Chapter 8

Summary and general discussion of the thesis
In this thesis, several endocrine disorders of the pituitary gland and/or their treatments, including thyrotrophin(TSH)-secreting pituitary adenomas (TSH-omas), adult growth hormone deficiency (GHD), growth hormone replacement therapy (GH-RT) and pituitary radiotherapy, are addressed. In addition, the possible associations of the age-related decline in the activity of the growth hormone (GH) - insulin-like growth factor 1 (IGF-1) axis with bone health and mood in community-dwelling older persons are explored.

In the following paragraphs, the main findings of the work presented in this thesis will be discussed. First, a summary of the main findings of the presented studies will be provided. Second, these main findings will be discussed and related to future perspectives for further research in a general discussion, which will also include a paragraph on methodological considerations. Finally, concluding remarks will be presented.

Summary of the main findings

In chapter 2, the long-term follow-up data of a cohort of 18 TSH-oma patients, evaluated in the VU University Medical Center (VUmc), the Academic Medical Center of the University of Amsterdam (AMC) and/or the Leiden University Medical Center (LUMC) between 1989 and 2011, were investigated, with a focus on long-term treatment outcomes. The majority of the patients had a macroadenoma with extrasellar tumor extension. Transsphenoidal surgery was performed in fourteen patients, resulting in initial postoperative clinical and biochemical remission in six (43%) patients. However, three of these patients subsequently developed recurrent hyperthyroidism. Adjuvant radiotherapy did not induce disease remission. Three patients were treated with somatostatin analogues (SSAs) only. In all three patients, the euthyroid state was achieved and maintained. One of these patients even appeared to be cured by SSA therapy \(^1\). In patients treated with pre- or postoperative SSA therapy, euthyroidism was restored, also in the long-term. During long-term follow-up, 72% of all patients received medical therapy, consisting of SSA therapy in most cases. At last follow-up, euthyroidism was present in all but one patient who refused all treatments.

In summary, the majority of TSH-oma patients, often presenting with macroadenomas and extrasellar tumor extension, required multimodality treatment, leading to adequate disease control in virtually all patients. Because of the disappointing results of pituitary surgery and radiotherapy and the excellent response to long-term SSA therapy, SSA therapy may be considered as primary...
therapy in more TSH-oma patients, especially in those harboring large macoradenomas with parasellar extension, in whom complete surgical removal is unlikely.

In chapter 3, patient characteristics and fracture occurrence, including potentially influencing factors, were investigated in adult GHD patients with previous Cushing’s disease (CD), acromegaly and nonfunctioning pituitary adenoma (NFPA), respectively, at the start of and during adult GH-RT. For this study, all adult GHD patients using ≥ 30 days of GH-RT with previous CD, acromegaly or NFPA were selected from the Dutch National Registry of Growth Hormone Treatment in Adults. Patients with previous CD (n = 180) or acromegaly (n = 65) were compared to those with previous NFPA (n = 783). At initiation of adult GH-RT, patients with previous CD had more often a history of osteopenia or osteoporosis, were younger and more often female compared to patients with previous NFPA, whereas patients with previous acromegaly had more often been treated with pituitary radiotherapy and a longer duration between pituitary tumor treatment and start of adult GH-RT. During follow-up, 3.8% of all patients had a fracture. Fracture risk did not significantly differ between the three groups during the first six years of adult GH-RT. In contrast, after six years of GH-RT patients with previous acromegaly, but not those with previous CD, had an increased fracture risk compared to patients with previous NFPA. Although further studies are needed to confirm these findings, our data suggest that patients with adult GHD due to previous acromegaly may have an increased risk of fractures during long-term GH-RT, compared to patients with adult GHD due to previous NFPA.

In chapter 4, the risk of cerebrovascular events (CVEs), secondary intracranial tumors and mortality was analyzed in a large cohort of NFPA patients who had or had not received pituitary radiotherapy. For this study, all patients from the Dutch National Registry of Growth Hormone Treatment in Adults with a NFPA were included. Irradiated (IRR) NFPA patients (n = 456) were compared to nonirradiated (non-IRR) NFPA patients (n = 350). During follow-up, 8.6% of all patients developed a CVE. The risk of a CVE was approximately three times higher in IRR men than in non-IRR men, whereas in women no such increased risk was observed. Seven patients, of which five had received radiotherapy, developed a secondary intracranial tumor during follow-up. Mortality did not significantly differ between IRR and non-IRR patients. It was concluded that pituitary radiotherapy was associated with an increased CVE risk in men. Although further research on the long-term effects of pituitary radiotherapy seems necessary, the benefits of pituitary radiotherapy should be carefully balanced against the potential risks. Long-term follow-up of IRR patients is recommended.

