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Chapter 1

General introduction and outline of this thesis
THE PITUITARY GLAND

The pituitary is a small gland that lies within the sella turcica, a recess in the sphenoid bone. Despite its small size, the pituitary gland is an important regulator of hormone homeostasis. Under the control of hypothalamic peptides, the anterior lobe, or adenohypophysis, synthesizes and secretes growth hormone (GH), prolactin, adreno-corticotroph hormone (ACTH), thyroid stimulating hormone (TSH), and the gonadotrophs LH and FSH. These hormones, in turn, stimulate their target glands, such as the adrenal cortex, thyroid, and ovaries/testicles to produce their respective end hormones: cortisol, thyroid hormone, estradiol/progesterone (in females) and testosterone (in males), respectively. The posterior lobe consists of axons of hypothalamic nerves expressing vasopressin and oxytocin. Vasopressin (also named anti-diuretic hormone ADH) is released in response to an increase in plasma osmolality resulting in increased renal water reabsorption. Oxytocin is released in large amounts during labour and causes contraction of the smooth muscle cells of the uterus. Furthermore it is responsible for the milk ejection reflex during lactation by contracting the smooth muscle cells of the mammary glands to release the milk into the duct system.

Disturbances in the secretion of pituitary hormones rapidly affect the levels of the hormones produced by their target glands. An increase in pituitary hormones leads to characteristic symptoms signs and phenotype, such as the Cushing phenotype in case of ACTH-induced cortisol excess or acromegaly in case of GH excess. Impairment in pituitary function is accompanied by non-specific complaints, such as tiredness, lack of concentration, and decreased physical tolerance and amenorrhoea. Furthermore, impaired bone mass will develop with a consequent increased fracture risk. (1) Disturbances in pituitary function have been shown to decrease overall survival, to cause metabolic dysregulation, as well as impaired quality of life. (2-4)

HYPOPITUITARISM

Hypopituitarism is the term used to describe insufficiency of pituitary hormone secretion and may affect anterior- or posterior pituitary function, or both. The reported incidence of hypopituitarism is around 12–42 new cases per million per year. The prevalence of hypopituitarism is 300–455 per million but this might be an underestimation as the disease is likely to be underreported since the clinical manifestations depend on the extent of hormone deficiency and are largely non specific, with complaints like fatigue, general unwell-being and cold intolerance. (5) The diagnosis of hypopituitarism relies on the measurement of basal and stimulated pituitary- and end-organ hormone secretion, and is more complicated than establishing the diagnosis of end organ deficiency.
INSUFFICIENCY OF THE GH-IGF-1 AXIS: GROWTH HORMONE DEFICIENCY

Growth Hormone (GH) plays an essential role in growth and maturation. Growth hormone is secreted in large amounts during childhood; and thereafter GH levels decline during aging.

In adults, Growth Hormone Deficiency (GHD) has been associated with hypercholesterolaemia and hypertriglyceridaemia. GHD is also associated with low muscle mass, a decrease in bone mass and diminished quality of life (QoL). It is generally accepted that 24-hour GH secretion poorly reflects GH status in adults. A number of tests evaluating GH secretory reserve may be used to diagnose GH deficiency (GHD).

The standard for diagnosing GHD is the Insulin Tolerance Test, or alternatively when contra-indicated a Growth Hormone Releasing Hormone/Arginine-test (GHRH/Arg) (with BMI-adjusted GH cut-offs). IGF-1 levels are not reliable to assess the GH/IGF-1 axis because normal levels do not exclude severe GHD. However, when IGF-1 levels are below -2 SD in the presence of 2 or more insufficient pituitary axes, severe GHD is present in almost all cases.

Adult Growth Hormone Deficiency will be more extensively discussed in Section II.

FIGURE 1.
GH/IGF-1 secretion
GH: Growth Hormone, GHRH: Growth Hormone Releasing Hormone, IGF-1: Insulin-like Growth Factor 1, GHRP: Growth Hormone Releasing hexaPeptide
INSUFFICIENCY OF THE HYPOTHALAMUS-PITUITARY-ADRENAL AXIS (HPA-AXIS): SECONDARY ADRENAL INSUFFICIENCY.

