Chapter 7

Discussion and summary
Introduction

The clinical approach to new patients in internal medicine proceeds according to a standard diagnostic sequence, before therapy can be instituted. This clinical process starts with a detailed medical history, followed by physical examination. Additional investigations, like laboratory and/or radiological tests, are based on the differential diagnosis made after these first steps. The results of these diagnostic tests enable to confirm the initial diagnosis or to limit the initial differential diagnosis. Sometimes additional tests are required. Finally, based on the principles of evidence-based medicine the patient will receive appropriate treatment. Unfortunately, this clinical approach is not always perfect and doctors need to know the imperfections of the diagnostic and therapeutic approaches. In this thesis some of these imperfections of the diagnosis, treatment and follow up are discussed, with a focus on clinical conditions characterized by growth hormone excess or -deficiency.

Acromegaly

Patients with acromegaly can only be cured by successful trans-sphenoidal surgery. However, this procedure cures only ~60 % of the patients with acromegaly. Moreover, during long term follow up of these initially cured patients, the disease may reoccur, resulting in an overall long term cure rate of only 40-50 %. Patients with persistent recurrent acromegalic disease require additional treatment to prevent increased morbidity and mortality. These additional treatments consist of somatostatin analogues, a growth hormone receptor antagonist, or radiotherapy. Several questions have not been resolved in detail. When is such operation successful? What are the criteria to decide that abnormal growth hormone secretion is well controlled? Which patients require adjuvant therapy? What is the relevance of discrepancies between GH and IGF-I levels? With respect to this last issue, several studies have demonstrated discrepancies between IGF-I and GH levels after surgery. For instance, one study showed that 19 % of the patients had
normal GH levels but high IGF-I, and 8% of the patients had elevated GH but normal IGF-I. In the group of patients with normal GH levels but high IGF-I another study showed that 50% had a normal glucose-mediated GH suppression after glucose tolerance test according to the current criteria.

Mortality studies showed that the control of GH hypersecretion leads to a mortality risk, that is not different from the normal population. Based on these studies the biochemical goals of treatment of acromegaly have been defined: random GH levels should be < 2.5 µg/L, the nadir GH levels during OGGT nadir should be < 1 µg/L and/or IGF-I levels should be in the normal range of age- and sex matched controls. The use of the mortality studies to define the criteria for well-control of GH excess has definite limitations. During the long term follow up required in these mortality studies, there is a lot of change in treatment modalities, e.g. better medication, change to more sensitive assays, loss of data, which influence the interpretation of the results. Therefore, the outcome of treatment in mortality studies is a reflection of older treatment modalities confounded by newer developments. Another problem is that these mortality studies used different biochemical parameters, e.g. random or postabsorptive GH measurements, GH levels after OGTT, and IGF-I levels, which make the comparison between the different studies not always straightforward. Also most studies used last known biochemical data what results in selection bias, because the subjects with the longest follow up will have the lowest biochemical parameters.

Somatostatin therapy is currently an accepted medical treatment used as adjunctive treatment after initial transsphenoidal treatment. Several studies have also advocated somatostatin analogues as primary treatment. In both conditions somatostatin analogues are effective in controlling GH excess in ~60% of the patients, according to the criteria derived from the mortality studies. At present two somatostatin analogues with slow release modalities are available: octreotide LAR and lanreotide Autogel. Instead of the parabolic increase of octreotide levels seen during 4 weeks after subcutaneous injection with octreotide LAR, lanreotide has a more log-linear decrease of its levels during 4 weeks after its
intramuscular injection. In chapter 2 a comparison was made between these two long acting depot preparations with respect to their ability to suppress GH levels in one group of well-controlled acromegalic patients. Both analogues have almost the similar binding capacities to somatostatin receptor subtype 2 and to a lesser extent to subtype 5. We used two different approaches to compare the efficacy of both methods. First, we measured mean fasting GH levels and IGF-I levels at 2, 4 and 6 weeks after injections of the analogues. Secondly, 24 h GH secretion profiles were compared at 4 weeks after administration of each analogue. There were no major differences between the effects of both analogues on GH levels or IGF-I concentrations. Although the number of subjects included in the study was limited, the detailed analysis of GH dynamics support the emerging notion that there are no major differences in efficacy between both somatostatin analogues, despite the difference in pharmacokinetics.

