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Acromegaly : irreversible clinical consequences

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Chapter 1.

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

INTRODUCTION

In this thesis a number of observations is described in acromegalic patients during long-term follow-up with cured or biochemically well-controlled disease. These observations focus on persistent consequences of the disease, which actually represent irreversible effects. In these studies we evaluate the acromegalic arthropathy, bone quality and fractures, colonic abnormalities, and quality of life. In addition, we study genotype-phenotype relationships of the exon-3 deleted growth hormone receptor (d3GHR) polymorphism on long-term clinical outcome in acromegaly.

Acromegaly

An introduction to the disease

Acromegaly is a disease of exaggerated somatic growth and distorted proportions arising from hypersecretion of growth hormone (GH) and insulin-like growth factor I (IGF-I). The clinical characteristics of acromegaly were first described more than 120 years ago by Pierre Marie¹ and are caused by hypersecretion of GH by a pituitary adenoma^{2,3}. If GH hypersecretion is present before closure of the growth plates, GH excess leads to a tall stature, this condition is referred to as gigantism rather than acromegaly.

Epidemiology

Acromegaly is a rare condition with a prevalence less than 70 cases per million and annual incidence of 3 to 4 cases per million^{4,5}. There are no known geographical and/or sex differences.

Pathogenesis

Both hypersecretion of GH or GH-releasing hormone (GHRH) can lead to acromegaly. Pituitary GH-secreting adenomas are responsible for 98% of acromegaly. In rare conditions, GHRH secreting tumors cause secondary somatotrope hyperplasia and acromegaly. These GHRH producing tumors can arise in the central nervous system (hypothalamic hamartoma, choristoma, and ganglioneuroma) and in peripheral organs (neuroendocrine tumors).

Familial syndromes associated with GH hypersecretion include multiple endocrine neoplasia type I^{6,7}, McCune-Albright syndrome⁸, and Carney complex⁹. Isolated familial

acromegaly is described with loss of heterozygosity in chromosome 11q13¹⁰ and, recently, low-penetrance germline mutations in the aryl hydrocarbon receptor-interacting protein gene were found in individuals who had familial pituitary adenoma predisposition^{11,12}.

Exogenous administration of GH to non-GH deficient (GHD) subjects as an athletic performance enhancer¹³ or anti-aging treatment¹⁴ has been a growing phenomenon during the last decade, exposing GH recipients to pathologies similar to those of patients who have endogenous GH hypersecretion. This comes into mind considering the facial appearance of the current governor of California.

Anatomy

The pituitary gland lies within the sella turcica, a recess in the sphenoid bone, close to the hypothalamus and the optic chiasm (*see Figure 1*). The pituitary weighs approximately 1 gram. It is connected to the hypothalamus consists of the adenohypophysis (80%) and the neurohypophysis (20%). The cell types in the anterior lobe of the pituitary are the somatotropes (50%) which produce GH, lactotropes (20%) which produce prolactin, corticotropes (10%) which produce adrenocorticotrophic hormone (ACTH), thyrotropes (10%) which produce thyroid stimulating hormone (TSH) and gonadotropes (10%) which produce follicle stimulating hormone (FSH) and luteinizing hormone (LH).

Pituitary tumors, including GH producing adenomas, are staged according to the Hardy-Wilson classification of pituitary tumors, based on the grade of sella turcica enlargement and invasion and suprasellar and parasellar extension. Most microadenomas (diameter < 1 cm) and macroadenomas (diameter > 1 cm) with suprasellar extension have a reasonable chance to be cured by surgery. Tumors invading the sellar floor of those with parasellar extension have a low chance to be cured by surgery.

Most GH producing pituitary tumors produce only GH, although mixed GH and prolactin production is present in 30% of the cases. A minority of GH producing tumors also produce TSH or α -subunits.

GH physiology

GH is a single chain polypeptide hormone that is synthesized, stored, and secreted by somatotrope cells in the pituitary gland. In plasma, GH circulated freely or is bound to GH-binding

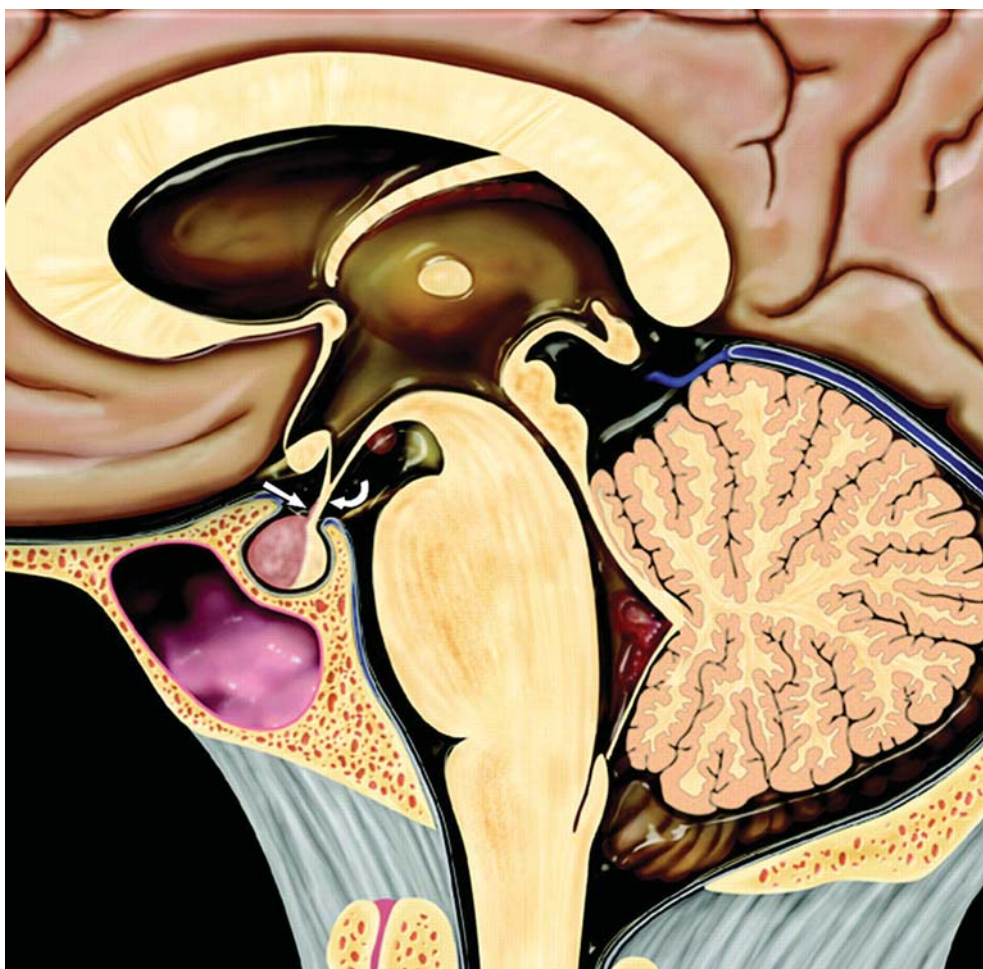


Figure 1. Localization of the pituitary gland: Head and neck digital teaching file. Salt Lake City, UT: Amirsys, 2002.

protein (GHBP). GH is cleared via renal and hepatic mechanisms.

