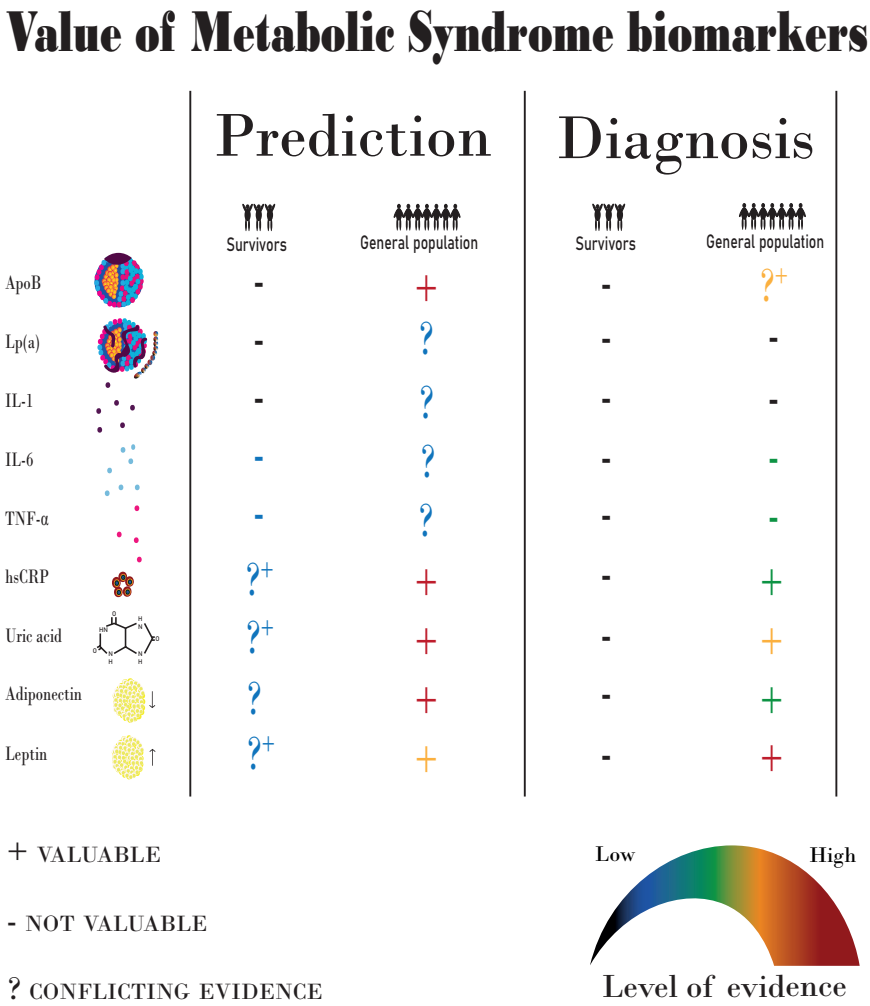
Design: A systematic literature review and meta-analysis on the diagnostic and predictive value of nine newer MetS related biomarkers (adiponectin, leptin, uric acid, hsCRP, TNF-alpha, IL-1, IL-6, apolipoprotein B (apoB), and lipoprotein(a) [lp(a)]) in survivors and adult non-cancer survivors was performed by searching PubMed and Embase. Evidence was summarized with GRADE after risk of bias evaluation (QUADAS-2/QUIPS). Eligible studies on promising biomarkers were pooled.

Results: We identified 175 general population, and 5 CCS studies. In the general population, valuable predictive biomarkers are uric acid, adiponectin, hsCRP and apoB (high level of evidence) and leptin (moderate level of evidence). Valuable diagnostic biomarkers are hsCRP, adiponectin, uric acid and leptin (low, low, moderate and high level of evidence, respectively). Meta-analysis showed OR for hyperuricemia of 2.94 (age-/sex-adjusted), OR per unit uric acid increase of 1.086 (unadjusted), and AUC for hsCRP of 0.71 (unadjusted).

Conclusions: Uric acid, adiponectin, hsCRP, leptin, and apoB can be alternative biomarkers in the screening setting for MetS in survivors, to enhance early identification of those at high risk of subsequent complications.

Keywords: childhood cancer survivors, the metabolic syndrome, biomarker, systematic review

Graphical abstract



Graphical abstract of systematic review for novel biomarkers for diagnosis and prediction of the metabolic syndrome in childhood cancer survivors and a young general population. Conclusions per biomarker are categorized as valuable, not valuable or conflicting evidence, and the level of evidence is expressed per color from low to high (black-blue-green-yellow-red; see figure on the lower right).

Introduction

Childhood cancer 5-year survival rates have increased from 5-30% in early seventies to more than 80% in the present time.[1, 2] Deployed therapies, such as chemotherapy, radiotherapy, and stem cell transplantation, better stratification and enhanced supportive care regimens, are responsible for increase in survival rates. However, intensification of treatment is also associated with long-term excess mortality and morbidities in survivors.[3] Survivors have a high level of frailty, suggesting their biological age progresses faster than their actual age. Consequently, survivors with an actual mean age of 33 have a biological age of 65 if they are compared to the general population.[4-9] At the age of 45-50 years, the prevalence of any chronic health condition is very high, from 95% up to 99%.[3, 10] One of these severe conditions is represented by cardiovascular disease (CVD), which is an important cause of premature death beyond 5 years cancer survival; the standardized mortality risk for CVD ranges from 1.9 to 12.7.[11-25]

This high risk of cardiovascular death is not only due to treatment effects, such as anthracycline exposure and cardiac irradiation;[26] survivors are also at high risk of type II diabetes mellitus (T2DM) and the metabolic syndrome (MetS).[11] These diseases are independent predictors of CVD and associated with factors such as adiposity, dyslipidemia, insulin resistance, and hypertension. These factors cluster together and form the 'deadly quartet', a MetS concept developed by Reaven in 1988.[27] The MetS had many definitions ever since.[11, 27-37] Patients with MetS carry a doubled risk of dying from cardio- and cerebrovascular disease.[11, 38] In addition, patients with the MetS are five times more likely to develop T2DM, which subsequently triples the risk of CVD.[11, 39-41]

As survivors develop cardiovascular complications at a relatively young age, there is a need for early diagnosis of MetS, to possibly prevent T2DM and CVD, and to improve long-term survival.[11] The occurrence of MetS may be underestimated especially in abdominally irradiated childhood cancer survivors (CCS), who have an unreliable waist circumference, while their MetS risk is even higher.[11, 42-44] Body mass index (BMI) and bioimpedance are alternative methods for

body composition measurement, but do not specifically measure abdominal fat, rely on hydration status and often underestimate body fat.[42, 45-47] Obviously, another alternative option to evaluate adiposity is measuring fat percentage by Dual-energy X-ray Absorptiometry (DXA) scan, which is the gold standard in case of suspected discordance of anthropomorphic measurements and adiposity.[42, 48, 49] However, performing DXA scans in all survivors on a routine basis is time-consuming and costly.[11] Additionally, there is currently no consensus for the threshold of fat percentage for diagnosing obesity.[50] Newer serum biomarkers may serve as another alternative for accurate early diagnosis or prediction of (disguised) MetS in CCS. Adult cardiologists currently apply multiple biomarkers that have been shown to improve risk estimation for CVD.[51]

Therefore, our primary objectives were to evaluate the value of the use of these newer serum biomarkers as (1) diagnostic marker, and as (2) additional independent predictor for the occurrence of MetS later in life, in survivors of childhood cancer specifically, as well as in a relatively young general, non-cancer population (studies with >75% of participants below 65 years). By including this selection of general population studies as well, we aimed to cover all available literature applicable and generalizable to young-adult survivors. To accomplish this, we performed a systematic literature search on adipokines adiponectin and leptin, uric acid, the inflammatory markers high sensitivity C-reactive protein (hsCRP), Tumor Necrosis Factor alpha (TNF-alpha), interleukin 1 (IL-1), and interleukin 6 (IL-6), and the lipid markers apolipoprotein B (apoB) and lipoprotein(a) [Lp(a)], and performed a meta-analysis of these outcomes for relevant recurrently published biomarkers. As secondary purpose, we screened for other new biomarkers that are not enlisted above, in order to reveal additional, potentially useful biomarkers.

Methods

The Systematic Search

A systematic literature review was performed in PubMed and Embase, to gather all published literature published between the first of October 2009 and September 3, 2020. Details of the search terms are available in Supplementary Table 1; in general, the search terms were related to adults/general population, as well as to (childhood) cancer survivors, and combined with all enlisted 9 separate biomarkers (adiponectin, leptin, uric acid, hsCRP, TNF-alpha, IL-1, IL-6, apoB and lp(a)) and the MetS. The AMSTAR checklist for systematic reviews was followed.[52] All titles and abstracts were screened by two independent reviewers (VP and SSvS), who were blinded to each other's judgement. Studies were included if they had the MetS as outcome, and one or more newer biomarker(s) as independent variable included in the model in predictive studies, or as discriminative variable in diagnostic studies. For studies performed in CCS, no limits were set for sample size or age. General population studies were eligible if the sample size was roughly 250 or larger and if 75% or more of this population was below 65 years of age, as they have comparable levels of frailty to a young adult survivor population.[5, 7, 8] We excluded studies with older adults since they are expected to have higher levels of frailty, comorbidities and aging factors, which may be confounders in the correlation between the newer biomarker and the metabolic syndrome. Multivariable analysis was mandatory for article inclusion of studies that investigated the prediction of MetS.

Studies were excluded if all included patients had an elevated biomarker; if all or none of the subjects had the MetS; if it was a selected cohort with pre-existing comorbidities (i.e. familial hypercholesterolemia, psoriasis, schizophrenia, polycystic ovary syndrome, obesity, hypertension); if all patients suffered from MetS or endpoint(s) such as T2DM, cardio- or cerebrovascular disease, or non-alcoholic fatty liver disease; if the article was a review, case study, expert opinion or conference abstract; if the article was written in a language other than English or Dutch, or if the full text was unavailable

(see Appendix A for an overview of selection criteria). Studies were only included if the outcome was presence or absence of MetS; those with separate MetS components or MetS risk score as outcome were out of the scope of this review. After all articles were screened based on title and abstract, the judgements were unblinded. Discrepancies were discussed and resolved by the two reviewers (VP and SSvS) and where necessary, two senior experts were consulted (MMvdHE and SJCMMN). A cross-reference check was performed with Scopus, to screen all forward and backward citations of included studies. The articles found by the cross-reference check were screened likewise. A flow diagram with the number of in- and excluded articles and reasons for exclusion illustrates this process (Figure 1).

Risk of bias assessment

The QUIPS tool was applied for critical appraisal of predictor studies[53, 54] (Supplementary Table 2) and QUADAS-2 tool for diagnostic studies (Supplementary Table 3). Definitions for low risk of bias judgement are shown in Appendix A. In case of doubt, the study was discussed with both reviewers and senior experts (VP, SSvS, MMvdHE, SJCMMN).

Data extraction enlisted novel biomarkers

Data of all included articles were extracted and summarized; the summaries of the enlisted newer biomarkers (adiponectin, leptin, uric acid, hsCRP, TNF-alpha, IL-1, IL-6, apoB and lp(a)) are depicted in Supplementary Table 4A-V. Data of interest are details regarding the size of the population and its type (survivors and their previous diagnosis, or general population), the study design (cross-sectional or longitudinal and retrospective or prospective), the biomarker (which and how it was measured), the exact outcome (MetS definition) and statistical analysis of choice. For studies investigating the diagnostic value of the biomarker for MetS, outcomes of interest were area under the curve (AUC) of receiver operating characteristic (ROC) curves, sensitivity and specificity. For the studies evaluating the predictive value of the biomarker of later development of the MetS, odds ratios (OR's) or beta-coefficients of multivariable logistic regression models, or hazard ratios (HR's) from multivariable Cox Proportional Hazards analysis were extracted from the publications.

Table 1 Commonly used metabolic syndrome definitions in selected studies

	NCEP ATP III	IDF 2006	Joint interim statement/ Harmonized definition	Japanese Obesity Society
Required for MetS diagnosis	3 or more criteria	Obesity plus 2 or more criteria	3 or more criteria	Obesity plus 2 or more criteria
Obesity	Waist circumference >102cm (men) or >88cm (women)	Waist circumference >90cm (men) or >80cm (women)	Waist circumference with ethnic-specific thresholds	Waist circumference >85cm (men) or >90cm (women)
Insulin resistance	Fasting plasma glucose ≥5.6 mmol/L or treatment	Fasting plasma glucose ≥5.6 mmol/L or treatment	Fasting plasma glucose ≥5.6 mmol/L or treatment	Fasting plasma glucose ≥6.1 mmol/L or treatment
Dyslipidemia	Triglycerides ≥1.7 mmol/L or treatment	Triglycerides ≥1.7 mmol/L or treatment	Triglycerides ≥1.7mmol/L or treatment	Triglycerides ≥1.7mmol/L, or HDL cholesterol <1 mmol/L (men) or <1.3 mmol/L (women), or treatment
	HDL cholesterol <1mmol/L (men) or <1.3 mmol/L (women) or treatment	HDL cholesterol <1mmol/L (men) or <1.3mmol/L (women) or treatment	HDL cholesterol <1mmol/L (men) or <1.3mmol/L (women) or treatment	
Hypertension	≥130/85mmHg or treatment	≥130/85mmHg or treatment	≥130/85mmHg or treatment	≥130/85mmHg or treatment

	Chinese Diabetes Society	Children and adolescents	Modified with BMI instead of waist circumference
Required for MetS diagnosis	3 or more criteria	3 or more criteria	
Obesity	Body mass index ≥25kg/m^2	Waist circumference ≥90th percentile	Body mass index ≥30 (Caucasians) or ≥25 (Asians) kg/m^2

Insulin resistance	Fasting plasma glucose ≥6.1 mmol/L or treatment	Fasting plasma glucose ≥5.6 mmol/L or treatment	
Dyslipidemia	Triglycerides ≥1.7 mmol/L, or HDL cholesterol <0.9 mmol/L (men) or <1.0mmol/L (women), or treatment	Triglycerides ≥1.7mmol/L or treatment	
		HDL cholesterol <1mmol/L or treatment	
Hypertension	≥140/90mmHg or treatment	≥130/85mmHg or treatment	

Table 2 Summary of outcomes

Summary of outcomes in diagnostic studies				
Biomarker	**Total number of studies and participants**	**Outcome**	**Number of studies**	**Range**
Leptin, in general population	6 studies, 8,209 participants[68,102,106,54,236,237]	AUC	5[68,102,106,236,237]	0.68-0.93
		Sensitivity	3[102,154,237]	48.0-92.6%
		Specificity	3[102,154,237]	56.3-72.0%
Uric acid, in general population	9 studies, 73,190 participants[66,101,150,237-242]	AUC	7[66,101,150,237,239,240,242]	0.56-0.85
		Sensitivity	3[237-239]	38.0-76.0%
		Specificity	3[237-239]	56.0-85.0%
Adiponectin, in general population	12 studies, 21,888 participants[63,65,67-69,102,106,140,143,243-245]	AUC	12[63,65,67-69,102,106,140,143,243-245]	0.55-0.92
		Sensitivity	2[102,243]	64.7-69.3%
		Specificity	2[102,243]	56.0-66.0%
hsCRP, in general population	7 studies, 18,211 participants[64,91,100,101,208,246,247]	AUC	6[64,91,100,101,208,247]	0.55-0.74
		Sensitivity	3[208,246,247]	51.0-69.0%
		Specificity	3[208,246,247]	56.6-72.0%
ApoB, in general population	1 study, 8,120 participants[111]	AUC	1[111]	0.68
TNF-alpha, in general population	1 study, 976 participants[64]	AUC	1[64]	0.54
IL-6, in general population	1 study, 976 participants[64]	AUC	1[64]	0.56
IL-1 and lp(a), in general population	No studies	n.a.	n.a.	n.a.

All biomarkers, in survivors	No studies	n.a.	n.a.	n.a.

Summary of outcomes in prognostic studies				
Biomarker	**Total number of studies and participants**	**Outcome**	**Number of studies**	**Range**
Uric acid, in general population	78 studies, 447,559 participants[71,72,75,77,82,88,90,92-96,98,99,101,150,207,210,238,239,241,242,248-303]	OR dichotomous	21[77,82,93-96,98,150,248,254,257,258,264,266,267,274,280,287,296,297,304]	1.00-5.17
		OR per unit	19[90,92,98,99,101,238,249,250,255,260,262,263,265,283,285,288,289,298]	1.001-2.14
		OR per unit logtransformed	2[239,302]	1.16, 2.08
		OR highest quantile	24[72,95,251,253,256-259,261,268,271,272,275,277-279,281,282,290-292,296,301,303]	1.00-8.04
		HR dichotomous	5[207,239,242,270,300]	1.06-2.99
		HR per unit	4[241,285,286,294]	1.10-2.35
		HR per SD	3[207,210,295]	0.86-1.36
		HR highest quantile	8[207,241,252,269,286,293-295]	0.74-3.47
		HR per unit longitudinal increase	2[207,285]	1.05, 1.31
		RR per unit logtransformed	1[276]	7.25 for men, 13.26 for women
		RR per SD	1[71]	1.10
		RR per 1.4mg/dl	1[88]	1.54 for men, 1.82 for women
		RR highest quantile	2[71,299]	1.69, 1.76
		PR	2[75,284]	1.47, 2.10
		IRR	1[75]	1.73

Uric acid, in survivors	2 studies, 390 survivors[58,59]	MetS prevalence in uric acid Q4 vs. Q1-3	1[59]	28.5% vs. 12.5% (P = 0.0044)
		MetS component(s) prevalence	1[58]	60% vs. 24% (P =0.04)
		high vs low uric acid		
Adipo-nectin, in general population	38 studies, 56,656 participants[65,67,69,70,73,74,76,78,81,102,103,105,140-148,159,245,305-319]	OR dichotomous (low adiponectin)	2[78,103]	0.90, 2.68
		OR per unit	9[67,73,76,141,144,148,159,309,314]	0.66-1.08
		OR per 5 units	1[69]	0.82 for men, 0.90 for women
		OR per unit logtransformed	4[74,146,245,306]	0.10-0.67
		OR per SD	2[315,317]	0.50-0.91
		OR per unit logtransformed Z-score	1[102]	0.76 for boys, 0.69 for girls
		OR highest quantile	13[69,105,140,142,143,145,147,305,308,315,317-319]	0.10-0.67
		OR lowest quantile	6[65,81,307,312,313,316]	1.82-18.6
		HR high baseline and increase during follow-up vs low baseline and decrease	1[311]	0.33
		HR decreased at follow-up	1[81]	4.37
		Time ratio of developing MetS Q1 vs Q4	1[310]	0.15 (=85% shorter time to develop MetS)

		Baseline ratio (value in	1[70]	1.27
		MetS subjects divided by value in non-MetS, adjusted for covariates)		
Adipo-nectin, in survivors	3 studies, 139 survivors[58,60,62]	OR highest quantile at baseline and follow-up	1[62]	0.5 (n.s.) for baseline, 0.9 (n.s.) for follow-up
		HR dichotomous (low adiponectin)	1[58]	6.7
		P-value of Kruskal-Wallis test median adiponectin in 0, 1, 2-4 MetS components	1[60]	n.s.
hsCRP, in general population	32 studies, 119,138 participants[70,74, 83-85,88,90,91,147,155,193, 195-199,208,246,249,265, 269,320-330]	OR dichotomous	2[155,196]	1.20, 2.74
		OR per unit	7[90,91,198,199,249, 328,330]	1.007-2.97
		OR per unit logtransformed	4[74,246,265,324]	1.15-3.2
		OR per SD	1[85]	1.21
		OR per unit logtransformed	2[208,325]	0.96, 1.07
		OR highest quantile	11[84,147,193,197,321-323,325-327,329]	1.07-7.11
		OR highest of three groups (<1.0, 1.0-3.0 and >3 µg/ml)	3[195,320,324]	1.65-18.86
		HR per unit logtransformed	1[269]	1.15
		RR per threefold increase	1[88]	1.13
		Baseline ratio	1[70]	0.80 (n.s.)
		P-value of likelihood test in multivariable model	1[83]	n.s.

hsCRP, in survivors	1 study, 87 survivors and 87 controls[61]	OR dichotomous	1[61]	7.26
ApoB, in general population	10 studies, 66,924 participants[74,79,82,86,87,108,109,331-333]	OR dichotomous	1[82]	2.55
		OR per unit	1[74]	2.99
		OR per 30mg/dl	1[87]	1.76 for men, 2.10 for women
		OR per SD	1[331]	1.56
		OR highest quantile	6[79,108,109,331-333]	0.96-6.03
		OR highest of three groups (<90, 90-119 and ≥120 mg/dl)	1[86]	2.69 for men, 1.69 for women
		RR per SD	1[331]	1.17 (n.s.)
		RR highest quantile	1[331]	1.79
ApoB, in survivors	No studies	n.a.	n.a.	n.a.
Leptin, in general population	17 studies, 28,797 participants[68,73,74,102,103,147-149,236,306,314,315,319,334-337]	OR dichotomous	1[103]	2.39
		OR per unit	4[73,148,314,336]	0.96-1.91
		OR per 10ng/ml	1[149]	1.06 (adjusted for WC), 1.22 (adjusted for BMI)
		OR per unit logtransformed	2[74,306]	1.47, 2.76
		OR per SD	3[68,315,335]	1.01-1.31
		OR per unit logtransformed Z-score	1[102]	1.81 for boys, 1.32 for girls
		OR highest quantile	6[147,236,315,319,334,337]	1.16-3.02

Leptin, in survivors	3 studies, 1 39 survivors [58,60,62]	OR highest quantile at baseline and follow-up	1[62]	4.8 for baseline, 5.7 for follow-up
		MetS component(s) prevalence high vs low leptin	1[58]	54% vs. 17% (P = 0.03)
		P-value of Kruskal-Wallis test median adiponectin in 0, 1, 2-4 MetS components	1[60]	n.s.
IL-6, in general population	5 studies, 3,370 participants[67,80,143,199,200]	OR per unit	2[67,199]	0.98-1.47
		OR highest quantile	2[143,200]	0.98 (n.s.), 4.10
		P-value in multivariable model	1[80]	n.s.
IL-6, in survivors	1 study, 87 survivors and 87 controls[61]	OR dichotomous	1[61]	1.53 (n.s.)
Lp(a), in general population	5 studies, 15,162 participants[89,320,338-340]	OR dichotomous	1[320]	8.27
		OR highest of three groups (<18.40, 18.40-33.84 and ≥33.85 µg/ml)	1[338]	0.82 (n.s.)
		OR per unit	1[339]	1.0 (n.s.)
		OR highest quantile	1[340]	0.45
		HR highest quantile	1[89]	1.01 (n.s.)
Lp(a), in survivors	No studies	n.a.	n.a.	n.a.