Although the patients described in chapter 2 were well controlled during treatment with somatostatin analogues according to accepted criteria, the study described in this chapter also showed that patients have persistently high GH levels during 24 h. This indicates that the definitions of biochemical control of GH excess derived from mortality studies should not be equated with normalization of GH secretion. In contrast, normalization of GH secretion occurs after successful transsphenoidal surgery. The question arises to what extent the subtle abnormalities in GH secretion that persist during somatostatin treatment translate into biological effects.

Adequate control of GH excess, employing the criteria derived from the mortality studies, normalizes the reversible manifestations of acromegaly such as sweating, carpal tunnel syndrome, diabetes mellitus, dyslipidemia, and soft tissue swelling. The problem with such parameters is, however, that they cannot easily be quantified by clinicometric or other methods. Therefore, in clinical practice we mostly rely on the effects of treatment on biochemical parameters (GH and IGF-I).

With respect to the heart, control of GH excess has clear effects, reflected
in a decrease of the increased left ventricular mass, improvement of systolic function at exercise and diastolic function. We wondered whether we could use the heart as a biomarker to compare the effects of different treatment modalities of GH excess in patients, who were well controlled for GH excess. Therefore, in chapter 3, we compared cardiac function between acromegalic patients cured by transsphenoidal surgery, acromegalic patients well controlled by somatostatin analogues, still active patients despite somatostatin analogues and de novo acromegalic patients prior to any treatment. We assessed cardiac parameters, using tissue Doppler assessment. The study showed that diastolic function was improved in patients who were no longer exposed to active disease. However, patients well- controlled by treatment with somatostatin analogues still had impaired diastolic function, indicating persistent effects of GH excess. This observation was present during tissue Doppler imaging, but not during conventional echographic assessment, reflecting the improved sensitivity of tissue Doppler imaging for detecting subtle differences in diastolic function. The clinical relevance of this subtle diastolic impairment is presently unclear. This was one of the first studies that differentiated patients with biochemical control of GH excess by dividing this group in well controlled and cured patients. By using a new technique to assess diastolic function we proved that some acromegalic patients well controlled according to the current biochemical criteria, derived from the mortality studies, still have slightly active disease. However, these patients had no other clinical symptoms and the clinical relevance of our observation for patient care is at present uncertain. Nonetheless, the observations in chapters 2 and 3 indicate, that the standard approach of the internist, proceeding from medical history, physical examination and appropriate diagnostic tests, fails to detect subtle, but persistent disease both with respect to biochemical parameters and with respect to the subtle effects on the heart.

During the studies described in the present thesis, we made an interesting observation. Although acromegaly was known from 1886, and cardiovascular disease plays an important role in the increased morbidity and mortality rate associated with acromegaly, it was astonishing to
conclude that there was hardly any documentation of the effects of GH excess on the function of the cardiac valves. We stumbled upon this question, when several of our patients had documented insufficiencies of the mitral and/or aortic valves. Despite long term follow up studies and many studies involving echocardiography there was no notion of a relation between acromegaly and cardiac valve disease. In chapter 4 we compared the prevalence of cardiac valve disease in acromegalic patients and matched controls. Therefore, we performed echocardiography in 40 patients with cured, well-controlled disease, or active acromegaly to assess if there was any valvular insufficiency compared with 120 healthy controls, matched for age, sex, blood pressure, and left ventricular systolic function. The prevalence of significant valvular insufficiency was more than threefold increased in the group of the acromegalic patients (22 % vs. 6.7 % in controls). Pathological aortic valve regurgitation was present in 20 % of the patients present compared with 4 % of the controls. Pathological mitral regurgitation was only present in 5 % vs. 0 % in controls. Interestingly, none of the patients with valvular insufficiency had symptoms or were previously known to a cardiologist. Nonetheless, the regurgitation found had clinical significance, according to the participating cardiologists. A longer duration of exposition to GH excess was associated with an increased prevalence of valvular insufficiency. We postulate that the damage that occurred to the cardiac valves is irreversible, in contrast to some other manifestations of acromegaly. This is based also on the histological examination of one of the valves obtained from an acromegalic patient after cardiac surgery. In conclusion, there is a high prevalence of valvular regurgitation in acromegalic patients, which most likely depends on the duration of GH excess. Apparently, the standard approach of the internist including medical history and physical examination has failed to detect this important complication of acromegalic disease in the 120 years after this disease was initially described. Therefore, patients with active acromegaly require echocardiographical examination to assess the valvular damage, because this may not be detected by a standard physical examination. This may have consequences for their treatment.
Growth hormone deficiency

