CHAPTER 12

Summary and general discussion of the thesis

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SUMMARY

The objective of this thesis was to investigate the highs and lows of GH. A cohort study, two large databases for epidemiological studies (Longitudinal Aging Study Amsterdam (LASA) and the Dutch National Registry of Growth Hormone (GH) treatment in Adults), and a randomized clinical trial, were used to learn more about the relationship of insulin-like growth factor-1 (IGF-1) with cardiovascular risk factors, morbidity and mortality in healthy elderly and in GH deficient adults. Characteristics of patients with GH deficiency of different underlying aetiologies were described, and the efficacy and safety of short- and long-term GH replacement therapy was extensively studied, and the optimal IGF-1 target level was investigated. Finally, treatment outcomes of patients with GH hypersecretion were explored.

In PART II, data from LASA, with a follow-up of almost 12 years, were used to study the association of IGF-1 levels with mortality and age-related diseases in a national representative sample of community-dwelling elderly. In Chapter 2, the longitudinal relationship of serum total IGF-1 concentration, divided into quintiles, with all-cause mortality, and fatal and non-fatal cardiovascular diseases and malignancies, were investigated. The lowest quintile of IGF-1 concentrations was associated with all-cause mortality compared to the middle quintile. Compared to the middle quintile, both the highest and the lowest quintile of IGF-1 concentrations were associated with a 2-fold increased risk of mortality due to cardiovascular disease (CVD). No association of IGF-1 with the development of fatal or non-fatal malignancies was found. In Chapter 3, the association of the IGF-1 concentration in quintiles with (components of) the metabolic syndrome was investigated and the role of the metabolic syndrome in the relationship of IGF-1 with developing CVD was examined in the same cohort. High-normal IGF-1 levels were associated with a higher probability of having the metabolic syndrome and the component high triglycerides, the latter particularly in women, compared to the lowest quintile. The role of the metabolic syndrome in the development of CVD was not mediator, but effect modifier. Subjects with the metabolic syndrome had the highest risk for developing CVD when having an IGF-1 level in the highest quintile, and subjects without the metabolic syndrome had the highest risk of developing CVD when having an IGF-1 level in the lowest quintile.

In conclusion, low IGF-1 levels are associated with all-cause mortality in healthy elderly. A U-shaped relationship of IGF-1 level with cardiovascular mortality was demonstrated. The metabolic syndrome was not a mediator of the U-shaped relationship with incident CVD, and the findings suggest different underlying pathophysiologic mechanisms for the association of high and low IGF-1 levels with CVD.

In PART III, the effect of decreasing and increasing GH dose to low-normal and high-normal IGF-1 target levels on different efficacy and safety outcome measures of GH treatment in GH deficient adults was investigated. An open-label, randomized clinical trial was conducted at the VUmc including 32 patients. In Chapter 4, the effect of in- or decreasing IGF-1 level on the primary outcome measures, lipids and body composition, as part of cardiovascular risk factors, next to physical performance and tolerability, was compared to establish a proper target level of IGF-1 during GH treatment. Although increasing GH dose to IGF-1 levels between 1 and 2 SDS improved waist circumference, safety was not guaranteed with the demonstrated effect on HDL cholesterol in men, and reported myalgia. In Chapter 5, the effect of in- or decreasing IGF-1 level during GH
treatment on cognitive function and wellbeing was studied. Increasing the GH dose resulted in increased vigor and impaired prefrontal memory functions in women. No effect was seen in men. In Chapter 6, the effect on (micro)vascular function and insulin resistance were investigated to further clarify the proposed different mechanisms for the relations of both low and high IGF-1 levels with CVD. Increasing IGF-1 levels was detrimental with respect to insulin resistance. The contribution of the neurogenic vasomotion domain increased in parallel, and could be explained by the favourable change in waist circumference.

In conclusion, although increasing the GH dose to IGF-1 levels between 1 and 2 SDS improved waist circumference, microvascular function and mood, safety was not guaranteed with the demonstrated effect on insulin resistance. Whether the increased insulin resistance has long-term consequences needs to be further investigated before a firm conclusion can be drawn about its contribution in the relationship between high IGF-1 levels and CVD. These results suggest that during GH treatment a “fine-tuned” intermediate IGF-1 target level may be the best option when balancing efficacy and safety outcomes.

