# Acromegaly : irreversible clinical consequences

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Chapter 13.

# GENERAL DISCUSSION, CONCLUSIONS, AND SUMMARY

# CONTENTS



## Part I. Introduction

In this thesis a number of observations have been described in acromegalic patients during long-term follow-up with cured or biochemically well-controlled disease. These observations focused on persistent consequences of the disease, which actually represent irreversible effects. In these studies we evaluated the acromegalic arthropathy, bone quality and fractures, colonic abnormalities, and quality of life. In addition, we studied genotype-phenotype relationships of the d3GHR polymorphism on long-term clinical outcome in acromegaly. Moreover, we have meta-analyzed the effect of this polymorphism on spontaneous and stimulated growth in (non)-GHD short children, in order to help us understand the ongoing effect of this polymorphism in acromegaly, even after long-term cured disease.

## Part II. Osteoartritis and joint-related problems in acromegaly

The prevalence of arthropathy in acromegaly is striking, also after long-term cure of GH overproduction. The aim of the study described in **Chapter 2** was the structural, clinical, and radiological assessment of the large joint-sites in 89 acromegaly patients with disease remission for a mean of 14 years after multimodality treatment, in comparison with 67 age-matched controls and a rheumatologic Dutch reference group.

The most frequent manifestation in our study was osteoarthritis, preferentially affecting the spine and even at remarkably young ages. The prevalence of clinical and radiological osteoarthritis of the hip, hand, and knee reached up to 80%. The prevalence of osteoarthritis in

patients exceeded the prevalence in controls at all joint-sites. The characteristical radiological changes observed in these patients with cured acromegaly consist of the combination of wide joint spaces and severe osteophytosis, which had not been described before.

This high prevalence of arthropathy in combination with the preservation of the extremely wide joint spaces, indicative of thickened cartilage, was previously thought to be present only in the active phase of the disease[1-5]. However, this case-control study demonstrated that prior GH excess has irreversible, deleterious late effects on clinical and radiological aspects of joints in patients with long-term cure of acromegaly.

The assumption is that persistent exposure of the tissues to pathologically elevated GH and IGF-I levels induces progressive changes in the joints. Cartilage proliferation occurs unevenly and produces a thickened, but mechanically unstable, joint surface[6,7]. In combination with laxity of periarticular ligaments and muscle weakness this leads to joint instability[6]. On the weight-bearing surfaces of the joints cartilage ulceration occurs and the reparative process deposits excessive amounts of fibrocartilage over the damaged areas. This is followed by development of osteophytes, formation of subchondral cysts, and joint space narrowing[6]. Ultimately, these pathophysiological processes become irreversible and self-perpetuating, with more mechanical trauma causing additional joint deformity that, in turn, leads to yet more structural damage to the articular tissues and after this point independently of the actual levels of GH and IGF-I. Our results support the hypothesis that the second step in the pathogenesis of osteoarthritis in acromegaly is independent of GH and IGF-I. Therefore, attention should be directed towards the recognition of joint-related problems in (long-term) cured acromegaly.

In conclusion, prior GH excess has irreversible, deleterious late effects on clinical and radiological aspects of joints in patients with long-term cure of acromegaly.

The few previous studies provided conflicting data on the impact of serum GH and IGF-I levels on clinical and radiological arthropathy. Moreover, these were mainly based on patient cohorts with active acromegaly. The study described in **Chapter 3** was conducted to identify factors influencing the development of radiological osteoarthritis during long-term control of acromegaly, focusing on disease specific parameters, GH and IGF-I concentrations and duration of the active disease, adjusted for the well-known determinants of primary osteoarthritis in 67 patients with long-term cured acromegaly.

This study documents that the risk to develop osteoarthritis in these patients is pre-

dicted by IGF-I concentrations at the time of initial diagnosis. An almost five-fold increase in risk for radiological osteoarthritis of the hip and hand was observed in patients in the highest tertile of pre-treatment IGF-I SD scores compared with patients in the lowest tertile of pre-treatment IGF-I scores. In addition, the extensiveness of osteoarthritis in all joints was associated with pre-treatment IGF-I SD scores. There were no other disease specific predictors for osteoarthritis