IL-1, in general population	4 studies, 1,594 participants[70,199,200,341]	OR per unit	2[199,341]	2.28 (IL-1 alpha), 1.009, 2.01 (IL-1 beta)
		OR highest quartile	1[200]	0.98 (n.s.)
		Baseline ratio	1[70]	1.17 (suggests effect in other direction)
TNF-alpha, in general population	3 studies, 1,458 participants[80,199,200]	OR per unit	1[199]	1.45
		OR highest quartile	1[200]	0.78 (n.s.)
		P-value in multivariable model	1[80]	n.s.
TNF-alpha, in survivors	1 study, 87 survivors and 87 controls[61]	OR dichotomous	1[61]	0.52 (n.s.)

Summary of evidence

The Grading of Recommendations Assessment Development and Evaluation (GRADE) tool was applied to summarize the quality of the evidence for each biomarker, per clinical research question (diagnosing or predicting MetS) and per population (general population and CCS).[55] The level of evidence was classified as insufficient, very low, low, moderate and high (Supplementary Table 4).[55] The applied thresholds for biomarkers are shown in Supplementary Table 5. An overview was made for studies assessing the same independent variables and outcome (Supplementary Table 6).

Data extraction non-enlisted biomarkers

As secondary objective we screened all articles for other biomarkers than the above enlisted nine biomarkers of our main interest (non-enlisted biomarkers). Details are discussed in Part 2 of the Appendix. These non-enlisted biomarkers were evaluated for presence of an effect if there were 4 or more publications with this biomarker in our search. As we did not search for these biomarkers systematically, evidence quality was not assessed with GRADE.

Meta-analysis

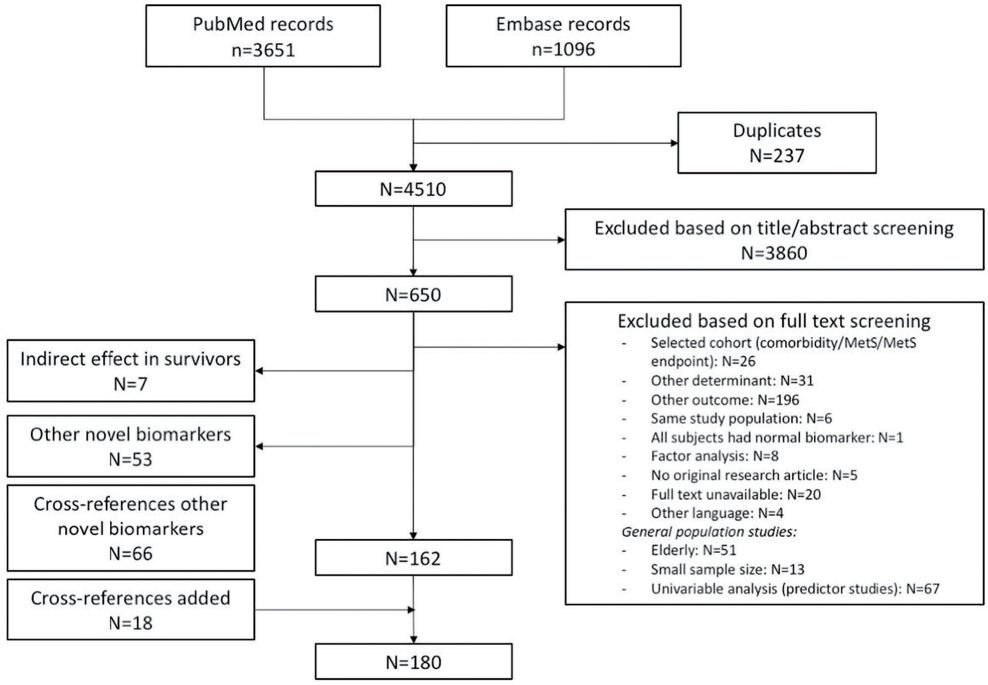
A meta-analysis was performed of relevant enlisted biomarkers with at least three publications on the same outcome measures and, if applicable, adjusted for the same covariates. Dichotomous outcomes were considered as comparable if the applied threshold differed less than the intra- and inter-assay variability for the biomarker as reported in literature. A random effects model with inverse variance weighting was used to estimate a pooled overall outcome measure. Overall heterogeneity (I-squared) and between-study variance (tau-squared) were calculated.[56] Meta-analysis was performed with the package *meta* in R.[57]

Results

Study selection

As shown in the flow chart (Figure 1), the literature search in PubMed and Embase yielded a total of 4,510 unique records. After title and abstract screening, 650 full-text articles were reviewed, after which 162 relevant studies remained. Backward and forward citation searching identified 18 additional studies. Hence, a total of 180 studies were identified that reported on the diagnostic and/or predictive value of one or more of the enlisted nine biomarkers of interest. Only five studies among the 180 were performed among a population of CCS.[58-62] All other studies were performed in the general population.

Figure 1 Flow chart of in- and excluded articles from the systematic literature search



Among 180 studies which included data regarding the 9 enlisted biomarkers, 60 also reported the value of other, non-enlisted newer biomarkers. Furthermore, we identified 119 other studies that only investigated non-enlisted newer biomarkers (other than the nine of our main interest), yielding a total of 179 studies for our secondary objective.

A detailed description of the critical appraisal of each of the 180 included studies for the nine predefined biomarkers is provided in the supplementary material (Supplementary Table 2 and 3).

Used metabolic syndrome definitions

In the included studies, a variety of MetS definitions was used of which the most common are described in Table 1 and the applied definition per study is depicted in Supplementary Table 4. The applied biomarker thresholds are summarized in Supplementary Table 5.

Evidence for newer, enlisted biomarkers as (additional) diagnostic criterion for metabolic syndrome

Twenty-nine studies reported on the diagnostic value of one or more of the nine enlisted newer biomarkers. These were all performed in the general population without a history of cancer. Six studies had a Caucasian study population.[63-68] The number of studies per biomarker ranged between zero [IL-1 and lp(a)] and twelve (adiponectin). The biomarker studied in the largest total number of participants was uric acid (73,190 participants). The relevant data extracted from each study, as well as the summary of evidence scored with the GRADE tool for each biomarker, are provided in the supplementary material (Supplementary Table 4). For each biomarker, a description of the number of studies and participants, and a summary of the several diagnostic outcomes, are provided in Table 2.

Whereas, ideally, the additional diagnostic value of a biomarker would be tested by comparing the AUC, sensitivity and specificity for a model containing only relevant covariates, versus a model containing

covariates and the newer biomarker, this method was used in only two of the 29 studies.[65, 69] One study compared the AUC of the biomarker with the AUC of waist circumference.[69] Most studies, however, only reported the AUC of the biomarker, either unadjusted or adjusted for age, sex, and sometimes BMI or waist circumference. Therefore, interpretation of the additional value is limited by detection and confounding bias for most of the biomarkers.

The overall summary of our findings, with a conclusion about the diagnostic value of each biomarker in the general population and in survivors based on the GRADE assessment, is shown in Figure 2. Of the nine investigated biomarkers, four were identified as valuable diagnostic biomarkers for MetS: leptin (high quality of evidence), uric acid (moderate quality), adiponectin, and hsCRP (both low quality). In addition, apoB may be valuable, although based on only one study with moderate quality of evidence. TNF-alpha and IL-6 appeared to be unusable, based on one low quality study testing both biomarkers. For IL-1 and lp(a), no studies were found.

Evidence for newer, enlisted biomarkers as independent predictor of metabolic syndrome

In total, 162 general population studies, and 5 survivor studies [two in acute lymphoblastic leukemia (ALL) survivors, two in survivors of hematological malignancies, one in survivors of heterogeneous tumors],[58-62] investigated the role of one or more of the nine enlisted, newer biomarkers as independent predictors of MetS. Twenty-six of the general population studies had a Western/Caucasian study population.[65, 67, 68, 70-92] The number of general population studies per biomarker ranged between 3 (TNF-alpha, 1,458 participants in total) and 78 (uric acid, 447,559 participants in total). Two of the survivors studies had a Western/Caucasian study population,[58, 59] the others were performed in Japan,[60] Malaysia,[61] and Mexico.[62] The number of survivors studies per biomarker ranged between zero [IL-1, apoB, and lp(a)] and 3 (adiponectin and leptin). The biomarker studied in the largest total number of survivors was uric acid (390 survivors). The

relevant data extracted from each study, as well as the summary of evidence scored with the GRADE tool for each biomarker, are provided in the supplementary material (Supplementary Table 4). For each biomarker, a description of the number of studies and participants, and a summary of the several prognostic outcomes, are provided in Table 2.

A common analysis strategy in these studies was to divide the biomarker value in quantiles, with thresholds that may differ per study. Not all participants in the highest or lowest quantile always had a biomarker value that would be classified as abnormal according to reference values. This may attenuate its value in predicting MetS. On the other hand, this bias towards the null hypothesis increases the effect of true positive findings. Also, several studies tested a dose-response effect by comparing the effect on MetS across the quantiles. Studies can be compared on whether a dose-response effect was observed or not.

Figure 2 Summary of conclusions: predictive and diagnostic value of novel 13 biomarkers for the MetS

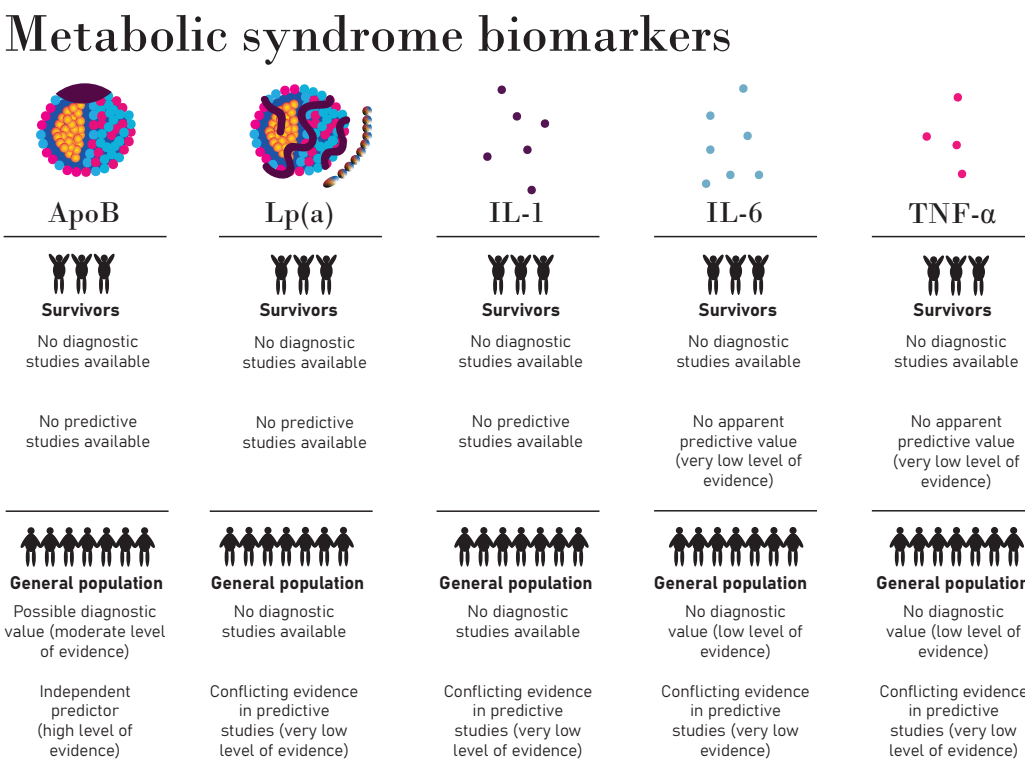


Figure 2 shows the overall summary of our findings, consisting of a conclusion about the role of each biomarker as independent predictor of MetS in the general population and in survivors, after GRADE assessment. Five biomarkers were identified as independent predictors of MetS in the general population: uric acid, adiponectin, hsCRP, apoB (all high quality of evidence), and leptin (moderate quality). There is conflicting evidence for the value of TNF-alpha, IL-1, IL-6, and lp(a) (very low quality of evidence). Among survivors, uric acid and hsCRP may be valuable as prognostic biomarkers, based on two and one studies, respectively, with very low quality of evidence. There is conflicting evidence for the prognostic value of adiponectin and leptin (very low quality). TNF-alpha and IL-6 appear not to be independent predictors, based on one very low quality study testing both biomarkers. For IL-1, apoB, and lp(a), no studies were found.

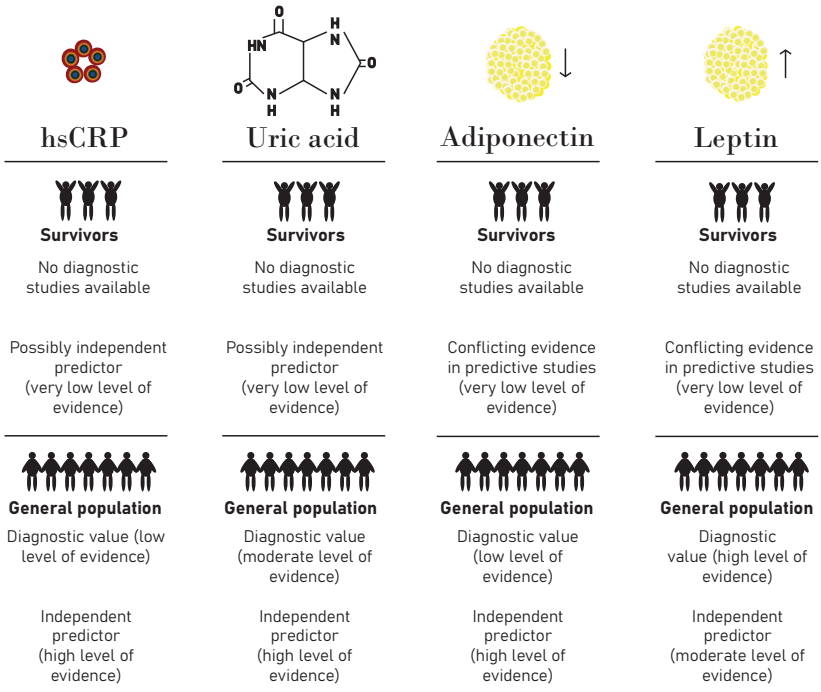
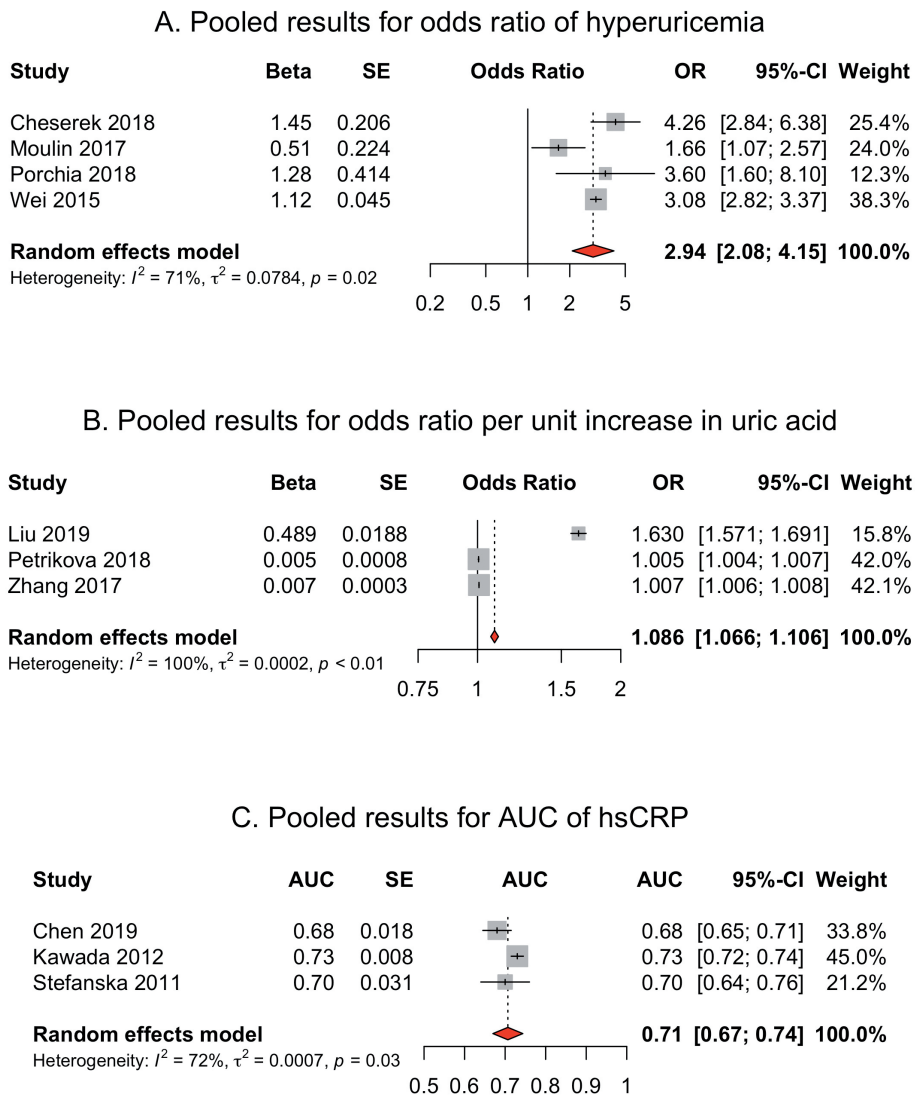


Figure 3 Forest plots for different study-specific outcomes



A. Odds ratio (OR) for hyperuricemia. B. OR for per unit increase in uric acid. C. Area under the curve (AUC) of hsCRP. The sizes of the square boxes on the forest plots are proportional to the total number of patients in the selected trials.