In PART IV, efficacy and safety of long-term GH treatment on different cardiovascular risk factors, morbidity and mortality was studied using data from the Dutch National Registry of GH treatment in Adults. In Chapter 7, patients with isolated GH deficiency were compared to patients with multiple pituitary hormone deficiencies at presentation and for the effect of long-term GH treatment. Patients with isolated GH deficiency had a less impaired metabolic profile than patients with multiple deficiencies. Both entities seemed to benefit from GH treatment with respect to lipid levels and blood pressure. The risk for CVD or diabetes mellitus during follow-up was not different between these groups. In Chapter 8, the effect of GH treatment on all-cause and cause-specific mortality was investigated in all patients included in the Dutch Registry. The primary control group (untreated GH deficiency) showed a higher mortality risk compared to the fully GH treated group after 5.5 years of follow-up, suggesting a positive effect of GH on survival. Additionally, mortality rates were compared to the general Dutch population. An increased mortality rate for all-cause mortality compared to the general population was demonstrated, especially in women and with a high mortality rate due to CVD. After excluding high-risk patients with an a priori increased mortality risk independent of GH deficiency (e.g. craniopharyngioma, or other possible malignant causes of hypopituitarism), only the increased mortality rate for CVD in women remained. The mortality rate due to malignancies was not increased. In Chapter 9, in a systematic review, the literature on long-term efficacy and safety of GH treatment in adult patients with GH deficiency was discussed, with particular emphasis on morbidity. A positive effect of GH treatment on the risk for CVD and fractures, especially in men, was concluded. The effect of GH treatment on stroke was less evident, but the underlying diagnosis for GH deficiency or the amount of cranial radiotherapy might have been influencing factors. GH treatment seemed safe with respect to regrowth and recurrences of (peri)pituitary tumors, and also to fatal and non-fatal malignancies, however, follow-up was still relatively short. From the studies on diabetes mellitus no firm conclusions could be drawn.

In conclusion, data from the Dutch Registry demonstrated that GH treatment was effective despite the extension of hypopituitarism (isolated GH deficiency or multiple pituitary hormone deficiencies) with respect to several cardiovascular risk factors, and in GH deficient men with
respect to mortality rate. In women, after exclusion of high-risk patients, mortality was not different from the background population except for CVD. This gender difference, while meriting further research, was also stated in some studies included in the systematic review on efficacy, where men seemed to respond better to GH treatment than women. Despite the still relative short follow-up, GH treatment was safe with respect to regrowth of pituitary tumors or developing a malignancy or dying from it.

In PART V, patients with GH hypersecretion from two different cohorts were described. In Chapter 10, patient and tumor characteristics in 30 acromegaly patients from the two University Hospitals in Amsterdam were investigated for predictive value on surgical outcome. Next to male sex, standardised revision of preoperative pituitary MRI scans showed tumor size above 20 mm, infrasellar extension, and probable extension into the cavernous sinus, tended to be independent predictors of persistent disease after initial surgery. In Chapter 11, data from the Dutch National Registry of GH treatment in Adults was used to describe the characteristics of patients with GH deficiency after treatment for GH hypersecretion, and to study the effect and safety of GH treatment compared to patients treated for a non-functioning pituitary adenoma. GH deficient patients with previous acromegaly had an unfavourable metabolic profile, which was worse than patients in a non-functioning pituitary adenoma for most variables. GH treatment was effective with respect to lipid profile, and did not lead to more CVD during follow-up. After excluding patients using antidiabetic medication, HbA1c increased more during GH treatment in patients with previous acromegaly than in patients with a non-functioning pituitary adenoma.

In conclusion, standardised evaluation of tumor characteristics could be helpful in predicting surgical outcome in acromegaly patients, especially in addition to the rising availability of different first-line treatment options, and evolving surgical techniques. GH deficiency after treatment for GH hypersecretion is an interesting condition due to the comparable metabolic changes in both entities. Data from the Dutch Registry demonstrated beneficial effect of GH treatment. However, glucose metabolism should be monitored closely.