IGF-I stimulates chondrocytes to synthesize extracellular matrix components in cartilage. The action of IGF-I is mediated through the type I IGF receptor[8;9]. IGF-I may also influence osteoarthritis by osteophyte formation[8;9]. In this context, it is interesting to note that Meulenbelt *et al.* observed that the IGF-I allele 3 is associated with radiological osteoarthritis in the general population at any joint site (knee, hip, hand, and spine), and that carriers of the IGF-I 3 allele were predisposed for radiological osteoarthritis at any possible joint[10]. This association was strongest in subjects with radiological osteoarthritis of the hip. In general, radiological osteoarthritis of the hip has a specific genetic and geographically prevalence pattern, which suggests the involvement of systemic factors[10;11]. Moreover, the hip is the joint, which is the least affected by occupational and physical causes of osteoarthritis[11]. Therefore, in long-term cured patients with acromegaly, the hip is also most prone to secondary osteoarthritis caused by systemic increase of levels of IGF-I during the active phase of the disease and, apparently, this mechanism influences the prevalence of osteoarthritis even after long-term cure.

Thus, the development and extensiveness of osteoarthritis in long-term cured acromegaly patients is predicted by IGF-I concentrations at the time of initial diagnosis.

Primary osteoarthritis preferentially affects post-menopausal women. However, acromegaly is equally distributed in men and women. In **Chapter 4** we evaluated whether female gender is also a risk factor for osteoarthritis in acromegaly.

We compared pain and stiffness, clinical parameters and radiographs of the knee, hand, and hip between 46 male and 43 female patients (mean age: 58 years) with controlled acromegaly for a mean of 14 years. In addition, the gender-specific prevalence of osteoarthritis was compared with age- and environment-matched controls and of radiological osteoarthritis in a Dutch population sample.

Radiological and symptomatic osteoarthritis of the knee, distal interphalangeal joint, and hip was equally prevalent in male and female patients. Clinical osteoarthritis was similar-

ly prevalent in both genders except for hand osteoarthritis, which was encountered more in women. In comparison with controls and the historical population sample, the prevalence of osteoarthritis was increased in women with acromegaly, and even more so in men with acromegaly.

In acromegaly, the prevalence of osteoarthritis at all joint sites is similar in male and female patients. The near equal gender distribution of osteoartrhitis in acromegaly contrasts with the gender difference that is observed in primary osteoarthritis in which post-menopausal women are more frequently affected than men[12], suggesting that the overproduction of GH and IGF-I overrules the potential role of risk factors, including hormonal factors, in primary osteoarthritis.

Estrogen deficiency has been implicated as a contributing factor in conditions such as osteoporosis, gout, and osteoarthritis[13]. Estrogens also have well-known effects on the somatotrope system, affecting both GH[14;15] and IGF-I secretion[16]. In the liver estrogens inhibit GH-dependent IGF-I production. Interestingly, in 1951, estrogens were proposed as the first medical treatment in women with acromegaly[17]. In acromegaly, both the protective effect of estrogens, which is also observed in primary osteoarthritis, and the inhibitory action of estrogens on IGF-I production resulting in less severe IGF-I exposure may relatively protect pre-menopausal women. However, the ultimate effects of acromegaly on joint pathophysiology appear to be so strong that the prevalence of osteoarthritis is highly increased in both male and female patients with acromegaly. This may explain the lack of gender difference in the prevalence of osteoarthritis.

We can conclude that in long-term cured acromegaly patients the prevalence of osteoarthritis is equally prevalent in male and female patients, which is in contrast to the prevalence pattern in primary osteoarthritis.

In **Chapter 5** we compared the distribution of osteophytes and joint space narrowing between patients with acromegaly and primary generalized osteoarthritis to gain insight into the pathophysiological process of GH and IGF-I mediated osteoarthritis.

Doubtful osteoarthritis (Kellgren and Lawrence score 1 or more) of hips and knees on radiographs were compared between 84 patients with controlled acromegaly for a mean of 14.0 years and 189 patients with primary generalized osteoarthritis.

The osteoarthritis phenotype in secondary osteoarthritis present in patients with

long-term cured acromegaly differs from that in patients with primary osteoarthritis with generalized nature, since hips and knees in patients with long-term cured acromegaly were characterized predominantly by osteophytes and these osteophytes were observed frequently without joint space narrowing indicating preservation of articular cartilage in these joints. Patients with acromegaly reported less functional disability of the hips and knees than patients with primary generalized osteoarthritis.