Meta-analysis of most relevant findings of enlisted biomarkers

We aimed to perform a meta-analysis of the most promising biomarkers: uric acid, adiponectin, leptin, hsCRP, and apoB. For diagnostic studies, only the AUC is suitable for meta-analysis, due to different thresholds used for sensitivity and specificity (Supplementary Table 6). For predictor studies, only dichotomous and continuous (per unit, or per unit log-transformed) studies are useful. Many studies use quantiles but these are unsuited for meta-analysis: cut-offs between the quantiles depend on the range and distribution in each study population, and are therefore insufficiently comparable between studies to perform a meta-analysis.

A wide variety of outcome measures was used in the studies, and many studies performed an analysis that was unsuited for meta-analysis. Also, there was variance in thresholds used for dichotomous outcomes, as well as in covariates in multivariable models. Therefore, we were unable to retain at least three sufficiently comparable studies for most biomarkers, and for most outcomes, in order to perform a meta-analysis. For a few biomarkers, enough studies were eligible for meta-analysis, because the authors also published crude outcomes, and outcomes that were only age- and sex-adjusted (Supplementary Table 6).

We were able to perform a meta-analysis for the prognostic value of uric acid (hyperuricemia and continuous uric acid levels), and for the diagnostic value of hsCRP. We estimated the pooled OR for the association between hyperuricemia and MetS, adjusted for age and sex (four studies,[93-96] with threshold variability accepted of 10%,[97] OR 2.94, 95% CI 2.08-4.15), the pooled OR per unit increase in uric acid, unadjusted (three studies,[90, 98, 99] OR 1.086, 95% CI 1.066-1.106), and the pooled AUC for hsCRP, also unadjusted (three studies,[91, 100, 101] AUC 0.71, 95% CI 0.67-0.74).[90, 99] Forest plots are shown in Figure 3. Unfortunately, many studies could not be included, and the reported estimators are not adjusted for relevant covariates, in particular age and sex for some, and overweight, insulin resistance, and smoking for all.

Other, non-enlisted biomarkers

In Supplementary Table 7, [179] articles for all other biomarkers for diagnosis or prognosis of MetS are enlisted and the main data is summarized. These included ratios of our studied biomarkers. All studies investigating leptin/adiponectin ratio as prognostic[62, 68, 73, 102-105] or diagnostic study[68, 102, 104-107] showed a possible relevance. Apolipoprotein A1 (apoA1) and apoB/apoA1 ratio seem valuable in predicting the MetS (6 studies with a protective effect of apoA1,[82, 86, 87, 108, 109] and 8 studies with an effect of increasing risk of increasing apoB/apoA1 ratio82,[108-114]). There are two studies reporting a diagnostic value of apoB/apoA1 ratio.[108, 111] Other recurrently reported, potentially useful biomarkers were Gamma GT, (non-high sensitivity) CRP, ferritin, leukocyte count, hemoglobin and urine pH and sodium excretion.

Discussion

This is the first systematic literature review investigating newer biomarkers for metabolic syndrome (MetS) in CCS, with the aim to obtain the highest level of evidence by including validated tools for risk of bias assessment and summary of evidence, and by performing a meta-analysis.

For five biomarkers, numerous studies with moderate to high quality of evidence were found for diagnosing and predicting MetS: uric acid, adiponectin, leptin, hsCRP, and apoB. The evidence was not sufficient to confirm the value of candidate biomarkers lp(a), IL-1, IL-6, and TNF-alpha.

Meta-analysis of eligible studies showed a predictive value of uric acid for MetS, with a positive association, and a diagnostic value for hsCRP.

These findings suggest that uric acid, adiponectin, leptin, hsCRP, and apoB may be used in a screening setting for CCS, in addition to standard MetS criteria, in order to provide better diagnosis and prediction of MetS (risk). Systematic reviews in other populations have identified not only elevated leptin,[115] uric acid,[115-118] and low (HWM) adiponectin,[115, 119, 120] but also Il-6[115] and TNF-alpha[115] as potential MetS biomarkers.

As anticipated, the number of publications for survivors on this topic was rather limited: we identified only five studies in CCS specifically, which found a possible predictive value for hsCRP and uric acid, and conflicting or no evidence for the value of adiponectin, leptin and TNF-alpha. Disadvantages of these survivor studies were low patient numbers and moderate to high (detection and confounding) bias risk. No studies investigated the diagnostic value of newer biomarkers. Survivor studies with information on altered biomarker values but no direct comparison between biomarker and MetS occurrence, were excluded.[60, 121-130] We expected to miss many relevant studies when designing the study, if we based our conclusions only on survivor studies. Therefore, evidence in the younger general adult population without childhood cancer history was included in our search as well, leading to 175 general population studies with relevant data which were generalizable to young adult survivors.

CCS can have an increased risk to develop MetS, in particular after treatment with cranial and/or abdominal radiotherapy, intensive chemotherapy, nephrectomy, adrenalectomy, or stem cell transplantation.[43, 131-139] These therapies can lead to several underlying conditions that can increase the risk for (components of) MetS, such as hypothalamic damage, growth hormone deficiency, pancreatic beta cell dysfunction, hypogonadism, hypothyroidism, and altered body composition with increased abdominal fat.[43, 131-139]

Furthermore, it is well acknowledged, that in CCS the biological age progresses faster than their true age, as can be derived from their high level of frailty.[4-9] Previous studies have shown, that the physiologic reserve of CCS with a median age of 33 is similar to that of adults in the general population who are aged 65 years.[6] For this reason, we included studies investigating biomarkers for MetS in the general population, with >75% of participants aged below 65 years, as may be very well applicable to CCS. We excluded studies investigating MetS biomarkers among elderly people on purpose, since they have an even higher level of frailty than CCS, comorbidities and aging factors, which may be confounders in the association between the newer biomarker and metabolic syndrome. We considered that extrapolating

conclusions from a general elderly population to CCS could draw invalid conclusions. Based on this approach, all available literature applicable to survivors is now discussed in this review, as it includes both survivor studies as well as all generalizable data from a reasoned selection of the general population studies.

On the other hand, several studies excluded people with certain chronic illnesses.[73, 101, 140-150] This may limit applicability of results to the population of CCS, in which the prevalence of comorbidities is high.[3, 25, 126, 151] This was taken into account when scoring the risk of bias. Additionally, childhood cancer (treatment) related long-term side effects, such as altered fat distribution, sarcopenic obesity, and hormonal disbalances, may play a survivor specific role in the pathogenesis of MetS;[11] development of future studies that apply the use of biomarkers in large cohorts of CCS is therefore important.

Due to differences in study designs and statistical analyses, a wide variety of outcome measures was used. There was also substantial diversity in follow-up time in longitudinal studies. By employing the GRADE tool for summarizing evidence, we were able to draw conclusions for each biomarker from this heterogeneity of results. The meta-analysis was based on few studies, as many studies could not be included. Also, heterogeneity was high in the meta-analysis on uric acid per unit increase, as the study of Liu et al. had a remarkably higher OR than the other two studies.[98]

Furthermore, although the ability of different MetS definitions to predict diabetes and CVD appears to be similar,[152, 153] the use of different definitions (Table 1) can lead to differences in occurrence of MetS. There are subtle differences between the definitions that were mostly used in the included studies (Table 1). The potential consequence of choice of definition is illustrated by studies that tested the biomarker use in diagnosing or predicting MetS according to multiple definitions, and sometimes found different results depending on the definition used.[67, 143, 154, 155] Therefore, comparing different studies and interpreting results of the meta-analysis requires some caution, as a full comparison of the studies is often not possible.

Adiposity, and hence the MetS, can be underdiagnosed in survivors, due to altered body composition after radiotherapy, stem cell transplantation, or amputations. For clinical applicability to survivors, it is important that newer biomarkers play an independent role in MetS, and measurement of newer biomarkers is only useful when their effect is not yet captured by established MetS components. Therefore, we did not investigate routine dyslipidemia and insulin resistance markers in our search (e.g., LDL, HOMA-IR). Although apoB and lp(a) are also lipid markers, they are of interest because they are better predictors of atherogenicity than triglycerides, HDL and LDL – particularly apoB, because it gives an estimate of the total number of circulating atherogenic particles.[156-158]

In this light, it is also favorable that studies adjust for MetS components, such as adiposity and insulin resistance, in order to adjust for potentially major correlations and interactions,[159-162] and to yield the independent/additional diagnostic and predictive value of the biomarker. Furthermore, it remains important to evaluate other traditional risk factors, including smoking, physical activity, socio-economic status, and family history.[78,163] In addition, genetic profile may still be relevant for MetS risk, although so far this is not included in standard screening.[164-166] Risk of detection and confounding bias remains high, especially in the diagnostic studies, as many studies did not adjust for MetS components and traditional risk factors. In particular for the diagnostic studies, a risk of (detection and) confounding bias remained.

The MetS is defined as a cluster of symptoms such as obesity, hypertension, impaired glucose tolerance and dyslipidemia.[11] These clustered symptoms are related to each other: an imbalance in energy intake and consumption causes a cascade of increased (visceral) adiposity, increased circulating free fatty acids and decreased adiponectin (which causes also an increase in insulin resistance), and high levels of pro-inflammatory and pro-thrombotic mediators, such as TNF-alpha, IL-1 and IL-6.[11, 34] Insulin resistance is associated with a lowered excretion of uric acid by the kidneys, and higher uric acid

production.[167, 168] The adipokines leptin and adiponectin are produced by adipocytes.[169] Low leptin values trigger metabolic, behavioral and endocrine responses that aim at a preservation of the fuel reserves of the body.[170] Adiponectin enhances insulin sensitization and suppresses inflammation and cell death.[170-173] Another important molecule is apoB: all atherogenic lipoproteins carry one single apoB molecule as their structural protein, and therefore apoB represents the atherogenic burden.[174] Serum apoB is a strong predictor of cardiovascular risks[156, 175, 176] and comes in as an important player for the MetS in this review as well. One of the low density lipoproteins carrying an apoB molecule, is Lp(a).[177] The interpretation of Lp(a) values in an individual can be difficult due to a high heterogeneity and wide distribution of Lp(a) concentrations.[178] Although evidence for relevance of Lp(a) for MetS evaluation in survivors was unavailable, it remains a marker of interest, since elevated Lp(a) levels were an independent predictor for cardio- and cerebrovascular outcomes[179-187] and were inversely associated with T2DM.[188]

An important inflammatory marker is (hs)CRP, which is synthesized by hepatocytes[189, 190] in response to infection, inflammation, tissue damage and malignant neoplasia.[189, 190] CRP binds to LDL[189, 191] and may have a causal role in atherogenesis,[189] as it is present in atherosclerotic plaques.[189, 192] Inflammatory markers may reflect a transient state instead of chronic state of inflammation.[193] Still, in the study of Oda et al., the diagnostic value of hsCRP was reproducible when the measurement was repeated after one year.[194] Many studies had a high CRP, or infection[100, 197-200] as exclusion criterion. Regarding inflammation; smooth muscle cells, endothelial cells and macrophages produce cytokines such as IL-1 and IL-6[201-203] in reaction to metabolic stress,[203, 204] by other inflammatory mediators such as interferon-gamma and TNF, and cholesterol itself.[203] Still, the evidence for the usefulness as marker for the MetS is rather limited.

Due to the systemic nature of MetS, our secondary objective to reveal other interesting biomarkers yielded many markers. Interesting markers for further research include Gamma GT, ferritin, leukocytes and hemoglobin. In several studies biomarkers were related to each other,

as MetS components are related as well.[205] In one study, leptin was inversely associated with uric acid excretion;[205] in another, a synergistic effect between hsCRP and high molecular weight adiponectin was found.[206] Also, ratios of biomarkers (e.g. leptin/adiponectin, apoB/apoA1) include extra information and may be better diagnostic or prognostic agents than single biomarkers. Future studies may investigate the value of combining biomarkers.

Some limitations are present in this systematic literature.

Many of the included studies had a cross-sectional design, which is suboptimal to investigate causality; this was taken into account for the GRADE and level of evidence. Some authors conducted prospective longitudinal studies[81, 193, 207, 208] and associated MetS risk at end of follow-up with baseline and/or change in biomarker level. Study designs even more suitable for determining prediction and causality include prediction models and Mendelian randomization.[209-212] These study designs require more time and financial resources, and large cohorts. These types of studies where either not performed or unsuitable for our research question.

Many studies were performed among Asian cohorts. Asian people are more susceptible to insulin resistance,[213, 214] which is accounted for in lower waist circumference thresholds. Additionally, there may be an ethnicity specific component in the relationship between biomarker and MetS.[215-222] This may limit the applicability to a Caucasian population.

For this literature study, we focused on diagnosis and prediction of the full MetS; other outcomes such as resolution of the MetS,[223] components of the MetS, CVD or T2DM were out of scope.[186, 224-235] Therefore, our findings do not provide a complete overview of the use of the newer biomarkers in diagnosing and predicting cardiovascular risk factors in CCS.

We have two suggestions for future research that are relevant for the implementations of our findings in the follow-up of CCS. The newer biomarkers could be added as a sixth criterion for MetS. This application

can be especially of value in cases of doubt of MetS diagnosis for individuals who had abdominal irradiation: it may be valuable to replace waist circumference with the adipokines leptin or adiponectin. This may identify MetS in more survivors, and can potentially improve the predictive ability for T2DM and CVD.[231]

An important requirement for the applicability of these newer biomarkers in such a screening setting for MetS (risk) in CCS, is the determination of a threshold. For uric acid, this is relatively well-established (Supplementary Table 5); for other biomarkers, this is less clear, as is illustrated by the range of applied thresholds (Supplementary Table 5). This is partly because of the use of different assays and testing of subfractions of a biomarker, such as high molecular weight adiponectin. Also, a tradeoff between sensitivity and specificity may influence the determination of an optimal threshold.

In conclusion, based on this systematic literature search, we suggest to consider the additional use of uric acid, adiponectin, hsCRP, leptin, and apoB in the screening setting for metabolic syndrome in CCS. As our conclusions are largely based on general population studies, studies in CCS are needed. Furthermore, future studies may specifically test the use of newer biomarkers as additional MetS components, and define optimal thresholds. The addition of one or more of these newer biomarkers as a criterion for MetS may lead to a newer and better classification and enhanced identification of risk of developing T2DM and CVD, especially in CCS in whom components are difficult to evaluate in the currently applied definitions. Early intervention can delay or prevent complications, and hence improve very long-term survival outcomes and quality of life.

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Supplementary material

Appendix A

Search terms
Criteria for article selection and risk of bias assessment
Critical appraisal of studies
Data extraction and GRADE for each research question per predefined biomarker
Data extraction non-predefined biomarkers

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7

Bariatric Surgery for Hypothalamic Obesity in Craniopharyngioma Patients: A Retrospective, Matched Case-Control Study

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Abstract

Context: Craniopharyngioma is a sellar tumor associated with high rates of pituitary deficiencies (~98%) and hypothalamic obesity (~50%).

Objective: To determine the efficacy regarding long-term weight loss after bariatric surgery in obese craniopharyngioma patients with hypothalamic dysfunction.

Design: Retrospective case control study.

Setting: Multicenter international study.

Patients: Obese craniopharyngioma patients (N = 16; of which 12 women) with a history of bariatric surgery [12 Roux-en-Y gastric bypass, 4 sleeve gastrectomy; median age of 21 years (range 15-52), median follow-up 5.2 years (range 2.0-11.3)] and age/sex/surgery/BMI-matched obese controls (N = 155).

Main outcome measures: Weight loss and obesity-related comorbidities up to 5 years after bariatric surgery were compared and changes in hormonal replacement therapy evaluated.

Results: Mean weight loss at 5-year follow-up was 22.0% (95% CI 16.1, 27.8) in patients versus 29.5% (28.0, 30.9) in controls ($P = 0.02$), which was less after Roux-en-Y gastric bypass (22.7% [16.9, 28.5] vs. 32.0% [30.4, 33.6]; $P = 0.003$) but at a similar level after sleeve gastrectomy (21.7% [–1.8, 45.2] vs. 21.8% [18.2, 25.5]; $P = 0.96$). No major changes in endocrine replacement therapy were observed after surgery. One patient died (unknown cause). One patient had long-term absorptive problems.

Conclusions: Obese patients with craniopharyngioma had a substantial mean weight loss of 22% at 5-year follow-up after bariatric surgery, independent of type of bariatric surgery procedure. Weight loss was lower than in obese controls after Roux-en-Y gastric bypass. Bariatric surgery appears effective and relatively safe in the treatment of obese craniopharyngioma patients.

Keywords: craniopharyngioma, hypothalamic obesity, hypothalamic dysfunction, bariatric surgery, weight loss, case-control study

Introduction

Craniopharyngiomas are rare brain tumors, which mostly affect children or older adults.[1-3] They are typically located in the sellar and suprasellar regions.[1,2] State-of-the- art treatment for craniopharyngiomas is tumor resection with or without radiotherapy.[2] Although craniopharyngiomas usually have a benign histology, treated patients often suffer from severe long-term sequelae as a result of hypothalamic dysfunction due to tumor localization or therapeutic interventions.[2-4]

Besides the necessity for life-long hormone replacement therapy due to hypopituitarism, hypothalamic dysfunction can also cause eating disorders such as hyperphagia, leading to obesity in 50% to 75% of the patients.[2,5,6] Energy expenditure may also be decreased and cognitive performance can be weak, which can interfere with conservative weight loss strategies.[2,7] Morbid hypothalamic obesity and associated complications like type 2 diabetes, hypertension, obstructive sleep apnea syndrome, hypersomnia and increased daytime sleepiness have a major impact on quality of life in patients with craniopharyngioma.[3,6,8-11] The morbid obesity and related comorbidities contribute to an increased cardiovascular mortality.[3,6,8-11]

Since pharmacologic treatment options are limited,[12] bariatric surgery might be a promising treatment strategy in combating obesity in patients with craniopharyngioma. Key to the effectiveness of bariatric surgery in the general obese population is a decrease in appetite, which is caused by changes in gastrointestinal hormones such as glucagon-like peptide 1 (GLP-1).[13,14] GLP-1 activates neurons in the hypothalamus that influence satiety, feeding, the sympathetic nervous system, and the pituitary.[12,13] Bariatric surgical procedures are not all equally effective – gastric bypass surgery seems to be the most promising option in the general population.[15-17] However, the question remains whether bariatric surgery is still effective if the hypothalamus is damaged, as is often the case in patients with craniopharyngioma.[2] Previously, studies that were hampered by a follow-up of ≤2 years reported a significant weight reduction following gastric bypass surgery in patients with severe hypothalamic obesity without postoperative impairment of oral

hormone replacement therapy for pituitary insufficiencies.[16-18]

In patients suffering from morbid obesity in the general population, bariatric surgery is an efficient treatment with sustained long-term weight loss.[19,20] However, data on the long-term effects of bariatric surgery in morbid hypothalamic obesity due to a craniopharyngioma are limited. This is a major barrier in providing evidence-based advice to patients. This study is therefore aimed at analyzing (medium) long-term weight reduction following gastric bypass and sleeve gastrectomy surgery in obese craniopharyngioma patients compared to a matched control group from a general obese population treated with bariatric surgery and at describing safety aspects regarding pituitary hormone replacement therapy.

Materials and methods

Study Design and Participants

In this international, multicenter, matched case-control study, patients with a history of craniopharyngioma and bariatric surgery to treat hypothalamic obesity were compared to bariatric surgery patients from a general obese population. Sixteen patients with histopathology-proven craniopharyngioma with ≥2 years follow-up were included from the Erasmus Medical Center, Rotterdam, The Netherlands (n = 4),[17] the Sahlgrenska University Hospital, Gothenburg, Sweden (n = 4),[17] the Medical University Hospital of Vienna, Austria (n = 5), University Hospital Erlangen, Erlangen, Germany (n = 2), and the Federal University of Parana, Curitiba, Brazil (n = 1). The study methods and the Dutch/Swedish patients have been previously described;[17] this report increased patient numbers by recruiting from additional centers and increased follow-up duration. This international study followed all national laws and recommendations in the country where the patient was treated concerning ethical approval and written consent. The study was approved by all local ethics committees. Two patients underwent a second bariatric surgery procedure; one had the Roux-en-Y gastric bypass ~20 months after a sleeve gastrectomy due to insufficient

weight loss and abdominal pain, and one patient had a Roux-en-Y gastric bypass ~6 years after gastric banding (the gastric banding was removed after 1 week due to abdominal complaints). Data from the second bariatric surgery onwards were applied in this analysis. Hypothalamic damage was defined as injury to the hypothalamus and/or third ventricle, diagnosed by neuroimaging and/or neurosurgery reports.[8] Patients with a history of radiotherapy were considered at high risk of hypothalamic dysfunction and therefore also included in the study if they met all other inclusion criteria.