Control of GH secretion is effectuated at the hypothalamic and the pituitary level by the interaction of stimulatory and inhibitory hormones resulting in a diurnal and pulsatile secretion pattern by which the majority of GH is released during sleep, stress and exercise^{15;16}. Thyroxine, sex steroids, cortisol, amino acids and fasting also enhance GH secretion. GH secretion is inhibited by meals, glucose, free fatty acids, glucocorticoid excess states and (visceral) adiposity. GH secretion is maximal in the late puberty and thereafter gradually decreases. Women have higher GH production than men^{15;17}.

The hypothalamic stimulatory (GHRH) stimulates GH gene transcription, GH cell

proliferation and GH release. The hypothalamic inhibitory hormone somatostatin acts via binding to somatostatin receptors and inhibits GH release from the secretory granules in the somatotropes and also inhibits GHRH release. Other negative feedback systems regulating GH secretion are GH at the hypothalamic level, and IGF-I at the hypothalamic and pituitary level. The physiological role of Ghrelin, the native substrate for the GH-releasing peptide (GHRP) receptor, is not fully elucidated, but high GH responses are induced by GHRP or Ghrelin infusion and these act synergistically to GHRH stimuli^{15,18-20} (see Figure 2).

GH stimulates the production of IGF-I in many organs, especially by the liver. IGF-I is a polypeptide belonging to the same family of growth factors as insulin. Serum IGF-I concentrations reflect the GH concentrations over 24 hours and, in general, is increased and decreased, when GH concentration is increased or decreased, respectively.

The primary and most obvious clinical effect of GH is the promotion of longitudinal growth. Most effects of GH are mediated via IGF-I¹⁷. The anabolic actions of GH and IGF-I involve many organs systems throughout life. These actions include stimulation of protein synthesis, increased lipolysis, and inhibition of protein catabolism. GH is involved in bone remodeling, muscle growth, and immunomodulation. GH stimulates the production of IGF-I, IGFBP-3, acid-labile subunit (ALS), and many other growth factors at a local level. GH antagonizes the actions of insulin resulting in glucose intolerance and hyperinsulinemia. In contrast, IGF-I has insulin-like effects by enhancing peripheral glucose uptake.

The GHR and the exon-3 deleted GHR polymorphism

The biological action of GH is mediated by the activation of a cell-surface receptor, the GHR. Without the functional GHR, the final height of patients does not exceed 70% to 80% of normal height. There are different molecular forms of the GHR, reflecting polymorphisms of the GHR gene. Of these GHR polymorphisms, three variants of the GHR, that differ in the presence or absence of exon-3 ($\text{GHR}_{\text{fl-fl}}$, $\text{GHR}_{\text{fl-d3}}$, and $\text{GHR}_{\text{d3-d3}}$), are frequent among the population²¹. The function of exon-3 is unknown, although the deletion is in close proximity to the GH binding site²². The loss of exon-3 appears to have little effect on the receptor as $\text{GHR}_{\text{fl-d3}}$ and $\text{GHR}_{\text{d3-d3}}$ are stable and functional receptors with no apparent differences in binding activity or internalization compared with $\text{GHR}_{\text{fl-fl}}$. While either allele alone is sufficient for normal growth²³, the presence of at least one deleted allele is thought to confer an increased growth response to GH therapy and *in vitro* associated with increased responsiveness to GH²⁴.

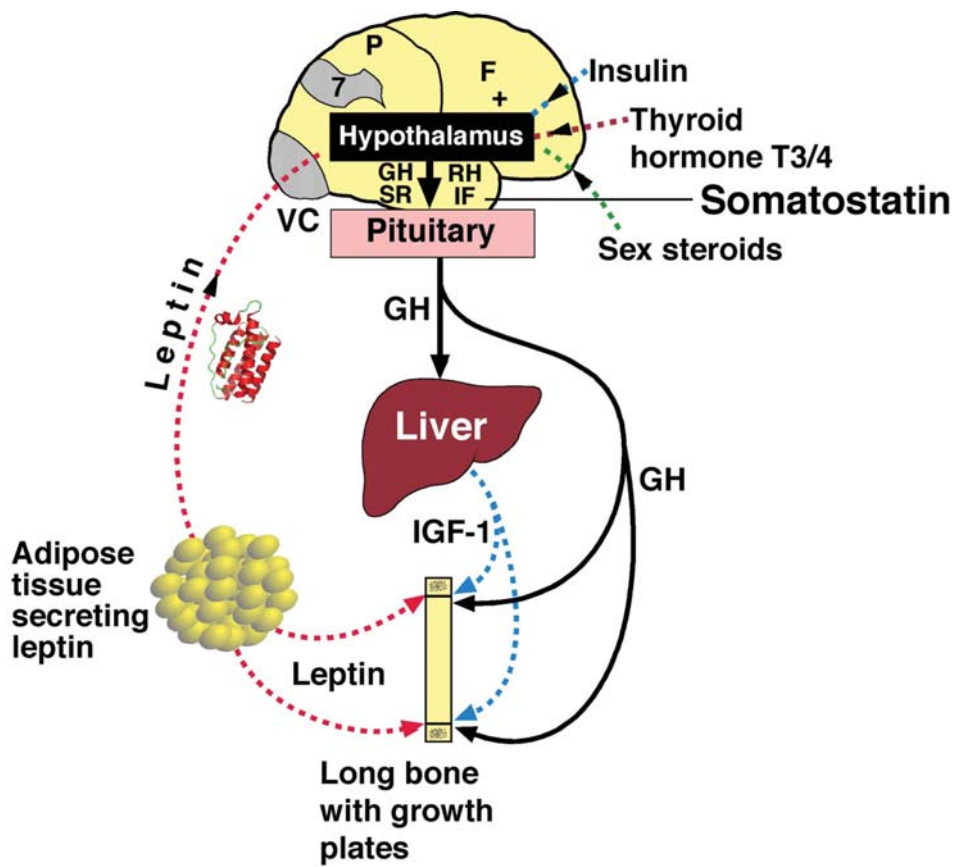


Figure 2. Regulatory mechanisms involved in the secretion of growth hormone: Burwell *et al. Scoliosis* 2009 4:24.