Arthropathy due to GH hypersecretion results in osteophytosis and, to a lesser extent, in joint space narrowing. This observation suggests that the GH-IGF-I system is mainly involved in bone formation resulting in osteophytosis but may protect against cartilage loss.

We assume that in well-controlled acromegalic patients, who had pathologically elevated levels of circulating GH and IGF-I in the past, and in whom predominantly osteophytosis without joint space narrowing is seen, GH and/or IGF-I are implicated in the initiation of osteophyte formation. Recently, the elevation of GH stimulated IGF-I expression in the synovial cells and peripheral cells adjacent to the articular cartilage seemed to lead to the initiation of osteophyte formation in mice[18]. This might suggest that other factors are involved in osteophyte formation rather than that osteophytes are merely a secondary feature following osteoarthritic changes[18]. In the active phase of acromegaly, arthropathy is associated with hypertrophy of cartilage and soft-tissue[19]. We are the first to demonstrate that in long-term cured acromegalic patients articular cartilage is maintained, reflected by the absence of joint space narrowing even despite the presence of severe osteophytes. In addition, these preserved joint spaces may protect against pain caused by osteophytes and, therefore, prevent acromegaly patients from a decrease in functional capability.

In conclusion, arthropathy caused by acromegaly results in osteophytosis and not in joint space narrowing.

Chapters 2-5 have shown that acromegalic arthropathy is an invalidating complication of acromegaly and although it shares features with primary osteoarthritis, joint space narrowing is infrequently seen in acromegalic patients[20].

Since the late effects of acromegaly on hand joints have not been characterized, the aims of **Chapter 6** were 1) to compare joint space width of hand joints between patients with long-term controlled acromegaly and age- and gender-matched controls, 2) to identify factors associated with increased joint space width, and 3) to assess the relation between joint space

abnormalities and complaints of joint pain in acromegalic patients.

In a cross-sectional study in 89 patients (age 58 ± 12 yr, 49% women) with long-term controlled acromegaly and 471 age- and gender matched controls without hand symptoms (age 46 ± 12, 42% women) radiological joint space width of hand joints were measured by automated image analysis[21].

Patients with long-term remission of acromegaly had 20-24% wider mean joint spaces at the MCP, PIP and DIP-joints. Mean joint space width of all hand joints exceeded the 95th percentile of controls in more than 60% of the patients. Only a small portion (9%) of the patients had mean joint spaces below the 50$^{th}$ percentile of controls. Higher GH and IGF-I concentrations at the time of diagnosis were associated with larger joint space width at the MCP-joints. However, age at diagnosis and duration of remission of acromegaly was not related to joint space. There was a gender difference since in males increased joint spaces were associated with more self-reported pain, which was not the case in females.

This new, semi-automated technique to quantify joint space width[21] to determine joint space narrowing in patients with osteoarthtritis was able to detect quantitative differences in joint space width in acromegaly patients compared with healthy controls. Moreover, within the group of acromegalic patients, this method was sensitive enough to relate joint space width to markers of disease severity of acromegaly. The large number of abnormally wide joint spaces, which we defined as higher than the 95$^{th}$ percentile of controls, may even be underestimated because of the lower age of the controls. Joints with increased joint space width were more frequently painful than joints within the range of normal, especially in male patients. In this patient group, cartilage loss is probably not the main cause of pain but, rather, the reverse, i.e. cartilage hypertrophy, should be recognized as a risk factor for pain. Additional studies are needed to assess which factors determine pain, such as osteophytosis, or instability of joints.

The increased joint spaces of the hand joints in long-term controlled acromegaly patients characterize an aspect of the late manifestations of well-controlled acromegaly and indicate persistent, possibly irreversible, cartilage hypertrophy.

Quality of life (QoL) is decreased in patients with long-term control of acromegaly[22]. In addition, these patients suffer from irreversible osteoarthritis. The aim **Chapter 7** was to assess the impact of joint-specific complaints, clinical and radiological signs of arthropathy on different aspects of QoL in patients with acromegaly after long-term disease control.

QoL was assessed in 58 long-term cured acromegaly patients by four health-related QoL questionnaires (HADS, MFI-20, NHP, SF-36) and one disease specific QoL questionnaire (ACROQOL). The outcomes of these questionnaires were compared with joint-specific self-reported complaints and clinical and radiological osteoarthritis.