GENERAL DISCUSSION OF THE THESIS
The highs and lows of GH and the cardiovascular system

Both GH hypersecretion and GH deficiency are associated with an increased cardiovascular risk, and treatment, with normalization of GH / IGF-1 levels, is demonstrated to reverse this outcome. Additionally, epidemiological evidence for a link between serum IGF-1 concentration and CVD in the general population has also been repeatedly demonstrated. In line with the increased risk in patients with pathologically high or low levels of GH or IGF-1, in this thesis, a U-shaped relationship of IGF-1 level –within the normal range in healthy elderly– and cardiovascular mortality was also shown. Several population-based prospective studies have suggested that low circulating levels of IGF-1 within the normal range may predict increased risk of ischemic heart disease, and ischemic stroke. On the other hand, both low concentrations and high concentrations of IGF-1 are found to be associated with chronic heart failure. There is sufficient evidence that the GH-IGF-1 axis is involved in aging and age-related diseases through complex mechanisms. It is possible that the results reflect a causal influence of IGF-1 concentration on mortality, although it cannot be excluded that some unadjusted confounders might influence the association. This thesis presents
the first study to include the role of the metabolic syndrome in the relationship of IGF-1 with CVD. Elderly with higher IGF-1 concentrations had an increased probability on prevalent metabolic syndrome. IGF-1 levels showed the same positive association with high triglycerides in women, but not in men. In cohorts with younger subjects the common finding is an association of low IGF-1 concentration and the metabolic syndrome, whereas in cohorts with older subjects the findings are more heterogeneous. There appears to be a difference in the association of IGF-1 and the metabolic syndrome in young and older persons. However, an association of neither the metabolic syndrome, nor of the individual components, with incident CVD could be demonstrated. Excluding subjects with prevalent CVD at baseline in an elderly cohort could have led to an underestimation of the association due to a “healthy survivor” bias. The metabolic syndrome was demonstrated to be an effect modifier in the relationship of IGF-1 with CVD. Subjects without the metabolic syndrome at baseline had an increased risk in developing CVD when they had an IGF-1 concentration within the lowest quintile. Subjects with the metabolic syndrome present at baseline had increased risk in developing CVD when they had an IGF-1 concentration in the highest quintile. This underlines the hypotheses that the increased risk for CVD for both low and high IGF-1 levels, even within the normal range, should be explained by different mechanisms. In addition, it would be interesting to investigate whether these associations can be found in a large cohort of younger adults where longer follow-up will be necessary.

Including the data from the clinical trial on the effect of high-normal and low-normal IGF-1 target levels during GH treatment in GH deficient adults, hypotheses about the underlying mechanisms of the relationships of both high and low IGF-1 levels with CVD could be further explored. High-normal IGF-1 values led to protection from cardiovascular disease through reduction of waist circumference, which contributed to improvement of vascular function through regulation of the activity of the sympathetic nervous system in the microcirculation. Next, a decrease in IGF-1 level was associated with a reduction of the contribution of endothelial activity to the vasomotion, which seemed to be independent of change in waist circumference or insulin resistance, perhaps due to the decreased formation of nitric oxide. However, increasing IGF-1 level led to a rise in insulin resistance which is known to have contrasting effects on the vasomotion. Data on the effect of GH treatment in adults with GH deficiency on glucose metabolism are controversial. On the one hand, GH has an anti-insulin effect. On the other hand, GH treatment reduces abdominal fat mass, and therefore might have a beneficial effect on insulin resistance. Nevertheless, in acromegaly, insulin resistance is demonstrated despite low abdominal fat mass. Whether the increased insulin resistance found in the clinical trial described in this thesis is due to the higher IGF-1 target level, or a direct effect of increasing GH dose with a significant amount, should be further investigated. Studies with very low GH dose (0.1 mg/day) demonstrate improved insulin sensitivity without affecting body composition. Authors postulate that this effect is mediated by the ability to increase bioavailability of IGF-1 in the absence of unfavorable lipolytic effects of higher doses of GH.