Matching Procedure for Controls

Controls were acquired from the Scandinavian Obesity Surgery Registry (SOReg), a Swedish nationwide registry. The patients were matched to controls from a sample of 69,672 individuals who were pre-selected from the total cohort of 75,600 SOReg participants after exclusion of subjects who were not Swedish, were reoperated, had surgery before 2007, or had a procedure other than gastric bypass surgery or sleeve gastrectomy. Controls had follow-up data on body weight (kg) available at 6 weeks, and at 1, 2, and 5 years after bariatric surgery. Patients had a considerable variation in follow-up duration due to the retrospective design. Missing data for 3- and 4-year follow-up in controls and 1- to 5-year follow-up in patients was interpolated linearly between the two closest available time points. The matching procedure was extensive: potential controls were first selected according to sex, type of bariatric surgery (Roux-en-Y gastric bypass or sleeve gastrectomy), pre-operative type 2 diabetes, and preoperative hypertension. Further matching was performed by year of obesity operation (10-year span category), age at obesity operation (10-year span category), and preoperative body mass index (BMI) (maximum of ±5 kg/m^2 different from the control). Controls were included only once. If less than ten controls were found, the criteria for matching age at bariatric surgery were extended to ±10 years of the patient's age instead of a certain age category, which was required in five patients. For one patient, the criteria for BMI were extended as this patient was an outlier due to extremely high BMI: the best-matched controls were chosen without a limit to BMI criteria. Ultimately,

all patients were each matched with ten controls except for two patients: nine controls were found for one and six controls were found for the extreme outlier. This resulted in the selection of 155 optimally matched controls (mean BMI difference –1.1 kg/m^2; maximum BMI difference between patient and control ranging from 0.04 to 12.6 kg/m^2)

Outcomes of Interest

Data were gathered retrospectively. Outcomes of interest were percentage weight change at 6 weeks, at 1, 2, 3, 4, and 5 years, and at last available follow-up after bariatric surgery. The presence of type 2 diabetes, hypertension, and dyslipidemia as comorbidities before bariatric surgery and during follow-up, and complications of the bariatric procedure were evaluated. We studied alterations in hormone replacement therapy for pituitary deficiency in patients with craniopharyngioma.[17] For insulin-like growth factor 1 (IGF-1) values, standardized deviation scores (SDS) were calculated if the applied assay and normative data were known.[21-24]

Statistical Procedure

Statistical analysis was performed using the Statistical Package for Social Sciences (IBM SPSS Statistics 25, Chicago, IL). Continuous data are represented as mean ± standard deviation (SD), or median and range; categorical data are represented as frequencies and percentages. Baseline statistics were compared between patients with obesity after craniopharyngioma and the matched controls from the SOReg database by Mann-Whitney U-test and Fisher's exact test for continuous and categorical data, respectively. Related continuous data were evaluated with Wilcoxon's rank test. A two-way analysis of variance was used to compare percentage weight change between patients and controls. In this procedure, a one-factor generalized randomized block design was applied with matched case-control units included as blocks. Percentage weight change was applied as the dependent variable and type of subject (patient with

craniopharyngioma or control) as the independent variable in the two-way ANOVA. Bootstrapping with 1,000 replicates was performed to meet the normality assumption related to the two-way analysis of variance test.[17]

Results

Patient Characteristics

The characteristics of the 16 craniopharyngioma patients treated with bariatric surgery are shown in Table 1. Twelve (75%) patients were female and 13 (81%) had childhood (<18 years) onset of disease. Initial treatment for craniopharyngioma was surgery (n = 13 [81%]), surgery and radiotherapy (n = 2 [13%]), and cyst aspiration (n = 1 [6%]). Two patients (13%) had a history of recurrence of craniopharyngioma twice and nine patients (56%) had residual tumor tissue on their last magnetic resonance imaging (MRI) scan. All patients had signs of either hypothalamic damage or third-ventricle involvement on MRI (n = 13 [87%, data missing for 1 patient]), or a history of radiotherapy (n = 7 [44%]). Two patients (13%) had used medication to treat obesity before bariatric surgery: sibutramine with no results, and sibutramine and orlistat with no results and no results/side effects, respectively. Twelve patients (75%) underwent Roux-en-Y gastric bypass and four patients (25%) underwent sleeve gastrectomy. Median follow-up duration of the patients since bariatric surgery was 5.8 years (range 2.0–11.3), hereafter being referred to as last follow-up.

A comparison of baseline characteristics of patients with craniopharyngioma and their controls with 'common' obesity matched for age, sex, comorbidity, BMI, and bariatric surgery is shown in Table 2. Baseline characteristics were comparable between patients and controls except for age at bariatric surgery (with a slightly lower mean age of 26 years [SD 12] in patients vs. 31 years [12] in controls; P = 0.03) and more frequent presence of dyslipidemia before surgery (4/16 [25%] in patients vs. 6/155 [4%] in controls; P = 0.008); the difference in the presence of dyslipidemia between patients and controls before

surgery was more pronounced in those undergoing sleeve gastrectomy (3/4 [75%] vs. 1/39 [3%]; $P = 0.001$]. The occurrence of dyslipidemia before bariatric surgery was higher in craniopharyngioma patients who had a gastric sleeve than in those who underwent gastric bypass (3/4 [75%] vs. 1/12 [8%]; $P = 0.03$).

Table 1 Baseline demographic and clinical characteristics of patients with craniopharyngioma

Characteristic	Craniopharyngioma patients (N = 16)
Sex, n (%)	
Women	12 (75)
Men	4 (25)
Median (range) age at first craniopharyngioma treatment (years)	12 (4–48)
Median age (range) at last follow-up (years)	33 (17–61)
Mean (SD) follow-up duration since craniopharyngioma surgery at last follow-up (years)	11.9 ± 3.8
Treatment for craniopharyngioma, n (%)	
Surgery	
Initially*	15 (94)
Ever	15 (94)
Median (range) number of craniopharyngioma surgeries	1 (1–6)
Radiotherapy	
Initially (in addition to surgery)	2 (13)
Ever	7 (44)
Mean (SD) cumulative radiotherapy dose (mGy)	4,225 ± 1,801
Hypothalamic damage, n (%)	9 (60)
Third-ventricle involvement, n (%)	9 (60)
Hypothalamic damage and/or third-ventricle involvement, n (%)	13 (87)

Hypothalamic damage and/or third-ventricle involvement and/or radiotherapy, n (%)	16 (100)
Pituitary deficiencies	
GH deficiency	
Frequency, n (%)	16 (100)
Median (range) age at occurrence (years)	13 (6–49)
GH replacement therapy at last follow-up, n (%)	14 (88)
TSH deficiency	
Frequency, n (%)	15 (94)
Median (range) age at occurrence (years)	14 (4–48)
Gonadal axis deficiency	
Frequency, n (%)	14 (88)
Median (range) age at occurrence (years)	13 (6–48)
Gonadal replacement therapy at last follow-up, n (%)	12 (75)
ACTH deficiency	
Frequency, n (%)	12 (75)
Median (range) age at occurrence (years)	12 (4–48)
ADH deficiency	
Frequency, n (%)	14 (88)
Median (range) age at occurrence (years)	12 (4–48)
Use of antiepileptic drugs, n (%)	2 (13)
Bariatric procedure	
Median (range) age at bariatric surgery (years)	21 (15–52)
Mean (SD) BMI before bariatric surgery (kg/m^2)	46.0 ± 8.0
Median (range) follow-up since bariatric procedure (years)	5.8 (2.0–11.3)

ACTH, adenocorticotropic hormone; ADH, antidiuretic hormone; BMI, body mass index; GH, growth hormone; TSH, thyroid-stimulating hormone. *Excluding one patient treated with cyst aspiration initially.

Table 2 Baseline characteristics of patients treated with bariatric surgery: craniopharyngioma-related hypothalamic obesity versus controls with 'common' obesity

Characteristic	Craniopharyngioma patients (N = 16)	Matched controls (N = 155)
Sex, n (%)		
Female	12 (75)	119 (77)
Male	4 (25)	36 (23)
Mean (SD) age at bariatric surgery (years)	26.4 ± 12.1	30.5 ± 11.5*
Bariatric procedure, n (%)		
Roux-en-Y gastric bypass	12 (75)	116 (75)
Sleeve gastrectomy	4 (25%)	39 (25)
Mean (SD) preoperative BMI (kg/m^2)	46.0 ± 8.0	45.1 ± 6.9
Roux-en-Y gastric bypass	45.4 ± 6.0	44.9 ± 5.6
Sleeve gastrectomy	48.0 ± 13.5	45.6 ± 9.7
Pre-operative diabetes mellitus, n (%)	1 (6)	10 (6)
Pre-operative hypertension, n (%)	4 (25)	35 (23)
Pre-operative dyslipidemia, n (%)	4 (25)	6 (4)†

BMI, body mass index. *P = 0.03, †P = 0.008.

Weight Change after Bariatric Surgery

Mean weight loss at 5 years after surgery was 22.0% (95% CI 16.1, 27.8) in craniopharyngioma patients compared to 29.5% (28.0, 30.9) in controls ($P = 0.02$; Table 3 and Figure 1). Patients had significantly less weight loss compared to controls from 1- to 5-year follow-up after any bariatric surgery procedure and from 2- to 5-year follow-up after Roux-en-Y gastric bypass specifically, but not after sleeve gastrectomy specifically. Mean weight loss at 5-year follow-up after Roux-en-Y surgery was less in patients compared to controls (22.7% [95% CI 16.9, 28.5] vs. 32.0% [30.4, 33.6]; $P = 0.003$) but was comparable at 5-year follow-up after sleeve gastrectomy comparing patients and controls, respectively (21.7% [−1.8, 45.2] vs. 21.8% [18.2, 25.5], $P = 0.96$). If the type of bariatric surgery is compared in patients or controls as a group, mean percentage weight loss at 4-year follow-up in controls was higher after Roux-en-Y gastric bypass compared to sleeve gastrectomy (33.0 [SD 7.8] vs. 24.0 [9.9]; $P < 0.001$), but not different when comparing these bariatric procedures in craniopharyngioma patients (21.8 [12.0] vs. 19.1 [5.7], $P = 1.00$). Figure 2 shows the percentage of patients and controls in 5% weight loss categories at 2- and 4-year follow-up. At last follow-up, eight (50%) of 16 patients had lost at least 20% of their original body weight, three (19%) between 10% and 15%, three (19%) between 5% and 10%, and one (6%) <5% weight loss, while one (6%) showed weight increase. Among the patients who used sibutramine, one had at least 20% weight reduction and the other had 5–10% weight loss at last follow-up. There was no significant difference in mean percentage weight loss at last follow-up comparing patients with (n = 13) and without (n = 2) hypothalamic damage or third-ventricle involvement (23.2% [SD 16.6] vs. 10.5% [5.4]; $P = 0.23$, one missing) and those with (n = 7) and without (n = 9) radiotherapy (16.6% [16.9] vs. 23.5% [15.7]; $P = 0.41$), respectively.

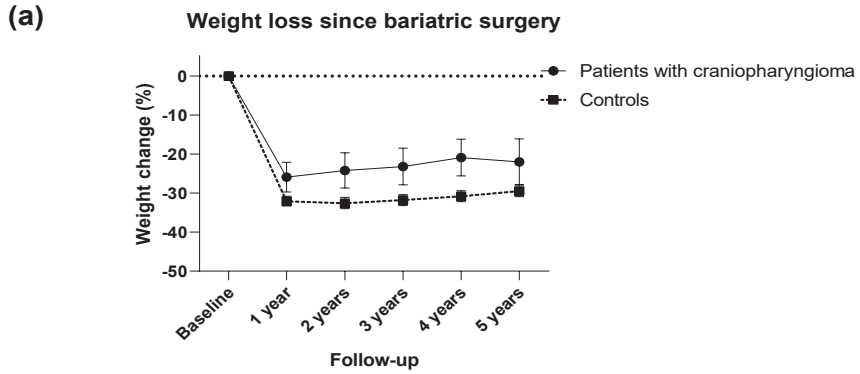
Table 3 Percentage weight loss after bariatric surgery of patients with craniopharyngioma and matched controls

Time after surgery	% Weight loss (95% CI)		
	Sleeve gastrectomy		
	Patients	Controls	*P*-value
6 weeks	18.1 (12.5, 23.7)	14.7 (12.9, 16.5)	0.25
1 year	25.3 (17.4, 33.2)	27.5 (25.0, 30.0	0.60
2 years	23.8 (14.6, 33.0)	27.1 (24.1, 30.0)	0.50
3 years	28.9 (18.4, 39.5)	25.5 (22.6, 28.4)	0.53
4 years	22.5 (8.9, 36.0)	24.0 (21.0, 26.7)	0.82
5 years	21.7 (–1.8, 45.2)	21.8 (18.2, 25.5)	0.96

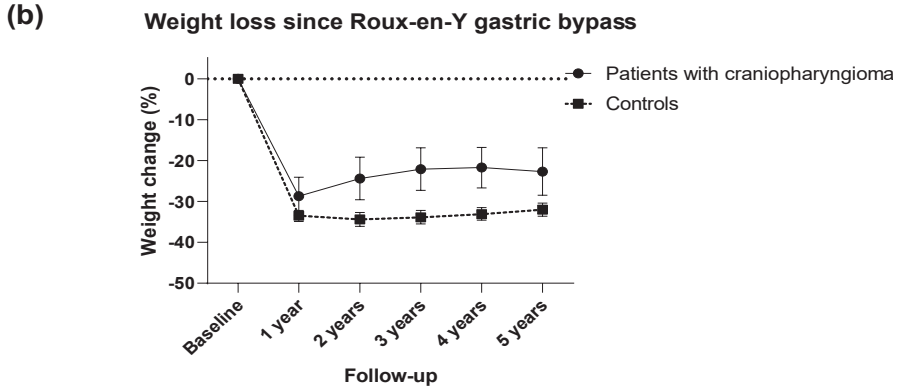
Time after surgery	% Weight loss (95% CI)		
	Roux-en-Y gastric bypass		
	Patients	Controls	*P*-value
6 weeks	15.0 (12.1, 18.0)	15.5 (14.6, 16.4)	0.74
1 year	28.7 (24.1, 33.4)	33.5 (32.2, 34.9)	0.05
2 years	24.4 (19.2, 29.6)	34.4 (32.7, 36.1)	<0.001
3 years	22.1 (16.9, 27.3)	33.9 (32.2, 35.5)	<0.001
4 years	21.7 (16.8, 26.7)	33.1 (31.5, 34.6)	<0.001
5 years	22.7 (16.9, 28.5)	32.0 (30.4, 33.6)	0.003

Time after surgery	% Weight loss (95% CI)		
	Any bariatric surgery procedure		
	Patients	Controls	*P*-value
6 weeks	15.8 (13.2, 18.4)	15.3 (14.5, 16.1)	0.71
1 year	25.9 (22.1, 29.7)	32.1 (30.8, 33.3)	0.003
2 years	24.2 (19.7, 28.7)	32.6 (31.1, 34.0)	0.001
3 years	23.2 (18.5, 27.9)	31.8 (30.4, 33.2)	0.001
4 years	20.9 (16.2, 25.6)	30.8 (29.4, 32.2)	<0.001
5 years	22.0 (16.1, 27.8)	29.5 (28.0, 30.9)	0.02

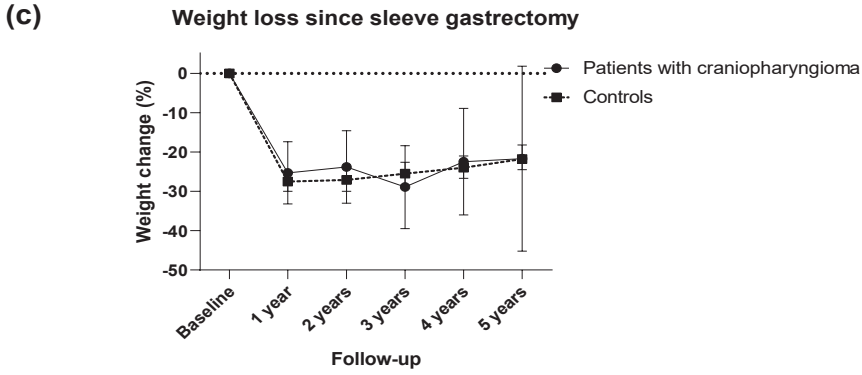
Figure 1 Weight loss up to 5-year follow-up after bariatric surgery



Patients with craniopharyngioma	n=16	16	16	15	13	10
Controls	n=155	155	155	125	124	96



Patients with craniopharyngioma	n=12	12	12	11	11	9
Controls	n=116	116	116	105	105	86



Patients with craniopharyngioma	n=4	4	4	3	2	1
Controls	n=39	39	39	29	19	10

Mean (SD) percentage weight loss in obese craniopharyngioma patients and matched controls after any bariatric surgery (A), Roux-en-Y gastric bypass specifically (B), and sleeve gastrectomy specifically (C).

Cardiometabolic Features

The prevalence of type 2 diabetes before bariatric surgery was similar in patients and controls (1/16 [6%] vs. 10/155 [6%]; *P* = 1.00). At last follow-up, type 2 diabetes had resolved in all subjects except for one control, resulting in similar percentages in patients and controls (0/16 [0%] vs. 1/155 [1%]; *P* = 1.00). Dyslipidemia occurred more often in patients than controls before bariatric surgery (4/16 [25%] vs. 6/155 [4%]; *P* =0.008) and at last follow-up (2/15 [13%; one missing data] vs. 2/155 [1%]; *P* = 0.04). Hypertension occurred at a similar prevalence in patients and controls before bariatric surgery (4/16 [25%] vs. 35/155 [23%]; *P* = 0.76) and there was no significant difference at last follow-up (0/16 [0%] vs. 18/155 [12%]; *P* = 0.22), although all cases of hypertension in patients were resolved at last follow-up.

Complications after Bariatric Surgery

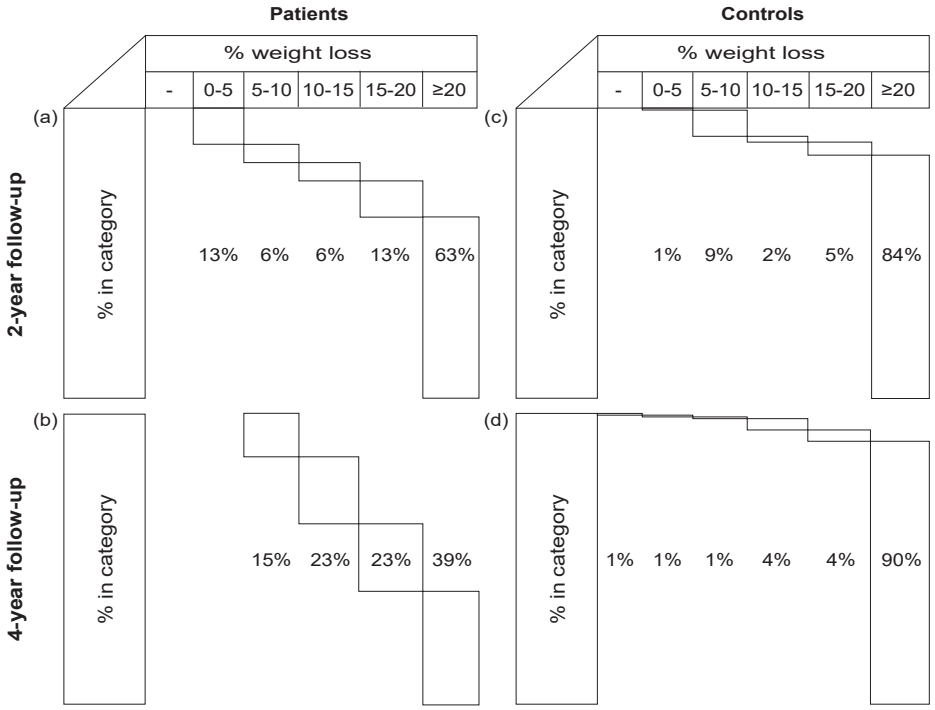
Five patients experienced short-term peri- and post-operative complaints or issues: post-operative abdominal pain (n = 1), dumping syndrome (n = 1), inability to eat solid food due to abdominal fullness (n = 1), stenosis of the anastomosis (n = 1), a generally complicated post-operative course with nephrolithiasis, pulmonary embolism, and post-infarction pneumonia (n = 1). Regarding long-term complications, one patient suffered from long-term severe absorptive problems ever since the bariatric surgery, which was accompanied by malnutrition and a low quality of life. One patient died at the age of 32 years, approximately 2.5 years after their second bariatric surgery; the cause of death was unknown. Since the cause of death could not be determined, an adrenal insufficiency cannot be excluded as a contributing factor to the fatality.