Diseases resulting in damage to the somatotrophic cells in the pituitary, cause GH deficiency. The syndrome of adult GH deficiency results in subtle changes in physical and biochemical parameters and in aspecific changes in quality of life. It is currently recommended to treat these patients with recombinant human GH (rhGH) aimed at IGF-I levels in the upper range of normal to improve cardiovascular morbidity. Because the complaints and physical effects of GH deficiency are subtle and aspecific, there are no good clinicometric or biochemical parameters to titrate the treatment with rhGH other than IGF-I concentrations. In addition, there are intrinsic imperfections with respect to physiological GH replacement. GH is secreted in a pulsatile fashion, which cannot be mimicked by a once daily injection of rhGH. Moreover, patients with pituitary insufficiency frequently have additional endocrine insufficiencies, with additional intrinsic limitations in physiological replacement. Despite adequate replacement of these endocrine insufficiencies, the quality of life of patients with pituitary disease may improve, but remains impaired to a certain extent.

In chapter 5 we evaluated quality of life in patients with long-term replacement with rhGH. A broad spectrum of quality of life parameters was investigated and compared to age- and sex-matched controls. In general, women had a greater impairment in quality of life parameters then men. In GH deficient female patients the domains physical functioning, role limitations due to physical and emotional problems, measured by the SF-36, and general and physical fatigue, measured by MFI-20, were worse than in controls. Moreover, both male and female GH deficient patients had problems in social functioning, together with impaired activation. The general health perception in men was impaired compared with controls. These results were interesting, because although most patients had a long-term follow up, we had limited knowledge of the quality of life of our patients. Apparently, the standard approach of internists is not suited to assess quality of life in patients, even though this is one of the main goals of treatment in patients with GH deficiency. Several years ago positive results of DHEA substitution were reported in subjects with primarily adrenal insufficiency. DHEA and its sulfate,
DHEA-S, are strange steroids. Although their concentrations are several folds higher than that of any other adrenal gland hormone, the function of these hormones is still not clear. In humans, no receptor has been found for DHEA or DHEA-S. It is postulated that they serve as precursors for active steroids intracellularly, for instance in the brain. By restoring DHEA to physiological levels, the quality of life improved. An interesting side effect was noticed in women consisting of a rise in IGF-I levels. Therefore, the question arose whether the improvement of quality of life and the rise of IGF-I were related to each other.

In chapter 5 the data are presented of a double blind crossover study of the effects of DHEA versus placebo in GHD patients to address this question. DHEA restored the adrenal gland hormone concentrations to normal levels. In general, the patients perceived a positive change in their health. Nonetheless, we observed that they were not able to describe exactly what aspects improved. The only positive change was observed in women who showed an improvement in the depression score (HADS). The general approach of internists of taking the medical history is inadequate for assessing subtle changes in quality of life, such as assessed by detailed questionnaires. Nonetheless, the use of questionnaires has limitations. Quality of life is something abstract that is difficult to determine and each subject may have slightly different interpretations of his/her quality of life. Another problem is related to the selection of the controls, which may be subject to bias. On the other hand, reference data from the literature may not be applicable to the study population. Therefore, we decided to use each subject as his/her own control.