The HPA-axis controls together with the sympathetic nervous system the stress response, and therefore, is of paramount importance for survival. Disruption or insufficient secretion of CRH and/or ACTH impairs adrenal glucocorticoid synthesis and secretion, a condition that is potentially lethal. In general, symptoms of secondary adrenal insufficiency are non-specific, but most patients with secondary adrenal insufficiency report fatigue and malaise (weight loss) characterized by abdominal discomfort and nausea. Blood pressure is usually normal or slightly decreased and since mineralocorticoid synthesis remains unaffected orthostatic hypotension will not occur until the maximal activation of the renin-angiotensin-aldosterone system (RAAS) cannot further compensate for electrolyte and fluid loss. In that case, an Addisonian crisis may develop.

The diagnosis of secondary adrenal insufficiency involves the evaluation of both basal (non-stimulated) cortisol concentrations as well as dynamic testing. Various dynamic tests have been developed to test the secretory capacity of the pituitary gland and are currently used in daily clinical practice. A single morning cortisol measurement after an overnight fast will already provide some information. In case of a fasting cortisol concentration > 500 nmol/l, in the absence of concurrent corticosteroid use or estrogen use, the chance of HPA-axis insufficiency is considered very low. Also, when cortisol concentrations are < 80 nmol/l, the diagnosis of AI is very likely and dynamic testing is generally considered not necessary. However, since basal cortisol concentrations are in the range between 80-500 in most cases, additional dynamic testing is crucial for the evaluation of corticotrope function. In the last decades several tests have been used to diagnose secondary hypocortisolism. To date, the insulin tolerance test (ITT) remains the golden standard for the evaluation of the HPA-axis. In case of contraindications for the ITT, such as epilepsy or coronary artery disease, alternative dynamic tests such as the corticotrophin releasing hormone (CRH) test, the metyrapone test, or the ACTH stimulation test can be used to assess adrenal function. The choice of test is made by the treating physician based on the patient’s clinical condition and one’s centers experience. Once diagnosed, hypocortisolism is treated with hydrocortisone replacement. Hydrocortisone therapy for hypopituitarism was associated with supraphysiological cortisol levels in the past, leading to adverse effects such as increased glucose intolerance, decline in bone mass and increased cardiovascular risk factors, such as hypertension and increased abdominal fat distribution. Decreasing the glucocorticoid dose from 20-30mg/day to 15mg/day was associated with beneficial effects in terms of body composition, lipid profile, and QoL. Current replacement doses are 20 mg divided in three doses. Unfortunately, to date there are no adequate methods to monitor over-replacement of hydrocortisone in routine clinical practice.
INSUFFICIENCY OF THE HYPOTHALAMUS-PITUITARY-GONADAL AXIS: SECONDARY- OR HYPOGONADOTROPIC HYPOGONADISM.

Hypogonadotropic hypogonadism is defined as the presence of low or normal gonadotropin levels, (luteinizing hormone (LH) and follicle stimulating hormone (FSH)) in the presence of low testosterone in males or estrogen levels/cyclic disturbances in pre-menopausal women. In pre-menopausal women, secondary hypogonadism manifests with (oligo-) amenorrhea, decreased libido as well as fertility and psychological disturbances. In post-menopausal women, hypogonadism might often be a-symptomatic and the absence of high serum LH/FSH values confirms the diagnosis. In males, hypogonadism presents with decreased libido, potency and fertility, and with increased prevalence of depressive like symptoms and other mood disturbances and osteoporosis. In males, testosterone replacement therapy is administered in the form of transdermal testosterone preparations allowing stable physiological serum testosterone levels whereas in pre-menopausal women, replacement therapy with oral estrogens alone or in combination with progestagens is administered.

