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Abnormal growth hormone secretion : clinical aspects

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Chapter 1

Introduction

Clinical aspects of abnormal GH secretion

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1. Introduction

This thesis describes several studies, which illustrate the physiology and pathophysiology of growth hormone. This chapter provides an overview of the concepts underlaying the studies.

1.1 Regulation of growth hormone secretion

Growth hormone (GH) is synthesized in the anterior pituitary gland by somatotropic cells. This gland is situated within the bony sella turcica and is overlain by the dural diaphragma sella, through which the stalk connects to the hypothalamus. Most of the functioning anterior pituitary cells consist of somatotroph cells (35-45 %)(1). In recent years, much knowledge has emerged on the embryogenesis of the pituitary. It has been discovered that the differentiation of pituitary stem cells into somatotroph cells is regulated by two transcription factors, PROP-1 and Pit-1 (2;3), which has clinical relevance for the understanding of congenital GH deficiency syndromes.

The two most important regulators of GH secretion are the hypothalamic peptides Growth Hormone Releasing Hormone (GHRH) and Somatostatin. Both hypothalamic peptides are secreted in independent waves and interact together to generate, and control, GH release. GHRH stimulates GH release, whereas somatostatin has an inhibitory effect. After GHRH is secreted by the hypothalamus, it is transported through the portal system to the somatotroph cells, where it binds to the GHRH receptor (1;4). Stimulation of the GHRH receptor results in the release of presynthesized GH, that is stored within the cells. In contrast to the GHRH receptor, of which no receptor subtypes are known, 5 different somatostatin receptor subtypes can be distinghuished. In the pituitary gland, the 2 most important somatostatin receptor subtypes are the subtypes 2 and 5 (5). After binding of somatostatin to its receptor, somatostatin inhibits GH secretion and/or cell proliferation (6).

In addition to the effects on the pituitary with respect to the release of GH, somatostatin and GHRH influence each other's release. GHRH stimulates somatostatin secretion, whereas somatostatin inhibits GHRH secretion (4). The integrated effect of GHRH and somatostatin on the pituitary gland ultimately leads to GH secretion. This is characterized by a pulsatile pattern with high amplitude pulses, especially at night, and low amplitude pulses predominantly during daytime.

GH secretion is regulated in a feedback system. The most important peptide in this system is Insulin-like-Growth factor I (IGF-I). Plasma IGF-I is predominantly produced by the liver, whereas IGF-I synthesis occurs in virtually all tissues and acts in a paracrine fashion. Most circulating IGF-I is bound to IGF-binding protein 3 (IGF-BP3) and acid labile sub unit (ALS). IGF-I is transported to the brain, where it has numerous effects. The most important action of IGF-1 in the brain is the stimulation of somatostatin production, which will eventually reduce GH production (7).

In addition to these important regulators of GH secretion, recently a novel potent GH secretagogue has been discovered, Ghrelin (1). Ghrelin appears to be the natural ligand of the growth hormone secretagogue receptor (GHS-R). Activation of this receptor by Ghrelin leads to potent GH secretion.

Ghrelin is predominantly produced by the stomach and released into the bloodstream. In addition to the GH releasing activity, it also stimulates the release of other pituitary hormones like cortisol and prolactin and plays a role in stimulating appetite, controling energy balance and gastric motility. Although Ghrelin is a potent GH releasing peptide, recent insight indicates that Ghrelin contributes more to the regulation of diverse functions of the gut-brain axis than to GH secretion *per se* (8).

1.2 GH and IGF-I

GH binds membrane-anchored GH receptors(9). The extra-cellular domain of this receptor can be released into the circulation and is referred to as growth hormone binding protein (GHBP), which may serve as a stabilizer of GH availability in the circulation (10). GH receptors are found in many peripheral tissues, especially in the liver. After binding of GH to the GH receptor, the receptor initiates a phosphorylation cascade involving a JAK/STAT pathway, which is ultimately leads to the biological actions of GH (11;12).

In general, GH acts on peripheral tissues by two mechanisms: 1) a direct effect, and 2) an indirect effect via IGF-I, produced, and secreted into the blood, by the liver or produced locally within a certain tissue. Of the circulating IGF-I, approximately 75 % is produced in the liver, the remainder being produced locally (13). IGF-I binds to the IGF-I receptor, which results in tyrosine phosphorylation to initiate its effect (14).