Thus, a U-shaped relationship of the GH-IGF-1-axis with cardiovascular risk factors and mortality is demonstrated, and different underlying pathophysiologic mechanisms are suggested. In GH deficiency or low-normal IGF-1 levels, this mechanism of developing CVD might be related to impaired microvascular function, dependent and independent of the unfavourable changes in body composition. In GH hypersecretion or high-normal IGF-1 levels, an important interaction with insulin resistance might contribute to the mechanism.
GH deficiency and its treatment options
GH deficiency in adults is associated with adverse clinical symptoms such as an abnormal body composition, reduced muscle strength and physical performance, decreased bone mineral density, an adverse lipid profile, and impaired cognitive functioning and quality of life. Although data on mortality was very limited, a study in 1990 in adults with hypopituitarism showed that life expectancy was reduced due to CVD, and the authors suggested that this was possibly a result of the untreated GH deficiency. Treatment with GH is reported to have beneficial effects on the above-mentioned symptoms in GH deficient adults. However, long-term data on GH replacement therapy in large patient groups is scarce, especially on effect on mortality. Data from the Dutch National Registry in GH Treatment in Adults demonstrated a mortality rate during GH treatment similar to the general population in men. Also in women, after exclusion of high-risk patients, mortality was not different from the general population, except due to CVD. Mortality due to malignancies was not elevated. These findings match the results in the study with healthy elderly, where the risk of all-cause mortality was highest in persons with the lowest concentration of IGF-1, and the risk of fatal or non-fatal cancer was not associated with IGF-1 concentration. At time, several review articles on mortality during GH treatment have been published. Pappachan et al. describe in their meta-analysis that patients with hypopituitarism have an increased mortality rate, being higher in women than in men. GH replacement improved mortality rate for both genders, but only in men mortality returns to that of the background population (figure 1).

A gender difference is more often described in studies on GH deficiency, on effects of GH replacement therapy, and on GH-IGF-1-axis in healthy older people. Mostly, sex hormone levels or substitution therapy are considered accountable for the gender differences. Nevertheless, when comparing men and postmenopausal women on, for example, responsiveness to GH replacement therapy, differences are also demonstrated. More research on this particular topic is warranted.

The heterogeneous aspect of GH deficiency in adults with respect to underlying aetiologies, their treatment modalities, and other confounding factors should be taken into account when studying this complex entity. This is demonstrated in the Dutch Registry, where sex, onset of GH deficiency, age, and underlying diagnosis were distinctive factors for the effect of GH treatment on mortality. To study the effect of other pituitary hormone deficits or their substitution therapies, patients with isolated GH deficiency were compared to patients with multiple pituitary hormone deficiencies. Before start of GH treatment the groups differed with a larger waist circumference, lower HDL cholesterol, and higher triglyceride level in patients with multiple pituitary hormone deficiencies. However, a favourable effect of GH treatment was demonstrated in both. GH seemed to protect against rising lipid levels and blood pressure over a follow-up period of 4.9 and 8.4 years respectively despite the aging-related weight gain. Patients with multiple pituitary hormone deficiencies demonstrated a favourable effect of GH treatment on triglyceride level, while patients with isolated GH deficiency did not. This difference was most prevalent in women. On the one hand, women with multiple pituitary hormone deficiencies could have experienced an interaction with estrogen replacement, inhibiting the lipolytic activity of GH. But, on the other hand, women with isolated GH deficiency received lower doses of GH than patients with multiple pituitary hormone deficiencies, which could have diminished this difference in effect. Subsequently to the increase in waist circumference, HbA1c increased equally in both groups. One might have expected a larger
increase in patients with isolated GH deficiency parallel to the increase in waist circumference. However, (female) patients with isolated GH deficiency received a lower dose of GH, which might have lead to a less detrimental effect on insulin sensitivity. Also, in patients with multiple pituitary hormone deficiencies a contributing unfavourable effect of for example glucocorticoid replacement therapy on glucose metabolism has to be considered. Despite the relatively short follow-up, the risk for CVD did not differ between patients with isolated GH deficiency and multiple pituitary hormone deficiencies. The incidence of diabetes mellitus was similar to the incidence reported by Attanasio et al.\textsuperscript{33} in a large international post-marketing database, and comparable to European reference data used in that study.