Replacement Therapies for Pituitary Deficiencies

Fifteen (95%) of the 16 patients needed minor-to-moderate changes of pituitary hormone replacement therapy during follow-up, the only exception being a patient only receiving growth hormone replacement

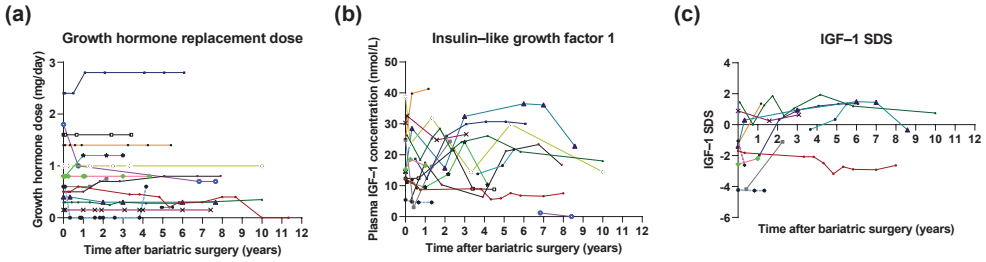
therapy (see Table 1 for baseline pituitary deficiencies, and Figures 3-4 for individual changes of replacement therapy). All patients were growth hormone deficient. Mean daily growth hormone dose was not significantly different before bariatric surgery versus last follow-up (0.92 [SD 0.65] vs.0.72 [0.88] mg; *P* = 0.50); similarly, mean IGF-1 (19.4 [10.1] vs. 34.0 [57.6] nmol/L; *P* = 0.72) and mean IGF-1 SDS values (–1.6 [1.6] vs. –0.7 [2.0]; *P* = 0.61) did not change significantly (Figure 3). One patient did not initially receive growth hormone replacement therapy due to fear of tumor growth but the patient reconsidered and decided to start during follow-up. Three patients stopped using growth hormone replacement therapy at some point during follow-up, one of which was due to diagnosis of a malignancy (Figure 3).

Figure 2 Waterfall plots of weight loss categories at 2- and 4-year follow-up after bariatric surgery.



Percentage of obese craniopharyngioma patients (A, B, n=16) and matched controls (C, D, n=155) in 5% weight loss categories for interpolated data at 2-year (A, C) and 4-year (B, D) follow-up after bariatric surgery. Percentages may not add up to 100% exactly due to rounding. Missing data at 4-year follow-up in three patients and one control.

Figure 3 Change in growth hormone replacement therapy and IGF-1 in obese craniopharyngioma patients following bariatric surgery

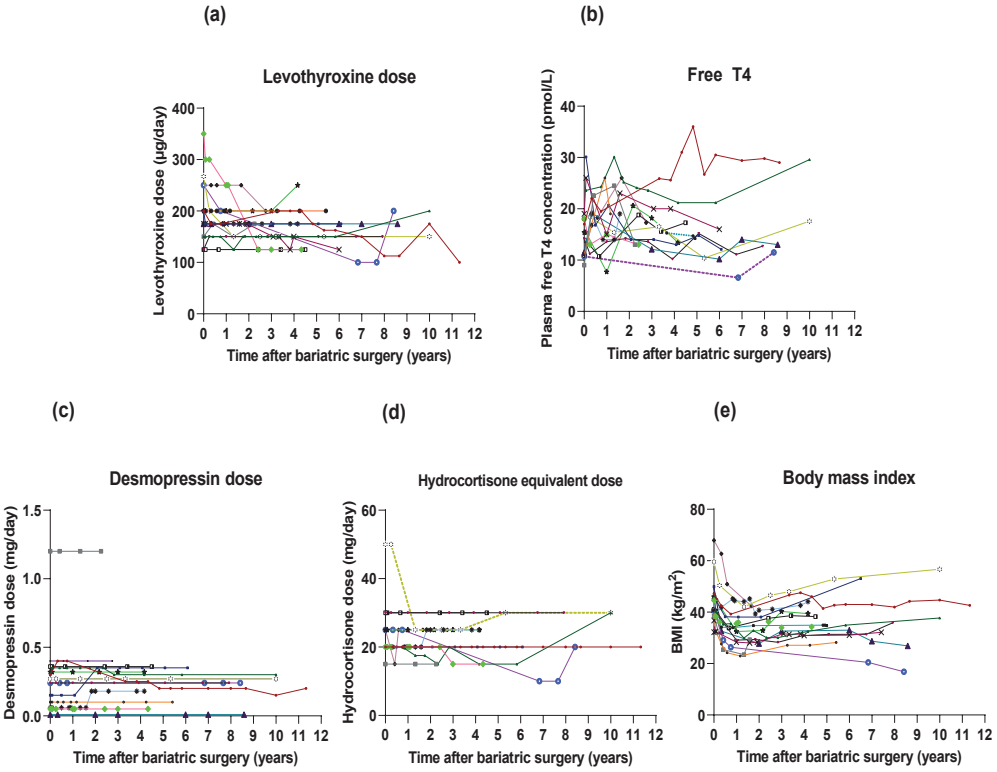


Spaghetti plots of changes in growth hormone replacement therapy daily dose (A), plasma IGF-1 (B), and IGF-1 SDS (C) for individual patients following bariatric surgery. A continuous line between observations represents patients using growth hormone replacement therapy and an interrupted line indicates patients who did not use growth hormone at last follow-up. IGF-1=insulin-like growth factor 1; SDS=standardised deviation score.

Fourteen (88%) of 16 patients had a gonadal hormone deficiency; eight had no change in their replacement therapy and one did not use any during follow-up. Three patients switched type of gonadal hormone replacement therapy (estradiol/dydrogesterone to ethinylestradiol/levonorgestrel at different doses; multiple esters of testosterone every 15 days intramuscular to testosterone undecanoate every 3 months; and gel application to injection). One patient required only a minor dose change. One patient stopped treatment due to a liver adenoma.

Thyroid hormone replacement therapy was needed in 15 (94%) of 16 patients, of which five had no changes in thyroid medication at all (Figure 4); mean daily levothyroxine dose was comparable before bariatric surgery and at last follow-up (199.5 [SD 59.8] vs. 171.2 [40.6] µg; $P = 0.23$). Mean cumulative daily 1-desamino-8-d-arginine vasopressin (DDAVP) doses for central diabetes insipidus remained similar comparing before surgery to last follow-up (0.29 [0.29] vs. 0.24 [0.10] mg; $P = 0.29$). DDAVP dose was unchanged in ten patients (Figure 4). Mean cumulative daily hydrocortisone dose did not change from before bariatric surgery to last follow-up (25.5 [9.3] vs. 24.2 [5.1] mg; $P = 0.85$).

Figure 4 Change in pituitary hormone replacement therapy, free T4, and BMI in obese craniopharyngioma patients following bariatric surgery



Spaghetti plots of changes in daily levothyroxine dose (A), plasma free T4 concentration (B), daily desmopressin dose (C), daily hydrocortisone dose (D), and BMI (E) for individual patients following bariatric surgery. A continuous line between observations represents patients with a deficiency for the particular pituitary hormone axis using hormone replacement therapy at last follow-up; an interrupted line is shown for patients who have a deficiency but do not use hormone replacement therapy at last follow-up; and a dotted line represents patients not known with this particular pituitary deficiency at last follow-up. BMI=body mass index, T4=thyroxine.

Discussion

This is the first long-term case-control study on the outcome of bariatric surgery in the largest cohort of patients with craniopharyngioma and hypothalamic dysfunction to date. It showed a mean ~22% weight loss 5 years after bariatric surgery. All patients required minor adjustments of hormonal replacement therapy after bariatric surgery, which were anticipated as most patients underwent a serious change in body weight. Although these results are encouraging, weight loss was significantly less pronounced, but still clinically relevant, compared to obese controls without a history of craniopharyngioma.

This less dramatic weight loss for craniopharyngioma patients compared to controls was, however, only observed after Roux-en-Y gastric bypass. This is in contrast to the results of our previous study in a smaller cohort,[17] when we found similar weight reduction after Roux-en-Y gastric bypass in patients with craniopharyngioma and controls, and less weight reduction in patients than controls after sleeve gastrectomy. The current study now includes the same Dutch and Swedish patients,[17] but the sample size has been enlarged by international cooperation, leading to a larger cohort of patients with a considerably longer follow-up after the bariatric procedure. The number of patients who underwent sleeve gastrectomy is, however, still relatively small (n = 4).

In a comparative effectiveness study in the general population, patients with Roux-en-Y gastric bypass had a greater mean weight loss (25.5%) than patients with sleeve gastrectomy (18.8%) at 5-year follow-up.[20] A previous meta-analysis showed that there were also better results at 5-year follow-up for Roux-en-Y gastric bypass compared to sleeve gastrectomy regarding not only weight loss but also remission of comorbidities such as hypertension, dyslipidemia, and type 2 diabetes.[19] The number of events in patients was too low in our study to compare decline in comorbidities between the two types of surgery. In the general population, Roux-en-Y gastric bypass patients had, on the other hand, a higher 30-day rate of major adverse events than those undergoing sleeve gastrectomy (5.0% vs. 2.6%).[20]

It seems that craniopharyngioma patients have a higher risk of post-operative adverse events than the general population, as five (31%) patients had problems shortly after surgery, of which two (13% of craniopharyngioma bariatric surgery patients) were serious adverse events. The risk-benefit ratio must especially be taken into account when applying bariatric surgery to underaged patients who may be unable to make a proper informed discussion. Considering our patients had similar weight loss compared to controls after sleeve gastrectomy and their weight reduction was similar after sleeve gastrectomy compared to Roux-en-Y gastric bypass as well as the lower adverse event rate with sleeve gastrectomy in the general population, sleeve gastrectomy may be considered a more advantageous strategy in patients with craniopharyngioma. Our study did not include laparoscopic gastric banding, which is another bariatric surgery procedure.[16] One patient included in our study was subject to a previous unsuccessful laparoscopic gastric banding (LAGB). Weismann et al. reported on 3 out of 6 described patients with LAGB that needed another bariatric surgery procedure.[16,25] LABG appears a less effective option in these patients.[25] Adjustable gastric banding is less effective in the general population as well: the PCORnet study described a mean five-year weight loss of 12% for LAGB, versus 26% after Roux-en-Y gastric bypass, and 19% for sleeve gastrectomy.[20] Only one patient was described to have had a biliopancreatic diversion.[25] In the general population, biliopancreatic diversion is not often performed as it is accompanied with very high rates of severe nutritional deficiencies and high rates of revisions.[26]

Although individual patients required adjustments of hormone replacement therapy during follow-up, mean doses did not change significantly. Despite growth hormone being administered subcutaneously and thus not being absorbed in the intestine, it is unsurprising some dose changes were needed during follow-up as growth hormone doses are known to be influenced by age and BMI.[27] Weight-based regimens have been proposed for glucocorticoid replacement, growth hormone replacement, and thyroid hormone replacement.[27,28] Changes in hormone replacement therapy can be considered as part of long-term practice in the care of patients with

hypopituitarism and are expected in the case of weight change; this did not lead to any confirmed major adverse events such as acute adrenal crisis. Our results suggest that bariatric surgery can be regarded as safe for patients with hypopituitarism and complementary replacement therapy, which is in line with previous research that found no major negative effects regarding hormone replacement therapy.[17,18,29,30] Wolf and colleagues[18] performed an oral thyroid/hydrocortisone/paracetamol absorption test in a patient who had undergone gastric bypass surgery and found sufficient gastrointestinal drug absorption. Hence, additional emphasis on individual drug management and adjustments, especially shortly after bariatric surgery, seems important.[29]

A limitation of our study is the retrospective design. Nevertheless, the study has several strengths. For such a rare disease, we report the largest sample size in the history of studies investigating bariatric surgery after craniopharyngioma and our study is unique in its duration of long-term follow-up. In addition, the cases were matched almost perfectly to controls from an average obese non-craniopharyngioma bariatric surgery population, thereby enabling an optimal comparison. Future research could investigate whether our data can be generalized to subjects with other causes of hypothalamic dysfunction.

Future studies that include even more patients and a longer follow-up as well as investigating differences between responders and non-responders to bariatric surgery with respect to weight loss will be able to show whether the observations from our study are sustained over time. Sleeve gastrectomy combines restriction of food intake with favorable hormonal alterations and Roux-en-Y gastric bypass adds a component of mild malabsorption to that in the general obese population.[29] As our study shows a similar weight loss effect in patients compared to controls with respect to sleeve gastrectomy but not after Roux-en-Y gastric bypass, it would be of interest to measure hormonal changes, such as GLP-1, related to bariatric surgery in future studies.[14] This would not only provide insight into the changed pathophysiology in patients with craniopharyngioma and hypothalamic dysfunction but also contribute to the exploration of other weight loss strategies for obesity in these

patients, such as GLP- 1 analogues.[31] In a small study of ten patients with different causes of hypothalamic obesity, treatment with the GLP-1 analogue exenatide resulted in weight stabilization or decrease.[31] It might also contribute to strategies to maintain weight loss after bariatric surgery: for example, the GLP-1 analogue liraglutide provided weight loss in a patient with craniopharyngioma whose bariatric surgery failed to be effective long term.[32]

In conclusion, patients with craniopharyngioma had a mean weight loss of 21% up to 5 years after bariatric surgery. Although weight loss was significantly less compared to matched obese controls, this was a clinically relevant reduction. Weight loss was only less in patients who underwent Roux-en-Y gastric bypass surgery while it was similar in those who underwent sleeve gastrectomy, compared to controls. Weight loss appears independent of bariatric surgery type. As for all patients with hypopituitarism, craniopharyngioma patients needed endocrinological follow-up and guidance with special attention for dose adjustment of their hormonal replacement therapy after bariatric surgery, but in this retrospective analysis no major changes were made in terms of dose and type of treatment. There were no confirmed cases of adrenal insufficiency. Bariatric surgery can therefore be regarded as a relatively safe and efficacious option in patients with craniopharyngioma who have no or mild cognitive decline and can cope with lifestyle restrictions after bariatric procedure. The possible downsides of bariatric surgery in craniopharyngioma patients are suboptimal weight loss compared to controls and the potential for absorption problems and perhaps more postoperative problems, which should be thoroughly discussed with patients before proceeding with this invasive intervention.[3]

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8

General Discussion

General discussion

The outcome of treatment of patients with tumors has improved over the past decades, which went hand in hand with a growing awareness for very long-term consequences regarding comorbidities and quality of life. This is especially true for children with cancer: they generally have an excellent short-term survival rates, and still have many years of living ahead thereafter. This awareness led to large cohorts of childhood cancer survivors being examined on a wide variety of long-term effects, such as the LATER study in the Netherlands.[1-3] A group for which appriate awareness is perhaps still lacking, although the attention is growing, are patients suffering from relatively benign neoplasms such as craniopharyngiomas, who often suffer from a compromised health.[4] Patients with craniopharyngioma have experienced similar therapeutic regimens as patients with a malignant disease, such as neurosurgery and radiotherapy. Also, this benign tumor lies very close to important neurological and vascular structures such as the hypothalamus, pituitary, carotid arteries and optic nerves, which can be damaged by the tumor and by treatment.[4] The hypothalamus and pituitary are important organs for the endocrine system and metabolism. Previous Dutch and Swedish studies already revealed, that craniopharyngioma patients had high rates of long-term sequalae like pituitary deficiencies (81-98%), visual deficiencies (75%), neurological deficits (34%) and obesity (56%).[5,6] The aim of this thesis was to further expand on identification of long-term endocrine, bone-related and metabolic alterations in those who suffer(ed) from a tumor, with a special focus on patients with benign tumors of the pituitary (craniopharyngioma and macro-adenoma). We aimed to determine risk factors as well as protective factors related to metabolic health and bone health, and evaluated the efficacy of current common methods for diagnosis and treatment of metabolic consequences.

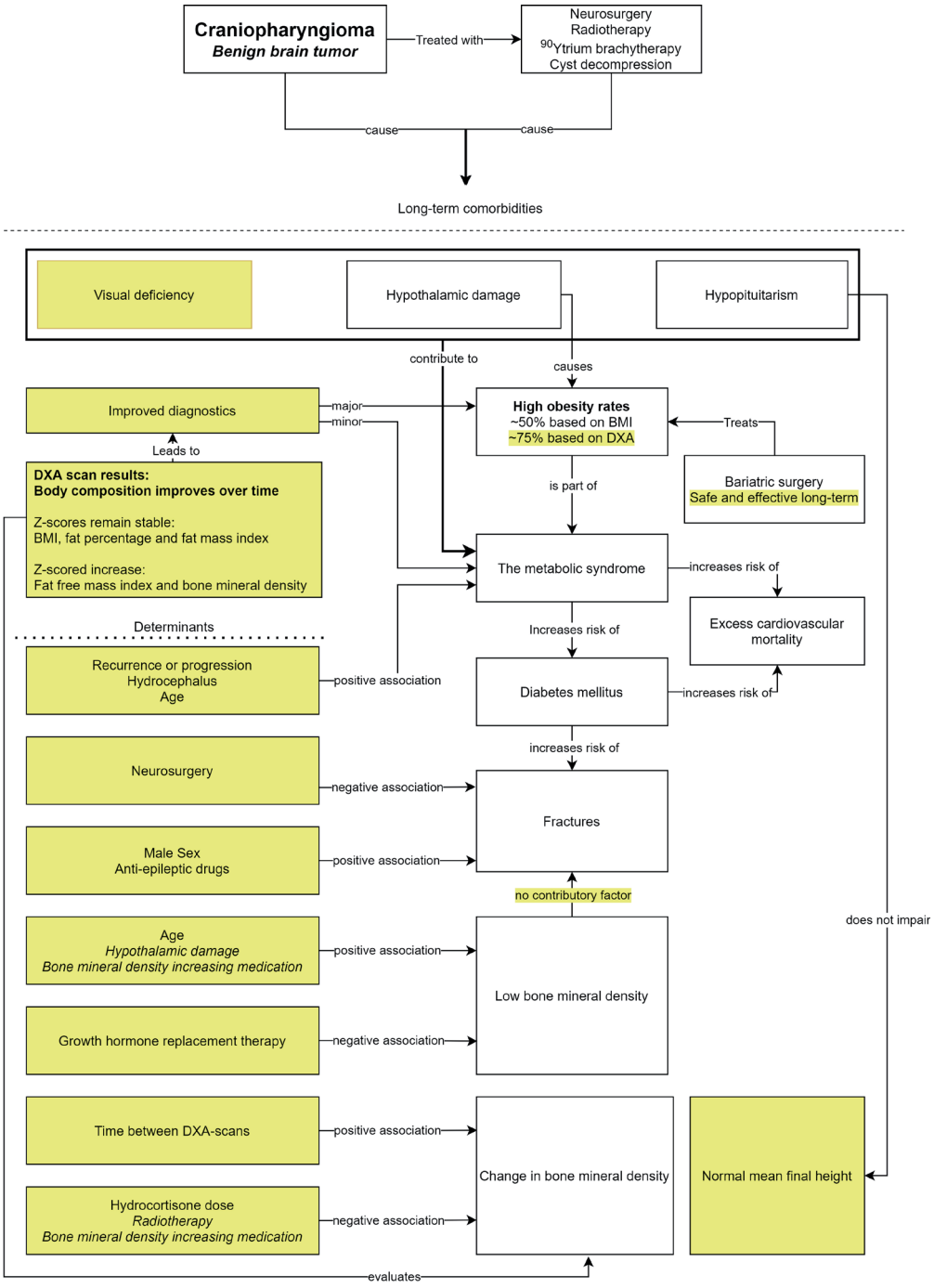
Tumors and bone

Non-malignant tumors can have a major effect on development and sustainment of bone. This is expecially the case after tumors in de sellar region that cause an increase or decrease in the secretion of pituitary hormones. First, we described the discovery of a novel *AIP* mutation, causing accelerated growth due to a growth hormone secreting adenoma with a complicated treatment in an exceptionally young boy. Thereafter, we described the impact on bone health in a large cohort of patients with craniopharyngioma and frequent occurrence of hypopituitarism, including fracture risk, bone mineral density (changes) and growth, and related risk- and protective factors (Figure 1).