1.3 Physiological effects of GH

The physiological actions of GH involve many organs and physiological systems. Although a complete overview of GH action falls beyond the scope of this chapter, important effects include longitudional bone growth, metabolism and - relevant for the scope of this thesis - the heart and general well-being.

GH plays an important role, through IGF-I dependent processes, in postnatal longitudinal bone growth and remodelling by inducing proliferation or/and differentiation of chondrocytes, osteoblasts, osteoclasts and collagen type I synthesis (15-18). In addition to bone

remodelling, IGF-I increases the fiber content and strength of skeletal muscles (19).

GH exerts many metabolic effects that persist throughout life. GH has a lipolytic effect in fat and muscle. After acute administration of GH, a rise in circulating free fatty acids (FFA) and glycerol is observed (20;21). Moreover, a reduction of LDL and elevations of HDL levels is observed with GH administration (22). Acute administration of GH causes a temporary effect on glucose uptake similar to insulin, whereas chronic GH administration leads to insulin resistance with hyperinsulinemia, due to a post receptor defect in insulin signaling (23). These effects may be partially explained by GH induced lipolysis and elevated plasma FFA, that inhibit insulin activity at its target tissues. GH therapy also increases lean body mass by enhancing protein synthesis, with a small inhibiting effect of protein degradation (24).

In addition to these metabolic effects, GH plays a role in immunomodulation, like B and T- cell proliferation, macrophage activity, immunoglobulin production etc. Therefore, GH exerts pleiotropic effects in many physiological systems. Remarkably, however, these effects are in general very subtle in adult patients and cannot be easily quantified by clinicometric approaches. This is probably the reason, that, in general, there is a long delay between the start of the disease acromegaly and the time of diagnosis (see below). In addition, the effects of GH substitution on GH deficient patients exemplify these subtle effects.

1.4 GH and the heart

The GH - IGF-I axis plays an important role in cardiac development and function. In cardiomyocytes both GH and IGF-I receptors are expressed (25). Interestingly, the GH receptor gene is expressed to a greater extent in the myocardium than in many other tissues (26). In hypophysectomized rats, GH induces cardiac IGF-I mRNA expression and increases cardiac IGF-I content. In turn, IGF-I increases the size of cultured cardiomyocytes and enhances myofibril development (27). Concomitantly, IGF-I down-regulates sms-actin, a protein that forms stress fiber-like structures (28). GH and IGF-I have a direct effect on myocardial contractility. By increasing the intracellular calcium content

and enhancing the calcium sensitivity of myofilaments in cardiomyocytes, GH and IGF-I promote the contractility of the myocardium (29;30). Thus, it appears that GH and IGF-I have positive inotropic effects on the heart by increasing cardiac growth and by increasing the sensitivity of the myofilament apparatus to Ca^{2+}.

1.5 GH and quality of life

As discused above, GH has effects in almost every organ system. These effects are translated in a subtle way into quality of life. Many studies on GH deficient subjects have shown that GH deficiency leads to impaired quality of life (31-33). In most studies, restoration of GH levels improves quality of life in the majority of the patients (34). GH may act directly or indirectly on neural sites. In the human hippocampus, putamen, thalamus, hypothalamus and pituitary, GH receptors are found, suggesting a direct role of GH in the brain (35;36). The hippocampus may be important with respect to neural effects of GH as this region plays an important role in memory, motivation and attention (37). The mechanism whereby GH exerts direct effects on psychological functions, is largely unresolved (38;39).

GH may enhance cognition by stimulating brain growth and development. Studies in GH deficient mice have shown impaired brain growth, glial and neuronal proliferation, and myelinisation. Conversely, brain size is increased in GH transgenic mice (37). Accordingly, GH plays an important role in neural function during brain injury. Studies in rats have shown that GH can prevent cell loss in the hippocampus (40), following hypoxic/ischemic injury. GH enhances cerebral blood flow and intracellular communication and, which improves neural function (41;42).

GH may be involved in normal sleep generation. In GH deficient patients decreased deep sleep, increased total sleep time and a decreased REM sleep have been observed, which could be reversed by restoration of GH levels (43;44). Nonetheless, the importance of GH in sleep generation has been questioned by other authors (45;46).