The patients reported high pain scores of the spine, knee, and hip which limited physical functioning and psychological well-being. Clinical osteoarthritis of the spine was associated mostly with impaired QoL scores. In addition to impaired physical and social functioning, spinal osteoarthritis was associated with emotional functioning, anxiety, and depression. Remarkably, radiological osteoarthritis was not associated with impaired QoL.

Our findings underscore the great importance of recognition of the complaints, pain management, and coping with pain in this patient group. Multimodality interventions directed towards reduction of pain and improvement of functional capacity and QoL should be developed and evaluated.





Physical symptoms, QoL, and psychological well-being are closely related. We demonstrated a relation between spinal complaints and osteoarthritis on anxiety, depression, and emotional problems. It has been reported that chronic pain of the lower back has clear functional and emotional impact since loss of vitality, persistent discomfort, sleeping difficulties, side effects of drugs, and economic and social concerns weighs heavily and cumulatively on affected individuals[28]. Furthermore, emotional disturbances (such as depression, increased somatic awareness, and anxiety reactions) were reactions to the presence of chronic pain. In addition, radiological osteoarthritis can be present without causing complaints of pain and stiffness, possibly due to an early stage of osteophytosis or relatively preserved joint-spaces.

Considering the impact of clinical osteoarthritis of the spine on Qol, we emphasize the recognition of these complaints and a focus on pain management and coping with pain in this patient group.

## Part III. Acromegaly; long-term disease outcome, not joint-related

Despite long-term disease remission or even cured disease, acromegaly patients suffer from a wide variety of co-morbidities. In addition to arthropathy, cardiovascular and metabolic abnormalities[23], hypertension[24;25], type 2 DM, and impaired glucose tolerance have been reported. Furthermore, active acromegaly is associated with increased prevalence of malignancies,

especially of the gastro-intestinal tract[26] and with altered bone mineral density and increased fracture risk. Chapters 7 and 8 focus on other complications of acromegaly, present even after long-term disease control.

The aim of the study described in **Chapter 8** was to establish the prevalence of osteoporosis, vertebral, and non-vertebral fractures in acromegaly patients with long-term controlled disease and factors potentially influencing the risk on fractures. Vertebral and non-vertebral fractures, bone mineral density (BMD), and markers of bone turnover were studied in 89 patients in comparison with data from a sample of the Dutch population.

The prevalence of vertebral fractures was almost 60% and was significantly increased when compared with controls. The prevalence of these fractures was independent of the duration of disease control, BMD, markers of bone turnover, and characteristics of acromegalic disease.

In this study, we demonstrated a very high prevalence of vertebral fractures in acromegalic women, and even more so in men, with long-term controlled disease. There was no relation between the vertebral fractures and BMD. In view of the significant morbidity and mortality associated with vertebral fractures in general and the apparent inability of BMD to predict fracture risk in these acromegalic patients, we propose to include vertebral fracture assessment in the screening of patients with acromegaly, both at diagnosis and during follow-up after establishment of disease control.

GH and IGF-I are important anabolic hormones for bone. In fact, most of the effects of GH are mediated by systemic and/or local IGF-I, which enhances the differentiated function of osteoblasts and bone formation, although GH may also act directly on cortical bone cells[27]. On the other hand, chronic GH and IGF-I excess, such as present in active acromegaly, may impair bone quality, independently of any change in BMD, and apparently increase the risk of fractures, the most important consequence of a decrease in bone quality. Since the clinical appearance of the fractures was asymptomatic, we were unable to discriminate fractures that had occurred at the time of active acromegaly from those which had occurred during the long period of disease control. Irrespective of this issue, these fractures may have significant clinical implications regarding morbidity and mortality, since vertebral fractures are associated with a decreased quality of life, an increased morbidity and mortality, and an increased risk of new (non)vertebral fractures[28-33]. At present, it is unclear what the optimal therapeutic strategy is to

decrease fracture risk in patients with acromegaly.

We conclude that there is a very high prevalence of vertebral fractures in acromegalic patients despite long-term controlled disease, which can cause increased morbidity and mortality.

In acromegaly, overproduction of GH and IGF-I cause abnormal extracellular matrix regulation. One of the pathophysiological changes in patients with Marfan's syndrome, a disease also caused by disturbed matrix regulation, is the development of colonic diverticula. In **Chapter 9** we hypothesize that abnormal matrix regulation in acromegaly may predispose to the development of colonic diverticula. Diverticula, dolichocolon, and colorectal polyps were assessed in 107 patients with cured and/or controlled acromegaly and in 214 age- and sex-matched controls. The findings were related to GH and IGF-I concentrations at the time of diagnosis of acromegaly.