Because the really important clinical endpoints are morbidities, next to mortality, and not just their surrogate markers, the long-term efficacy and safety of GH replacement therapy was broadly discussed in the systematic review. In short, a positive effect of GH treatment with respect to CVD and fractures, and safety with respect to neoplasia, could be concluded but the limitations of the study design have to be considered. The retrieved cohort and case-control studies were of fairly good quality, but eight of the 21 studies retrieved originated from two post-marketing databases (KIMS and HypoCCS). Conflicts of interest, overlap of patients, lack of important data on for instance missing data, and not always having an adequate control group, make these observational studies susceptible to bias. Ideally, a large randomized placebo-controlled trial is needed to explore the effect of GH treatment. However, when investigating morbidity and mortality, this is both unpractical and unethical.

In clinical practice it is still unclear how to dose GH and how to choose the appropriate target level for IGF-1 in adult GH deficiency. In the current clinical practice guideline on GH treatment in adult GH deficiency a recommendation for a target level of IGF-1 is not given or only supposed with no supporting scientific evidence.\textsuperscript{34} Earlier dose comparison studies have been conducted comparing the effect of low and high GH doses compared to GH deficiency at baseline.\textsuperscript{35,36} A beneficial effect
of GH treatment was demonstrated in both treatment arms with no significant difference between the groups. IGF-1 was never used as a treatment target but indirectly, correlations of IGF-1 level with several outcome measures were investigated and were not found. This thesis includes the first prospective, open-label, randomized clinical trial to compare low-normal and high-normal IGF-1 target levels on various clinical endpoints during GH treatment. Although increasing GH dose to IGF-1 levels between 1 and 2 standard deviation score (SDS) (adjusted for age and gender) improves waist circumference, microvascular function, and the patient's wellbeing, safety is not guaranteed with the demonstrated (gender-dependent) effect on cholesterol, insulin resistance, and reported myalgia. In addition, when investigating cognitive function and mood the adjustment of the GH dose in female patients also seems to have a narrow window. A dose too high may impair prefrontal cognitive functioning, while a dose too low may result in decreased vigor. An IGF-1 target level between -1 and 1 SDS seems advisable; however, more scientific evidence is still warranted for use in current clinical practice. The study design included a relative rapid increment of the GH dose which might have led to more adverse events, including insulin resistance, compared to when the GH dose is increased more gradually. Next to the relatively small sample size, which decreases the statistical power, especially when stratification for gender is necessary, an important limitation is the open-label design, in particular when investigating patient satisfaction. Future prospective studies should take this into account if possible. Unfortunately, due to the proven benefit of GH replacement therapy in adults, placebo-controlled study designs are nowadays considered unethical.

Thus, treatment of GH deficiency is demonstrated to be effective with respect to surrogate markers of CVD and mortality. The optimal treatment dose of GH should be selected individually where a high-normal target level of IGF-1 improves cardiovascular risk, but conversely could also worsen cognitive function and insulin sensitivity. The factors sex, extension of hypopituitarism, age, and underlying diagnosis influence the response to GH replacement therapy underlining a personalized approach when treating patients with GH deficiency. In contrast to the impaired glucose metabolism, the fear for an increased rate of neoplasia is not demonstrated as important safety issue of GH treatment.

**GH hypersecretion and its treatment options**

Therapies for GH hypersecretion have the aim of reducing or controlling tumor growth, inhibiting GH secretion, and normalizing IGF-1 levels. Although treatment of choice for most microadenomas and some macroadenomas, approximately 40-60% of macroadenomas are unlikely to be controlled with surgery alone (especially invasive adenomas). The success of neurosurgery is dependent upon the availability of skilled and experienced surgeons and multimodality teams. However, the influence of tumor characteristics such as size and extension on surgical outcome is still unclear. The retrospective study in this thesis evaluated predictors of surgical outcome in 30 acromegaly patients and included an overview of the literature at time specifically investigating predictive tumor characteristics for surgical outcome based on pituitary imaging. Together, when trying to specify which radiologic measurements are distinctive, the results were not conclusive. Tumor size ranging from 10 to 20 mm, extension including involvement of the third ventricle and the cavernous sinus, measured in many different ways, were all independent predictors. A standardized classification system for defining tumor size and invasiveness is needed as stated by the guidelines for acromegaly.
management, especially in a time when more alternative treatment options are becoming available for GH-secreting adenomas. First-line drug treatment, with or without primary surgical debulking, is suggested for patients with a low probability of surgical cure. Together with improvements in radiotherapeutic techniques, these developments have led to the idea of refraining from surgery in the cavernous sinus. However, alternative surgical techniques, including new endoscopic approaches to the cavernous sinus, have demonstrated positive results with low complication rates, resulting in pleas for re-evaluation of the role of surgery in the multidisciplinary approach to these invasive adenomas. Therefore, there is a need for a practical radiologic classification system, and even more; comparative studies on different first-line treatment options in these tumors are warranted.