INSUFFICIENCY OF THE HYPOTHALAMUS-PITUITARY-THYROID AXIS: SECONDARY HYPOTHYROIDISM

Symptoms of hypothyroidism are associated with complaints of tiredness, edema (especially periorbital), constipation, weight gain and depression. The symptomatology of secondary hypothyroidism does not differ from primary hypothyroidism, but may be masked by other concomitant pituitary insufficiencies. A diagnosis of secondary hypothyroidism is confirmed by the presence of a low serum FT4 levels and inappropriately normal or low TSH levels. TSH levels are non-diagnostic in secondary hypothyroidism. In case of multiple pituitary hormone deficiencies, secondary hypothyroidism should also be suspected when FT4 levels are within the lower tertile of the reference ranges. L-thyroxine is the treatment of choice but under-replacement is often the case resulting in a negative cardiovascular profile, although the awareness for the risks of chronic under-replacement is rising. (17)

Concomitant corticotropin deficiency should be excluded in order to avoid acute adrenal insufficiency before starting replacement therapy and retesting of the HPA-axis should be considered after re-institution of normal thyroid hormone values.

With the exception of congenital forms hypopituitarism is largely caused by pituitary tumours, or by the consequent treatment of those tumours with surgery or radiotherapy. Hypopituitarism may also arise after traumatic brain injury or vascular insult and after radiotherapy for non-pituitary tumours. In the course of treatment in various tumours like for instance nasopharyngeal carcinoma (NPC) the pituitary is within the radiation field of the primary tumour resulting in a high dose to the pituitary and the risk of
hypopituitarism. The aim of this thesis was, first of all, to critically evaluate the available literature on the long-term consequences of cranial irradiation, and subsequently to evaluate the prevalence of pituitary insufficiency in our tertiary referral center using state of the art endocrine evaluation (Section I). In addition, we aimed to investigate the metabolic phenotype of the adult GHD patient in more detail after long-term rGH replacement given the unknown contribution of growth hormone replacement therapy.

**Section I: Radiation Induced Hypopituitarism**

Irradiation of the hypothalamic-pituitary region is thought to result in a characteristic pattern of decline of pituitary function, explained by the cell content in the pituitary with growth hormone (GH) secretion declining first, followed by ACTH, gonadotrophins and TSH. (18)

Radiation-induced pituitary insufficiency is a dose-dependent late sequel of radiotherapy for pituitary tumours with prevalence rates for one or more pituitary insufficiencies of around 50% after 5 years, arising up to 75% after 10 years, following a total dose of 40-45Gy Figure 2. (19-21) The prevalence of insufficiencies is correlated with the total radiation dose to the hypothalamic/pituitary region.

![Probability of normal pituitary function after irradiation for pituitary tumours with 40 Gy adapted from Littley et al.](image)

**FIGURE 2.**
Probability of normal pituitary function after irradiation for pituitary tumours with 40 Gy adapted from Littley et al.10
Data from historical cohorts indicate that a total dose of 7-24 Gy delivered to the pituitary/hypothalamus may cause growth hormone deficiency only whereas dosages as high as 50-60 Gy will most certainly cause multiple pituitary hormone deficiencies. (22) The incidence of multiple pituitary deficiencies thus increases both in time and with higher doses. (18, 23) The hypothalamic region is suggested to be more radiation sensitive causing elevated prolactin levels after irradiation in the presence of still intact pituitary function. This is indicative of a decreased dopaminergic inhibition by the hypothalamus and thus prolactin release, however hypothalamic dysfunction is difficult to observe since its hormones (GnRH, TRH, CRH, GHRH) are difficult to measure. The pathophysiological basis of the effect of irradiation is DNA damage, strand breaks, both in healthy- as well as in tumour tissue. This damage is generated by direct 3-dimensional dysfunctional changes in DNA as well as by the indirect negative effect of production of free radicals from water molecules in the cell. (24) These strand breaks may have direct lethal effects or will have accumulating sub-lethal effects that eventually will restrict potential cell replication. After radiation cell death occurs in the mitotic phase of the cell cycle (late G2-earlier phase) providing a partial explanation for the delayed onset of hormonal failure in slowly replicating tissue, such as that of the neuroendocrine tissue of the hypothalamus and pituitary. (25) Figure 3

Ionising irradiation also induces degenerative changes in surrounding glia cells, causing decreased trophic support and demyelination resulting in chronic neuronal damage.

