CHAPTER 1

General introduction and outline of the thesis

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GENERAL INTRODUCTION

Growth Hormone

Growth hormone (GH) is synthesized, stored, and excreted by the somatotrope cells of the anterior lobe of the pituitary gland. The pituitary gland lies within the sella turcica, a recess in the sphenoid bone, nearby the hypothalamus and the optic chiasm (figure 1). It is connected to the hypothalamus with the pituitary stalk and consists of the adenohypophysis (anterior lobe 80%) and the neurohypophysis (posterior lobe 20%). The cell types in the anterior lobe of the pituitary are: the somatotropes (50%), lactotropes (20%), corticotropes (10%), thyrotropes (10%), and gonadotropes (10%), all producing their specific hormones: GH, prolactin, adrenocorticotrophic hormone (ACTH), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH), respectively. Two hypothalamic hormones control the secretion of GH: GH releasing hormone (GHRH) which stimulates GH secretion, and somatostatin which inhibits the secretion (figure 2). GH is released from the anterior pituitary in a pulsatile manner with the majority occurring at night. Physiological stimuli enhancing GH secretion are sleep, hypoglycaemia, and exercise. Inhibitors of GH are, amongst others, meals, glucose, and adiposity. Women have a higher GH production than men. In 1910 hypophysectomy was shown to arrest growth, and in 1912 it was demonstrated that the main action of GH was to promote longitudinal bone growth. However, as normal growth occurs over a relatively short time period and GH secretion continues throughout life, it is not surprising that it has many other functions. Most, but not all, effects of GH are mediated via insulin-like factor-1 (IGF-1), a pathway named the GH-IGF-1-axis. IGF-1 is the active metabolite of the axis and is produced in many organs, but mainly in the liver. IGFs and their associated binding proteins (IGFBPs) also play important
roles in normal development and growth. Next, the anabolic actions of GH (and IGF-1) include stimulation of protein synthesis, increased lipolysis, muscle growth, and immunomodulation. GH directly antagonizes the actions of insulin leading to glucose intolerance. In contrast, IGF-1 has an insulin-like effect and enhances peripheral glucose uptake. Also, IGF-1 is a key regulator of cell proliferation and an inhibitor of cell apoptosis and necrosis. The serum IGF-1 concentration reflects the GH concentration over 24 hours and normal values are different for age and sex. Therefore, it is common practice to express IGF-1 level as standard deviation score (SDS) with normal values between -2 SDS and +2 SDS (adjusted for age and sex).

Figure 2. The GH-IGF-1 axis

The GH-IGF-1-axis and age-related diseases

GH secretion is maximal in the late puberty, and afterwards GH and IGF-1 levels in healthy individuals gradually decline with age. This phenomenon of relative GH and IGF-1 deficiency during normal aging has been named the "somatopause" and is often ascribed to the reduced activity of the hypothalamic-GH-IGF axis. Survival and age-related diseases (e.g. cardiovascular diseases (CVD), stroke, and malignancies) have often been associated with this axis. On one hand, in the cardiovascular system, IGF-1 is postulated to protect against endothelial dysfunction, atherosclerotic plaque development and ischemic myocardial damage (figure 3). Endothelial cells have high-affinity IGF-1 binding sites, and IGF-1 stimulates nitric oxide (NO) formation by endothelial cells and vascular smooth muscle cells (VSMC). Arterial endothelial dysfunction can cause arterial stiffness, which is a risk factor for atherosclerosis, and subsequently CVD. Another possible pathway of the relationship of IGF-1 with CVD is through the relationship of IGF-1 with (components of) the metabolic syndrome. The metabolic syndrome is a cluster of cardiovascular risk factors, including hypertension, abdominal obesity, unfavourable lipid profile and hyperglycaemia. Older persons with metabolic
syndrome are more likely to experience any CVD than subjects without metabolic syndrome.\textsuperscript{6,7} Low-normal IGF-1 levels have also been shown to be associated with development of ischemic heart disease and stroke in several epidemiological studies.\textsuperscript{8-10} In two studies on the association of IGF-1 with the metabolic syndrome in older populations U-shaped relationships have been reported.\textsuperscript{11,12} Others report low IGF-1 values to be related to a greater metabolic burden.\textsuperscript{13-16} On the other hand, high levels of IGF-1 have been expected to activate survival pathways that would make programmed cell death of damaged cells slightly less probable, which suggests a possible role in carcinogenesis. In a population-based studies high-normal levels of IGF-1 have been reported to be associated with a moderately increased risk of cancer.\textsuperscript{17} Some epidemiologic data show that a high level of serum IGF-1 is associated with increased risk for some specific cancers, namely lung, prostate, colorectal, and premenopausal breast carcinoma.\textsuperscript{17-20} If low IGF-1 activity is associated with an increased risk of developing CVD and high IGF-1 activity with an increased risk of developing cancer one hypothesis might be that there is an optimal set point for the GH-IGF-1-axis associated with survival.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Several effects of IGF-1 on cardiovascular function have been identified that could explain the epidemiologic link between low IGF-1 and the occurrence of CVD (adapted from: Kaplan et al. ref: 5).}
\end{figure}