Pituitary adenoma and growth

An example of a tumor in the sellar region with high secretion of hormones and obvious influence on bone, is a growth hormone secreting adenoma. **Chapter 2** describes the discovery of a novel truncating *AIP* mutation (p.Tyr202x) in a case of growth hormone secreting adenoma with an unexpected course of disease, and with an onset at an extraordinarily young age. The 7-year old boy presented with a strongly reduced intake of nutrients, which could have led to failure to thrive and decelerated growth. Instead, the tumor caused an excess growth hormone before closure of the epiphysis and led to an accelerated growth.[7] In all pituitary adenomas, only 5% of the cases relate to a genetic alteration; therefore not all cases need genetic screening.[8] However, the chances of identifying a genetic cause increase especially in case of familial predisposition, and in pediatric acromegaly.[8] In case of gigantism or familial predisposition in familial acromegaly in Familial Isolated Pituitary Adenomas (FIPA) kindreds, 50% of the patients have a causative mutation.[8,9] It is important to screen high-risk populations of mutations, as it allows earlier diagnosis in relatives and a better choice of therapy.[9,10] *AIP* mutated adenomas seem to have a suboptimal response to treatment with 1st generation somatostatin analogues, but a good response to 2nd generation somatostatin analogues.[11,12] Second generation somatostatin analogue pasireotide has the highest affinity for

Figure 1 Summary of the findings in craniopharyngioma patients of this thesis



Findings are marked in yellow if they are newly discovered by the projects presented in this thesis. Scentences in italic represent findings in univariable analysis or with unlikely causal relationship.

somatostatin receptor (SSTR) 5, followed by SSTR2, SSTR3 and SSTR1 thereafter.[13] Despite the highest affinity for SSTR5, pasireotide resistance is mostly related to SSTR2 expression instead of SSTR5 in the general acromegalic population.[14,15] In the patient of **Chapter 2**, tumor growth continued despite treatment with neurosurgery and second-generation somatostatin analogues. The pathology reported presence of SSTR2 expression, and loss of SSTR5 expression at the third operation – a possible decline starting from the first surgery could not be demonstrated due to lack of available tissue for examination. Furthermore, *in vitro* experiments showed a resistance for pasireotide. This suggests that it could be preferable to test the *in vitro* response of tumor tissue to growth hormone secretion instead of assessing somatostatin receptor expression to improve the predicted reponse *in vivo*.[15] This is because the functional test combines the presence of the receptors with their down-stream function. The aberrant course of disease in this patient underlines importance of individualized, tumor-specific treatment.

Craniopharyngioma and bone health

Growing towards an adequate height

While the patient in **Chapter 2** had an increased growth due to high growth hormone levels, on the other side of the spectrum a growth hormone deficiency can cause an impaired growth. Growth is an important aspect of bone health. Infant growth partially determines the acquired bone mass of the adult.[16] Size, or final height, also matters for metabolic properties of an individual.[17] Healthy taller persons have larger total resting energy expenditure, but a relatively lower mass-specific resting energy expenditure compared to smaller persons.[17-19] Lastly, height is of importance in the evaluation of bone mineral density: smaller bones with a comparable volumetric bone mineral density appear to have a lower areal bone mineral density, as a two-dimensional image does not incorporate the depth of bone.[20,21]

Impaired growth due to growth hormone deficiency in the context of hypopituitarism can occur when a benign tumor grows near the

pituitary, or when this tumor is treated with surgery or radiotherapy.[22,23] In **Chapter 3**, we performed one of the largest studies investigating bone health in patients with craniopharyngioma with a median follow-up of 16 years. In this retrospective study, growth appeared normal, as both childhood and adulthood onset patients achieved a mean final height despite high frequencies of pituitary deficiencies: a pituitary deficiency of at least one axis occurred in 92% of the cases, with growth hormone deficiency in 85% in this cohort. In the literature, certain studies[24] were consistent with finding a normal mean final height. However, one study still showed short stature in 31% of the cases,[25] and in a very large cohort of 393 craniopharyngioma patients, patients with childhood-onset disease were slightly (0.6 SDS) shorter.[26] The size of this cohort was even larger than our cohort, which enables to find a significant difference when the difference between two groups are relatively small.

Proper treatment with growth hormone therapy is likely the most important contributor to achieving a normal final height,[27] as growth acceleration is observed after initiating growth hormone therapy.[28,29] Still, patients with craniopharyngiomaq seem to have a better growth after growth hormone therapy than growth hormone deficient patients with other types of brain tumors, regardless of cranial radiotherapy.[30] Perhaps, the 'growth without growth hormone syndrome', plays a role in adding extra centimeters of achieved height on top of the results from growth hormone treatment. This 'growth without growth hormone syndrome' supposedly relates to hypothalamic damage, which occur at a high rate (~45%) in patients with craniopharyngioma.[31] In the International Registry of Hypothalamic Obesity Disorders (IRHOD), craniopharyngioma was even the most common type of brain tumor causing hypothalamic obesity.[32] Craniopharyngioma patients with grade 2 hypothalamic damage were taller than patients with grade 0 or 1 hypothalamic damage.[25] The precise mechanism of 'growth without growth hormone syndrome' is not yet elucidated, but it appears that hypothalamic damage and related obesity play a central role, as they lead to insulin resistance, initiating high insulin levels and a mitogenic effect,[33,34] and to elevated leptin levels which affects the bone growth center.[35-40] Besides hypothalamic damage, another theory suggests the

existence of yet undiscovered hormones and growth factors, other than growth hormone, which cause the unexpected pursued growth.[35-40] Growth without any growth hormone replacement indeed occurred in patients with craniopharyngioma.[33,34,36,41-44]

Bones breaking bad: fractures and bone density in patients with craniopharyngioma

Risk factors for fractures in the general population were low bone density, hypogonadism, poor physical function, chronic health problems, anticonvulsants, corticosteroid use and estrogen replacement therapy.[45] These risk factors are all potentially applicable in patients with craniopharyngioma.[6,31] **Chapter 3** describes the first study investigating determinants of fracture risk of patients with craniopharyngioma, and one of few studies investigating determinants of low bone mineral density.

The occurrence of bone fractures in 18% of the craniopharyngioma patients in **Chapter 3** appears much higher than the cumulative incidence of 8-10% in a general European population.[26] Fracture risk was especially high in men and patients who received medication for epilepsy, while previous surgery as craniopharyngioma therapy was a protective factor. The mean bone density values of the cohort were in the normal range, but 24% still had values in the osteoporotic range due to a wide spread. Factors associated with higher risk of osteoporotic bone mineral density values were age and bone mineral density increasing medication.

Despite the apparent high fracture rate in this study, patients with craniopharyngioma did not have more fractures than healthy controls in a previous comparison.[31] The craniopharyngioma patients were of mixed Dutch and Swedish descent, while the reference population was a general Swedish population.[31] However, an increased fracture risk was found in a cohort with solely Swedish patients compared to a Swedish reference group.[5] This difference may be explained by the choice of the reference cohort: people from Scandinavian countries

were reported to generally have a higher fracture risk than people from countries in Western Europe.[46] A reference cohort from the same geographic location would be preferable, but a suitable Dutch healthy reference cohort was unfortunately unavailable for the study of Wijnen et al.,[31] and for the study described in **Chapter 3**. The cause of high geographical heterogeneity is unknown, but may relate to lack of sun exposure and relating vitamin D deficiency risks,[47] differences in diet or physical activity, or registration bias. Vitamin D is formed in the skin under sun exposure (UV-B).[47] A higher fracture risk of hip fracture risk in the winter was observed in Sweden, especially at higher latitudes.[47] In this study, there was a significant interaction with seasonal effect and latitude for fracture risk, which suggested the vitamin D levels to relate to the fracture risk.[47] Vitamin D combined with calcium suppletion gives a small reduction in fracture risk in elderly.[48] This may not be a causal relationship, as vitamin D correlates inversely with body mass index (BMI) as well.[49] As many patients with craniopharyngioma are obese, they may be at high risk of vitamine D deficiency. To our knowledge, vitamin D deficiency was not evaluated in cohorts of patients with craniopharyngioma, nor is the effect of vitamine D suppletion evaluated in a randomized controlled trial in this population.

In a population with growth hormone deficient subjects due to causes other than craniopharyngiomas, the fracture rate was even higher, at 28-29%.[50] However, fracture rate was equal in craniopharyngioma patients and non-functioning pituitary adenoma patients who were both using growth hormone replacement therapy for two years.[51] The fracture rate described in **Chapter 3** is still likely an underestimation due to the retrospective design, which could partially explain the apparent lower fracture rate compared to other growth hormone deficient subjects.

Another factor that potentially protects patients with craniopharyngioma to fractures compared with other growth hormone deficient populations, is the high rate of obesity.[52] The risk of fractures in case of obesity in the general population is controversial: mostly, obesity is regarded as protective factor against fractures,[53] particularly hip and vertebral fractures in adults.[54] On the other hand, fracture risk

may be site and subpopulation dependent, as obesity was found as a risk factor[55,56] for humerus, finger and ankle fractures,[53,54,57] and in older men.[58] Obesity increases the risk of type II diabetes, which may increase the fracture risk despite a high bone mineral density, as it increases the risk of falling due to retinopathy and autonomic dysfunction.[59] In **Chapter 3**, BMI was not significantly protective against fractures in patients with craniopharyngioma, although a trend for a mild protective association was apparent in univariable analysis. Probably, the protective factors of high BMI are annuled by the risk factors. The protective factors may related to higher absorption of falling forces by soft tissue padding and increased bone density due to skeletal loading, but high BMI is accompanied with an increased risk of type II diabetes mellitus and increased forces of impact after a fall.[60]

People with a low bone density may have a high risk of fractures of nearly all types.[61-64] Osteoporotic fractures are most typically located at the hip, spine, distal radius and (proximal) humerus, but it can also occur at other sites such as the ankle, ribs or pelvis.[61] In **Chapter 3**, the fractures of craniopharyngioma patients were most often situated in the long pipebones or vertebrae (in 52%). Surprisingly, osteoporotic bone density values did not relate to an increased fracture risk in these patients when evaluated in a logistic regression mode. Possibly, the risk is overrulled by other determinants.

Also, no association was found between fractures and pituitary deficiencies, which is likely due to an appropriate hormonal replacement. This assumption is further substantiated by the described normal growth regardless of high rates of growth hormone deficiency in childhood onset disease, and high rates of pituitary replacement therapy. In a female general population, premenopausal women still had a lower risk of fractures than postmenopausal women using hormonal replacement therapy and calcium and vitamin D suppletion.[65] This suggests that in general, age still plays an important role besides hormonal status. Age did however not show as an important factor in our cohort, probably because other factors have a bigger impact.

Age could also explain higher fracture risk of men compared

to women in **Chapter 3**. The median age in the craniopharyngioma cohort was 45 years. In the general population, the lifetime risk of fractures is much higher in women than in men.[66] However, in the age category below 50 years, men have a higher fracture risk due to risk of trauma.[66-69] A higher fracture risk in men than women with craniopharyngioma can therefore be regarded as 'normal'. The difference between men and women of the craniopharyngioma may turn around when the cohort increases further in follow-up duration: in a general population in a postmenopausal age category, women have a higher fracture risk than men of a similar age.[67-69] Also, although not significantly different, men in our craniopharyngioma study had a 10% higher rate of corticotrophic deficiency. In the general population, oral corticosteroid use had a dose-dependent positive relationship with fractures.[70] However, in patients with hypopituitarism and loss of endogenous production of glucocorticoids, replacement therapy did not relate to an increased fracture risk.[71] This small potential difference in corticotropic deficiency therefore unlikely explains the different fracture rate between men and women with craniopharyngioma. A better explanation may be formed by a difference in behaviour potentially leading to traumatic injury from factors such as use of alcohol, work activity, recreational or sports activity, and even in making choices when crossing a road.[66,72,73] Unfortunately, we were unable to investigate behavioral factors in patients with craniopharyngioma within the current design of the study.

Despite a higher fracture risk in men, women in the cohort more often received medication aimed to improve bone density. One could argue, that this may have reduced the fracture risk. However, in the logistic regression model, bone mineral density improving medication was not a significant factor for determining the fracture risk. Although bone mineral increasing medication was prescribed, our study did not evaluate the compliance of the use. In the general population, women tended use more unique medications, but were less compliant than men when using medication chronically.[74]

In **Chapter 3**, craniopharyngioma patients using antiepileptic drugs had tripled odds of having a fracture compared to patients who did

not use any antiepileptic drugs. Generally, patients with epilepsy are at high risk of fractures. The fractures are caused by falls and seizures; the falls may or not may relate to the seizure, and the seizures may or not may relate to a fall.[75,76] Even strong muscular contractions during a seizure without a fall can infrequently cause fractures, which occurred more often in men.[75] Falling may be caused by seizures, coexisting neurological deficits, and by ataxia, clumsiness and poor balance due to antiepileptic drugs.[75] Furthermore, antiepileptic drugs can give an accelerated bone loss, low bone density and hyponatremia, and increase fracture risk.[77-79] In our study, the presence of epilepsy itself was not a significant factor in predicting fracture risk. Craniopharyngioma patients with epilepsy who do not use antiepileptic drugs may represent a subset of patients who suffer little from seizures and therefore not require therapy.

It is not entirely clear why in **Chapter 3** surgical craniopharyngioma treatment was observed as protective factor for fractures. Perhaps patients had a generally low performance due to severe comorbidities, which could form a contra-indication for major surgery and relate to a higher fracture risk as well. Another theory is that this is related to treatment with cyst aspiration; initial treatment with cyst aspiration was associated with lower recurrence- or progression-free survival in a previous study of the cohort.[6] This may lead to more damage to neurovascular structures. Also, previous treatment with radiotherapy tended to relate with lower fracture risk. In the past years, a shift occurred from extensive surgery (gross total resection) towards more partial resection, combined with radiotherapy, to avoid hypothalamic obesity.[6] Radiotherapy could be a related to a more limited surgery, resulting in less damage of neurovascular structures, and therefore diminishing risks of falling and diabetes mellitus type 2.

For low bone density, mineral density increasing medication was identified as 'risk factor', but that is unlikely to be causally related: probably the patients with low bone density were starting treatment for the purpose of increasing their bone density. Also, in univariable analysis, hypothalamic damage was confirmed as a risk factor for low bone density. This is in line with the findings of Holmer et al., who

found hypothalamic involvement of the tumor with consequently leptin resistance, and additionally, insufficient gonadal replacement therapy were previously found as risk factors for reduced bone mineral density.[80,81] In our analysis, insufficient gonadal replacement therapy was not confirmed as risk factor for low bone density; however, almost all patients received gonadal replacement therapy when applicable. Leptin resistence may explain why in our study BMI did not have a significant negative relationship with osteoporotic bone density values, while in the general population obese adults have a lower osteoporosis risk than health weight individuals.[82] Leptin correlates positively with BMI as it is produced by adipose tissue.[83-85] Leptin has a direct anabolic effect on bone, but the overall effect may be bimodal as the hypothalamus exerts a central effect as well.[86] This balance may be disrupted in patients with craniopharyngioma and hypothalamic damage.

In the general population, the fracture risk is assessed with the FRAX to estimate the 10-year probability of major osteoporotic fractures or hip fractures.[87] Suggestions have been made to improve the estimation by FRAX in men, by adding comorbidities, medication and behavioral factors. [87] Many of the classical risk factors for osteoporosis of which some are implemented in FRAX, such as smoking, high alcohol consumption, nutrition, inactivity and family history,[81,88] could not be evaluated in the craniopharyngioma cohort described in **Chapter 3**, as the study had a retrospective design and these factors were often poorly described in the medical files. Our research however shows that non-classical risk factors are involved. Application of the FRAX in craniopharyngioma patients could therefore not give a good estimation.

Future studies could be aimed at prospectively investigating fracture rates and influential factors for fractures including classical risk factors such as smoking and alcohol use, but also bone quality and leptin levels. The validity of fracture risk assessment by FRAX could be evaluated in patients with craniopharyngioma, and perhaps adjusted with novel found risk factors to evaluate the risk in patients of this population specifically. Studies would preferably be performed multiple, different cohorts of patients with craniopharyngioma to validate the results of

the current study. The effect of bone density increasing medication on fracture risk could be evaluated in these patients, especially in men.

Longitudinal changes in bone density of patients with craniopharyngioma

Chapter 4 is the first longitudinal study investigating bone density changes over time as evaluated with DXA-scan and determinants bone density changes in a large cohort of patients with craniopharyngioma. This retrospective study showed that 60% of the patients had a low bone mineral density at first evaluation, but fortunately a significant increase in bone mineral density Z-scores is shown after a median time of 10 years between the first and last DXA-scan. The improvement in bone density was stimulated by use of growth hormone therapy, while radiotherapy and medication to improve bone density related to a decrease in bone density.

Our findings were for the most part in line of expectation of previous studies in craniopharyngioma or patients with hypopituitarism. The high rates of low bone density were similar to a smaller study of Andereggen et al., who found pathological bone density in 53% of patients with craniopharyngioma.[89] In the Pfizer International Metabolic Database study, growth hormone deficient patients with craniopharyngioma or pituitary adenoma were observed, who were receiving growth hormone replacement therapy.[90] Here, patients with radiotherapy had a lower bone mineral density than patients without radiotherapy, despite a higher fat mass.[90] This probably relates to hypothalamic dysfunction after radiotherapy.[91,92]

Other studies studies indeed showed an increase in bone density if growth hormone replacement therapy was given in case of a growth hormone deficiency (not specifically in craniopharyngioma).[93-97] Aside from the importance of growth hormone for bone mass acquisition during growth, it plays an important role in bone mass maintenance due to bone remodeling.[98] Additionally, growth hormone has an anabolic effect on muscle mass,[99] which also improved as is discussed in the next

paragraph. These findings underline the importance of growth hormone replacement therapy. Although malignant neoplasms were a concern for the application of growth hormone therapy for a long time, this does not appear to be an important concern: the incidence of malignant neoplasms in case of hormone replacement therapy were low, and reported between 6-27 per 100,000 person-years.[28,100,101]

The negative association of medication to improve bone density and change in bone density appeared odd at first; however, bone density improving medication is more often given to patients with impaired bone health, and again this association is not likely a causal relationship.

As is further elaborated below, the general improvement of bone mass was accompanied by an improvement of muscle mass in the cohort. This improvement of bone and muscle mass may correlate: high-impact exercise, such as jumping, causes an increase in bone density.[102] Our study did not evaluate lifestyle aspects such as exercise. Patients with craniopharyngioma have a low aerobic capacity, potentially related to hypothalamic involvement.[103,104] This low aerobic capacity may be a barrier in the performance of physical activity, as well as many other factors including psychosocial difficulties, increased daytime sleepiness, growth hormone and gonadal deficiency, neurological and visual deficits, decreased motor profiency and working memory.[44,104] Other studies have indeed observed a decreased physical activity in children with craniopharyngioma compared to obese and normal weight controls.[105-107] Physical activity in patients with craniopharyngioma is often not a sustainable way to achieve a weight reduction, not even when combined with a diet and pharmacotherapy.[108]

It would be of interest to investigate whether physical activity does improve bone strength and reduce fracture risk, as is the case in the general population.[109] These and other potential factors such as neurological deficits, exercise and diet, and potential weight loss (i.e. after bariatric surgery) that may influence bone health could be investigated, and previous findings may be validated in another cohort.