In chapter 5, the occurrence of tumor recurrence or regrowth in NFPA patients using GH-RT for GHD was investigated from the start of (baseline) and during GH-RT in adulthood. For this study, all NFPA patients using ≥ 30 days of GH-RT (n = 783) from
Both tumor recurrence in patients without residual tumor at baseline and tumor regrowth in patients with detectable residual tumor at baseline were defined as tumor progression. During follow-up, tumor progression occurred in 12.1% of all patients. Patients who had received radiotherapy as part of their prior NFPA treatment, had a significantly decreased risk of tumor progression compared to those who had not received radiotherapy. The presence of residual tumor at baseline significantly increased the risk of tumor progression. The tumor progression rates observed in our study were similar to or lower than those reported in NFPA patients not treated with GH-RT in literature. Although comparisons should be performed with caution, findings indicate that GH-RT does not appear to increase the risk of tumor progression in NFPA patients.

In chapter 6, cross-sectional associations between serum IGF-1 concentration and measurements of bone health, including quantitative ultrasound (QUS) and bone mineral density (BMD), were examined in community-dwelling older persons. Moreover, prospective associations between serum IGF-1 concentration and three-year change in BMD and ten-year osteoporotic fracture incidence, respectively, were studied. This study included 627 men and 656 women from the Longitudinal Aging Study Amsterdam (LASA). Measurements included baseline IGF-1 concentration, baseline QUS of the heel (consisting of broadband ultrasound attenuation (BUA) and speed of sound (SOS)), BMD of the total hip, femoral neck, total lumbar spine and total body at baseline and after three years, fracture incidence over ten years and various relevant confounders. Compared to women in the highest quintile of IGF-1 concentration, women in the lowest quintile of IGF-1 concentration had significantly lower BUA and a greater three-year decline in total hip BMD. Additionally, compared to women in the highest quintile of IGF-1 concentration, women in the combined four lowest quintiles of IGF-1 concentration had a higher ten-year fracture risk. None of these associations were observed in men. It was concluded that there appears to be a consistent gender difference in the relationship between IGF-1, bone health and fractures. Furthermore, our findings support the hypothesis that the GH-IGF-1 axis may be involved in the maintenance of bone health in older persons, particularly women.

In chapter 7, both cross-sectional and longitudinal associations between serum IGF-1 concentration and minor and major depression were investigated in community-dwelling older persons. This study included 1188 participants from the LASA study. Measurements included baseline IGF-1 concentration, minor and major depression (MDD), assessed with the Center for Epidemiological Studies-Depression Scale (CES-D) and the Diagnostic Interview Schedule (DIS) at baseline and after three years, and various relevant confounders. MDD was diagnosed according to the DIS,
whereas minor depression was defined as a CES-D score ≥ 16 but not fulfilling the criteria for MDD.

At baseline, compared to men with an IGF-1 concentration in the high-normal range, men with an IGF-1 concentration in the mid-normal range had a decreased probability of prevalent minor depression. Compared to women with an IGF-1 concentration in the high-normal range, women with an IGF-1 concentration in the low-normal range tended to have an increased probability of prevalent MDD. At three-year follow-up, no significant prospective associations were observed in men. Compared to women with an IGF-1 concentration in the high-normal range, women with an IGF-1 concentration in the mid-normal range had a decreased likelihood of developing minor depression during follow-up. In this first large population-based study examining the relationship between IGF-1 and minor and major depression in older persons, observed associations differed across the two genders. Although cross-sectional results may indicate a possible acute role of IGF-1 in depression, the inconsistency between cross-sectional and longitudinal findings suggest that IGF-1 may not play an important predictive role in late-life depression.

**General discussion and future perspectives**

**TSH-secreting pituitary adenomas**

In chapter 2, clinical, biochemical, radiological and treatment characteristics of TSH-oma patients were investigated, with a focus on long-term treatment outcomes.

The size of our study population, 18 patients, is in line with those of other published series of TSH-omas, reflecting the rarity of the disease. Although two larger studies with 70 and 90 cases, respectively, have recently been published (both in 2014), the number of diagnosed TSH-oma patients between 1990 and 2010 in a national Swedish registry study was only 28. In that same study, an increase in the incidence of TSH-omas, from 0.05 per million person per year in 1990 - 1994 to 0.26 per million persons per year in 2005 - 2009, was reported. This increase has been attributed to both improvements in diagnostic instruments and increased practitioner awareness. These factors have also been held accountable for the higher proportion of microadenomas diagnosed in more recent years.

GH and prolactin (PRL) are the most common cosecreted hormones in TSH-omas, which may be due to a shared nuclear transcription factor, i.e. Pit-1. Pit-1 is a pituitary-specific factor that plays a major role in differentiation and expression of TSH, GH and PRL. Similar to other types of pituitary adenomas (PAs), the pathogenic mechanisms leading to TSH-oma formation are largely unknown. In search of candidate genes that
may be involved in the pathogenesis of TSH-omas, the Pit-1 gene has been screened for mutations. Overexpression, but not mutation, of the Pit-gene has been observed in TSH-omas. Although based on these observations it has been hypothesized that Pit-1 may play a role in the heterogeneous hormone expression of TSH-omas as well as in cell proliferation of TSH-omas, the possible role of Pit-1 in tumor formation remains to be clarified.