\textbf{The Longitudinal Aging Study Amsterdam (LASA)}

The database used in this thesis to investigate the relationship of IGF-1 level with age-related diseases and mortality is the Longitudinal Aging Study Amsterdam (LASA). LASA is an ongoing multidisciplinary cohort study on predictors and consequences of changes in physical, cognitive, emotional and social functioning in older people in The Netherlands. A sample of older men and women (aged 55-85 years at baseline), stratified by age, sex, urbanization grade, and expected
5-year mortality, was drawn from the population registers of 11 municipalities in three regions in The Netherlands, thereby creating a representative sample of the Dutch population. LASA is carried out at the VU University and VU University Medical Center and was initiated by the Ministry of Health, Welfare and Sports in The Netherlands. At baseline (1992/1993) and every three years thereafter, subjects participated in an interview and a physical examination performed by trained nurses at the subject’s home. Studies in this thesis were performed in a subgroup of the LASA population (n=1319), including participants from the second cycle (1995/1996) because at this cycle IGF-1 measures from blood samples were available in participants aged 65 years or older.

**Growth hormone deficiency in adults**

The prevalence of severe GH deficiency in adults in The Netherlands is approximately 175 per 1,000,000 people. The most common underlying causes of GH deficiency in adults are pituitary adenomas or the consequences of their treatment modalities such as surgery and radiotherapy. In about one quarter of the adult patients, GH deficiency is of childhood onset, and multiple pituitary hormone deficiencies are present in the majority.\(^1\) The clinical manifestations of GH deficiency in humans are variable, depending on the age of onset. GH deficiency in adults does not present with impaired growth as in childhood, but as a syndrome with specific (clinical) characteristics.\(^2\) In 1990 it was demonstrated that adult patients with GH deficiency had a decreased life expectancy due to an increased mortality from cardiovascular diseases.\(^2\) Important changes in cardiovascular risk factors, such as adverse lipid profile, increased body mass index, and hypertension in GH deficiency are reported, but also a reduced bone mineral density, exercise tolerance, muscle strength, cognitive function and quality of life.\(^2\) Since then only few studies have addressed the question whether this impaired metabolic profile leads to higher cardiovascular morbidity.\(^2\) It did tended to be increased, though more in women than in men. A gender difference has been described several times.\(^2\) Other pituitary hormone deficiencies or their replacement therapies might influence the relationship of GH deficiency with different outcome measures studied. Next to the higher metabolic burden, probably leading to more cardiovascular morbidity and mortality, it has been demonstrated that the consequence of GH deficiency in adults results in elevated direct and indirect health care costs, including increases of in-patient care, use of disability pension, and sick leave compared to the general population.\(^2\) Together, this makes GH deficiency a rare but important, complex and challenging entity to study.