Consecutive bone density measurements should then preferably be performed with the same DXA-scanner to avoid a potential systematic bias, as the DXA-scanner type may influence the measurements[110] (although agreement between DXA-scans is still high).[111]

Metabolic long-term effects

Fat and muscle: body composition changes in patients with craniopharyngioma

Chapter 4 is the first study evaluating body composition changes in patients with craniopharyngioma, by comparing DXA-scan results, which are the gold standard to evaluate body composition.[112-114] Previous studies investigating body composition in patients with craniopharyngioma were only small cohorts or did not use the DXA-scan,[26,115,116] and barely evaluated change over time.[51] Although most patients in **Chapter 4** had a high mean fat percentage and fat mass index, change in these adiposity indicators over a median time of ten years was comparable to an age- and sex-matched reference population, while their fat free mass improved over time. Still 55% of the craniopharyngioma population of **Chapter 4** is obese, based on their BMI at last follow-up.

The increase in muscle mass could be explained by the frequent application of growth hormone replacement therapy. Body composition is influenced by all pituitary hormones, but particularly growth hormone.[117-119] In another study with craniopharyngioma patients, growth hormone replacement therapy for a duration of two years did not induce a decrease in fat percentage, while patients with non-functioning pituitary adenoma lowered in fat percentage.[51] The increase in fat-free mass and lipids after growth hormone replacement was however visible in craniopharyngioma patients as well.[51]

Other observations show an increase in BMI (Z-scores) which occur mostly before or in the first years after treatment.[24,120] In **Chapter 4**, an increase in BMI is observed as well, but BMI Z-scores did not change,

nor did the fat percentage Z-score. The evaluations in our cohort are however presumably performed in long-term follow-up. The observed increase in fat-free mass could potentially contribute to ceasing a further increase of fat mass. In the general population, resting energy rate is dependent on fat-free mass, fat mass, sex and height;[17,18,121] the fat-free mass is perhaps the most important indicator, and relates to skeletal muscle mass.[122-126] Low resting energy expenditure is a major contributor to obesity in patients with craniopharyngioma.[107,116,127] Multiple studies showed this low resting energy expenditure occurred regardless their high fat-free mass.[44,106,107,115,116,127] The low resting energy expenditure appears most influenced by the degree of hypothalamic damage[4,128] which may give a dysregulation of the autonomous nervous system.[129-131] It is unclear whether an increase in muscle mass would result to an increase in resting energy expenditure in patients with craniopharyngioma, as the previous studies did not evaluate a change in time. Nor has it been investigated whether the improved fat-free mass relates to a change in habits of physical activity. Future studies could focus on these research questions, with sequential use of the same DXA-scanner preferably. This is especially important when evaluating body composition, as especially lean body mass measurements are dependent on the carbohydrate intake and (related) hydration status of the person.[110,132] The hydration status of craniopharyngioma patients may be altered due to their risk of hypopituitarism,[133-136] including growth hormone deficiency and diabetes insipidus. These deficiencies require replacement therapy that may not match the normal physiology and may differ per patient due to individualized therapeutic schedules.

Application of the DXA-scanner in diagnosis of obesity and the metabolic syndrome

Obesity and low relative skeletal muscle mass are important factors in metabolic dysregulation and the metabolic syndrome.[123,137-143] **Chapter 5** is the first study in patients with craniopharyngioma that shows a major improvement in the diagnostics of obesity by evaluating body composition with the DXA-scanner. The obesity rate was as high as 75% based on fat percentage. Apparently other metabolic

alterations resulting in metabolic syndrome components were very frequent, as the improved obesity diagnostics only led to a minor improvement in the metabolic syndrome evaluation.

In **Chapter 5**, childhood onset patients had a higher obesity rate based on body fat percentage than adulthood onset patients. This probably relates to previous findings of Wijnen et al.[6] and Gautier et al.,[144] who observed that childhood onset patients have higher rates of panhypopituitarism, diabetes insidipidus.[144] and are more frequently treated with radiotherapy[144] than adulthood onset patients. Diabetes insipidus and radiotherapy can relate to hypothalamic dysfunction.[91,92,145]

Risk factors for the metabolic syndrome in uni- and multivariable logistic regresson analysis in **Chapter 3** were visual impairment, and age at last DXA-scan, recurrence or progression of disease, and hydrocephalus. Wijnen et al. found visual impairment as risk factor for the metabolic syndrome as well in a larger cohort of which the current study is a subset.[52] Visual impairment relates to low levels of physical activity.[146] Recurrence of disease will require more medical interventions such as neurosurgery and radiotherapy, which may cause a further damage of neurological structures. Radiotherapy and hydrocephalus may relate to a decline in IQ, which occurred in survivors of brain tumors.[147] It may be harder for patients with a low IQ to adhere to lifestyle advices. Low IQ was also related to development of obesity in a general population.[148]

BMI misclassified obesity if compared to fat percentage in 15% of men and 9% of women in one study in Denmark, and 25% of men and 48% of women in another study in the general population of the United States.[149,150] Both studies handled a threshold of fat percentage of 25% for men and 30% for women to identify obesity; there may however be a difference in the studied population. The population from Denmark is probably more suitable to compare with Dutch patients, as it is a European population as well, with a similarly described obesity rate of 17% in a cohort in 2015.[151] In **Chapter 5**, craniopharyngioma patients were misclassified in 29%, which appears to be in between the study from Denmark and the United States. Perhaps the different percentage

is due to the geographic difference, due to the high prevalence of hypopituitarism in patients with craniopharyngioma or the different definition for obesity. Currently, the consensus for the threshold of fat percentage for diagnosing obesity is not entirely formed.[152] This is still one of the drawbacks of the application of the DXA-scan for evaluation of body composition. Furthermore, DXA-scans are relatively expensive and time-consuming.[153] Future studies could therefore compare evaluation of obesity by DXA-scan measured fat percentage with other modalities, for example by muscle to visceral fat ratios by DXA-scan,[142] bio-impedance, perhaps even the simple waist circumference, or biomarkers (as is elaborated on in the next paragraph). The cost-effectiveness of performing DXA-scans remains to be determined before general clinical use in CP survivors can be recommended for this application. It may be useful to measure body composition components before performing interventions for obesity or low muscle mass such as growth hormone replacement to evaluate the effect, and in cases who have a BMI in an uncertain range, and if the DXA-scan is performed for another indication (to evaluate bone health).

Application of biomarkers in the diagnosis of the metabolic syndrome in childhood cancer survivors

The DXA-scan is the gold standard when an altered body composition is suspected. An altered body composition occurs in patients with craniopharyngioma, as described in **Chapter 4** and **Chapter 5**, but **Chapter 6** shifts the focus to another group at risk of an altered body composition: the childhood cancer survivors. Body composition is especially altered in childhood cancer survivors with metabolic alterations due to pituitary deficiency after high doses of cranial radiotherapy, abdominal radiotherapy and corticosteroids,[117,154-160] which contributes to their high risk of cardiovascular death.[153,161] Frail obese childhood cancer survivors with inadequate muscle mass are subject to the doubled jeopardy of sarcopenic obesity.[162]

The obesity rate is underestimated in childhood cancer survivors when conventional measuring methods such as BMI and waist hip ratio are used instead of fat percentage, measured by DXA-scan.[112] Therefore, the metabolic syndrome risk may be underestimated as well, as obesity is one of the criteria for the metabolic syndrome. For childhood cancer survivors it can be argued as well, that although the DXA-scan could provide information on body composition and give a better estimate of obesity, a routine application remains costly and time-consuming.[153] As alternative, we investigated the role of biomarkers to identify the metabolic syndrome in survivors in **Chapter 6**. We performed the first systematic review and meta-analysis to find novel biomarkers to diagnose or predict the metabolic syndrome in childhood cancer survivors, or a young general population from which the results were applicable to survivors. Although studies in childhood cancer survivors were very rare,[163-167] still 180 studies performed in the general population reported information on potentially useful biomarkers. For the prediction of the metabolic syndrome, identified valuable biomarkers were uric acid, adiponectin, hsCRP, leptin and apoB. For the diagnosis of the metabolic syndrome, uric acid, leptin, adiponectin and hsCRP were considered valuable. This study is a very important first step towards early identification of the metabolic syndrome in childhood cancer survivors. In the next step, optimal thresholds should be determined for most biomarkers, and the biomarkers should be tested specifically in this population and included in a prediction model. Therafter, the model can be validated in another survivor cohort, and the effect of early treatment of the metabolic syndrome on long-term vascular complications and mortality can be determined. It may offer a major improvement in long-term survival of childhood cancer survivors, as patients with metabolic syndrome have twice the risk of dying from cardio- and cerebrovascular disease compared to patients without the metabolic syndrome.[153,168] Application of these biomarkers for determination of the metabolic syndrome could be of interest as well for survivors of pediatric benign tumors, such as craniopharyngioma.

Metabolic surgery in patients with craniopharyngioma and severe obesity

The medical society is still in search of treatment options to lower risk of cardiovascular mortality in patients with craniopharyngioma, by lessening risk factors such as obesity.[4,31,169] Treatment of obesity is an very challenging in patients with craniopharyngioma and related hypothalamic damage. There is only limited evidence for the efficacy of pharmaceutical therapies.[170] Generally, severe obesity can be treated with metabolic surgery, also called bariatric surgery.[170-174] These types of operations are performed on the intestine and stomach and cause an decreased volume of the stomach, increased satiety, mild malabsorption of nutrients and consequently significant long-term weight loss in the general obese population. The changes in appetite are caused by hormonal changes, such as gut hormone glucagon-like peptide-1 (GLP-1), which acts on the hypothalamus.[170,171,175] However, the hypothalamus and pituitary are very frequently dysfunctioning in patients with craniopharyngioma, making the efficacy of bariatric surgery questionable.

In **Chapter 7** we present a study with the largest population of 16 craniopharyngioma patients who underwent bariatric surgery, with the longest follow-up to date. The study showed a mean loss of 22% after 5 years in craniopharyngioma patients, which is considerable but was less than 155 matched controls if patients received a Roux-en-Y gastric bypass.

In previous studies, including one with the Dutch and Swedish patients of our cohort and two years follow-up, the result was the opposite, with equal weight loss after Roux-en-Y gastric bypass and less weight loss after sleeve gastrectomy.[169] The current study contains more patients and has a longer follow-up. This study is therefore a better representation of the craniopharyngioma population and suggests that craniopharyngioma patients gain more weight long-term than a general population after bariatric surgery. The weight loss between patients with craniopharyngioma was comparable for Roux-en-Y gastric bypass and sleeve gastrectomy (23% versus 22%) in

Chapter 7, while in another study in a general obese population Roux-en-Y gastric bypass causes a higher weight loss than sleeve gastrectomy (26% versus 19%).[174] The weight loss therefore appears independent of the type of bariatric surgery in craniopharyngioma patients. Sleeve gastrectomy and Roux-en-Y gastric bypass both give a restriction in food intake with favorable hormonal alterations, but the Roux-en-Y gastric bypass has also a component of mild malabsorption.[172] It is possible that this malabsorption component does not add much in patients with craniopharyngioma because the hypothalamic damage dysfunction prevents an even larger effect. Still, the observation of 22% weight loss after five years suggests that hormonal alterations still exert an effect, probably in different brain centers. GLP-1 receptors are for example also located in the medulla and parietal cortex.[176] GLP-1 analogue liraglutide resulted in a decreased response to desirable food with high content of fat or sugar in the parietal cortex on functional MRI in a diabetic population.[176] It would be of interest to evaluate GLP-1 changes in patients with craniopharyngioma after bariatric surgery, and their effect in the brain.

Safety remains an issue in surgical procedures. The fear of complications is even larger when the surgery induces malabsorptions in patients with hypopituitarism, who depend on their replacement therapy with their lives. Short-term, 13% of craniopharyngioma patients with any type of bariatric surgery procedure had serious adverse events in **Chapter 7**. This appears higher than in the general population, who have a 30-day rate of major adverse events of 5% after Roux-en-Y gastric bypass, and of 3% after sleeve gastrectomy.[174] Perhaps the sleeve gastrectomy should be of small preference, as the safety profile in general is better and our patients had as much weight loss as after Roux-en-Y gastric bypass. The apparent good efficacy of sleeve gastrectomy must however be regarded with caution, as this studied subgroup was much smaller than the subgroup who had a Roux-en-Y gastric bypass.

Regarding long-term safety, one patient had severe absorptive issues and another died of unknown cause. The mean doses of pituitary replacement therapy did not change. All necessary changes in pituitary replacement therapy were within expectation of long-term care in

patients with changing age and weight. Other studies have indeed found no large negative effects on hormone replacement therapy.[169,172,177,178] One study even performed an oral thyroid/hydrocortisone/paracetamol absorption test after Roux-en-Y gastric bypass in one patient, which showed sufficient absorption of each drug.[178] Therefore, bariatric surgery was considered relatively safe if evaluated long-term in these patients. Future studies can focus on achieving even larger cohorts with a longer follow-up duration, and evaluate the differences between responders and non-responders of bariatric surgery, including evaluation of gastric hormones and the response of the brain by functional MRI.

Future perspectives for patients with craniopharyngioma

Targeted therapy before neurosurgery to protect neurovascular structures

This thesis underlines the importance of avoiding further damage of the hypothalamus and other brain structures due to treatment. A way of avoiding surgical damage, is to apply novel targeted molecular therapy to reach tumor shrinkage in advance of neurosurgery. In oncology, neo-adjuvant and targeted therapies are already often applied.[179] As explained in **Chapter 1**, there are two different histopathological subtypes of craniopharyngioma: the papillary and adamantinomatous subtype.[4] It is still unclear whether histological subtype and/or biological characteristics such as age of onset have any influence on survival rates. It seems that papillary craniopharyngioma patients have a better outcome than adamantinomatous craniopharyngioma patients regarding tumor size and recurrence rate, but this remains controversial.[180,181] The histopathological background may also be important for application of targeted therapy. For papillary craniopharyngioma, there is limited experience with *BRAF* inhibitors such as dabrafenib and bemurafenib, often combined with MEK inhibitors such as trametinib, in tumors carrying *BRAF*^{V600E} mutations.[182-189] The choice for dual therapy with *BRAF* and MEK

inhibitors, is made due to better survival when applied for melanoma compared to monotherapy.[187,190] Dual BRAF/MEK inhibitory therapy is proposed as neoadjuvant therapy or treatment option in complicated cases of papillary craniopharyngioma, but was only applied in a few cases so far.[182] Randomized controlled trials for evaluating the value of neoadjuvant application are still lacking. Also, papillary craniopharyngioma only account for 1 out of 10 craniopharyngiomas, which means this targeted therapy is only an option in 10% of the cases at best.[4,191] Targeted molecular therapies for adamantinomatous craniopharyngioma are being developed and relate to IL-6, PD1/PD-L1, MEK, IDO-1, but need further research as well before they can be applied in daily clinical practice.[192] New treatment modalities such as monoclonal antibodies may co-occur with currently unknown late effects.[193]

GLP-1 analogues for hypothalamic obesity

Still, the development of targeted therapies will be too late for many patients that have already been diagnosed. They may already suffer from hypothalamic obesity. Although **Chapter 7** shows promising results of bariatric surgery for hypothalamic obesity, not all obese patients will opt for this: patients may not comply with the indications for surgery, and importantly every surgery comes with a risk of complications, while not all patients had beneficient results in our research. Application of GLP-1 analogues may be a viable pharmaceutical alternative in these patients as primary treatment or after ineffective bariatric surgery. A study with one year open-label exenatide showed no significant weight loss, but still stabilisation or decreasing weight in 75% of a small group of patients with hypothalamic obesity.[194] Ultimately, even more effective GLP-1 analogues with more advantageous administration such as semaglutide[195] could be tested in patients with hypothalamic damage in a randomized controlled trial. It could as well be investigated whether GLP-1 analogue response predicts the efficacy of bariatric surgery in these patients. Since craniopharyngioma is a rare disease, international cooperation is essential in finding solutions for the health problems of the patients.

COVID-19

Current affairs bring new challenges: in 2020, the world news is dominated by a pandemic of coronavirus disease 2019 (COVID-19). Long-term health care had to make way for the acute COVID-19 issues; for example, osteoporosis care in the Netherlands temporarily suspended.[196] Health care professionals involved in endocrinological care were unavailable for active medical practice related to the COVID-19, due to illness or due to work related to COVID-19.[197] Patients with craniopharyngioma may have a more frequent occurrence of serious COVID-19 disease, as people with severe obesity more easily evolve towards respiratory failure.[197] It is still uncertain to what extend the COVID-19 pandemic has an influence on survival rates in these high risk patients. Regarding childhood cancer survivors, there did not seem to be a large effect so far on survival.[198] Still, the social isolation could potentially aggravate mental issues in survivors.[199,200] Only time will tell what the long-term effects of the pandemic are on the lives of these vulnerable people.

Conclusion

Mortality from cancer has declined in the past decades,[201] with the largest victory in childhood onset cancer, of which the 5-year survival rate is now 80%.[202,203] Still, the previous disease and treatment (especially radiotherapy) remain a continuous threat due to late effects and shorter lifespans.[204] Radiotherapy is also applied in patients with craniopharyngioma, who are generally regarded as subject to a benign tumor.[4] Despite the benign aspect of this rare tumor, patients are still at risk of a wide variety of long-term health issues and increased mortality.[31] The health issues presented in this dissertation relate to impaired endocrine, metabolic and bone-related health. Craniopharyngioma should therefore be regarded as a chronic disease, which requires life-long follow-up from a multidisciplinary team in expert centers. The performance of research in this rare disease requires international collaboration, for which we have found a great partner

in the Sahlgrenska University Hospital in Gothenborg, Sweden, and extended this collaboration in the past years with Erlangen University Hospital in Erlangen, Germany, the Medical University of Vienna in Vienna, Austria, and the Federal University of Parana in Curitiba, Brazil. We are very thankful for this co-operation and hope the future will bring an even more extensive collaboration. Ultimately, research should have the purpose of serving the patient a tailored therapy, to achieve an optimal life span and quality of life.

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9

Summary
Samenvatting

Summary

A major improvement in survival rates after tumors has been accomplished by the medical field, especially in pediatric cancer. This led to an increased awareness for the still suboptimal very long-term survival, and for frequently occuring late effects after treatment of neoplasms. The aim of this thesis was to further examine long-term endocrine, bone-related and metabolic alterations in those who suffer(ed) from a tumor, with a particular focus on patients with craniopharyngioma.

Accelerated growth after acromegaly due to *AIP* mutation

We describe a case of a 7-year old boy with accelerated growth, despite decreased food intake, due to excessive growth hormone production of a pituitary adenoma. Patients presenting with acromegaly at a young age or family members with acromegaly, are tested for genetic mutations. This should lead to early diagnosis of relatives and a better choice of therapy. In this exceptionally young patient, a new germline, paternally inherited *AIP* mutation (p.Tyr202x) was identified. *AIP* mutated somatotropinomas present mostly in young adolescent males and typically have an aggressive phenotype. Multiple surgeries and 1st and 2nd generation somatostatin analogues did not lead to cure, and the patient will require radiotherapy. In general, *AIP* mutated somatotropinomas may be more sensitive to 2nd generation somatostatin analogues, but it proves ineffective in our patient, which corresponded with in vitro insusceptability of the tumor to pasireotide. In vitro susceptibility of tumor tissue to somatostatin analogues may serve as a guide for the expected efficacy in the patient. This underlines the importance of targeted, tumor-specific therapy and combining treatment options.

Fractures, bone mineral density, growth, body composition and the metabolic syndrome in patients with craniopharyngioma

Craniopharyngioma is a benign neoplasm that lies close to the pituitary, hypothalamus and optic nerve. It often requires surgery and radiotherapy, which can lead to major long-term complications, including pituitary deficiences, visual impairments, neurological damage and obesity due to hypothalamic dysfunction. Together, this may influence bone health of these patients. We retrospectively studied bone health of Dutch and Swedish patients with craniopharyngioma. This population (with a median age at follow-up of 45 years) reached a normal mean final height, despite a high frequency of growth hormone deficiency (85%) and even after childhood-onset of disease. The cumulative incidence of fractures in patients with craniopharyngioma was 18%, as opposed to 8-10% in a general European population. Osteoporotic bone mineral density values occurred in 24%. Osteoporotic bone density values and pituitary deficiencies did not predict fracture risk; growth hormone replacement therapy protected against low bone mineral density. Fracture risk was especially high in patients using anti-epileptic drugs, and in men, while men received interventions (i.e. vitamin D or bisphosphonates) to improve bone mineral density less often than women. In addition, we evaluated the change in bone mineral density and body composition in patients with craniopharyngioma with a median time of 10 years between the first and last DXA-scan. The bone mineral density Z-scores of total body, L2-L4 and femur neck and fat-free mass index Z-scores increased significantly, while Z-scores of BMI and fat-related measures remained stable. This suggests bone density and body composition improve over time. A positive association with increasing bone density was found for growth hormone replacement therapy, while a negative association was found for radiotherapy, glucocorticoid dose and medication to improve bone mineral density. Obesity was better evaluated when applying fat mass index or fat percentage as derived by DXA-scan compared to body mass index. Obesity is one of the components of the metabolic syndrome (together with dyslipidemia (low HDL and high triglycerides), high glucose levels and hypertension). The metabolic syndrome is

associated with cardiovascular disease and is diagnosed if patients meet at least three out of five criteria of an altered metabolic profile. Even though more patients were diagnosed with obesity by DXA-scan, many patients had already met enough criteria to be already diagnosed with the metabolic syndrome. Their metabolic profile was so impaired that improved diagnosis of obesity did not give a major improvement the diagnosis of the metabolic syndrome. Risk factors for the metabolic syndrome were recurrence or progression of disease, hydrocephalus and age.