The estimated average surgical cure rate of TSH-omas is around 30 - 40%, although several recent studies have reported higher cure rates of 58%, 73% and even 84%. In the study with a surgical cure rate of 84%, the success was partly attributed to more aggressive surgical resection. However, there are indications that more aggressive surgery may lead to higher complication rates.

SSA treatment has shown satisfactory results in TSH-oma patients, which is in accordance with findings in our study. In the future, the role of SSA therapy in the management of TSH-omas may be similar to the one already established in the treatment of GH-secreting pituitary adenomas. Of course, the cost-effectiveness of such a treatment, especially if long-term treatment is indicated, also has to be taken into account. A remarkable observation in our study was the achievement of apparent cure by SSA therapy in one of our patients. More studies are required to confirm this finding. Also, potential mechanisms behind these findings remain to be elucidated. Furthermore, reliable factors that could predict in which patients SSA therapy could be successfully withdrawn would have to be identified.

TSH-omas express various somatostatin receptors (SSTs) as well as dopamine receptors. In the context of a possible functional interaction between SSTs and dopamine subtype 2 (D2) receptors, combined treatment with SSAs and dopamine agonists (DAs) or with a chimeric compound that binds to SSTs as well as D2 receptors has recently received more interest. In a recent study, it was suggested that combination therapy with the already clinically available SSAs and DAs may be considered in a subset of TSH-oma patients, whereas further investigations into the new chimeric compounds are needed.

Since the first published case reports of TSH-omas in the 1960s, the number of studies on TSH-omas in literature has progressively increased. Despite this increase, much still remains to be elucidated, which is mainly due to the rarity of the disease. The observed increase in the incidence of TSH-omas in more recent years, may facilitate the collection of larger patient groups. In addition, the set-up of multicenter studies through (inter-) national collaboration may also advance scientific and clinical knowledge on TSH-omas. Studies exploring the pathogenic mechanisms leading to TSH-oma formation, may provide new insights for therapies. Also, further investigations...
of newly developed therapies, such as the chimeric compounds targeting both SSTs and D2 receptors, may improve TSH-oma management. Furthermore, although the efficacy of SSA therapy has been increasingly recognized, more research into the (very) long-term effects of SSA treatment is needed. To firmly establish the place and role of SSA therapy in the management of TSH-omas, randomized controlled trials in larger patient populations with sufficient follow-up time should be performed. Hopefully, this will be feasible in the future.

Fractures in adult GHD patients with previous CD, acromegaly and NFPA using GH-RT

In chapter 3, patient characteristics and fracture occurrence were examined in a large cohort of adult GHD patients with previous CD, acromegaly and NFPA, respectively. Both GH and IGF-1 are important regulators of bone metabolism and have the potential to modulate bone remodeling, a process continuously taking place in the highly dynamic skeletal tissue \(^24-26\). Bone remodeling, important for the maintenance of bone, is a coordinated process of coupled osteoclast-mediated bone resorption followed by osteoblast-mediated bone formation \(^26\). GH and IGF-1 may not only increase bone resorption, but also bone formation, leading to an overall increase in bone remodeling \(^24,25\). Patients with GHD have a low bone turnover and a decreased BMD, probably due to decreased bone formation \(^24-27\). Treatment of adult GHD patients with GH-RT leads to an increase in BMD if the treatment is continued for a long enough period of time \(^28-30\). Nevertheless, little is known about the risk of fractures in untreated and treated adult GHD patients \(^24,25,27,28\). The limited available data suggest that untreated GHD patients have an increased fracture risk compared to healthy controls \(^25,31-33\). Recently, a first attempt was made to prospectively assess the effect of long-term GH-RT on fracture risk in GHD adults. The Hypopituitary Control and Complication Study (HypoCCS), an international post-marketing surveillance study, found a significantly decreased annual clinical fracture incidence in GHD adults treated with GH-RT compared to GHD adults not treated with GH-RT \(^34\). Because in this study, as in other studies, the study population consisted of patients with different causes of GHD, very little is known about the potential influence of different underlying etiologies of GHD on fracture risk \(^32-36\). To the best of our knowledge, our study is one of the first to specifically explore fracture occurrence over a considerable period of time in a large group of adult GHD patients categorized according to underlying cause of GHD, i.e. acromegaly, CD or NFPA. As both acromegaly and CD are known to affect
skeletal health, adults with GHD due to (treatment of) these diseases were compared to those with GHD due to previous NFPA, thus to patients with a comparable condition.