Diagnosis

Signs and symptoms

Due to the insidious clinical manifestation of GH excess, acromegaly is a disease with a typically delayed diagnosis, approximately 10 years from the onset of the symptoms²⁵. Changes in appearance are the reason to seek medical care in only 13% of the acromegaly patients²⁶, even though these changes account for 98% of presenting features²⁷.

Changes in appearance derive from skeletal growth, and soft-tissue enlargement. Facial changes include enlarged lips and nose and macroglossia which can cause excessive snoring and sleep apnea syndrome, frontal skull bossing and cranial ridges, mandibular overgrowth with prognathism, maxillary widening with teeth separation, jaw malocclusion, and overbite. Increased ring and shoe size are often reported²⁶.

Arthropathy of the large peripheral and axial joints is a common feature of the disease, occurring in approximately 70 to 80% of patients, even in patients with cured disease. The stature of the patient is characterized by kyphoscoliosis, and weight is increased²⁸. Patients suffer often from carpal tunnel syndrome.

Skin thickening, due to accumulation of glucosaminoglycans, is noticed mainly in the face, hands, and feet. Hypertrophy of and hypersecretion by sebaceous and sweat glands result in oily and sweaty skin, respectively. Other symptoms associated with acromegaly are a low voice, tiredness, paresthesias, and hirsutism.

Hyperprolactinemia with or without galactorrhea develops in approximately 30% of patients because of pituitary stalk compression in the case of macro adenomas or mixed secretion of GH and prolactin by the pituitary adenoma²⁹. Hypopituitarism ensues by mass compression of normal pituitary tissue by macro adenomas in approximately 40% of patients³⁰; amenorrhea or impotence³¹ or secondary thyroid³² or adrenal failure can develop. Other local tumor effects include headache, visual field defects with typical hemianopsia, and sporadically dysfunction of cerebral nerves, especially of the trigeminal, trochlear or abducens nerves.

Important cardiovascular and metabolic manifestations of acromegaly are acromegalic cardiomyopathy, valvular abnormalities³³, hypertension^{34,35}, type 2 diabetes mellitus, and impaired glucose tolerance. Furthermore, acromegaly is associated with increased prevalence of malignancies, especially of the gastro-intestinal tract³⁶. Patients with active acromegaly have a two- to three-fold increased mortality risk due to cardiovascular and respiratory diseases and cancer^{5;37-45}.

Biochemical markers

Basal plasma GH and IGF-I concentrations are elevated in most cases of acromegaly. However, high GH concentrations can also be found in healthy subjects, owing to the episodic nature of GH secretion, that can fluctuate between undetectable levels and peaks up to 100 µg/L. Therefore, a confirmatory test is required. The glucose tolerance test (GTT) is the golden standard for the diagnosis of GH excess. In healthy controls, after an oral glucose load of 75 grams, the serum GH level is suppressed to low levels. In contrast, in acromegaly, the serum GH concentration is insufficiently suppressed after glucose loading. GH measurements after an GTT are unreliable in patients who have uncontrolled diabetes mellitus or liver or renal diseases, in patients receiving estrogens, or in patients who are pregnant and during late adolescence⁴⁶. In

our centre, the normal suppression of GH after GTT is $< 1 \text{ mU/L}$ (or $< 0.38 \text{ } \mu\text{g/L}$), measured by IFMA, highly sensitive for the 22 kDa protein (Wallac, Turku, Finland).

Imaging

Pituitary MRI with contrast enhancement is most sensitive for determining a pituitary adenoma, with detection limits of tumors as small as 2 mm. MRI can also visualize tumor dimensions, invasiveness and proximity to the optic chiasm. In the rare case when the GH source is extra-pituitary, CT, MRI, or both can be used to localize the ectopic source⁴⁷.

Treatment

Treatment should aim at managing the tumor mass and GH hypersecretion, to prevent morbidity and increased mortality while preserving normal pituitary function.

Surgery

Transsphenoidal selective adenomectomy is the preferred approach for treating most patients. Serum GH levels are controlled within an hour after complete removal of the GH-secreting adenoma⁴⁸. This approach, in the hands of experienced neurosurgeons, cures the majority of patients who are harboring a well-circumscribed micro adenomas or small macro adenomas^{49,50}. Cure rates are approximately 75% for micro adenomas and 50% for non-invasive macro adenomas. The long-term biochemical results of surgery are excellent in most patients with initial cure, although a minority (5-15%) develop (late) recurrence of disease. Life-long follow-up is required because of this chance for recurrence.

Peri-operative mortality is low and there is a low incidence of morbidity postoperatively, including meningitis and cerebrospinal fluid leaks ($< 1\%$), transient diabetes insipidus and (partial) hypopituitarism ($< 10\%$).

Pharmacotherapy

Somatostatin analogs

Somatostatin analogs are the first-choice pharmacotherapy for acromegalic patients, which can be used as primary or pre-operative treatment or as secondary treatment after unsuccessful surgery. Two formulas are available for treatment of acromegaly: octreotide (Sandostatin ® Novartis) and lanreotide (Somatuline ® Ipsen), which inhibit GH secretion mainly via the

somatostatin receptor subtypes 2 and 5⁵¹. The half-life of these drugs is increased in comparison with native somatostatin. Both somatostatin analogs are available in depot preparations, using release from microspheres (Sandostatin LAR and Somatuline SR) or an aqueous substance (Lanreotide Autogel). Depot preparations are administered every 4 weeks (Sandostatin LAR or Lanreotide Autogel). Side effects of these drugs are mostly explained by the physiological action of somatostatin. These include bile stone formation, inhibition of insulin secretion and therefore a slight deterioration in glucose tolerance in a minority of patients, and (mostly transient) abdominal pain, diarrhea and nausea.

Reduction of GH and IGF-I levels during treatment with somatostatin analogs is observed in many patients, but control of disease depends on octreotide sensitivity (determined by somatostatin subtype status of the adenoma) and baseline serum GH concentrations. In most studies ~60% of patients are well controlled by somatostatin analog treatment, when used as primary or adjuvant treatment after surgery. Tumor volume reduction of GH adenomas occurs in 20-50% of acromegalic patients during somatostatin analog treatment⁵². Medical pre-treatment before surgery of especially macroadenomas, however, does not clearly improve outcome⁵³.

There is no contra-indication for long-term (life-long) use of these analogs. However, this is expensive, since treatment with somatostatin analogs costs 10.000-26.000 euro per patient per year.