1.6 Pathophysiolocal effects of GH: GH excess

Acromegaly is a rare disorder of GH excess, first described by Pierre Marie in 1886. This syndrome is characterized by elevated GH and IGF-I levels and by progressive somatic disfigurement and systemic manifestations. The prevalence is currently approximately 40 cases per million subjects with an estimated annual incidence of three to four patients per million subjects (47-49).

In almost all cases, GH excess is caused by a GH -secreting pituitary adenoma. In very rare cases, the syndrome is caused by extra-pituitary production of GH or GHRH in neuroendocrine tumors, like carcinoid tumors (50).

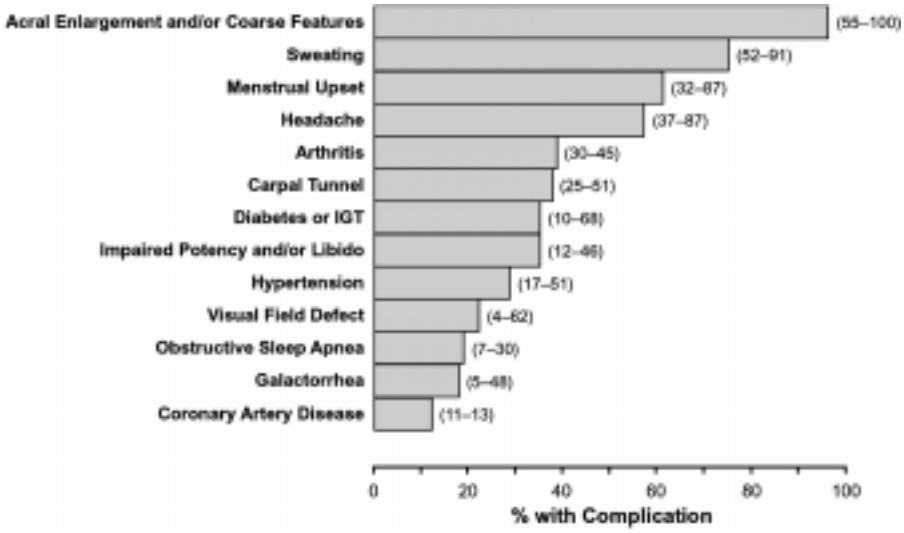

Fig. 1 Clinical features of acromegaly

Acromegaly is a disease that develops slowly, with only little and subtle clinical symptoms in the beginning (see Figure 1). Therefore, there is an average delay of 8 years in the diagnosis of acromegaly. At the time of diagnosis patients have coarsened facial features, soft tissue hypertrophy and exaggerated growth of hands and feet. Other characteristics consist of an increased number of skin tags, sleep apnoe, colonic polyps, insulin resistance, carpal tunnel syndrome and

cardiovascular disease like hypertension and cardiac hypertrophy (50-52).

The treatment of first choice is still trans-sphenoidal surgery, with success percentages ranging 60-70 % on the short term (53-56). The success of surgery depends on the skill and experience of the surgeon. Side effects of the surgical procedure are related to the size of the tumor and on the invasiveness of the tumor into adjacent structures. The most important side effects are hypopituitarism and permanent diabetes insipidus (57). Meningitis is a direct and serious surgical complication. After a follow up of more than 10 years, recurrences occur in 19 % of the patients, resulting in a 10 year cure rate of only 40 % (55). Therefore, adjuvant treatment is necessary in many patients to treat persistent or recurrent disease.

The first choice of adjuvant therapy is medical therapy. Current medical treatment options are mostly based on the fact that somatotroph adenomas express high levels of somatostatin receptors subtypes 2 and 5 (58;59). By stimulating these receptors, GH secretion will be suppressed, leading to decreased IGF-I levels. Two long-acting somatostatin analogues, octreotide and lanreotide, are currently available, which have a high binding affinity to somatostatin receptor subtype 2 and to a lesser extent subtype 5 (5). With the introduction of the octreotide long acting repeatable (LAR) formulation, patients only require an intramuscularly injection once monthly. In approximately 60 % of the patients octreotide treatment decreases GH levels beneath 2.5 μg/L and normalizes IGF-I levels (60;61).

In clinical practice, octreotide LAR appeared to be more effective in suppressing GH secretion than the slow release (SR) preparation of lanreotide (62-65). Lanreotide (SR) had to be injected every 2-3 weeks and effectively controlled GH and IGF-I levels in fewer patients. Recently, a new slow release depot preparation of lanreotide was introduced, Lanreotide Autogel (66). This new depot formula of lanreotide has to be injected subcutaneously only once a month. **Chapter 2** of this thesis describes a prospective study in which the efficacy of octreotide LAR and lanreotide Autogel in suppressing GH and IGF-I levels was compared in patients with active acromegaly.