A major finding in our study was the increased fracture risk in adult GHD patients with previous acromegaly. Active acromegaly is associated with increased bone turnover. Although the effect of this increased bone turnover on bone mass remains controversial, acromegaly has been associated with an increased vertebral fracture risk, even after biochemical control of the disease. The reason for this possible increased fracture risk is unclear, but it has been speculated that the microarchitecture of bone, particularly trabecular bone, may be negatively affected by GH excess, leading to an increased fracture risk. As severe GHD has also been associated with increased fracture risk, it may hypothesized that the combined deleterious effects of longstanding GH excess and GHD on bone homeostasis in adult GHD patients with previous acromegaly may cause the observed increased fracture risk. As acromegaly is an insidious disease that may be difficult to diagnose, the GH excess associated with the disease may exist for a long time. Moreover, following treatment of acromegaly, GHD may remain undiagnosed for a considerable time, which for instance may be due to decreased physician awareness of GHD in patients with previous acromegaly.

Many aspects regarding adult GHD, underlying causes of adult GHD, GH-RT and bone health remain open for further investigations. The possible protective effect of GH-RT on fracture risk in adult GHD patients in general still has to be confirmed, as previous studies have shown several limitations such as a short follow-up time, a retrospective design, a heterogeneous study population or no hard clinical endpoints. A prospective randomized controlled clinical trial, comparing a homogenous population of adult GHD patients with GH-RT to those without GH-RT on fracture incidence may provide definite answers, but has not yet been performed. However, ethical and practical constraints complicate the performance of such a trial. More data from large prospective observational studies, using clinical endpoints instead of surrogate markers such as BMD, may provide a useful alternative.

Furthermore, as mentioned above, data on long-term fracture risk in adult GHD with previous acromegaly or CD are lacking. To enhance our knowledge on these specific patient groups and to optimize their treatment, further research on the long-term effects of GH-RT in these patients is required. More long-term studies are needed to confirm our findings. Also, a study specifically investigating vertebral fracture incidence with systematic radiological imaging in GHD patients with previous acromegaly would be informative. In addition, pathophysiological mechanisms underlying impaired bone health in GH excess and GHD remain to be elucidated.
Long-term safety of radiotherapy for NFPA

In chapter 4, the occurrence of CVEs, secondary intracranial tumors and mortality were analyzed and compared between NFPA patients who were or were not treated with pituitary radiotherapy.

In a considerable proportion of NFPA patients, especially in those with large macroadenomas expanding into the cavernous sinus, complete surgical removal may not be accomplished. In these patients as well as in patients with tumor recurrence, pituitary radiotherapy may offer an effective treatment option to induce tumor control. Nevertheless, radiotherapy is nowadays less frequently used than previously, which is probably due to improvements in surgical and imaging techniques. Furthermore, fear of long-term side effects of radiotherapy probably has also limited its use. Therefore, the optimal use of radiotherapy in the management of NFPPAs is still a matter of debate. By far the most common long-term side effect of pituitary radiotherapy is hypopituitarism, which has been attributed to direct damage to pituitary cells, vascular damage eventually leading to cell death and hypothalamic damage. The loss of anterior pituitary hormones following radiotherapy appears to occur in a classical pattern with GH being the most radiosensitive, followed by luteinizing hormone (LH)/follicle-stimulating hormone (FSH), adrenocorticotropic hormone (ACTH) and TSH. New hormonal deficiencies may develop up to 20 years after radiotherapy. In our study, an increased CVE risk was observed following pituitary radiotherapy, which is accordance with most, although not all, data in literature. Although the pathophysiology of this increased risk remains to be clarified, radiation-induced effects on the cerebral vasculature probably play a role. Following radiotherapy, various effects have been described in the microvascular bed, including increased capillary permeability, dilatation, telangiectasia, occlusion and ischemia leading to necrosis and compensatory endothelial cell proliferation. In medium and larger blood vessels, radiation insult mainly leads to occlusion, due to atherosclerotic processes.