Growth hormone receptor antagonists

Pegvisomant (* Pfizer) is a pegylated GHR antagonist approved for treatment for acromegaly that interferes with the signaling of the GH receptor, and that inhibits subsequent IGF-I generation. Pegvisomant binds through a high affinity site 1 to one GHR dimer subunit but cannot bind through a mutated site 2 to the second GHR dimer subunit, resulting in failure to initiate subsequent GH signal transduction pathways⁵⁴. Although GH concentrations increase due to a decreased feedback signal, IGF-I is effectively reduced in almost all patients¹⁶. Pegvisomant is administered via daily subcutaneous injections. Pegvisomant improves insulin sensitivity and glucose tolerance, reflected in reduced fasting serum insulin and glucose levels. Few side effects have been observed, but at present long-term safety data are lacking. A major concern with pegvisomant treatment is the possible growth of the pituitary adenoma due to disrupted feedback systems. However, with the short-term use of this drug and the application of the drug in mostly operated and irradiated patients, tumor growth has been

observed in only a very small number of patients, which may reflect more the aggressive nature of the GH producing adenoma than true side effects of pegvisomant. Another side effect is the development of transient increases of liver enzymes. Pegvisomant is very expensive and cost 28.000-115.000 euros per patient per year.

Dopamine agonists

Bromocriptine and cabergoline have been used as adjuvant therapy for acromegaly⁵⁵ and in patients with mixed GH/prolactin producing adenomas. Bromocriptine suppresses serum GH levels to less than 5 µg/L in less than 15% of patients who have acromegaly when used in high doses (up to 20 mg per day). Cabergoline is a long-acting dopamine agonist that reduces serum GH levels to less than 2 µg/L and normalizes IGF-I in approximately 30% of patients. Side effects include gastrointestinal discomfort, transient nausea and vomiting, nasal congestion, dizziness, postural hypotension, headache, and mood disorders⁵⁶. In light of recent studies demonstrating increased incidence of valvular heart disease with high doses of cabergoline^{57,58}, dopamine agonists should be prescribed with caution in this patient group already at risk for valvular disease due to the growth hormone excess.

Radiotherapy

Radiotherapy is presently reserved for patients with post-operative persistent or recurrent tumors with resistance to, or intolerance for, medical treatment, although it has been used routinely in the past to treat persistent disease. Conventional external deep X-ray therapy administered by a linear accelerator usually is given in 1.8 Gray (Gy) doses to a maximum accumulating dose of 40 to 50 Gy fractionated in at least 20 sessions. After radiotherapy, the decline in serum GH levels is delayed to ~50% within the first 2 years and 75% after 5 years⁵⁹ and dependent on the pre-radiation serum GH concentrations. Remission rates of radiotherapy seem to depend on the extent of surgical intervention (debulking) prior to radiotherapy. The incidence of hypopituitarism increased with the duration of follow-up after radiotherapy and occurs in 60% of the patients during follow-up for 10-15 years⁶⁰. A lower incidence of hypopituitarism is potentially observed when a smaller dose of 20 Gy, instead of 40 Gy, is used⁶¹. Secondary intracranial tumor formation or visual impairment is not observed when the radiation dose does not exceed 45 Gy and the fractional dose is less than 2.5 Gy⁶². Secondary carcinogenesis is very rare, in the range of less than 2% in 20 years⁶³.

Another irradiation technique is stereotactic radiosurgery using gamma knife, which

delivers a single tumor-focused radiation fraction. Gamma knife radio-surgery requires precise delineation of the tumor target to allow exact focusing with minimal surrounding tissue exposure, especially to the optic tract. GH decline is faster than with conventional techniques. It is presently unclear whether this technique is associated with decreased incidence of hypopituitarism compared with conventional radiotherapy, but long-term studies are not available^{64;65}.

Definition of disease control/disease remission

From an international consensus point of view, absolute numbers are used when discussing control rather than cure. Nadir GH levels should be below 1 µg/L, preferably less than 0.41 µg/L, in the 2 hours after 75-g oral glucose load during the GTT⁴⁶. Age- and gender-adjusted serum IGF-I levels should be within normal ranges. Since IGF-I has a long half-life and stable serum levels, it allows for assessment of disease activity. Circadian periodicity, nutrition, blood glucose levels, steroids, and age effect serum GH and IGF-I levels and have to be taken into account when interpreting IGF-I concentrations⁶⁶. Mean GH concentrations < 2.5 mcg/L are used in many studies as an supportive marker of disease control.

Ideally, both GH and IGF-I values should be obtained to complement evidence for assessing disease activity; however, a discrepancy between abnormal GH levels coexisting with normal IGF-I serum levels is encountered in 30% of patients⁶⁷.

Disease recurrence

Recurrences may be re-growth of post-operatively non-detectable tumor remnants or new monoclonal cell expansions. Following surgery recurrences develop in 5 to 15% of patients, in the course of 15 years post-operatively⁶⁸. Following radiotherapy, recurrences are rarely observed. During chronic somatostatin analog treatment, tumor growth is rarely observed.

Patients who have recurrent GH-producing adenomas usually are considered for pharmacotherapy, unless there are clear indications for second surgery.

Osteoarthritis

An introduction to the disease

Osteoarthritis is a slow progressive degeneration of articular cartilage and related changes in the underlying bone at the joint margins^{28;69}. Soft-tissue structures in and around the joints are also often affected. These include the synovium that may show signs of inflammation, the surroun-

ding ligaments, which are often lax and bridging muscles which become weak⁷⁰.

Epidemiology

Osteoarthritis is the most prevalent joint disorder in the world. The prevalence of osteoarthritis in the general population increases with age and is higher in women than in men, especially among the elderly⁷¹. The joint groups most often affected by osteoarthritis are the hand, knees, hips, metatarsophalangeal joints, and the apophyseal joints, and intervertebral discs of the spine. The prevalence of radiological osteoarthritis differs per joint site and ranges in a random population in Rotterdam (The Netherlands) from 10% in the hips to 69% in the hands in post-menopausal women⁷². Clinical osteoarthritis is less common than radiological osteoarthritis. Disc degeneration is very common.

The articular manifestations of acromegaly have been recognized since the classical description by Marie in 1886 and are present in most patients with untreated disease^{1;73;74}. Both weight and non-weight bearing joints are affected, including shoulders, wrists, knees, hips, and the spine^{28;73;75;76}. The long-term effects of acromegaly on arthropathy are not known.

Pathogenesis of osteoarthritis in the general population

In human cartilage, chondrocytes are responsible for the generation of the extra-cellular cartilage matrix and the maintenance of tissue homeostasis⁷⁷. In osteoarthritis, destruction and failure of the extra-cellular matrix takes place, as a result of imbalance in the physiochemical resisting properties of the articular cartilage and applied mechanical stress. This osteoarthritic cartilage degeneration consists of a three-step cellular reaction pattern, not necessarily in sequence. First, chondrocytes activate or deactivate their synthetic-anabolic activity. Second, chondrocytes undergo phenotypic modulation, leading to an altered gene-expression profile of the cells in the diseased tissue. Third, the chondrocytes can die or proliferate in an attempt to compensate for cell loss or in order to increase their synthetic activity⁷⁸.