Surgery or radiotherapy as treatment modalities for GH-secreting adenomas may be complicated by the development 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. Because of overlapping characteristics of GH hypersecretion, GH deficiency and GH replacement therapy (figure 2) this subgroup of patients in the Dutch Registry was of particular interest with respect to this thesis. GH deficient patients with previous acromegaly had an unfavorable metabolic profile comparable with, or worse than, GH deficient patient who were previously treated for a non-functioning pituitary adenoma, which could partly be explained by a longer duration of GH deficiency before commencing GH treatment. GH treatment led to a significant improvement of the lipid profile in both groups, even after excluding patients using lipid-lowering medication. Remarkably, after excluding patients using antidiabetic medication, in patients with previous acromegaly, HbA1c increased significantly more than in patients with a non-functioning pituitary adenoma. After treatment for acromegaly the insulin insensitive state characteristic for active acromegaly apparently does not recover, suggesting either a persistently increased pancreatic islet β-cell mass and / or peripheral insulin resistance. This might have preconditioned patients with previous acromegaly for a steeper increase in HbA1c during GH treatment than patients with a non-functioning pituitary adenoma. This provides another reason to monitor glucose metabolism closely during GH treatment, especially in this particular subgroup of patients with GH deficiency. During follow-up no increased risk for developing fatal or non-fatal CVD was observed. Normann et al. were the first to raise questions about safety of GH treatment in patients previously treated for acromegaly. They described three vascular events during a two year follow-up period of 10 patients with previous acromegaly while no events in patients with a non-functioning pituitary adenoma were recorded. However, two of the three events were cerebrovascular infarctions two and six weeks after start of GH treatment and both patients had received cranial radiotherapy. Therefore, whether the increased rate of vascular events was due to the impaired metabolic profile or to other patient characteristics at baseline or due to GH treatment itself was not conclusive.

Thus, in GH hypersecretion the surgical outcome can be predicted by tumor characteristics, such as size and extension. Since more first-line treatment options arise, there is a need for a practical radiologic classification system. GH treatment is effective and safe in GH deficiency after treatment for GH hypersecretion, but glucose metabolism should be monitored closely.
Strengths and limitations

Several strengths of this thesis can be identified. First, this thesis includes both epidemiological and clinical studies to explore the highs and lows of GH. For example, in a large cohort of healthy elderly, the epidemiological evidence for a link between IGF-1 and CVD is provided and further investigated by looking at the association with specific cardiovascular risk factors. The U-shaped association of IGF-1 with CVD as demonstrated in the epidemiological studies was than further explored in the clinical trial on GH treatment in GH deficient patients. Several specific cardiovascular function tests were executed to hypothesize about the possible mechanisms responsible for the association found between IGF-1 and CVD.

Second, studies in this thesis included many covariates that could be considered. Since IGF-1 levels are affected by many factors, and GH deficiency is an entity that is complex due to the co-existence with other hormone deficits or substitution therapies, these confounding factors need to be acknowledged. Next, when investigating the cardiovascular system this is also the case. Co-morbidities and co-medication are important to take into account when interpreting treatment effect on cardiovascular risk of GH replacement therapy. In the LASA study many variables have been registered and data collection was done in a standardized way and thoroughly. The Dutch National Registry of GH treatment in Adults with almost 2900 patients made it possible to describe different aspects of the complex entity of GH deficiency in adults. For a median of six years of GH treatment, patient data was recorded, including pre-treatment data. Since data collection also included co-medication, the effect of GH treatment on lipid levels, blood pressure, and glucose metabolism could be investigated taking this into account. This aspect is usually missing from other observational studies.48
And last, this thesis describes and investigates data representative for clinical practice. The cohort study with acromegaly patients from the two University Hospitals in Amsterdam assessed predictors of surgical outcome. It meets the stated lack of a practical classification system for pituitary tumors in the current clinical guideline. Also, the clinical trial with GH treated GH deficient adults was conducted to meet the lack of scientific evidence for target levels of IGF-1 in the current clinical guideline. To do this, measurements which were easy to use were chosen, and which did not rely on sophisticated techniques which can only be used in research settings. The two large databases both contain interesting subjects for clinical practice. One represented the healthy aging population and the other a substantial national cohort of GH deficient adults. The Dutch Registry is unique in its kind due to the independent nature (no finances from pharmaceutical companies) and the national coverage, including all GH deficient adults intended to treat with GH treatment. This database made it possible to look at different subgroups of interest for the endocrinologist treating these patients. The results could help to treat patients with GH deficiency more tailor-made. Additionally, the systematic review provides an overview of the literature on the most relevant outcomes for clinical practice, namely morbidities.