The prevalence of diverticula, dolichocolon, and adenomatous polyps was increased in patients when compared with controls. Diverticula were associated with both GH and IGF-I concentrations at the time of diagnosis of acromegaly, when adjusted for the duration of active disease. The presence of dolichocolon and adenomatous polyps was associated with higher IGF-I concentrations at diagnosis.

Acromegaly is associated with an increased prevalence of colonic diverticula. In addition to the known irreversible effect of GH excess on collagen of joints and cardiac valves, this observation indicates an irreversible effect of GH and/or IGF-I on the collagen of the colon.

Support for a pathophysiological role of alterations in connective tissue characteristics in diverticula are derived from observations in patients with connective tissue diseases like Marfan's and Ehlers-Danlos syndromes, who develop diverticula throughout the colon at a precocious age[34-37]. Diverticula in Marfan's syndrome are caused by an abnormally weak bowel wall, due to a mutation in the fibrillin gene, leading to disturbed connective tissue[35]. This same mechanism also leads to degeneration of cardiac valves and aortic root in these patients[38]. GH is also involved in matrix regulation. GH increases gene expression of the matrix metalloproteinases (MMPs), which are capable of altering the composition of the extracellular matrix[39]. In acromegaly, this altered matrix is thought to be responsible for changes found in heart valves and the aortic root[40], a mechanism known from Marfan's syndrome[38]. A crucial role of GH and IGF-I in the regulation of matrix regulation is further strengthened by the observations that

both cardiac valve pathology and the presence of diverticula are strongly associated with the duration of exposure to abnormal GH and IGF-I concentrations in acromegaly[41].

Therefore, we conclude that there is an irreversible effect of excessive exposure to GH and/or IGF-I in acromegaly on collagen in the colon, resulting in the development of diverticula. Diverticula are another, hitherto unrecognized, feature of acromegaly.

## Part IV. Different effects of the exon-3 deleted growth hormone receptor polymorphism

In 2004 Dos Santos *et al.* described an increased growth response in carriers of the d3GHR polymorphism ($GHR_{d3}$ compared with $GHR_{wt-wt}$) in children born small for gestational age (SGA) and with idiopathic short stature (ISS) in response to rhGH treatment[42]. In addition, they documented increased receptor activity of $GHR_{d3}$ compared $GHR_{wt}$ in vitro[41]. Since 2004, several studies have addressed the possible influence of this common polymorphism of the GHR (d3GHR), present in 35% of the normal population, on the growth response to recombinant human GH (rhGH) treatment in children with different clinical conditions, including GHD[43-48], SGA[42;49-53], ISS[42;54;55], and Turner syndrome[56]. However, the results of these studies are remarkably inconsistent, because 6 reports[45;47;53;55;56] confirmed the findings of Dos Santos *et al.*[42], whereas another 8 reports[43;44;46;48;49;51;52;54] could not demonstrate a significant effect of the exon-3 deleted genotype ($GHR_{d3}$) on the growth response to rhGH.

In **Chapter 10** we hypothesized that the discrepancies between these studies might be explained, at least in part, by the relatively small numbers of patients included in these studies, precluding sufficient statistical power. Therefore, we conducted a structured meta-analysis on the 15 studies, which assessed the effect of $GHR_{d3}$ on baseline height and the 1$^{st}$ year's growth response to rhGH treatment in pre-pubertal GHD and non-GHD children with short stature.

We demonstrate that the growth response during the first year of rhGH treatment is significantly increased in pre-pubertal short children with the $GHR_{d3}$ genotype in comparison with the $GHR_{wt-wt}$ genotype. Moreover, there is an association between the stimulatory effect of the $GHR_{d3}$ genotype and baseline height in children with GHD. Both findings are in line with the differences in activity between both GH receptor variants *in vitro*[42]. In addition, a lower rhGH dose and a higher age at onset of rhGH treatment were associated with a larger diffe-

rence in growth response between $GHR_{wt-wt}$ and $GHR_{d3}$ genotypes.

This meta-analysis in prepubertal children with short stature indicates that $GHR_{d3}$ is associated with increased baseline height in GHD, but not in non-GHD. Furthermore, $GHR_{d3}$ stimulates growth velocity by an additional effect of ~0.5 cm during the first year of rhGH treatment and this effect is more pronounced at lower doses of rhGH and higher age.