The vascular system is also compromised by the release of pro-inflammatory cytokines such as Necrosis Factor-kappa beta (NF-κB). Due to radiation induced oxidative stress
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NF-κB causes endothelial proliferation by promoting the release of anti-inflammatory cytokines and adhesion molecules. Inflammatory cells are subsequently recruited, promoting foam cell formation which results in increased collagen synthesis, and thus of atherosclerosis. (26) Clinical studies performed in patients previously treated for e.g. lymphoma, breast cancer or head and neck cancer have demonstrated an increase in cardiovascular risk, also after adjustment for classic cardiovascular risk factors. Depending on the study, the relative risk of a clinical cardiovascular event (i.e., myocardial infarction, stroke) to be related to irradiation ranged from 1.5- to 4.0-fold, and this risk was even higher in the presence of traditional cardiovascular risk factors. (27,28)

Other reported late effects of cranial radiotherapy include a decline in neurocognitive function resulting in a decreased quality of life (29-31). In larger studies however the contributory role of cranial radiotherapy to the risk of cerebrovascular incidents was not higher than that of surgical trauma or glucocorticoid over-replacement or of undiagnosed hypopituitarism. (32)

Pituitary insufficiency is a well known late onset complication of cranial irradiation in children treated for cerebral tumours or after total body radiotherapy.(33-41) In the Childhood Cancer Survivor Study (CCSS) 43% of children treated for cerebral tumours had one or more endocrinopathies. Consequently, virtually all follow-up protocols for childhood cancer survivors include endocrine assessments as the development of hypopituitarism can still occur years after the initial treatment, especially in the doses < 45 Gy. Over the past decades, survival rates of patients treated with cranial radiotherapy for malignant or benign tumours have substantially improved by the introduction of new surgical, radiotherapy, and chemotherapy options. In contrast to the long-term survivors of cranial radiotherapy in childhood, endocrine surveillance programs have not been routinely incorporated in adults treated with cranial radiotherapy. The prevalence of hypopituitarism after cranial radiotherapy is influenced by a number of factors. First, the time interval between radiotherapy and the assessment of pituitary function is important, since the development of pituitary failure is likely to increase in time after radiotherapy. (42-44) Second, hypothalamic and pituitary insufficiencies are more likely to develop with increasing radiation exposure.

Furthermore, studies in survivors of childhood acute lymphoblastic leukaemia as well as in childhood brain cancer demonstrated an increased risk of metabolic and cardiovascular late effects after cranial irradiation, including effects on body composition, insulin resistance and hyperleptinaemia. Patients treated with radiotherapy for pituitary tumours had higher visceral to subcutaneous fat ratios when compared with controls who did not receive radiotherapy. (47) Further studies are needed to determine the clinical significance of these findings and, where clinically relevant, whether cardiovascular outcomes may be modulated by additional therapy.
A number of non-pituitary tumours, such as nasopharyngeal carcinomas, meningiomas or primary cerebral tumours are treated with high dose radiotherapy. Most often treatment schedules comprise multiple fractions of 2 Gy, with a boost sometimes additionally delivered to the primary tumour. Depending on the tumour localisation, the pituitary/hypothalamic region will receive some dose despite improved radiotherapeutic techniques. Figure 4. In nasopharyngeal carcinoma, the total dose on the primary tumour area will be at least 6-70 Gy in fractions of 2 Gy. Depending on the location of the primary tumour this might result in an estimated dose of > 40 Gy to the pituitary gland, predicting a very high probability of pituitary insufficiency, as depicted in Figure 2. Structured follow up for pituitary function is not routinely incorporated in the long term monitoring of these patients. Since the overall survival of stage I and II NPC patients has improved throughout the years to a total of > 80% 5 year survival rate, structured monitoring of pituitary function is advisable. (48,49)

**FIGURE 4.**

Figure 4A and 4B show the position of the primary tumour (yellow line), the radiation field (red line) and the pituitary region (green line). Figure 4C shows the isodose lines of 66.5 Gy (purple), 57.75 Gy (Cyan) and 30 Gy (blue) in the same patient, notice the position of the pituitary region (green) within the radiation field.