Another new perspective in somatostatin analogue treatment is the development of SOM 230 (67). This novel drug has a broader binding affinity for somatostatin receptor subtypes. Compared with octreotide it has higher binding affinity to somatostatin receptor subtype 5, and to a lesser extent also to somatostatin receptor subtypes 1 and 4 (5;68). Preliminary data are promising, but further investigations are needed to establish the additional value of this new drug in the treatment of acromegaly (69).

In the development of drugs aimed at decreasing GH levels in acromegalic patients, recently a new approach was introduced. Pegvisomant is a competitive inhibitor of the GH receptor. Pegvisomant is highly effective and normalizes IGF-I levels in 97% of the patients (70;71). One of the concerns of this new drug is that by blocking the GH receptor the patient may become GH deficient. The clinical value of this drug in acromegaly has therefore to be studied in long-term studies (72). Currently, Pegvisomant is used in patients who do not effectively respond to treatment with somatostatin analogues.

The last therapeutical option in acromegaly is the use of radiotherapy. Although effective in reducing GH secretion, the response is slow and takes many years (73). After 6 years, 70% of the patients have normal IGF-I levels, whereas after 10 years, 10-15 % of the patients still have high levels of GH (73;74). One of the major side effects of radiotherapy is hypopituitarism, which develops in almost 55 % of the patients after 10 years (75). Lethargy, impaired cognitive function and personality changes are also observed in patients who were treated with radiotherapy (76). Therefore radiotherapy is currently used as an adjuvant therapy in acromegaly only when surgical and/or medical therapy have failed.

The goal of therapy in acromegaly is biochemical cure (according to consensus defined as GH levels below 2.5 µg/L (or 5 mU/L) and IGF-I levels in the normal age and sex adjusted range. These criteria are based on historical outcome parameters of therapy in acromegaly: Mortality risk normalizes when these treatment goals ar reached (53;77;78). The morbidity that accompanies acromegaly, like impaired glucose tolerance, an adverse lipid profile, sleeping disorders and acromegalic arthropathy (e.g. osteoartrithitis, cartilage thickness)

improves, when effective treatment is instituted. Also the cardiac abnormalities observed in active acromegaly, like biventricular-concentric hypertrophy, diastolic dysfunction at rest, systolic dysfunction at exercise and diastolic heart failure improve or normalize after curation (26;79-81). The above defined biochemical criteria for cure are supported by a recent study that showed that GH secretion in cured acromegalic patients assessed by with detailed 24-hour GH secretion profile did not differ from normal subjects (82).

Patients, in whom the biochemical treatment goals can only be reached by continuous treatment with medicial therapy, have so called "well-controlled disease". Studies have shown that morbidity in these well controlled patients improves to the same extent as in cured acromegalic patients: after 12 months of somatostatin therapy, a decrease in left ventricular mass, an improvement in diastolic function and - to a lesser extent - systolic function is observed (51), despite the fact that 24-hour GH secretion is not completely restored like in cured acromegalic patients (83). The question, therefore, remains, whether these patients still have persisting subtle effects of GH overproduction.

Moreover, most studies investigating the effect of treatment on cardiac function in acromegaly used heterogeneous groups, including de novo acromegaly patients in combination with uncontrolled treated patients, or well-controlled patients in combination with cured patients for analyses (81;84-89). One study used a homogenous group of patients (90), but did not include all relevant diastolic and systolic parameters. In **Chapter 3** it is investigated whether cardiac function in well-controlled acromegalic patients is really normalized as compared with cured patients, using 2 dimensional echocardiography, as well as Tissue Doppler echography, which allows detailed measurement of diastolic function.

A remarkable lack in the knowledge on cardiac consequences of acromegaly is that despite the many investigations on cardiac function in these patients, (26;51;79;80;91-93) little is known about cardiac valve function. It is known that GH excess changes the cardiac structure and diastolic function in acromegalic patients. It is also known that GH excess affects the composition and structure of collagenous tissue in

general. Heart valves consist mainly of collagen but it is has not been documented whether GH excess has any effect on cardiac valves. **Chapter 4** addresses this issue in different groups of acromegalic patients.