In women, the small improvement in quality of life was not associated with the increase of IGF-I levels. Remarkably, IGF-BP3 levels, the major GH binding protein in the plasma, did not increase, indicating that the increase in IGF-I levels was not merely the result of increased binding proteins. Because all patients had a fixed dose of rhGH, increased GH availability was another unlikely explanation of the increase in IGF-I levels. We studied only postmenopausal women with hypopituitarism without hormone replacement therapy, whereas we studied men with hypopituitarism who were all on testosterone substitution. We speculate that this difference in hormone substitution between men and women...
and/or gender may have been involved in the discrepant results of DHEA substitution on IGF-I levels. Nonetheless, from a practical perspective, at present postmenopausal women do not receive standard estrogen supplementation, whereas men above the age of 50 years still receive testosterone supplementation.

In chapter 6 the date are presented of a prospective, randomised, controlled study on the effects of GH substitution in patients with ischemic cardiac failure. The basic concept derived from other studies was that cardiomyocytes have receptors for GH and IGF-I and that GH treatment may be of benefit in certain patients with impaired cardiac function. The patients received rhGH in dosages normally given to GH deficient patients. Unfortunately, there was no effect on cardiac function after 6 months of treatment. This randomised study proved that GH substitution in patients with normal endocrine functions is not of benefit for ischemic cardiac dysfunction. The question arises whether the initial ideas of performing such studies in this group of patients without any endocrine dysfunction were solid. In the early nineties observational studies of rhGH treatment were reported in small groups of patients with heart failure, which demonstrated a positive change in left ventricular mass and systolic function. Moreover, there were suggestions that these patients had a disturbed GH-IGF-I axis reflected in decreased IGF-I levels. Subsequently, a large study in intensive care patients proved that GH substitution caused excessive mortality. In this respect, a parallel with the effects of thyroid hormone substitution in patients with non-thyroidal illness can be made. In these patients so far no consistent clinical benefit of thyroid hormone substitution has been demonstrated. The changes in hormone concentrations in response to non-endocrine disease reflect the adaptive capacity of the human body. Before interfering in the human body, one should understand the underlying pathophysiological mechanisms of the changes observed. It is interesting that all the studies performed in cardiac failure with GH were based on one uncontrolled study, and that later this hype was finished by prospective, randomised studies.
Concluding remarks

Internists use a standard approach to evaluate signs and symptoms of patients, supplemented by diagnostic tests, in order to make a diagnosis, to assess the activity of the disease and to evaluate the effects of appropriate treatment. Against this background the clinical syndromes of GH excess and GH deficiency impose several difficulties. With the exception of advanced cases of acromegaly, the signs and symptoms of both syndromes can be subtle and aspecific. Consequently, they cannot easily be quantified by clinicometric methods.

The studies described in the current thesis highlight several limitations of the standard approaches of internists. The association between acromegaly and valvular heart disease escaped the attention of the attending physicians for more than 120 years (chapter 4). In the assessment of disease activity and of the effects of treatment we have to rely on biochemical criteria for both GH excess and GH deficiency. For the treatment goals of acromegaly, the current criteria have been derived from mortality studies. However, acromegalic patients still have subtle GH overactivity during treatment with somatostatin analogues despite being “well controlled” according to these criteria. We obtained evidence for biological effects of this subtle GH overactivity at the level of the heart, i.e. diastolic dysfunction was present in these patients, but not in patients cured from active acromegaly by surgery (chapter 3). There appeared to be no difference between two different somatostatin analogues with respect to biochemical control of active acromegaly (chapter 2).

The studies in the patients with GH deficiency indicate that our current clinical approaches are not able to assess the effects of treatment with respect to the effects on quality of life. Using structured questionnaires, we were not able to show improved quality of life in GH deficient patients with secondary adrenal insufficiency by adding DHEA substitution although patients experienced a subjective change (chapter 5). Finally, our treatment of diseases should be based on solid evidence of underlying pathophysiological mechanisms. GH substitution in subjects without endocrine disease but with ischemic cardiomyopathy did not have major effects (chapter 6). However, in retrospect the
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evidence for the involvement of GH in the pathophysiology of heart disease in patients without GH deficiency or overproduction was only circumstantial.