With all highs come lows, so also a few limitations need to be addressed. First, the use of serum total IGF-1 concentration as a marker for IGF-1 status is a matter of debate. Total IGF-1 may not fully represent the bioactive IGF-1 level and many of the immunoassays used for measuring IGF-1 are hampered by interference of IGF binding proteins (IGFBPs) remaining after extraction. The IGF-1 kinase receptor activation assay (IGF-1 KIRA) has been investigated as alternative approach. However, total IGF-1 is still the marker used in clinical practice today. Therefore, the results presented in this thesis can be extrapolated to current clinical practice.

Second, owing to the observational nature, in both the cohort study of acromegaly patients and in the Dutch Registry, data was retrieved from medical records. All available data was judged thoroughly, but availability and accuracy of the reported data depended on the attending physician and made it impossible to standardize diagnostic testing. There was a diversity of incorporated laboratory methodologies that could have influenced between-group and even within-individual analyses. And last, unfortunately, a large control group of untreated GH deficient adults was missing. When investigating the effect of GH replacement therapy on, for instance, cardiovascular risk factors it is interesting to compare to a similar cohort of untreated patients to reliably draw a conclusion on the contribution of GH treatment in preventing CVD in GH deficient adults. When the lack of improvement on a specific outcome measure in a GH treated group cannot be compared to deterioration in untreated patients, the conclusion of a beneficial effect can be missed. However, desired randomized controlled trials on long-term treatment effect and safety are both impractical and nowadays considered unethical.

Implications for clinical practice
How does this thesis contribute to current clinical practice? First, the data in this thesis contradicts the idea of GH treatment being the “fountain of youth”. High-normal IGF-1 levels in healthy elderly were not associated with the development of malignancies, nor was long-term GH treatment in GH deficient adults. However, a high-normal IGF-1 concentration did not seem to fully protect
against cardiovascular mortality. In addition, in GH treated GH deficient adults, higher IGF-1 levels (within the reference range) appeared to improve cardiovascular risk factors and function. Nevertheless, increasing the GH dose did also lead to more insulin resistance. Endocrinologists prescribing GH should be aware of these findings as strict dosing becomes even more important. Next, the heterogeneity of patients with GH deficiency should be taken into account. The underlying aetiologies of GH deficiency, extension of hypopituitarism, age, and gender seem to be important factors and treatment effect can differ individually. Both arguments underline the focus of GH treatment in adults to be more and more directed to tailor-made dosing and monitoring. In addition, more research is needed to predict which subgroup of patients with GH deficiency would benefit from GH replacement therapy and which group would less or not.

Future perspectives

As stated above, the use of serum total IGF-1 concentration as a marker for IGF-1 status is a matter of debate. Total IGF-1 may not fully represent the bioactive IGF-1 level. The IGF-1 receptor stimulating activity has been investigated as alternative marker and compared to total IGF-1 in GH deficiency and GH hypersecretion. One study evaluated the value of this new marker for monitoring GH therapy and concluded that despite normalization of total IGF-1, the IGF-1 receptor stimulating activity remained subnormal in a substantial proportion of patients. However, the consequences for clinical practice remain to be elucidated.