**Growth hormone replacement therapy**

Until 1985, only small quantities of human pituitary GH from cadavers were available, and therefore treatment with GH was restricted to children with severe GH deficiency. In 1985, four patients who were previously treated with human GH were reported to have died of Creutzfeldt–Jakob disease.\(^3\) Treatment with pituitary GH was banned immediately. However, simultaneously recombinant human GH became available in large amounts, and as a result, GH therapy became a treatment option to consider for more patients. Subsequently, in 1995, GH treatment in adults with severe GH deficiency was approved in Europe.\(^3\) This approval was based on numerous short-term studies that have shown beneficial effects of GH replacement therapy in adult GH deficient patients.\(^3\) Only few really long-term studies have demonstrated lasting positive effects on several efficacy
measurements. Most long-term data come from observational studies, mainly post-marketing surveillance databases (KIMS Study Group and Hypopituitary Control and Complications Study (HypoCCS)), and some national registries. Data from these studies, together with a placebo-controlled crossover trial, which demonstrated deterioration of metabolic factors with ceasing GH treatment, underline the necessity of long-term treatment. However, whether GH treatment has implications for the incidence of relevant clinical endpoints, e.g. CVD, and subsequently mortality, remains to be established. Next to efficacy, more data is awaited on safety measures. In children with GH treatment more long-term and safety data is available. Few studies describe an increased incidence of secondary neoplasia or mortality risk due to bone tumors. However, other studies found no evidence for an increased risk of cancer compared to the normal population. Next, data on the effect of GH treatment on glucose metabolism in adults with GH deficiency are contradictory. It has been suggested that GH treatment may increase the risk of developing diabetes mellitus because, on the one hand, GH causes insulin resistance. On the other hand, GH treatment reduces abdominal fat mass, and therefore is proposed to have a beneficial effect on insulin resistance, and it could improve glucose homeostasis. In children who have received GH treatment in childhood the incidence of type 2 diabetes was sixfold higher than in children not treated with GH. An acceleration of the disorder in predisposed individuals is suggested. However, these findings cannot be extrapolated to adult patients as it has to be realized that children are receiving considerably higher doses of GH than adults. Adults with severe GH deficiency inject themselves subcutaneously with GH daily, with a starting dose between 0.10 and 0.30 mg/day. The maintenance dose may vary considerably from person to person and seldom exceeds 1.0 mg/day. To date, only a few studies in GH deficient adults on dose-effectiveness have been conducted. These earlier studies led to the advice to individualize GH dose instead of using a fixed dose, adopted from pediatric practice. The current guidelines on GH treatment in adults state, next to individualized dosing, that the goals should be an appropriate clinical response, avoidance of side effects, and an IGF-1 value in the age-adjusted reference range. A remark is placed saying that the used target for IGF-1 is commonly the upper half of that range, although no published studies offer specific guidance in this regard. So, scientific evidence is warranted. Since (U-shaped) associations of IGF-1, within the normal range, have been found with cardiovascular risk factors and disease in the general population, it would be interesting to investigate if this association can also be found in GH deficient adults treated with GH. Individualized and strict dosing of GH to prevent over- or undertreatment may become even more important in the near future.

The Dutch National Registry of Growth Hormone Treatment in Adults

The database used in this thesis to investigate the characteristics of GH deficiency, and efficacy and safety of long-term GH treatment in adults, is the Dutch National Registry of GH treatment in Adults. After 1985, GH was no longer scarce, and there was fear of misuse of GH in non-GH deficient patients or even the emergence of a “black market”. Therefore, the Dutch National Registry was established in 1998 as an initiative of the Ministry of Health, Welfare and Sports. In The Netherlands, only adults who met the criteria for severe GH deficiency were eligible for reimbursement of the costs of GH treatment by the health insurer. Approval of the indication for GH treatment was linked to the database, and judged by an independent board of endocrinologists. Severe GH
INTRODUCTION AND OUTLINE

Deficiency was defined according to the consensus guidelines of the GH Research Society for the diagnosis and treatment of adults with GHD, published in 1997. The insulin tolerance test (ITT) is considered to be the ‘gold standard’ to diagnose severe GH deficiency in adults. The combined GHRH-arginin test is a good alternative if ITT is contraindicated. For ITT, a peak GH response of <3 µg/l (<9 mU/L) was used to diagnose severe GH deficiency. For the GHRH-arginine test, a peak GH response of <9 µg/l (<27 mU/L) was used as cut off value. Nowadays, BMI-adjusted cut off values are proposed for the GHRH-arginin test. When two or more pituitary deficiencies are present and the IGF-1 level is below the lower reference range for age and gender, GH deficiency can be assumed, since the probability of severe GH deficiency increases with an increasing number of pituitary hormone deficits. Therefore, these patients do not require further testing.