The problem of insufficient statistical power in the individual studies is illustrated by the fact that the pharmacogenetic effects are largely consistent among the different studies, even though these effects were small and not always statistically significant. The $GHR_{d3}$ genotype is not expected to be associated with physiological variations in human growth or to be a primary cause of short-stature in humans, since potential variations in GH sensitivity due to genotypic differences in GHR activity can be compensated by alterations in endogenous pituitary GH secretion, which might mask the effect of the GHR polymorphism on spontaneous growth. We hypothesized that in patients with GHD this compensatory effect within the GH-IGF-I axis did not function properly and, as we expected, the $GHR_{d3}$ genotype was associated with increased baseline height in GHD patients. As expected, this genotypic effect was not demonstrated on baseline height in non-GHD children

In conclusion, the $GHR_{d3}$ is associated with increased baseline height in GHD, but not in non-GHD children. Furthermore, $GHR_{d3}$ stimulates growth velocity by an additional effect of ~0.5 cm during the first year of rhGH treatment.

In analogy with Chapter 10, we evaluated the impact of the genomic deletion of exon 3 of the growth hormone receptor on long-term clinical outcome of acromegaly in a well-characterized cohort of patients with long-term remission of acromegaly in **Chapter 11**.

The genetic distribution of the d3GHR was assessed in 86 acromegalic patients in long-term disease control and related to anthropometric parameters, cardiovascular risk factors, osteoarthritis, bone mineral density, colonic polyps and diverticula, and dolichocolon.

The d3GHR polymorphism is associated with more severe complications of acromegaly, reflected in an increased prevalence of osteoarthritis, colonic polyps, and dolichocolon. Other co-morbidities such as metabolic syndrome, type 2 DM, changes in BMD, or (non)vertebral fractures are unaffected by the d3GHR polymorphism. Apparently, the ultimate impact of the d3GHR polymorphism on long-term complications of acromegaly is evident only on the irreversible effects of previous GH excess.

It has frequently been assumed that the prevalence of colonic polyps and dolichocolon in acromegaly was correlated to IGF-I concentrations[57-60]. A more active signal transduction of GH in $GHR_{d3}$ patients is concordant with the finding of an increased prevalence of both adenomatous polyps and dolichocolon. Acromegaly is associated with increased BMD in combination with a high prevalence of vertebral fractures, especially with coincident hypogonadism[61]. Up till this study, a relation between pre-treatment GH or IGF-I concentrations and these co-morbidities had not been reported, which is consistent with the lack of difference between the d3GHR genotypes[27;62]. This study shows that co-morbidities including joint-complaints, osteoarthritis, hypertension, and colonic abnormalities are highly prevalent in patients with acromegaly despite long-term cured disease[20;63-65]. The effect of the d3GHR polymorphism had no effect on DM. This is explained by the fact that type 2 DM is frequently observed in active disease, but is potentially reversible since disturbances in glucose metabolism normalize after cure and the prevalence of type 2 DM is not increased in patients with (long-term) disease remission[63-66].

In conclusion, the d3GHR polymorphism is associated with more severe outcome of acromegaly for the irreversible complications of GH excess, but not for the reversible complications.

Since the first publication on enhanced growth in children with the $GHR_{d3}$ genotype in 2004, several studies were performed evaluating the effect of this polymorphism in various clinical conditions. We systematically reviewed these studies in **Chapter 12**, in order to establish the functional consequences of the exon 3 deleted GHR polymorphism.

Discrepancies exist between different studies on the effect of the d3GHR on the GH-IGF-I axis in GHD and acromegaly, and no evident effect of the $GHR_{d3}$ genotype on the GH and/or IGF-I concentrations could be established evaluating these studies[43;46;67]. The presence of d3GHR had a small effect on clinical outcome; including increased growth velocity in (non)-GHD children treated with rhGH treatment, and increased basal height in GHD children. In acromegaly, the d3GHR was associated with a worse outcome of irreversible complications of acromegaly (more osteoarthritis, dolichocolon, and adenomatous polyps). In addition, the polymorphism was associated with a better treatment response to somatostatin analogs or Pegvisomant. The effects of the d3GHR on the response to rhGH treatment in GHD adults were less evident. However, it is more complicated to establish clear genotype-phenotype

relationships in adults, since the treatment endpoints of rhGH in adults are less clear than in children with GHD treated with rhGH.