When hypopituitarism develops in the course of treatment for an underlying disease, such as nasopharyngeal carcinoma, the symptoms of hypopituitarism may mimic those of
residual symptoms after chemotherapy, surgery or cranial irradiation and may therefore be easily overlooked. Cranial radiotherapy may also induce cognitive impairments, which may mask symptoms of hypopituitarism. Diagnosing hypopituitarism can be very difficult especially for physicians not familiar with endocrine pathology such as radiation oncologists and Ear-Nose-and Throat specialists. Even a trained endocrinologist cannot diagnose pituitary failure only on the basis of clinical signs and symptoms. Since hypopituitarism will develop several years after radiotherapy most patients will not consult an internist, and therefore the diagnosis may be easily overlooked. Despite the fact that there are many ways to screen for pituitary dysfunction, the evaluation of the effects of radiotherapy on pituitary or hypothalamic function in adult patients who were treated with cranial irradiation for different causes has not been incorporated into standard patient care. In addition, there are no protocols for standardizing the endocrinological evaluation or follow up for these patients.

In Chapter 2 and appendix 1 of this thesis a review and meta-analysis of the published English literature is presented, whereas Chapter 3 and the appendix 1 address the prevalence and time frame of onset of pituitary insufficiency after irradiation for head and nasopharyngeal tumours, including a proposed algorithm for standardized follow up.

Section II: Growth hormone secretion and growth hormone deficiency

The regulation of GH secretion is controlled by the net balance between stimulatory hypothalamic peptides such as GHRH and GHrelin, and on the other hand the inhibitory tone of somatostatin. The net result is a pulsatile secretion of GH, which is important because most of the secretion occurs in bursts. The magnitude of GH bursts correlates with somatic growth and with the hepatic actions of GH. Activation of the GH-receptor in the liver induces key intracellular signaling pathways such as PI3Kinase, MAP Kinase, and STAT5b, the latter resulting in the transcriptional activation of the IGF-1 gene. Together with IGF-1, GH exerts its anabolic effects on target tissues. (52) GH, as well as sex hormones, are thus extremely important for skeletal growth and maturation throughout puberty.

The largest amount of growth hormone is secreted during adolescence; with a further progressive decline in GH secretion throughout life.

Growth Hormone Deficiency (GHD) has been associated with an adverse metabolic profile and with an increased cardiovascular mortality due to abdominal obesity, hypercholesterolaemia and hypertriglyceridaemia in adults. (1-3) Untreated GHD is also characterized by a decrease in muscle bone mass, decreased bone turnover and increased fracture risk. (7,8) GHD is also associated with an overall decrease in quality of life. (51-53)
In 1990, Rosen et al. reported increased mortality in patients with hypopituitarism, due to cardiovascular disease (CVD), particularly cerebrovascular disease, which was attributed, at least in part, to GHD. (2,54) Over the following decades a number of studies from 4 different cohorts compounding approximately 2000 patients with hypopituitarism, have reported increased mortality in these patients treated historically with conventional hormone replacement therapy, none of these patients were treated with recombinant GH (rGH) replacement. These studies only included patients with surgically resected non-secreting pituitary adenomas and craniopharyngiomas and excluded patients with Acromegaly and Cushing’s disease, since it was assumed already that these specific diseases would increase mortality risk, as demonstrated by Dekkers et al. in 2006 and 2008. (3,55-58) A significant number of these patients also received additional cranial irradiation, and the majority of pre-menopausal women were not treated for gonadotropin deficiency.