The main goals of the Dutch National Registry were to gain more insight into long-term efficacy, safety and costs of GH replacement therapy in GH deficient adults in The Netherlands. Treatment data of all registered patients were collected (bi-)annually since 2002 from medical records by trained monitors. This included data on medical history, diagnostic procedures, medical treatments, physical and laboratory investigations, bone mineral density, concomitant medication, GH treatment, and adverse events. All data were collected on a paper case report form and checked by the same or another monitor before entry into the database and afterwards. When GH treatment was started before 1998 or the first monitor visit, patient data and data on GH treatment were collected retrospectively. This national registry is not financially supported by pharmaceutical companies, which makes it quite unique. Until 2009 almost 2900 patients were entered in the database.

The characteristics of all registered patients are presented in table 1. Table 2 shows the underlying causes of GH deficiency in the total group of patients registered in the database.

The patients registered in the database can be subdivided into three different groups, i.e. a treatment group, a primary control group and a secondary control group. Patients in the treatment group have received GH treatment until the end of follow up. Patients in the primary control group have been diagnosed with severe GH deficiency, however, for different reasons GH

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics of the total group of patients registered in the Dutch National Registry of GH treatment in Adults (adapted from: van Nieuwpoort et al. ref: 69)</th>
<th>N/mean</th>
<th>%/range</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
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</tr>
<tr>
<td>Age (years)</td>
<td>43.5</td>
<td>13.9-86.5</td>
</tr>
<tr>
<td>Sex</td>
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<td></td>
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<tr>
<td>Male</td>
<td>1475</td>
<td>51.0</td>
</tr>
<tr>
<td>Female</td>
<td>1416</td>
<td>49.0</td>
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<tr>
<td>Onset GHD</td>
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<td></td>
</tr>
<tr>
<td>CO</td>
<td>626</td>
<td>21.7</td>
</tr>
<tr>
<td>AO</td>
<td>2265</td>
<td>78.3</td>
</tr>
<tr>
<td>Hormonal deficiencies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGHD</td>
<td>311</td>
<td>10.8</td>
</tr>
<tr>
<td>MPHD</td>
<td>2580</td>
<td>89.2</td>
</tr>
</tbody>
</table>

GHD: growth hormone deficiency; CO: childhood-onset; AO: adult-onset; IGDH: isolated growth hormone deficiency; MPHD: multiple pituitary hormone deficiencies.
treatment was not started, but patient data have been collected. The secondary control group consists of patients that have been treated with GH in adulthood, but in whom treatment with GH was discontinued for various reasons during follow up. These three groups could only be defined retrospectively, since patients entered the Registry with the intention to treat with GH, or as patients for the primary control group (severe GHD without the intention to treat).

**Growth hormone hypersecretion**

A GH-secreting pituitary adenoma leads to the clinical picture of acromegaly. The prevalence of acromegaly is approximately 40 per 1,000,000 people. Symptoms and signs of GH hypersecretion can range from subtle acral overgrowth or soft tissue swelling to diabetes and cardiac failure. Visual field defects and headache, accompanying an expanding tumor, may be part of this presentation. Acromegaly is considered a serious disorder, which – if left untreated – is associated with an increased morbidity and mortality. Associations of pathologically high GH and IGF-1 concentrations with CVD, cerebrovascular disease, and diabetes mellitus are also described. Therefore, the aim of