Pituitary radiotherapy aims to deliver an effective radiation dose to tumor tissue, while at the same time minimizing the dose to normal surrounding tissue. In the last decades, several new radiation technologies have been developed. Conventional radiotherapy, the ‘oldest’ radiation technique, is delivered in multiple, usually daily, small doses over a period of weeks. The more recently developed stereotactic radiation techniques enable more precise tumor localization and radiation dose delivery, thereby achieving a steeper dose gradient between the tumor and normal surrounding tissue. Stereotactic radiotherapy may be either delivered in a single dose, which has been termed stereotactic radiosurgery (SRS), or in multiple
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doses, which is referred to as fractionated stereotactic radiotherapy \(^{45,47}\). Because the delivery of a single high dose, instead of the equivalent dose in multiple fractions over time, is potentially more toxic to tumoral tissue as well as normal tissue, SRS is reserved for patients with small tumors not located nearby critical structures \(^{43}\). In contrast, fractionated radiotherapy modalities are suitable for all sizes of PAs as fractionation of the total dose lowers radiation toxicity. Currently, randomized controlled trials comparing the efficacy and safety of newer and older radiation techniques are lacking. Indeed, for all radiation techniques, including conventional radiotherapy, there is a paucity of prospective randomized studies \(^{45,47}\). This is not surprising, given the ethical implications of withholding radiotherapy in patients with large postoperative tumor remnants and the general difficulties related to conducting studies in patients with a disease with a long natural history \(^{47}\). As a result, most evidence comes from nonrandomized retrospective studies and systematic reviews of these studies. Although these provide useful information, they likely suffer from selection bias \(^{45}\). Furthermore, difference in follow-up time and study endpoints also complicate the comparison of studies. Despite these limitations, overall evidence suggests that, compared to conventional radiotherapy, the newer radiation techniques, especially the fractionated techniques, appear to have a similar efficacy in terms of tumor control and a similar or even lower occurrence of hypopituitarism \(^{54}\). However, it is not clear whether the latter is due to shorter follow-up time or a true reduction in toxicity \(^{45,54}\).

In the future, more follow-up data regarding the overall safety of radiotherapy in the very long term are awaited, as current evidence suggests that symptoms and signs of radiation toxicity may manifest even years after the radiotherapy has taken place. Because it is unlikely that long-term prospective, randomized controlled trials comparing IRR and non-IRR NFPA patients will be performed, large observational studies, such as the Dutch National Registry of Growth Hormone Treatment in Adults, will be of great value to assess these long-term risks. In addition, more investigations on the relationship between pituitary radiotherapy and cerebrovascular disease are required. Especially underlying mechanisms of this relationship, such as radiation-induced vascular damage, have to be further elucidated. Furthermore, the long-term effects of the newer radiation techniques have to be assessed, as these may possibly reduce the risk of adverse events. In addition, the exact time and place of radiotherapy, especially of these newer techniques, in the treatment algorithm of NFPAs remain interesting subjects for further research.

Tumor recurrence or regrowth in NFPA patients using adult GH-RT

The development of tumor progression in NFPA patients using adult GH-RT for GHD was investigated in chapter 5.
As it has been hypothesized that GH-RT may stimulate tumor formation or growth, some concerns have been raised about the long-term safety of GH-RT \textsuperscript{55-57}. This may be particularly relevant for NFPA patients because postoperative tumor remnants and tumor recurrence are frequently encountered in these patients\textsuperscript{41,58}. The hypothesis that GH and IGF-1 may affect tumor growth is partly based on observations from experimental studies, demonstrating the potentially mitogenic, proliferative and antiapoptotic properties of GH and IGF-1, and making the involvement of the GH-IGF-1 axis in tumor development plausible \textsuperscript{55,57,59-63}. However, these findings from animal studies may not be directly translated to the human setting \textsuperscript{55}.

Studies in the general human population examining the possible association between IGF-1 concentration and cancer have shown variable results. In a systemic review and meta-regression analysis of epidemiological studies, it was concluded that high-normal IGF-1 concentrations are associated with various types of common cancers, such as prostate and breast cancers, but associations were modest and variable between sites \textsuperscript{64}. In addition to epidemiological studies in the general population, studies in patients with acromegaly may also provide more insight, as acromegaly represents a 'natural' model to study the effects of high GH and IGF-1 concentrations. In acromegalic patients, increased risks of colonic polyps and possible colorectal cancer have been described \textsuperscript{65,66}. However, the effects of the pathologically increased GH and IGF-1 concentrations in acromegalic patients, may not be directly compared with those in adult GHD patients treated with GH-RT, as GH-RT aims to achieve physiological IGF-1 concentrations. More evidence on the long-term effects of GH-RT comes from studies in GHD children treated with GH-RT. Previous beliefs of an increased risk of leukemia in these patients, were not confirmed in subsequent studies \textsuperscript{67,68}. Recent studies indicate that, although specific populations may be at increased risk, the overall safety profile of GH-RT in children is favorable \textsuperscript{68-70}. Likewise, studies in adult GHD patients using GH-RT suggest that the risk of fatal and nonfatal malignancies is not increased, but with the caveat that longer follow-up studies are needed \textsuperscript{71-77}. In a recently published report from the HypoCCS, the risk of breast, prostate or colorectal cancer, was not increased in GHD adults treated with GH-RT in comparison to the general population or untreated GHD adults. Moreover, the recurrence rate of PAs did not differ between untreated and treated GHD patients. However, the study population included patients with different etiologies of GHD \textsuperscript{78}.