The classical clinical features of the adult patient with GHD is that of a patient suffering from overweight, with predominantly abdominal obesity, decreased muscle strength, reduced exercise intolerance and depressed mood. Additional investigations would reveal elevated serum lipids, particularly LDL cholesterol, reduced lean body/increased fat mass and reduced bone mineral density. In the mid 1990’s, human recombinant growth hormone (rGH) became available for the treatment of adults with severe GHD. Since then, consistent beneficial effects of replacement therapy with rGH have been reported on body composition and lipid profile, resulting in reduction of fat mass combined with an increase in lean body mass, and a reduction in total cholesterol (TC) levels, as meta-analysed and summarized by Maison et al. (6) Favourable effects were also reported on bone turnover, bone mineral density (BMD), muscle strength, cognitive function and QoL.(6, 59, 60)

In cross-sectional studies, beneficial effects of rGH replacement have been reported to sustain for at least 5 years of treatment; data with a longer follow-up duration are scarce. With respect to cardiovascular risk profile, a direct improvement of several cardiovascular risk factors was noted within the first year of treatment, which persisted during long-term rGH treatment. (61,62) A sustained improvement of lipid spectrum and diastolic blood pressure (DBP) was reported in a small study over 7 and 10 years of treatment, suggesting on-going beneficial effects of rGH even beyond 5 years. However whether rGH replacement has favourable effects on the incidence of cardiovascular events, including cardiovascular death is yet to be established.

GROWTH HORMONE AND THE SKELETON

The skeleton consists of cortical bone and trabecular (cancellous) bone. Cortical bone, which comprises 80% of the skeleton, is designed to provide rigidity and strength and
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is predominantly found in the long bones, e.g. at the femur. Cancellous bone has a more flexible design with interconnecting trabecles, and is metabolically more active than cortical bone. There are three types of bone cells: osteoclasts, responsible for bone resorption, osteoblasts, responsible for bone formation and osteocytes that are the mechano-sensors of the skeleton. The three types of bone cells form the main components of the so-called basic multicellular unit (BMU). In a healthy adult there are more than 1 million BMU’s, which are mostly active in cancellous bone. In a BMU bone resorption takes 3 weeks to be completed whereas bone formation may last up to 9 months. The balance between formation and resorption is essential for maintaining a normal bone mass and skeletal integrity. Disruptions in the ratio of bone formation and resorption in favour of resorption will ultimately lead to progressive bone loss and increased bone fragility.

GH and IGF-1 play an important role in bone growth and metabolism throughout the life span of an individual. IGF-1 mediates skeletal growth by promoting endochondrial ossification in cartilage and by enhancing osteoblast formation and differentiation of both osteoblasts as osteoclasts, GH also exerts direct effects on bone. Both GH and IGF-1 act as anabolic hormones on bone by stimulating proliferation, and to some extent, differentiation of osteoblasts. IGF-1 promotes osteoblast differentiation through the mTOR pathway. This has been demonstrated in an IGF-1 knock-out mouse model in which decreased bone formation and subsequent decreased bone mass has been observed. Up-regulation of IGF-1 mediated pathways in osteoblasts results in widening of the cortex and in an increase in the length of the long bones, whereas trabecular bone is hardly affected by these pathways. In osteocytes, knocking out IGF-1 results in a decrease in calvarial bone growth rate. IGF-1 is also a co-regulator in osteoclast differentiation by induction of Receptor Activator of Nuclear factor kB Ligand (RANK-L) expression. RANK-L is a stimulator of osteoclast differentiation, proliferation and activation and thus prolongs the lifespan of the osteoclast resulting in an overall increase in bone remodelling. In contrast GH promotes the production of osteoprotegerin (OPG) which binds to RANK-L and inhibits osteoclast formation and differentiation. The ratio between RANK-L and OPG is critical for optimal balance between bone formation and resorption. After the menopause for example, OPG levels drop tremendously due to estrogen deficiency, the most important stimulator of OPG formation, leading to a marked increase in bone loss particularly within the first year after the menopause.

IGF-1 knockout models have also shown that IGF-1 is required for adequate function of parathyroid hormone (PTH). In the absence of IGF-1, PTH does not longer have a stimulating effect on bone formation rates. IGF-1/GH plays a key role in bone cell growth and differentiation.
In humans with growth hormone insensitivity due to inactivating mutations in the gene encoding the GH receptor (Laron syndrome) GH levels are very high and IGF-1 levels are reduced by more than 80%. These individuals are extremely short of stature due to short long-bones. In patients with Laron syndrome the cortex is of normal thickness and there is no increased incidence of osteoporosis or fractures. (70) In contrast, untreated GHD is characterized by low bone turnover, decreased bone mineral density (BMD) and increased fracture risk (1,7). Recombinant human GH (rGH) replacement therapy has been shown to increase bone turnover as reflected by an increase in bone formation and bone resorption markers, resulting in an initial decline in (or unchanged) BMD, followed by a small increase of about 1-2% in the first 2 years of rGH replacement due to a positive balance in favor of bone formation. (71,72)