Biomarkers for the metabolic syndrome in childhood cancer survivors

Childhood cancer survivors have a high risk of metabolic alterations due to their past cancer treatment, while assessment of the metabolic syndrome can be difficult. This is especially the case after abdominal radiotherapy, which increases the risk of the metabolic syndrome while introducing a bias in waist circumference evaluation. In a systematic review and meta-analysis in childhood cancer survivors and a representative general population, hsCRP, adiponectin, uric acid and leptin were identified as useful biomarkers to diagnose and predict the metabolic syndrome, and apoB as additional predictive biomarker.

Long-term efficacy and safety of bariatric surgery in obese patients with craniopharyngioma

Treatment with bariatric surgery for obese patients with craniopharyngioma may have unsatisfactory results, as the hypothalamus is often damaged and insusceptible to the change of appetite-regulating hormones that occur after bariatric surgery. In this thesis we describe the first long-term case-control study, showing patients with craniopharyngioma had a mean weight loss of 22% at 5 years after bariatric surgery. Although average weight loss was lower in patients than in controls, especially in case of Roux-en-Y gastric bypass, the achieved weight loss was clinically meaningful. Bariatric surgery appeared relatively safe. Dose adjustments to hormonal replacement therapy were within the limits of expectation in the light of changing BMI and age.

In summary, craniopharyngioma patients are at high risk of impaired bone health, obesity and the metabolic syndrome; awareness and interventions to overcome the metabolic syndrome and consequent co-morbidities are warranted. For that purpose, international co-operation is needed to develop systemic therapies, for treatment of hypothalamic obesity and metabolic consequences, and for neo-adjuvant therapy targeted at the histopathological background of the craniopharyngioma.

Samenvatting

De verbeterde behandeling van tumoren heeft in de afgelopen decennia tot een duidelijke toename in de overleving geleid, met name onder kinderen. Daardoor is er in toegenomen mate aandacht gekomen voor de gezondheid van overlevenden van kanker op de langere termijn; late effecten komen frequent voor. In dit proefschrift zijn de botgezondheid, en endocriene en metabole status bij patiënten met een tumor onderzocht. Hierbij werden risicofactoren en beschermende factoren voor langetermijngevolgen en de wijze van diagnostiek bestudeerd. De onderzoeken werden met name gericht op patiënten met een craniopharyngioom.

Versnelde groei bij acromegalie door een *AIP* mutatie

We beschrijven de casus van een 7-jarige jongen met een versnelde lengtegroei, ondanks dat hij weinig eetlust heeft, door excessieve productie van groeihormoon vanuit een hypofyse-adenoom op een uitzonderlijk jonge leeftijd. Bij acromegalie patiënten die erg jong zijn bij ontstaan van de ziekte, of die familieleden met acromegalie hebben, dient te worden getest op genetische mutaties zodat familieleden vroegtijdig gediagnosticeerd kunnen worden en er gerichtere keuzes voor therapie gemaakt worden. Bij onze patiënt was sprake van een nieuwe, vanuit vaders zijde overgeërfde truncerende *AIP* mutatie (pTyr202x). *AIP* gemuteerde adenomen komen vooral voor bij mannelijke adolescenten en worden gekenmerkt door een agressief phenotype. Meerdere hersenoperaties en 1e en 2e generatie somatostatine analogen leidden bij onze patiënt niet tot genezing, en deze patiënt zal radiotherapie nodig hebben. Tweede generatie somatostatine analogen lijken in het algemeen effectief bij *AIP* gemuteerde adenomen, maar waren ineffectief in deze casus, wat overeen kwam met de ongevoeligheid van het tumorweefsel voor pasireotide bij vitro analyse. Deze casus onderschrijft het belang van een specifieke, tumorgerichte therapie en het combineren van behandelopties.

Botbreuken, botdichtheid, groei, lichaamscompositie en het metabool syndroom in patiënten met een craniopharyngioom

Het craniopharyngioom is een zeldzame goedaardige hersentumor, gelegen nabij de hypofyse, hypothalamus en optische zenuw. Deze tumor wordt meestal behandeld met een hersenoperatie en radiotherapie en wordt gekenmerkt door een breed spectrum aan complicaties op lange termijn, waaronder hormoonuitval door hypofysebeschadiging, visuele beperkingen, neurologische schade en obesitas door schade aan de hypothalamus. Dit zijn factoren die van invloed kunnen zijn op de botgezondheid. In een retrospectieve cohortstudie hebben we de botgezondheid onderzocht in Nederlandse en Zweedse patiënten met een craniopharyngioom (mediane leeftijd bij follow-up 45 jaar). Deze patiënten bereikten gemiddeld een normale lichaamslengte, ook wanneer de ziekte op de kinderleeftijd geconstateerd was. Botbreuken kwamen voor in 18% van de patiënten, terwijl dit percentage in de algemene Europese bevolking op 8-10% ligt. Gebruikers van medicijnen tegen epilepsie en mannen liepen een hoger risico op botbreuken, terwijl mannen minder medicatie gebruikten om de botdensiteit te verhogen (bijv. vitamine D en bisfosfonaten). Zeer lage botmineraaldensiteit, passend bij botontkalking, kwam voor bij 24%. Groeihormoonbehandeling leek beschermend tegen een lage botdichtheid. Een verbetering van botdichtheid en lichaamscompositie werd geobserveerd met DXA-scans met een mediane tijd van 10 jaar tussen de metingen. Er was een significante toename zichtbaar van de Z-scores voor botdichtheid van de botten in het hele lichaam, in de lage rugwervels (L2-L4) en de femurhals, en voor vetvrije massa index, terwijl Z-scores voor body mass index en vetgerelateerde waarden stabiel bleven. Er was een positieve associatie met botdichtheidstoename voor groeihormoontherapie, en een negatieve associatie met radiotherapie, glucocorticoïd dosering en botdichtheidsverhogende medicatie. Obesitas bleef echter een veelvuldig voorkomend probleem, en is een van de onderdelen van het metabool syndroom (naast afwijkende vetten in het bloed (laag HDL en hoog triglyceriden), een hoge bloeddruk en verhoogde bloedglucosewaarden).

Het metabool syndroom wordt gediagnosticeerd als aan minimaal drie van de vijf onderdelen voldaan wordt. Het metabool syndroom geeft een verhoogd risico op hart- en vaatziekten en diabetes mellitus. Het meten van vetpercentage en vet massa index met een DXA-scan verbeterde de diagnostiek van obesitas ten opzichte van body mass index. Echter, veel patiënten hadden al veel afwijkende bevindingen voor de andere onderdelen van het metabool syndroom, waardoor deze verbeterde diagnose van de component obesitas slechts beperkte waarde had voor de diagnose van het metabool syndroom. Risicofactoren voor het metabool syndroom waren progressie van ziekte, hydrocephalus (ophoping hersenvloeistof) en leeftijd.

Diagnostiek en voorspelling van het metabool syndroom met biomarkers in overlevenden van kinderkanker

Kinderen die kanker overleefd hebben, hebben ook een verhoogd risico op het metabool syndroom, terwijl de diagnose van obesitas en daarmee metabool syndroom bemoeilijkt wordt, met name na radiotherapie op de buik. Hierbij kan de buikgroei beperkt zijn, waardoor de buikomvang klein is ondanks een verhoogd vetpercentage. Bij een systematisch literatuuronderzoek naar het toepassen van biomarkers voor de diagnose en voorspelling van het metabool syndroom, werden studies onder overlevenden van kinderkanker en een representatieve gezonde populatie gebruikt. Aan de diagnose van het metabool syndroom konden de biomarkers hsCRP, adiponectine, urinezuur en leptine bijdragen. Het voorspellen van het ontstaan van het metabool syndroom werd voorspeld door dezelfde biomarkers, en daarnaast ook apoB.

Effectiviteit en veiligheid op de lange termijn van bariatrische chirurgie voor obese patiënten met een craniopharyngioom

De behandeling van obesitas bij patiënten met een craniopharyngioom met bariatrische chirurgie (maagverkleiningsoperaties) leidt potentieel tot matige resultaten. De hypothalamus reguleert het lichaamsgewicht

maar is frequent beschadigd bij deze patiënten, en kan hierdoor verminderd gevoelig zijn voor hongergevoel-regulerende hormonen. We presenteren de eerste studie die het gewichtsverlies van craniopharyngioom patiënten op lange termijn onderzoekt. Na vijf jaar hebben patiënten gemiddeld een gewichtsverlies van 22%. Dit is een goed resultaat, maar het is minder dan in gematchte controlepatiënten (bariatrische chirurgiepatiënten zonder craniopharyngioom). Er waren geen grote wijzigingen noodzakelijk in de medicatie voor de hypofyse-uitval. Bariatrische chirurgie lijkt een veilige therapeutische optie voor obesitas in deze patiënten.

De toekomst brengt hopelijk systemische therapieën die gericht zijn op het verminderen van hypothalame obesitas en op tumorverkleining voorafgaand aan operatie, gebaseerd op de histopathologie van het craniopharyngioom. Bij het onderzoek naar deze zeldzame ziekte is internationale samenwerking noodzakelijk.

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About the Author

About the author

Selveta Sanne (Selvetta) van Santen was born on April 24th in Dordrecht, the Netherlands. She graduated from high school in 2010 (CSG De Lage Waard, Papendrecht). She immediately enrolled in the Bachelor study in Medicine, followed by her Master's, for which she received her degree in 2017. During her training period, she performed research into cardiovascular risk related to apoB at the Department of Internal Medicine/Vascular diseases of Sint Franciscus Gasthuis, Rotterdam, under the direction of Doctor M. Castro Cabezas and Doctor M. de Vries. After her graduation, she worked as a physician for the inpatient clinic at the department of Internal Medicine of the Albert Schweitzer Ziekenhuis, Dordrecht for 7 months, until she decided to focus on research again. She started her PhD in September 2017, of which the results are presented in this thesis. Selvetta thankfully received guidance from her promotor A.J. Professor van der Lelij and copromotor Doctor S.J.C.M.M. Neggers, both specialized in endocrinology (Department of Medicine – Endocrinology, Erasmus Medical /Pituitary Center Rotterdam), and her promotor Professor van den Heuvel-Eibrink, who is specialized in pediatric oncology (Princess Máxima Center for Pediatric Oncology and Department of Pediatric Oncology/Hematology Erasmus Medical Center). During her training, she worked as a physician at the Late Effects clinic of the Erasmus University Medical Center and Princess Máxima Center for Pediatric Oncology, and treated adult survivors of childhood cancer for long-term complications of their disease and previous treatment. After finishing her PhD training in March 2021, she returned to the Albert Schweitzer Ziekenhuis to work as a physician at the Department of Internal Medicine again under the supervision of Doctor P.J.H. Smak Gregoor, with the ultimate goal of entering a traineeship in Internal Medicine.

PhD Portfolio

Name PhD student: Selveta Sanne van Santen

Erasmus MC department: Medicine, section Endocrinology – Pituitary Center Rotterdam
Research school: Netherlands Institute for Health Sciences
Other affiliation: Princess Máxima Center for Pediatric Oncology

PhD period: September 2017 – March 2021

Promotors: Prof. dr. A.J. van der Lelij
Prof. dr. M.M. van den Heuvel-Eibrink
Copromotor: Dr. S.J.C.M.M. Neggers

	Year	ECTS
General courses		
Basic course for Clinical Investigators (BROK)	2017	2.0
NIHES Biostatistical Methods I: Basic Principles (CC02) (grade 9.0)	2017	5.7
Systematic literature research Pubmed I and II, Medical Library Erasmus MC	2017	0.33
Systematic literature research Multiple databases, Medical Library Erasmus MC	2017	0.33
Endnote course, Medical Library Erasmus MC	2017	0.33
Open Clinica, Erasmus MC	2017	0.3
Logframe course, Erasmus MC	2017	0.2
Masterclass acromegaly (partially completed)	2017	0.2
Course basic life support (pediatrics), Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands	2018	0.2

Excel basic course, Medical Library Erasmus MC	2018	0.3
Excel advanced course, Medical Library Erasmus MC	2018	0.4
Access basic course, Medical Library Erasmus MC	2018	0.3
Access advanced course, Medical Library Erasmus MC	2018	0.4
NIHES ESP66 Logistic Regression (summer course)	2018	1.4
NIHES ESP09 Regression Analysis (summer course)	2018	1.4
Scientific writing (partially completed)	2018	-
Time management and negotiating, Erasmus MC	2018	1
Postgraduate Course, GH and Growth Factors – Metabolic Disorders, Gothenburg, Marstrand, Sweden (with case presentation)	2018	2
25th ESE Postgraduate Training course on Endocrinology, Diabetes and Metabolism, Rotterdam, the Netherlands	2019	0.9
Research Integrity Course, Erasmus MC	2019	0.3
Pituitary Masterclass, Milan, Italy	2019	0.5
NIHES Survival Analysis for Clinicians (EWP24) (grade 9.5)	2020	1.9
NIHES Advanced Topics in Clinical Trials (EWP10)	2020	1.9
Pituitary Society fellowship course (online)	2020	0.3
Postgraduate Craniopharyngioma Course: New developments and challenges in the treatment of Childhood Craniopharyngioma; striving for optimal balance	2021	0.6
Research skills		

Weekly research meeting Endocrinology Laboratory (with 10 oral presentations)	2017-2021	4.5
Weekly research meeting Princess Máxima center for Pediatric Oncology - van den Heuvel-groep and Late Effects of Childhood Cancer (with 2 oral presentations)	2020-2021	2.0
Seminars, meetings and workshops		
Scientific Endocrinology meetings (Internal Medicine Research Meeting, Erasmus Lectures on Endocrinology and Workdiscussions with once an oral presentation)	2017-2020	1.5
PhD day: a Healthy PhD, Rotterdam, the Netherlands	2018	0.2
ESP64 Summer lectures (summer course)	2018	0.2
Van den Heuvel group retreat "Fier op Schier", Schiermonnikoog, the Netherlands	2019	1.0
Van den Heuvel group retreat (online)	2020	0.5
National and international conferences		
JNVE meeting, Nijmegen, the Netherlands (with oral presentation)	2018	2.0
European Congress of Endocrinology, Barcelona, Spain (poster presentation)	2018	1.0
Pancare, Prague, Czech Republic	2018	1.0
Wetenschapsdagen (with oral presentation)	2019	2.0
Dutch Endocrine Meeting, Noordwijkerhout, the Netherlands (poster presentation with oral pitch)	2019	1.0
ENDO, New Orleans, USA (poster presentation, nominated for presidential poster)	2019	1.0
European Congress of Endocrinology, Lyon, France (poster presentation)	2019	1.0
EYES, Athens, Greece (oral presentation)	2019	2.0

Wetenschapsdagen, Sint-Michielsgestel, the Netherlands (poster presentation)	2020	1.0
Dutch Endocrine Meeting, Noordwijkerhout, the Netherlands (poster presentation with oral pitch)	2020	1.1
ENDO (Online)	2020	1.0
European Congress of Endocrinology (online, with poster presentation)	2020	1.0
SIOP (with poster presentation; online)	2020	1.0
ICCBH (with poster presentation)	2020	1.0
Dutch Endocrine Meeting (online)	2021	0.3
Clinical meetings and participation		
Outpatient clinic for long-term complications of childhood cancer treatment	2017-2020	40
Teaching activities		
Lecture "Late effects after treatment of childhood cancer" for medical students in the second year of their study.	2018	1.0
Skills education "Hypercortisolism" for medical students in the first year of their study.	2018	1.0
Lecture "Late effects after treatment of childhood cancer" for medical students in the second year of their study.	2019	1.0
Lecture "Late effects after treatment of childhood cancer" for medical students in the second year of their study.	2020	1.0

List of publications

1. Klop B, van der Pol P, van Bruggen R, Wang Y, de Vries MA, **van Santen S**, O'Flynn J, van de Geijn GJ, Njo TL, Janssen HW, de Man P, Jukema JW, Rabelink TJ, Rensen PC, van Kooten C, Cabezas MC. Differential complement activation pathways promote C3b deposition on native and acetylated LDL thereby inducing lipoprotein binding to the complement receptor 1. Journal of Biological Chemistry 2014; 289(51): 35421-30.

2. de Vries MA, Alipour A, Birnie E, Westzaan A, **van Santen S**, van der Zwan E, Liem AH, van der Meulen N, Cabezas MC. Coronary leukocyte activation in relation to progression of coronary artery disease. Frontiers in Medicine 2016; 10(1): 85-90.

3. de Vries MA, **van Santen SS**, Klop B, van der Meulen N, van Vliet M, van de Geijn GM, van der Zwan-van Beek EM, Birnie E, Liem AH, de Herder WW, Castro Cabezas M. Erythrocyte-bound apolipoprotein B in atherosclerosis and mortality. European Journal of Clinical Investigation 2017; 47(4): 289-96.

4. **van Santen SS**, Olsson DS, Hammarstrand C, Wijnen M, van den Heuvel-Eibrink MM, Van der Lely AJ, Johannsson G, Janssen J, Neggers S. Diagnosing Metabolic Syndrome in Craniopharyngioma Patients: Body Composition versus BMI. European Journal of Endocrinology 2019;181(2):173-183

5. **van Santen SS**, Olsson DS, van den Heuvel-Eibrink MM, Wijnen M, Hammarstrand C, Janssen J, Johansson G, van der Lely AJ, Neggers S. Fractures, Bone Mineral Density, and Final Height in Craniopharyngioma Patients with a Follow-up of 16 Years. The Journal of Clinical Endocrinology & Metabolism 2020;105(4):e1397-e1407

6. **van Santen SS**, Olsson DS, Hammarstrand C, Wijnen M, Fiocco M, van den Heuvel-Eibrink MM, Johannsson G, Janssen JAMJL, van der Lely AJ, Neggers SJCMM. Body Composition and Bone Mineral Density in Craniopharyngioma Patients: A Longitudinal Study Over 10 Years. The Journal of Clinical Endocrinology & Metabolism 2020;105(12):dgaa607.

7. Pluimakers VG, **van Santen SS**, Fiocco M, Bakker MCE, van der Lelij AJ, van den Heuvel-Eibrink MM, Neggers SJCMM. Can biomarkers be used to improve diagnosis and prediction of metabolic syndrome in childhood cancer survivors? A systematic review. Obesity Reviews 2021; 22(11): e13312.

8. **van Santen SS**, Wolf P, Kremenevski N, Boguszewski CL, Beiglböck H, Fiocco M, Wijnen M, Wallenius VR, van den Heuvel-Eibrink MM, van der Lely AJ, Johannsson G, Luger A, Krebs M, Buchfelder M, Delhanty PJD, Neggers SJCMM, Olsson DSO. Bariatric Surgery for Hypothalamic Obesity in Craniopharyngioma Patients: A Retrospective, Matched Case-Control Study. Journal of Clinical Endocrinology & Metabolism 2021; 106(11): e4734-e4745.

9. **van Santen SS**, Daly AF, Buchfelder M, Coras R, Zhao Y, Beckers A, van der Lely AJ, Hofland LJ, Balvers RK, van den Heuvel-Eibrink MM, Neggers SJCMM. Complicated clinical course in incipient gigantism due to a treatment resistant, *AIP*-mutated pediatric somatotropinoma. *Submitted.*

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