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Non-secreting pituitary adenoma</td>
<td>898</td>
</tr>
<tr>
<td>Secreting pituitary adenoma</td>
<td>471</td>
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<tr>
<td>ACTH</td>
<td>204</td>
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<tr>
<td>Prolactin</td>
<td>189</td>
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<td>GH</td>
<td>72</td>
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<tr>
<td>FSH/LH</td>
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<tr>
<td>TSH</td>
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<tr>
<td>Craniopharingioma</td>
<td>314</td>
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<td>Radiotherapy other than for pituitary disease</td>
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<td>Congenital anomalies of the pituitary region</td>
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<tr>
<td>Sheehan’s syndrome</td>
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<tr>
<td>Non-pituitary tumor of the pituitary region</td>
<td>82</td>
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<tr>
<td>Empty sella syndrome, pituitary hypoplasia</td>
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<tr>
<td>Other</td>
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</tr>
<tr>
<td>Cystic lesion pituitary region</td>
<td>54</td>
</tr>
<tr>
<td>Head trauma</td>
<td>52</td>
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<tr>
<td>Infection pituitary gland</td>
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</tr>
<tr>
<td>Birth trauma</td>
<td>40</td>
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<tr>
<td>Genetic cause</td>
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<tr>
<td>Unknown</td>
<td>27</td>
</tr>
<tr>
<td>Meningioma</td>
<td>19</td>
</tr>
</tbody>
</table>

IGHD: isolated growth hormone deficiency; ACTH: Adrenocorticotropic Hormone; GH: Growth Hormone; FSH: Follicle Stimulating Hormone; LH: Luteinizing Hormone; TSH: thyroid stimulating hormone. Three patients had a secreting pituitary adenoma that produced two different pituitary hormones. In two patients there was combined secretion of GH and prolactin, in one patient ACTH and prolactin.
treatment for acromegaly, next to reducing or controlling tumor growth, is to normalize IGF-1 values. The treatment of choice is transsphenoidal surgery (TSS). The first pituitary surgery for acromegaly was performed in 1893 in England, while the first transsphenoidal successes were obtained in 1907 by, among others, Harvey Cushing in the United States. Nowadays, large series have shown that TSS is an effective therapy with acceptable low complication and mortality rates. One of the largest cohorts demonstrated remission rates of non-invasive adenomas of 72.2%, dropping to 21.6% for invasive adenomas. In the United Kingdom it was shown that surgical outcome varied widely between centres (20–60%) and that surgical experience was an important determinant. However, the influence of tumor characteristics, such as tumor size and extension, on surgical outcome is still unclear. Figure 4 shows the anatomical relations of the pituitary gland. Macroadenomas (≥10 mm) with cavernous sinus invasion are unlikely to be controlled by surgery alone. Magnetic resonance imaging (MRI) is now the reference standard for analysing pituitary adenomas, providing invaluable information about tumor size and extension. However, a practical classification system for accurately defining tumor size and invasiveness is needed as exemplified by the recently updated guidelines for acromegaly management.

Figure 4. Anatomical relations of the pituitary gland.

Surgery or radiotherapy as treatment modalities may be complicated by the incidence of pituitary hormone deficiencies, including GH deficiency. Ronchi et al. stated that the prevalence of severe GH deficiency is 60% in patients treated for acromegaly by surgery alone or surgery followed by radiotherapy. Because acromegaly and GH deficiency may yield adverse consequences on similar target systems, it is interesting to investigate whether post-acromegaly GH deficiency also benefits from GH replacement therapy. Only few studies have investigated the characteristics of patients with GH deficiency after treatment for GH hypersecretion and an impaired metabolic profile has been suggested. Subsequently, a positive effect of GH treatment has been demonstrated. However, contradicting results have also been published, and really long-term data are lacking.
The Highs and Lows of Growth Hormone

Various highs and lows of GH and its axis will be addressed in this thesis: GH hypersecretion and GH deficiency, high-normal versus low-normal IGF-1 target levels, but also relations of the axis with survival and morbidity, and efficacy and safety of GH replacement therapy.

The objective of this thesis was to investigate the relationship of IGF-1 with cardiovascular risk factors, morbidity and mortality in healthy elderly and in GH treated GH deficient adults. Characteristics of GH deficiency in different underlying aetiologies are described and efficacy and safety of short- and long-term GH replacement therapy has been extensively studied, including the search for the optimal IGF-1 target level during treatment. Finally, treatment outcomes of patients with GH hypersecretion have been explored. A cohort study, two large databases for epidemiological studies, and a randomized clinical trial, have been used to gain more knowledge about the rather young, complex entity of GH deficiency in adults, its treatment, and the association of GH and IGF-1 levels with different clinical endpoints. At times, when vivid discussions arise on health care costs and on drug safety, a broad scope on GH and its axis is warranted. Thereby, this thesis aims to contribute to the existing knowledge needed to provide wise, and possibly more personalized, health care in the near future.