The $GHR_{d3}$ genotype seems to affect metabolism. In patients with DM type I and II and with IGT the frequency of the $GHR_{d3}$ genotype is significantly lower than in the normal population. In addition, in a cohort of healthy Caucasian children and adolescents higher insulin secretion was demonstrated in the presence of the d3GHR[68]. These findings suggest that increased bioactivity associated with this allele confers a protection function against type II DM due to increased IGF-I levels as a result of increased GH sensitivity that promotes glucose uptake and decreased insulin sensitivity[68].

The $GHR_{d3\text{-}d3}$ isoform is more frequently present in patients suffering from starvation, indicating that both the elevated GH gene expression and increased GHR-mediated GH responsiveness may constitute adaptive responses to the effects of persistent malnutrition, since increased circulating GH appears to form part of a physiological response to nutrition deprivation. The prevalence of the $GHR_{d3}$ isoform in well-fed populations is currently unknown. However, in patients with type II DM and IGT, the $GHR_{d3}$ isoform is associated with more severe obesity than in patients with the other isoforms. Additional research on this interesting topic is required.

We conclude that the effect of the d3GHR polymorphism is not limited to subtle variations in growth parameters in (non)-GHD children with short stature treated with rhGH, but the effect affects many pathophysiological processes in which the GH-IGF-I axis is involved to some extent, despite the fact that the effect of the d3GHR on the GH-IGF-I axis itself is not yet completely elicidated. From a clinical perspective, the effects of the presence of the d3GHR are so small that it does not affect diagnostic or therapeutic approaches.

## Part V. General discussion and concluding remarks

Acromegaly is a slowly progressive disease of exaggerated somatic growth and distorted proportion arising from hypersecretion of GH and IGF-I. The active phase of the disease causes enormous morbidity, including phenotypic changes, arthropathy, cardiovascular and pulmonary complications, and malignancies. Nowadays treatment options have been well established and almost all patients reach a state of controlled or cured disease. However, the studies described in this thesis document that there are severe long-term consequences of acromegaly, despite accu-

rate disease cure or control, which are, to a more or lesser extent, immobilizing for the patients.

Athropathy was the most reported long-term consequence by the patients and showed to have great impact on QoL. Arthropathy was the consequence of severe osteoarthritis at multiple joint-sites. Osteoarthritis was equally prevalent in males and females. The extend and severity of osteoarthritis was related to the plasma levels and duration of GH and IGF-I excess during the active phase of the disease. The characteristics of the osteoarthritis were very typical and consisted of severe osteophytosis in the absence of joint space narrowing, which contrasts with joint space narrowing in primary osteoarthritis. Joint space widening was already known to be present in the active phase of acromegalic disease, but we described that despite long-term disease control and severe osteophytosis, this joint space widening persists, reflecting persistent cartilage hypertrophy.

Colonic abnormalities, including diverticula, adenomatous polyps, and dolichocolon were highly prevalent in acromegaly patients and associated with the duration and amount of GH and IGF-I excess.

The prevalence of vertebral fractures was very high en increased, compared with controls. Vertebral fractures were not associated with any acromegalic disease characteristic and were independent of BMD and gonadal status.

Finally, we meta-analyzed differences in growth response to rhGH treatment in GHD and non-GHD short children. This variation is growth response was partly explained by a polymorphism in the d3GHR. In addition, we investigated the effect of this polymorphism on the long-term consequences of acromegaly. This polymorphism of the d3GHR was associated with more severe complications of acromegaly, reflected in an increased prevalence of irreversible complications of the disease, such as osteoarthritis, colonic polyps, and dolichocolon. The reversible complications, i.e. DM type II, metabolic syndrome and changes in BMD, were not affected by this polymorphism.

In view of the significant morbidity in acromegaly patients, both at diagnosis and during long-term follow-up after establishment of disease control, we propose that screening for osteoarthritis, and vertebral fractures should be included in the follow-up of acromegalic patients. In addition, clinicians should be aware of the increased prevalence of diverticula in the colon, which may be associated with increased complications and complaints.

It is essential to recognize these long-term consequences in order to establish appropriate follow-up and (multidisciplinary) care in these patients to limit the persisting complex

morbidity. Both doctors and patients should be aware of these persisting consequences to prevent inappropriate expectations with respect to the long-term results of treatment.

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