Etiology

Osteoarthritis is a disease with a complex etiology. Systemic factors determine the susceptibility to the impact of local biomechanical factors in developing osteoarthritis as shown in *Figure 3*. Well-known systemic factors include age, female sex, and genetic predisposition⁷⁰. Up till now, it is unknown whether excessive concentrations of circulating GH and/or IGF-I are included



Figure 3. Pathogenesis of osteoarthritis with putative risk factors: Felson *et al.*, Ann Intern Med 2000; 133(8): 635-46.

in the systemic factors that render patients more susceptible to osteoarthritis. Of the local biochemical factors, physically demanding occupations⁷⁹, a history of joint trauma⁸⁰, and obesity are factors most commonly associated with osteoarthritis⁸¹.

Diagnosis

Clinically, osteoarthritis is characterized by joint pain, tenderness, limitations of movement, crepitation, and occasional effusion. The golden standard measurement is radiographic examination⁸². There are several radiographic classifications of osteoarthritis, including the classifications according to Kellgren and Lawrence⁸³ and OARSI⁸⁴, which are widely used. Criteria for clinical/symptomatic osteoarthritis were established by the Diagnostic and Therapeutic Criteria Committee of the American College of Rheumatology, and the major criterion for classification of osteoarthritis is joint pain on most days of the prior month in combination with structural changes, like radiographic abnormalities or the presence of bony swellings⁶⁹.

In osteoarthritis there is a poor association between clinical symptoms and radiological deformities. Since cartilage does not sense pain, cartilage degeneration itself cannot lead to pain. The origin of pain is thought to be due to stimulation of pain receptors in the synovium and surrounding tissues, such as periost, subchondral bone, entheses and tendons.

Treatment

At present, there is no medical treatment available to prevent the onset of osteoarthritis or to cure or delay the structural progression of osteoarthritis. Treatment of osteoarthritis remains

symptomatic aiming at controlling pain and maintaining or improving joint function. In case of persisting severe joint complaints, replacement surgery can be taken into consideration.

Acromegalic arthropathy

Two steps are encountered in the pathogenesis of arthropathy in acromegaly. First, elevated GH and IGF-I levels promote growth of the articular cartilage and periarticular ligaments, leading to thickening of the cartilage lining and congestion of the joint space with ensuing limitation in the range of motion. Radiological changes in this phase are joint space widening and periarticular soft tissue hypertrophy. These early changes are, at least partially, reversible upon adequate disease control^{73-75;85}. Second, the altered joint geometry results in repeat intra-articular trauma and exuberant reparative reactions, which leads to scar, cyst, and osteophyte formation with further deterioration of joint geometry. At this point, the disease acquires the characteristics and the features of degenerative joint disease^{86;87}.

OUTLINE OF THIS THESIS

Part II. Osteoarthritis and joint-related problems in acromegaly

Acromegaly is a rare disease, but associated with significant morbidity, including arthropathy. The articular manifestations have been investigated in the past, but mostly in patients with untreated or treated, but still active acromegaly^{28;76;88;89}. After treatment resulting in short-term biochemical remission, reversibility without normalization of the joint complications was observed⁷³⁻⁷⁵. The consequence of long-term cure or biochemical control on joint manifestations was not studied in detail previously. Therefore, in **Chapter 2** we studied the prevalence and characteristics of arthropathy measured by standardized self-reported questionnaires, structured joint assessment, and radiographic joint examination in patients with long-term cure for acromegaly and compared the data with those obtained in controls.

Activation of the GH-IGF-I axis is a key-factor in the development of the degenerative joint disease in acromegaly, since acromegaly is associated with a very early onset of osteoarthritis. Therefore, in **Chapter 3** we aimed to identify parameters of acromegaly at the time of diagnosis associated with manifestations of secondary osteoarthritis in patients with long-term

cure of acromegaly.

The exact pathogenesis of primary osteoarthritis is unknown, but ample evidence suggests that systemic, hormonal, and genetic factors are involved. Female gender is one of the most important risk factors for primary osteoarthritis, especially after the menopause. In contrast, in acromegaly there are no known gender differences in disease prevalence or characteristics^{26;90;91}. Therefore, in **Chapter 4** we studied whether the effects of gender and menopause as observed in primary osteoarthritis are also present in patients with secondary osteoarthritis, caused by acromegaly. This study was performed in order to obtain more insight both in pathophysiological processes that play a role in osteoarthritis in acromegaly in particular and in osteoarthritis in general.

Osteoarthritis in acromegaly is associated with osteophytosis but in contrast with primary osteoarthritis not with joint space narrowing *per sé*. Therefore, in **Chapter 5** we compared the radiographic appearances of osteoarthritis in patients with long-term cured acromegaly with a well-described cohort of patients with (generalized) primary osteoarthritis.

Although acromegalic arthropathy shares features with primary osteoarthritis, joint space narrowing is infrequently seen in acromegalic patients⁹². In order to gain more insight on this topic, we compared joint space width of the hand between acromegaly and primary osteoarthritis in **Chapter 6**. Our aim was to assess the extend of joint space width, to identify factors associated with joint space width, and to assess the relation between these joint space width and self-reported pain.

Quality of life (QoL) in acromegaly is impaired in patients with untreated and treated disease⁹³⁻⁹⁷, even after long-term biochemical remission⁹⁸⁻¹⁰⁰. Unsubtle and not joint-site specific self-reported joint-complaints predict impaired physical and mental QoL in controlled acromegaly¹⁰¹. Therefore, in **Chapter 7**, we studied the impact of joint specific complaints, radiological and clinical osteoarthritis on the different aspects of QoL in patients with long-term cured acromegaly.

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

In untreated acromegaly, high circulating concentrations of GH and IGF-I are associated with an increase in bone turnover and in cortical bone mineral density (BMD), but with variable changes in trabecular BMD that have been found to be either increased or decreased¹⁰²⁻¹⁰⁶. We have previously reported normal trabecular BMD measurements in a cross-sectional study of largely eugonadal patients with a mean remission of 10 years after successful treatment of acromegaly¹⁰⁷. The study in **Chapter 8** aimed to assess whether the changes observed after a mean duration of 10 years after cure of acromegaly were sustained in the longer-term by evaluating BMD 7 years after initial assessment. In addition, we assessed the incidence of vertebral and non-vertebral fractures after long-term remission of acromegaly.