In our study, the effect of GH-RT on tumor progression was specifically investigated in NFPA patients only. Our findings support those of other studies examining this specific patient group, that GH-RT does not appear to increase the risk of NFPA tumor progression \textsuperscript{79-81}. Nevertheless, the biological growth behavior of NFPAs is variable and difficult to assess, partly because a fully reliable biochemical or histopathological
predictor for NFPA growth has not yet been identified. It has been suggested that ‘silent corticotroph adenomas’, i.e. adenomas immunohistochemically expressing but not biochemically or clinically overproducing ACTH, tend to behave more aggressively \(^{41,82}\). Many other potential markers have also been examined, but with disappointing results. A marker that has frequently been investigated in NFPAs is Ki-67, a nuclear antigen expressed by proliferating cells. Although Ki-67 labeling indices have proved useful in predicting clinical and biological behavior of several tumors, results in NFPAs are conflicting \(^{82-85}\).

Despite the generally encouraging data with regard to tumor recurrence or regrowth in NFPA patients treated with GH-RT, more long-term follow-up data, ideally from prospective comparative studies, are needed in the future to draw more robust conclusions. Unfortunately, ethical and practical constraints severely compromise the performance of prospective randomized controlled studies. Thus, hopefully more follow-up reports of large surveillance studies will emerge in literature. In addition, because nowadays lower GH dosages are being used in adult GHD patients than in earlier years, it would be interesting to study the safety profile of GH-RT in more recently treated patients. It may be expected that the number of adverse events will be lower. Also, further research aiming at the identification of a reliable prediction marker for NFPA biological behavior would be of great value to guide important treatment decisions in the management of NFPA patients.

The ‘somatopause’ and bone

In chapter 6, the cross-sectional associations of IGF-1 with measurements of bone health, including QUS and BMD, as well as the longitudinal associations of IGF-1 with three-year change in BMD and ten-year fracture risk, respectively, were studied in community-dwelling older persons. Only few other studies have explored the relationship between IGF-1 and QUS measurements \(^{86-88}\). BMD is more widely used because it is currently considered one of the main determinants of osteoporotic fracture risk. However, it has been suggested that the skeletal fragility associated with osteoporosis may not only be dependent on bone density, but also on bone microarchitecture \(^{88}\). Dual X-ray absorptiometry (DXA), used to measure BMD, may not assess bone microarchitecture as well as QUS \(^{89}\). QUS techniques were introduced in the mid-1980s, based on earlier observations that when sound waves travel through bone, the patterns of the waves are modified by various characteristics of bone such as elasticity, stiffness, volume and density \(^{89,90}\). The properties of bone alter the shape, intensity and speed of the sound waves that are used for QUS measurements, which are therefore expressed in terms of velocity (SOS) and attenuation (BUA) \(^{91}\). Assessment of QUS has several advantages over DXA,
because QUS scanners are transportable and do not involve radiation, which makes them usable outside hospitals. Additionally, QUS measurements are less expensive and generally less time-consuming. These advantages may be particularly useful for population-based studies in older persons. Nevertheless, QUS is currently not widely used in clinical practice, partly due to the absence of standardization. As a consequence, QUS measurements acquired on machines from different manufacturers cannot easily be compared.

In line with the hypothesis that the ‘somatopause’ contributes to osteoporosis and osteoporosis-related fractures, it has been suggested that GH and IGF-1 may serve as therapeutic agents in the prevention and treatment of osteoporosis. Currently, the medical treatment of osteoporosis mainly relies on agents with primarily antiresorptive properties, such as estrogens and bisphosphonates. The development of agents with anabolic properties that stimulate bone formation could be of additional value. In that regard, GH and IGF-1 have received considerable interest. A landmark study published by Rudman et al. in 1990, 12 healthy older men treated with recombinant GH for six months were compared with 9 healthy older men not treated with GH-RT. Although BMD of the radius or femur did not significantly change, lumbar BMD significantly increased in the treatment group. After publication of this report, several other studies have consistently demonstrated that GH treatment increases markers of bone formation and resorption in younger and older healthy persons with or without osteoporosis. In contrast, the effects of GH on BMD are heterogeneous in different studies, which may be due to short follow-up times of most of these studies. In a recent follow-up of a double-blind placebo controlled study including 80 women with postmenopausal osteoporosis who had been treated with GH or a placebo, it was concluded that GH treatment was beneficial for bone and fracture outcomes. Several studies have explored the effects of recombinant IGF-1 on bone. One study reported that recombinant IGF-1 in combination with insulin-like growth factor-binding protein 3 (IGFBP-3) was well tolerated and showed beneficial effects on bone mass, muscle strength and functional ability in osteoporotic patients with a recent hip fracture. Others have described increased markers of bone turnover during IGF-1 treatment in healthy older or osteoporotic persons, but the clinical relevance of this finding remains to be established.