1.7 Pathophysiological effects of GH: GH deficiency

GH deficiency occurs when the pituitary secretes an insufficient amount of GH levels. This occurs in congenital pituitary deficiencies, like a Pit-1 or PROP-1 mutation, or in macroadenoma of the pituitary, (e.g. non-functional adenoma), or through other factors that damage the pituitary and/or hypothalamus (e.g. trans-sphenoidal surgery, or irradiation). Interestingly, disturbances in the GH-IGF-I axis can also occur in patients with a normal hypothalamus/pituitary axis but with a chronic disease, e.g. chronic heart failure or obesity.

Patients with adult-onset GH deficiency have many signs and symptoms (Table 2). GH deficiency is associated with a twofold increased risk of death from cardiovascular disease as compared with healthy controls (94-98). The high cardiovascular mortality risk is associated with an favourable metabolioc profile (abdominal obesity, insulin resistance, an abnormal lipid profile, atherosclerosis, endothelial dysfunction and hypercoagulability) and abnormal cardiac function (decreased cardiac function, with reduced left ventricular mass, left ventricular diameters resulting in an impaired systolic function at exercise). Other abnormalities are reduced pulmonary function, muscle dysfunction and decreased performance capacity (80;93;99-104).

Background
- Need for GH treatment as a child (GHD proven on retesting)
- Known pituitary pathology ± previous treatment
- Full "conventional" pituitary hormone replacement

Symptoms
- Abnormal body composition
  - Reduced lean body mass
  - Increased abdominal adiposity
- Reduced strength and exercise capacity
- Impaired psychological well-being
  - Reduced vitality and energy
  - Depressed mood
  - Emotional lability
  - Impaired self-control
  - Anxiety
  - Increased social isolation

Signs
- Overweight, with predominantly central (abdominal) adiposity
- Thin, dry skin; cool peripheries; poor venous access
- Reduced muscle strength
- Reduction exercise performance
- Depressed affect, labile emotions

Investigations
- Stimulated GH level below 3 μg/L
- Low or low-normal serum insulin-like growth factor-I (IGF-I)
- Elevated serum lipids, particularly low-density lipoprotein (LDL) cholesterol
- Reduced lean body mass/increased fat mass
- Reduced bone mineral density

Table 2. GH deficiency: Signs and symptoms (ref.108)

The introduction of recombinant human GH (rhGH) has been an important development for the treatment of GH deficiency. RhGH therapy restores IGF-I levels into the normal range (105;106). However, physiogical GH profiles cannot be restored, as GH levels after rhGH administration follow a pharmacological pattern with a T max of 2-4 hours with a slightly down slope GH level during 24 hour (107). Restoration of normal IGF-I levels, and to a lesser extent GH levels, result in an improvement of many organ functions, including insulin tolerance, lean body mass, lipid metabolism, exercise tolerance, bone mass, and cardiac function (102;108-110). When rhGH was introduced as a treatment for adult GH deficiency, studies suggested that quality of life (QoL) also improved. However, all these studies were limited with respect to the fact, that they only focussed on one dimension of QoL (see the review of Hull et al. (34)). There are only a few studies that studied different aspects of QoL, like depression and general well being

(114-116) . In addition, most studies investigated QoL in GH deficiency patients before and after rhGH administration, but did not compare QoL with healthy subjects (114). **Chapter 5** will address the QoL in GHD patients on long-term treatment with rhGH as compared to healthy subjects.

In patients with panhypopituitarism currently not all deficient hormones are replaced. The adrenal cortex produces more hormones than cortisol, which is the only adrenal hormone that is substituted in patients with ACTH insufficiency. One of the key products of the adrenal gland is the hormone DHEA (di-hydro-epi-androsterone) and its sulfate DHEA-S, from which many other steroid hormones are synthesized through intracrine pathways (117;118). Using DHEA replacement in patients with *primary* adrenal insufficiency, an improvement in quality of life, and sexual functioning was observed (119-121). Interestingly, some studies also showed, that DHEA replacement increased IGF-I levels (120;122-124). It was unclear, however, whether the increase in IGF-I levels was due to altered GH secretion and/or to an effect of DHEA on IGF-I production. We hypothesized that patients with secondary adrenal insufficiency will benefit of DHEA replacement, and that the increase of IGF-I could play a role in this improvement. In **chapter 5** the effect of DHEA replacement on QoL and IGF-I will be described in GH and ACTH deficient patients, treated with a fixed dose of rhGH.