Colonic diverticular disease is common in Western and industrialized societies¹⁰⁸ and are most often found in the sigmoid and descending colon¹⁰⁹. The pathophysiology of colonic diverticular disease is yet incompletely understood, but aging and dietary factors resulting in weakening of the colonic wall are thought to be contributing factors. Marfan's syndrome, a connective tissue disorder, is associated with colonic diverticular disease^{110;111} and with heart valve abnormalities¹¹². Acromegaly is also associated with heart valve abnormalities¹¹³, possibly due to effects of GH, which has altered the extracellular matrix¹¹⁴. Based on these partial similarities between acromegaly and Marfan's syndrome, we hypothesized that acromegaly might be associated with increased prevalence of colonic diverticula. Therefore, in **Chapter 9** we determined whether characteristics of acromegaly, especially GH and/or IGF-I concentrations at diagnosis, were associated with colonic diverticular disease. In addition, we also assessed the prevalence of dolichocolon and colonic polyps.

Part IV. Effects of the exon-3 deleted growth hormone receptor polymorphism

The effect of the deletion of d3GHR has been investigated in several clinical conditions, some focusing on the single or double deletion of exon 3 as one genotype (GHR_{wt} *vs.* GHR_{d3}), and some regarding the single or double deletion of exon 3 as two different genotypes (GHR_{wt-wt} *vs.* GHR_{wt-d3} and GHR_{d3-d3}). In children the genotype-phenotype relationships of the GHR polymorphisms can more easily be assessed by growth velocity, which is not possible in adults. Therefore, in **Chapter 10** we focused on the overall effect of the GHR_{wt-d3} and GHR_{d3-d3} geno-

type on growth in children treated with human GH in a structured meta-analysis.

We hypothesized that the GHR_{d3} genotype would render the patients more susceptible for the long-term complications of acromegaly. Therefore, in **Chapter 11** we determined whether the d3GHR polymorphism may have rendered acromegalic patients more susceptible for the long-term, irreversible effects of GH, by assessing long-term clinical outcome, including body composition, cardiovascular risk factors, the metabolic syndrome, joint-related problems and colon pathology.

Since the first publication on enhanced growth in children with the GHR_{d3} genotype in 2004, several studies assessed the effects of this polymorphism in various clinical conditions. We systematically reviewed all these studies in **Chapter 12**, in order to establish the functional consequences of the exon-3 deleted GHR polymorphism in more detail.

REFERENCES

- (1) Marie P. On two cases of acromegaly: marked hypertrophy of the upper and lower limbs and head. *Rev Med* 6, 297-333. 1886.
- (2) Cushing H. III. Partial Hypophysectomy for Acromegaly: With Remarks on the Function of the Hypophysis. *Ann Surg* 1909; 50(6):1002-1017.
- (3) Evans HM, Long JA. Characteristic Effects upon Growth, Oestrus and Ovulation Induced by the Intraperitoneal Administration of Fresh Anterior Hypophyseal Substance. *Proc Natl Acad Sci U S A* 1922; 8(3):38-39.
- (4) Alexander L, Appleton D, Hall R, Ross WM, Wilkinson R. Epidemiology of acromegaly in the Newcastle region. *Clin Endocrinol (Oxf)* 1980; 12(1):71-79.
- (5) Ritchie CM, Atkinson AB, Kennedy AL, Lyons AR, Gordon DS, Fannin T *et al.* Ascertainment and natural history of treated acromegaly in Northern Ireland. *Ulster Med J* 1990; 59(1):55-62.
- (6) Chandrasekharappa SC, Guru SC, Manickam P, Olufemi SE, Collins FS, Emmert-Buck MR *et al.* Positional cloning of the gene for multiple endocrine neoplasia-type 1. *Science* 1997; 276(5311):404-407.
- (7) Teh BT, Kytola S, Farnebo F, Bergman L, Wong FK, Weber G *et al.* Mutation analysis of the MEN1 gene in multiple endocrine neoplasia type 1, familial acromegaly and familial isolated hyperparathyroidism. *J Clin Endocrinol Metab* 1998; 83(8):2621-2626.
- (8) Weinstein LS, Shenker A, Gejman PV, Merino MJ, Friedman E, Spiegel AM. Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. *N Engl J Med* 1991; 325(24):1688-1695.
- (9) Boikos SA, Stratakis CA. Carney complex: the first 20 years. *Curr Opin Oncol* 2007; 19(1):24-29.
- (10) Gadelha MR, Prezant TR, Une KN, Glick RP, Moskal SF, Vaisman M *et al.* Loss of heterozygosity on chromosome 11q13 in two families with acromegaly/gigantism is independent of mutations of the multiple endocrine neoplasia type I gene. *J Clin Endocrinol Metab* 1999; 84(1):249-256.
- (11) Vierimaa O, Georgitsi M, Lehtonen R, Vahteristo P, Kokko A, Raitila A *et al.* Pituitary adenoma predisposition caused by germline mutations in the AIP gene. *Science* 2006; 312(5777):1228-1230.
- (12) Daly AF, Vanbellinghen JF, Khoo SK, Jaffrain-Rea ML, Naves LA, Guitelman MA *et al.* Aryl hydrocarbon receptor-interacting protein gene mutations in familial isolated pituitary adenomas: analysis in 73 families. *J Clin Endocrinol Metab* 2007; 92(5):1891-1896.
- (13) Nelson AE, Ho KK. Abuse of growth hormone by athletes. *Nat Clin Pract Endocrinol Metab* 2007; 3(3):198-199.
- (14) Perls TT, Reisman NR, Olshansky SJ. Provision or distribution of growth hormone for "antiaging": clinical and legal issues. *JAMA* 2005; 294(16):2086-2090.
- (15) Giustina A, Veldhuis JD. Pathophysiology of the neuroregulation of growth hormone secretion in experimental animals and the human. *Endocr Rev* 1998; 19(6):717-797.
- (16) Kopchick JJ, Parkinson C, Stevens EC, Trainer PJ. Growth hormone receptor antagonists: discovery, development, and use in patients with acromegaly. *Endocr Rev* 2002; 23(5):623-646.
- (17) Le RD, Bondy C, Yakar S, Liu JL, Butler A. The somatomedin hypothesis: 2001. *Endocr Rev* 2001; 22(1):53-74.