A beneficial effect of GH replacement therapy in adults has been demonstrated in this thesis and by others. Nevertheless, GH therapy is expensive and has potential risks. Therefore, it is becoming increasingly important to identify those patients or patient groups who will benefit most from GH replacement. This thesis described the effect of GH treatment in different subgroups, and demonstrated relevance of diverse patient characteristics (e.g. sex, age, onset of GH deficiency and underlying diagnosis) on the effect of GH replacement on mortality. Recently, Schneider et al. proposed a generalized criterion of clinical response to GH treatment using values from simple measurements, obtained from the KIMS study, and identified factors at baseline and during the first six months of treatment that could predict that proposed clinical response. This predictive model had some important limitations and needs to be validated in an external cohort. The influencing factors on GH treatment effect described in this thesis and the exploration of predictors for clinical response could be interesting new ideas for future research with data from the Dutch Registry. One of the most striking finding was the difference encountered more than once for gender. Gender is known to affect GH and IGF-1 secretory patterns in both healthy subjects as in GH deficiency or hypersecretion. However, the mechanisms are not fully understood. GH secretion is higher in healthy women than in men, whereas IGF-1 levels are similar or higher in men. Due to the proposed lower sensitivity to GH, women affected by GH deficiency and receiving oral estrogen replacements need higher GH doses than men to achieve normal IGF-1 levels. The fact that in some studies there were no differences between women with or without estrogen replacement suggests that there must be additional factors involved. More detailed investigations are needed to clarify the mechanism and more attention is needed for the described remaining increased mortality rate due to CVD during GH treatment in GH deficiency during follow-up in clinical practice. Also, more information is needed on the effect of GH treatment on different morbidities, such as CVD, diabetes,
fractures and neoplasia. Unfortunately, due to withdrawal of the health insurers data collection for the Dutch National Registry of GH Treatment in Adults was ended in 2009. If data collection in the registered patients can be restarted, follow-up will be beyond ten years which is imperative for studies on the incidence of morbidities, and more knowledge on these clinically relevant outcomes can be generated.

With respect to GH hypersecretion, next to medical treatment and new surgical approaches, new diagnostic modalities are being investigated. Prompt diagnosis and complete resection of a GH-secreting adenoma, when possible, are crucial to an optimal outcome. The hormonally active state allows GH secreting tumors to exert significant clinical phenotypic changes while small in size which challenges early detection by imaging. Nowadays, more insight is provided about the applicability of metabolic imaging with positron emission tomography (PET). With all studied labeled molecules, \(^{11}\text{C}-\text{L-methionine (MET)}\) demonstrates high sensitivity in detection of GH secreting adenomas. MET-PET scans are thought to correlate with protein synthesis, representing active hormone production by the tumor, and can discriminate active tumors from fibrosis and cysts. Combined PET/MRI in acromegaly offers great potential for disease monitoring in addition to traditional anatomic tools. However, further evolution of currently available scanning modalities and available tracers is needed to optimize use of this technology.
Concluding statements on the highs and lows of GH

- There is U-shaped relationship of IGF-1 level with CVD in healthy elderly
- Different mechanisms are responsible for the association of high and low IGF-1 with cardiovascular risk factors and disease
- During GH treatment a high-normal IGF-1 target level seems beneficial with respect to body composition and mood, but a detrimental effect on insulin sensitivity should be feared
- Long-term GH treatment is favorable with regard to mortality, CVD, and fractures
- During long-term GH treatment women continue to have an increased mortality rate due to CVD
- High-normal IGF-1 levels in healthy elderly and long-term GH treatment are safe with respect to neoplasia
- Patients with isolated GH deficiency are less metabolically impaired than patients with multiple pituitary hormone deficiencies, but both benefit from GH treatment
- Patients with GH deficiency after treatment for GH hypersecretion are more metabolically impaired than patients with a non-functioning pituitary tumor
- GH treatment for GH deficiency after treatment for GH hypersecretion is beneficial and safe with respect to CVD, but has a detrimental effect on glucose metabolism
- GH secreting pituitary tumors of >20 mm, with infrasellar extension and extension into the cavernous sinus tend to be predictors of persistent disease after transsphenoidal pituitary surgery
- Focus of GH treatment in adults should be more and more directed on “tailor-made” dosing and monitoring
- The gender difference merits further attention
- More research is needed to predict which subgroups of patients with GH deficiency would benefit from GH replacement therapy and which groups would not
REFERENCES