OUTLINE OF THE THESIS

PART I contains the general introduction and outline of the thesis.

In PART II, the GH-IGF-1-axis is studied in a national representative sample of community-dwelling older persons using data from the Longitudinal Aging Study Amsterdam. Survival and age-related diseases have often been associated with the altered activity of the hypothalamic-GH-IGF axis due to natural aging. In chapter 2, the relationship of IGF-1 concentration with fatal and non-fatal CVD, cancer and all-cause mortality was studied. In chapter 3, the association of IGF-1 with (components of) the metabolic syndrome was reported and the involvement of the metabolic syndrome in the relationship of IGF-1 with CVD was assessed.

In PART III, the effect of low-normal and high-normal IGF-1 concentrations on different efficacy and safety outcome measures was studied in GH deficient adults on different GH treatment regimens for 24 weeks in a randomized clinical trial conducted at the VUmc. In chapter 4, parameters mostly used in clinical practice were studied and the lack of data on the proper target level of IGF-1 as stated in the current guidelines on GH treatment in adults was addressed. In chapter 5, the effect of low-normal and high-normal IGF-1 concentrations on cognitive function and wellbeing in men and women from the same cohort has been described. Chapter 6 focused on the effect of changing IGF-1 level on cardiovascular function with an attempt to learn more about the underlying mechanisms of the suspected contradictory relationship of both high and low levels of IGF-1 with CVD.

In PART IV, efficacy and safety of long-term GH treatment on different cardiovascular risk factors, morbidity and mortality was studied. In chapter 7, data from the Dutch National Registry of GH Treatment in Adults was used to investigate the difference in clinical presentation at the start of GH treatment, and the effect of GH treatment on cardiovascular risk factors and morbidity, in patients with isolated GH deficiency compared to multiple pituitary hormone deficiencies. In chapter 8, the effect of long-term GH treatment on mortality in the total cohort of GH deficient adults in
the Dutch National Registry was investigated. All-cause and cause-specific, e.g. malignancy and CVD, mortality rates were compared to the general Dutch population. Subsequently, in the review in chapter 9, the literature on long-term efficacy and safety of GH treatment in adult patients with GH deficiency was discussed, with particular emphasis on morbidity: fatal and non-fatal CVD and stroke, fractures, fatal and non-fatal malignancies and tumor recurrences, and diabetes mellitus.

In PART V, patients with GH hypersecretion from two different cohorts were described. In chapter 10, the surgical outcome in a group of acromegaly patients was reviewed retrospectively. These patients underwent endoscopic surgery in the two university hospitals in Amsterdam from 2001 until 2009. Patient and tumor characteristics were investigated for predictive value on initial surgical outcome. In chapter 11, using data from the Dutch National Registry of GH Treatment in Adults, the characteristics of patients with severe GH deficiency after treatment for acromegaly was described, and the safety and efficacy of long-term GH treatment with respect to cardiovascular outcomes was compared with patients previously treated for a non-functioning pituitary adenoma.

In PART VI, a summary of the presented research is provided and conclusions from this thesis are drawn and discussed. In addition, directions for future research will be provided. The thesis ends with a brief summary of the presented research in Dutch.
REFERENCES


54. Mo D, Hardin D, Erfurth E, Melmed S. Adult mortality or morbidity is not increased in childhood-onset growth hormone deficient patients who received pediatric GH treatment: an analysis of the Hypopituitary Control and Complications Study (HypoCCS). *Pituitary* 2013.


60. Newman CB, Frisch KA, Rosenzweig B et al. Moderate doses of hGH (0.64 mg/d) improve lipids but not cardiovascular function in GH-deficient adults with normal baseline cardiac function. *J Clin Endocrinol Metab* 2011;96:122-132.


5. Toogood AA, Beardwell CG, Shalet SM. The severity of growth hormone deficiency in adults with pituitary disease is related to the degree of hypopituitarism. *Clin Endocrinol (Oxf)* 1994;41:511-516.