In patients with alterations in the GH-IGF-I axis, like chronic non-endocrine disease, or even elderly subjects, the idea emerged that restoration of GH levels would benefit the patients. In line with this assumption, studies performed in the early nineties suggested that patients with idiopathic dilated cardiomyopathy or ischemic cardiac failure would benefit from the positive effects of GH on cardiac muscle (125;126). The idea was, that by improving the strength of the cardiac muscle cardiac function improves. Studies indeed showed promising results, but most studies were only observational. Randomised (controlled) studies could not confirm the results (127-129). These studies mainly focused on the systolic function, although the majority of patients with cardiac failure have diastolic dysfunction (130). Therefore, in **chapter 6**, the effect of rhGH in ischemic cardiomyopathy

on cardiac function with special focus on diastolic function is described.

1.8 Aims of this thesis

GH plays an important role in the human body, by direct and/or indirect mechanisms. The aim of this thesis is to focus on different clinical aspects of the physiological role of GH in humans, with a special focus on three different models. The first model is the model of GH excess: acromegaly. In this model we compared the effects of two somatostatin analogues on GH secretion, the effect of the treatment of acromegaly on cardiac function and on cardiac valves. In the second model, GH deficiency, the investigations focused on the effects of DHEA replacement on quality of life and IGF-I concentrations. The third and last model is the model of relative GH deficiency in a chronic non-endocrine disease (ischemic cardiomyopathy), where we tested the hypothesis that restoring GH levels could have beneficial effects on cardiac function.

In **chapter 2** data are presented of a comparison between a new depot somatostatin analogue, Lanreotide Autogel, and the only other available depot preparation, Octreotide LAR. Lanreotide Autogel is a new slow-release depot preparation that requires monthly injections. To compare the two medications in effectively suppressing GH levels, seven patients were first analysed during treatment with octreotide LAR before they were analysed on the new drug. The effects of GH suppression was analysed with two different approaches. First using GH profiles (an average of GH levels taken every 30 minutes for 3,5 hour) assessed 2, 4 and 6 weeks after an injection. Secondly, we compared GH secretion characteristics in detail via deconvolution analysis of 24 h plasma GH concentration profiles.

Chapter 3 presents data of cardiac function in patients with so-called well-controlled acromegaly during treatment with somatostatin analogues compared with other therapeutic modalities. One of the remarkable observations presented in chapter 2 is that although patients are well controlled by somatostatin analogues according to strict biochemical criteria, the total 24-hour GH production remains relatively

high, in comparison to acromegalic patients cured by surgery, who exhibit normal 24 GH secretion. It is uncertain, whether this difference in GH levels translates into biological effects. A sensitive organ that reacts to GH excess is the heart. Therefore, *de novo*, active and well-controlled patients, as well as cured acromegalic patients, underwent echocardiography to compare systolic and diastolic function in detail. Although there are many studies that assessed cardiac function in acromegaly patients, this is the first study in which diastolic and systolic functions in the four categories of therapeutic modalities were compared with each other.

Chapter 4 presents data of an observational study on the prevalence of myocardial valve dysfunction in acromegaly. Despite some case reports, the prevalence or incidence of valvular insufficiency has not been documented in acromegalic patients. To investigate the effects of active acromegaly on valvular insufficiency both active (*de novo* and treated active patients) and inactive (cured and well-controlled) patients were investigated.

In **chapter 5** the results of a double-blind, placebo controlled randomised cross-over study are presented. In this study the effects of DHEA on IGF-I and QoL were investigated in patients with GH deficiency and secondary adrenal failure, who were on stable hormone substitution. Any difference in QoL, measured with a broad spectrum of parameters, was assessed. Together with a general test (SF-36), the effects on depression, and anxiety (HADS), fatigue (MFI-20) and sexual functioning were investigated.

In **chapter 6** the data are presented of a randomised study in which rhGH in a fixed dose was given for 6 months to patients with ischemic cardiac failure. At baseline and after 6 months cardiac function was assessed using MR cardiac imaging. The goal was to investigate the change in systolic and diastolic function after rhGH therapy, as was suggested in a few studies with patients with dilated cardiomyopathy.

In **chapter 7** the data of the studies presented in this thesis are summarized and discussed.

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