- (18) Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature* 1999; 402(6762):656-660.
- (19) Gualillo O, Lago F, Gomez-Reino J, Casanueva FF, Dieguez C. Ghrelin, a widespread hormone: insights into molecular and cellular regulation of its expression and mechanism of action. *FEBS Lett* 2003; 552(2-3):105-109.
- (20) Petersenn S. Growth hormone secretagogues and ghrelin: an update on physiology and clinical relevance. *Horm Res* 2002; 58 Suppl 3:56-61.
- (21) Urbanek M, Russell JE, Cooke NE, Liebhaber SA. Functional characterization of the alternatively spliced, placental human growth hormone receptor. *J Biol Chem* 1993; 268(25):19025-19032.
- (22) Kratzsch J, Wu Z, Kiess W, Dehmel B, Bosse-Henck A, Reuter W *et al.* The exon 3-retaining and the exon 3-deleted forms of the growth hormone-binding protein (GHBP) in human serum are regulated differently. *Clin Endocrinol (Oxf)* 2001; 54(1):61-68.
- (23) Pantel J, Grulich-Henn J, Bettendorf M, Strasburger CJ, Heinrich U, Amselem S. Heterozygous nonsense mutation in exon 3 of the growth hormone receptor (GHR) in severe GH insensitivity (Laron syndrome) and the issue of the origin and function of the GHRd3 isoform. *J Clin Endocrinol Metab* 2003; 88(4):1705-1710.
- (24) Dos SC, Essioux L, Teinturier C, Tauber M, Goffin V, Bougneres P. A common polymorphism of the growth hormone receptor is associated with increased responsiveness to growth hormone. *Nat Genet* 2004; 36(7):720-724.
- (25) Jadresic A, Banks LM, Child DF, Diamant L, Doyle FH, Fraser TR *et al.* The acromegaly syndrome. Relation between clinical features, growth hormone values and radiological characteristics of the pituitary tumours. *Q J Med* 1982; 51(202):189-204.
- (26) Nabarro JD. Acromegaly. *Clin Endocrinol (Oxf)* 1987; 26(4):481-512.
- (27) Molitch ME. Clinical manifestations of acromegaly. *Endocrinol Metab Clin North Am* 1992; 21(3):597-614.
- (28) Scarpa R, De BD, Pivonello R, Marzullo P, Manguso F, Sodano A *et al.* Acromegalic axial arthropathy: a clinical case-control study. *J Clin Endocrinol Metab* 2004; 89(2):598-603.
- (29) Barkan AL, Stred SE, Reno K, Markovs M, Hopwood NJ, Kelch RP *et al.* Increased growth hormone pulse frequency in acromegaly. *J Clin Endocrinol Metab* 1989; 69(6):1225-1233.
- (30) Greenman Y, Tordjman K, Kisch E, Razon N, Ouaknine G, Stern N. Relative sparing of anterior pituitary function in patients with growth hormone-secreting macroadenomas: comparison with nonfunctioning macroadenomas. *J Clin Endocrinol Metab* 1995; 80(5):1577-1583.
- (31) Kaltsas GA, Mukherjee JJ, Jenkins PJ, Satta MA, Islam N, Monson JP *et al.* Menstrual irregularity in women with acromegaly. *J Clin Endocrinol Metab* 1999; 84(8):2731-2735.
- (32) Eskildsen PC, Kruse A, Kirkegaard C. The pituitary-thyroid axis in acromegaly. *Horm Metab Res* 1988; 20(12):755-757.
- (33) Lie JT. Pathology of the heart in acromegaly: anatomic findings in 27 autopsied patients. *Am Heart J* 1980; 100(1):41-52.

- (34) Pietrobelli DJ, Akopian M, Olivieri AO, Renauld A, Garrido D, Artese R *et al.* Altered circadian blood pressure profile in patients with active acromegaly. Relationship with left ventricular mass and hormonal values. *J Hum Hypertens* 2001; 15(9):601-605.
- (35) Minniti G, Moroni C, Jaffrain-Rea ML, Bondanini F, Gulino A, Cassone R *et al.* Prevalence of hypertension in acromegalic patients: clinical measurement versus 24-hour ambulatory blood pressure monitoring. *Clin Endocrinol (Oxf)* 1998; 48(2):149-152.
- (36) Colao A, Spinelli L, Marzullo P, Pivonello R, Petretta M, Di SC *et al.* High prevalence of cardiac valve disease in acromegaly: an observational, analytical, case-control study. *J Clin Endocrinol Metab* 2003; 88(7):3196-3201.
- (37) Alexander L, Appleton D, Hall R, Ross WM, Wilkinson R. Epidemiology of acromegaly in the Newcastle region. *Clin Endocrinol (Oxf)* 1980; 12(1):71-79.
- (38) Bengtsson BA, Eden S, Ernest I, Oden A, Sjogren B. Epidemiology and long-term survival in acromegaly. A study of 166 cases diagnosed between 1955 and 1984. *Acta Med Scand* 1988; 223(4):327-335.
- (39) Etxabe J, Gaztambide S, Latorre P, Vazquez JA. Acromegaly: an epidemiological study. *J Endocrinol Invest* 1993; 16(3):181-187.
- (40) Rajasoorya C, Holdaway IM, Wrightson P, Scott DJ, Ibbertson HK. Determinants of clinical outcome and survival in acromegaly. *Clin Endocrinol (Oxf)* 1994; 41(1):95-102.
- (41) Swearingen B, Barker FG, Katznelson L, Biller BM, Grinspoon S, Klibanski A *et al.* Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. *J Clin Endocrinol Metab* 1998; 83(10):3419-3426.
- (42) Bates AS, Van't HW, Jones JM, Clayton RN. An audit of outcome of treatment in acromegaly. *Q J Med* 1993; 86(5):293-299.
- (43) Wright AD, Hill DM, Lowy C, Fraser TR. Mortality in acromegaly. *Q J Med* 1970; 39(153):1-16.
- (44) Orme SM, McNally RJ, Cartwright RA, Belchetz PE. Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. *J Clin Endocrinol Metab* 1998; 83(8):2730-2734.
- (45) Beauregard C, Truong U, Hardy J, Serri O. Long-term outcome and mortality after transsphenoidal adenomectomy for acromegaly. *Clin Endocrinol (Oxf)* 2003; 58(1):86-91.
- (46) Melmed S. Medical progress: Acromegaly. *N Engl J Med* 2006; 355(24):2558-2573.
- (47) Melmed S, Casanueva F, Cavagnini F, Chanson P, Frohman LA, Gaillard R *et al.* Consensus statement: medical management of acromegaly. *Eur J Endocrinol* 2005; 153(6):737-740.
- (48) van den BG, van DH, Frolich M, Meinders AE, Roelfsema F. Can intra-operative GH measurement in acromegalic subjects predict completeness of surgery? *Clin Endocrinol (Oxf)* 1998; 49(1):45-51.
- (49) Gittoes NJ, Sheppard MC, Johnson AP, Stewart PM. Outcome of surgery for acromegaly--the experience of a dedicated pituitary surgeon. *QJM* 1999; 92(12):741-745.
- (50) Kreutzer J, Vance ML, Lopes MB, Laws ER, Jr. Surgical management of GH-secreting pituitary adenomas: an outcome study using modern remission criteria. *J Clin Endocrinol Metab* 2001; 86(9):4072-4077.
- (51) Hofland LJ, Lamberts SW. The pathophysiological consequences of somatostatin receptor internalization and resistance. *Endocr Rev* 2003; 24(1):28-47.
- (52) Freda PU. Somatostatin analogs in acromegaly. *J Clin Endocrinol Metab* 2002; 87(7):3013-3018.