In the future, research could focus on the possibilities of QUS measurements in daily clinical practice. First of all, a method enabling comparison of QUS measurements derived from different machines from different manufacturers has to be developed. Furthermore, more studies with a longer follow-up duration are needed to assess the predictive value of QUS on long-term fracture risk. Additionally, the possible place of QUS in fracture risk assessment in clinical practice has not yet been fully
established. For instance, it has been suggested that QUS may be used alone or in conjunction with DXA for fracture risk assessment in subgroups of patients, such as elderly women or men. With regard to GH or IGF-1 administration for prevention or treatment of osteoporosis, more research is needed to conclude whether this is safe and effective in older persons with or without osteoporosis. Although an association between low-normal IGF-1 concentration and osteoporosis has been observed in several large epidemiological studies, clinical implications of this finding are still unclear. Result from studies investigating GH and/or IGF-1 administration in older persons or persons with osteoporosis appear encouraging, but follow-up times were usually short. In addition, in several studies side effects, such as soft tissue edema were observed. Possibly, combined treatment with antiresorptive agents may have favorable effects, but future research is clearly needed to investigate the possibilities of GH and/or IGF-1 treatment in osteoporosis management.

The ‘somatopause’, mood and longevity

In chapter 7, cross-sectional as well as longitudinal associations between IGF-1 and prevalent and incident minor and major depression were investigated in community-dwelling older persons.

Although many environmental and biological causes have been related to depression, to date the etiology of depression remains elusive. Throughout the years the understanding of depression has gradually evolved. The initial observation that symptoms of depression can be alleviated by agents that increase the synaptic concentrations of monoamines led to the so called ‘monoamine hypothesis of depression’, which proposes that deficiencies in serotonin, norepinephrine and/or dopamine levels, form the basis of depression. Although this hypothesis has been of great importance for the understanding and management of depression, it does not seem to provide a complete pathophysiological explanation. It has been suggested that more complex neural mechanisms, such as neurodegeneration or aberrant neuronal network functioning, may also be involved. According to the so called ‘neurotrophic hypothesis of depression’, reductions in the expression and function of growth and/or neurotropic factors may contribute to the development of depression. One of the factors that has received scientific attention in that regard is IGF-1, as the GH-IGF-1 axis influences several important processes such as neuronal growth, differentiation and maturation, and has shown neuroprotective properties.

Most evidence concerning the potential involvement of IGF-1 in depression comes from animal studies, indicating that depression is associated with decreased IGF-1. However, to date only few studies have been conducted in humans, with heterogeneous
results. Indeed, to our knowledge, our study is the first to prospectively investigate this potential relationship in community-dwelling older persons. Nevertheless, based on the results from previous nonhuman studies, the question whether IGF-1 may exert antidepressive effects has been addressed in literature. Administration of IGF-1 has been tested in several animal models of depression, with consistent positive results. In line with these findings, intranasal administration of IGF-1 in humans has been discussed as a plausible treatment option of depression in a recent review, proposing the set-up of clinical trials. However, based on clinical evidence so far this seems preliminary.

The observations that adult GHD and normal aging share phenotypic similarities, that GH and IGF-1 secretion decrease with advancing age, and that GH-RT has beneficial effects in GHD adults, have prompted the question whether GH administration in healthy older persons may reverse or prevent symptoms and signs associated with normal aging. In the first clinical report addressing this question, the aforementioned study by Rudman et al., it was postulated that the effects of six months treatment with GH were equivalent in magnitude to changes incurred during 10 to 20 years of aging. Results of this study elicited an enormous general interest in GH as an antiaging drug. Since then, a number of clinical studies have investigated this subject. A recent systematic review of randomized controlled clinical trials evaluating GH therapy in healthy elderly, concluded that GH minimally alters body composition, but does not improve other clinically relevant or functional outcomes in healthy elderly. Furthermore, persons treated with GH were more likely to experience side effects such as soft tissue edema and arthralgia than nontreated persons. In addition, no study included in the analysis lasted longer than one year. Thus, based on the available evidence so far, administration of GH as an antiaging therapeutic in normally aging persons does not seem indicated. Indeed, it has been questioned whether GH administration in healthy older persons may not even be deleterious rather than beneficial for human lifespan. This hypothesis is based on results from studies in various species showing that decreased GH or IGF-1 signaling leads to extended longevity. Numerous studies have found that mice with mutations causing reduced activity of the GH-IGF-1 axis have an increased lifespan compared to controls. These data led to the suggestion that lowering GH concentrations could possibly slow the aging process in humans. Nevertheless, so far data concerning the role of the GH-IGF-1 axis in longevity in humans are scarce and inconclusive.