Data on the effects of long-term rGH replacement on BMD are, however, scarce. Previous studies reported that rGH replacement induces a progressive increase in BMD and BMC up to 5-7 years of treatment, followed thereafter by a maintenance of BMD up to 7 years of treatment. (72-74) Götherström et al. found an increase in total body and lumbar spine BMD and BMC up to 10 years of rGH replacement, whereas femoral neck BMD and BMC reached a peak value after 5-7 years. Only one study has reported the effects of 15 years of rGH supplementation. This study reported a sustained increase in total body and lumbar BMD and BMC over 15 years, whereas femoral neck BMD and BMC returned towards baseline values after 7 years. (59)
Another important issue regarding long-term rGH replacement therapy in adults is the potential association between growth hormone/IGF-1 and cancer risk, which is an on going topic of debate. A number of animal studies as well as epidemiological studies in humans examined the relationship between low IGF-1 as well as reduced cancer risk and cardiovascular risk. The activity of the GH/IGF-1 axis decreases with ageing, yet smaller individuals within a species usually live longer (including ponies and small dogs). (75) Life span is also longer in mice lacking GHR, resulting in low IGF-1 levels. Although some of these mutant mice were also deficient in other hormones, such as TSH, their longevity is thought to be primarily due to their Growth Hormone Deficiency (GHD), since restoration of GH levels reverted their longevity to match that of non-mutants. (76,77)

Reduced IGF-1 levels as well as reduced IGF-1 signalling has been associated with reduced cancer risk in humans. For instance, cancer was virtually absent in a Ecuadorian cohort of patients with severe GHD due to GHR gene mutations). (78) Another cohort of patients with Laron syndrome showed a general identical clinical picture. (79) To date, only one case of (non-lethal) cancer has been reported in both Laron cohorts.

Whether IGF-1 per se alters longevity in humans remains questionable. Among others, the Leiden Longevity study showed that the relation between longevity and IGF-1 may be through insulin sensitivity. Rozing et al. showed a lower prevalence of diabetes, and non-fasted serum glucose levels in the offspring of familial nonagenarians compared to their partners although IGF-1 and IGFBP3 did not differ between both groups (80). It was already shown in the 90’s that sporadic long-lived centenarians were very sensitive to insulin compared to young adults and that insulin sensitivity decreases with age. (81) A recent meta-analyses of IGF-1 in the general population showed an increase in mortality in both high as well as in the population with low IGF-1 levels, hazard ratio (HR) 1.18, (95%CI 1.04-1.34). (82) This U-shape relationship was present for both cancer and cardiovascular mortality. In addition, several other epidemiological reports showed an association of both low and high IGF-1 levels with DM2, sarcopenia, osteoporosis and cardiovascular disease. (75,83) However, this by no means proves that low and high IGF-1 levels are related to increased specific morbidity or mortality.

Taken together, these data do suggest that optimizing the activity of the GH/IGF-1 axis to promote healthy aging in humans is more complex than originally appreciated, and requires a greater understanding of its array of interactions and tissue specificity.

Chapter 4 describes the results of an extended literature search on long-term growth hormone replacement in adults beyond 5 years of treatment. In Chapter 5 the changes in metabolic profile after initiation of growth hormone replacement within a group of long-term recombinant GH therapy users are presented and discussed. In Chapter 6, the difference in metabolic profile of GHD patients on stable, defined as > 5 years, rGH replacement therapy to the metabolic profile of the general population will be
addressed. Chapter 7 discusses whether long-term rGH replacement has any beneficial effect on bone metabolism. Finally, in Chapter 8, a systematic literature search and cohort study is performed investigating the metabolic effects of discontinuing rGH replacement.
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Chapter 1