In the future, many aspects regarding the etiology and pathophysiology of depression in general, and the potential involvement of the GH-IGF-1 axis in depression in particular, remain to be elucidated. Despite the reasonable body of evidence linking
the GH-IGF-1 axis to mood in animals, data from human studies are scarce. Therefore, more prospective observational studies in humans are needed. Although basic studies indicate a potential antidepressive effect of IGF-1, research on the antidepressive effects of IGF-1 administration in humans seems preliminary at this point. Furthermore, the possible influence of the GH-IGF-1 axis in the normal aging process in humans remains to be established. Altering GH concentration to slow or reverse aging in healthy older persons cannot be recommended before more studies have elucidated the mechanism through which GH and IGF-1 affect aging. In addition, more clinical long-term data are required to conclude whether long-term GH administration or inhibition of GH action is effective and safe in older persons.

Methodological considerations

A large part of the data presented in this thesis were derived from two large cohort studies: the Dutch National Registry of Growth Hormone Treatment in Adults (chapters 3, 4 and 5) and the Longitudinal Aging Study Amsterdam (chapters 6 and 7). Below several limitations of these studies will be addressed.

The Dutch National Registry of Growth Hormone Treatment in Adults

Although the Dutch National Registry of Growth Hormone Treatment in Adults has many strengths, one of its major limitations is the retrospective and nonrandomized design, which is inherent to the observational nature of the study. Treatment decisions, such as whether or not a patient would receive radiotherapy, were made by the physicians of the patients and therefore likely subject to selection bias. In addition, due to the low number of patients without GH-RT in the database, comparisons between adult GHD patients with or without GH-RT could not be made. As mentioned before, conducting a prospective randomized controlled clinical trial in these patients is unfortunately difficult due to practical and ethical constraints. Currently, many data on the long-term effects of adult GH-RT are based on two large observational international databases, i.e. the HypoCCS and the KIMS database (Pfizer International Metabolic Database). In that context, our nationwide financially independent database is of great additional value.

The Longitudinal Aging Study Amsterdam

The Longitudinal Aging Study Amsterdam is an ongoing multidisciplinary cohort study in which many data regarding emotional, cognitive, physical and social functioning of community-dwelling older persons are collected. Despite this large amount of collected data, one major limitation with regard to the studies presented in this thesis is the lack of information on bioactive IGF-1 concentration. Only total serum IGF-1 was measured,
whereas most IGF-1 is bound to IGF-binding proteins (IGFBPs) in the circulation. These IGFBPs may modulate the bioactivity and availability of IGF-1. In addition, local tissue IGF-1 concentrations, for instance in bone or brain, were not measured. However, with current available techniques these types of measurements are difficult to perform and unpractical in such a large population-based study in which so many data are collected.

A general concern of studies including participants with an older age is attrition. In LASA, attrition has mainly been due to mortality. However, this does not necessarily influence the representativeness of the study sample as mortality also occurs in the general older population.

**Concluding remarks**

In this thesis, several endocrine disorders of the pituitary gland and their associated treatments as well as the possible relationships between the 'somatopause' and bone health and depressive disorders, respectively, were investigated.

First, it can be concluded that TSH-omas still are rare tumors, despite the reported increase in incidence in recent years. Multimodality treatment is often required, but results in clinical remission in virtually all TSH-oma patients. Although pituitary surgery is still considered the treatment of first choice, surgical outcomes are heterogeneous. In contrast, SSA therapy shows a high efficacy. SSAs may therefore be considered as first-line therapy in selected TSH-oma patients, especially in those with large adenomas and parasellar extension.

Second, an increased fracture risk was observed in adult GHD patients with previous acromegaly, but not in those with previous CD, compared to those with previous NFPA. Our study is one of the first to find this increased fracture risk in patients with previous acromegaly. More studies are required to clarify this finding.

Third, an increased risk of CVEs was demonstrated in IRR men compared to non-IRR men in a large cohort of NFPA patients. In contrast, secondary intracranial tumors and mortality were not associated with radiotherapy. As our data suggest an increased risk of CVEs following pituitary radiotherapy, a careful assessment of the risk versus benefit profile should be performed in NFPA patients. Long-term follow-up of NFPA patients who have received radiotherapy is required.

Fourth, tumor progression occurred in 12.1% of NFPA patients using long-term GH-RT for adult GHD. The risk of tumor progression was decreased by previous pituitary radiotherapy, but increased by the presence of residual tumor. Although more long-term follow-up data are needed, our findings support the current view that adult GH-RT is safe with regard to tumor progression in NFPA patients.
Fifth, low-normal IGF-1 concentrations were associated with lower BUA, greater three-year decrease in total hip BMD and increased ten-year fracture risk in community-dwelling older women, but not in community-dwelling older men. Although these findings support the hypothesis that the GH-IGF-1 axis influences bone health in older persons, especially women, clinical implications are uncertain.

Finally, several associations, which differed across the two genders and over time, were observed between serum IGF-1 concentration and prevalent and incident minor and major depression. As our study was, to our knowledge, the first to examine these associations in community-dwelling older persons, further studies are needed to investigate the seemingly complex relationship between IGF-1 and late-life depression.
References


Summary and general discussion


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Summary and general discussion