- (53) Ben-Shlomo A, Melmed S. Clinical review 154: The role of pharmacotherapy in perioperative management of patients with acromegaly. *J Clin Endocrinol Metab* 2003; 88(3):963-968.
- (54) Schade R, Andersohn F, Suissa S, Haverkamp W, Garbe E. Dopamine agonists and the risk of cardiac-valve regurgitation. *N Engl J Med* 2007; 356(1):29-38.
- (55) Maffei P, Martini C, Pagano C, Siculo N, Corbetti F. Lipohypertrophy in acromegaly induced by the new growth hormone receptor antagonist pegvisomant. *Ann Intern Med* 2006; 145(4):310-312.
- (56) Colao A, Ferone D, Marzullo P, Di SA, Cerbone G, Sarnacchiaro F *et al.* Effect of different dopaminergic agents in the treatment of acromegaly. *J Clin Endocrinol Metab* 1997; 82(2):518-523.
- (57) Abs R, Verhelst J, Maiter D, Van AK, Nobels F, Coolens JL *et al.* Cabergoline in the treatment of acromegaly: a study in 64 patients. *J Clin Endocrinol Metab* 1998; 83(2):374-378.
- (58) Muratori M, Arosio M, Gambino G, Romano C, Biella O, Faglia G. Use of cabergoline in the long-term treatment of hyperprolactinemic and acromegalic patients. *J Endocrinol Invest* 1997; 20(9):537-546.
- (59) Cannavo S, Almoto B, Cavalli G, Squadrito S, Romanello G, Vigo MT *et al.* Acromegaly and coronary disease: an integrated evaluation of conventional coronary risk factors and coronary calcifications detected by computed tomography. *J Clin Endocrinol Metab* 2006; 91(10):3766-3772.
- (60) Biermasz NR, van DH, Roelfsema F. Ten-year follow-up results of transsphenoidal microsurgery in acromegaly. *J Clin Endocrinol Metab* 2000; 85(12):4596-4602.
- (61) Howard GM, English FP. Occurrence of glaucoma in acromegalics. *Arch Ophthalmol* 1965; 73:765-768.
- (62) Zanettini R, Antonini A, Gatto G, Gentile R, Tesei S, Pezzoli G. Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Engl J Med* 2007; 356(1):39-46.
- (63) Brada M, Ford D, Ashley S, Bliss JM, Crowley S, Mason M *et al.* Risk of second brain tumour after conservative surgery and radiotherapy for pituitary adenoma. *BMJ* 1992; 304(6838):1343-1346.
- (64) Landolt AM, Haller D, Lomax N, Scheib S, Schubiger O, Siegfried J *et al.* Stereotactic radiosurgery for recurrent surgically treated acromegaly: comparison with fractionated radiotherapy. *J Neurosurg* 1998; 88(6):1002-1008.
- (65) Attanasio R, Epaminonda P, Morti E, Giugni E, Ventrella L, Cozzi R *et al.* Gamma-knife radiosurgery in acromegaly: a 4-year follow-up study. *J Clin Endocrinol Metab* 2003; 88(7):3105-3112.
- (66) Clemmons DR. IGF-I assays: current assay methodologies and their limitations. *Pituitary* 2007; 10(2):121-128.
- (67) Freda PU, Nuruzzaman AT, Reyes CM, Sundeen RE, Post KD. Significance of "abnormal" nadir growth hormone levels after oral glucose in postoperative patients with acromegaly in remission with normal insulin-like growth factor-I levels. *J Clin Endocrinol Metab* 2004; 89(2):495-500.
- (68) Ben-Shlomo A, Melmed S. Acromegaly. *Endocrinol Metab Clin North Am* 2008; 37(1):101-22, viii.
- (69) Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K *et al.* Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum* 1986; 29(8):1039-1049.
- (70) Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM *et al.* Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Ann Intern Med* 2000; 133(8):635-646.

- (71) van Saase JL, Vandenbroucke JP, van Romunde LK, Valkenburg HA. Osteoarthritis and obesity in the general population. A relationship calling for an explanation. *J Rheumatol* 1988; 15(7):1152-1158.
- (72) Bijkerk C, Houwing-Duistermaat JJ, Valkenburg HA, Meulenbelt I, Hofman A, Breedveld FC *et al.* Heritabilities of radiologic osteoarthritis in peripheral joints and of disc degeneration of the spine. *Arthritis Rheum* 1999; 42(8):1729-1735.
- (73) Colao A, Marzullo P, Vallone G, Marino V, Annecchino M, Ferone D *et al.* Reversibility of joint thickening in acromegalic patients: an ultrasonography study. *J Clin Endocrinol Metab* 1998; 83(6):2121-2125.
- (74) Colao A, Marzullo P, Vallone G, Giaccio A, Ferone D, Rossi E *et al.* Ultrasonographic evidence of joint thickening reversibility in acromegalic patients treated with lanreotide for 12 months. *Clin Endocrinol (Oxf)* 1999; 51(5):611-618.
- (75) Colao A, Cannavo S, Marzullo P, Pivonello R, Squadrito S, Vallone G *et al.* Twelve months of treatment with octreotide-LAR reduces joint thickness in acromegaly. *Eur J Endocrinol* 2003; 148(1):31-38.
- (76) Layton MW, Fudman EJ, Barkan A, Braunstein EM, Fox IH. Acromegalic arthropathy. Characteristics and response to therapy. *Arthritis Rheum* 1988; 31(8):1022-1027.
- (77) Hedbom E, Hauselmann HJ. Molecular aspects of pathogenesis in osteoarthritis: the role of inflammation. *Cell Mol Life Sci* 2002; 59(1):45-53.
- (78) Aigner T, Vornheim SI, Zeiler G, Dudhia J, von der MK, Bayliss MT. Suppression of cartilage matrix gene expression in upper zone chondrocytes of osteoarthritic cartilage. *Arthritis Rheum* 1997; 40(3):562-569.
- (79) Maetzel A, Makela M, Hawker G, Bombardier C. Osteoarthritis of the hip and knee and mechanical occupational exposure--a systematic overview of the evidence. *J Rheumatol* 1997; 24(8):1599-1607.
- (80) Englund M, Paradowski PT, Lohmander LS. Association of radiographic hand osteoarthritis with radiographic knee osteoarthritis after meniscectomy. *Arthritis Rheum* 2004; 50(2):469-475.
- (81) Hart DJ, Doyle DV, Spector TD. Incidence and risk factors for radiographic knee osteoarthritis in middle-aged women: the Chingford Study. *Arthritis Rheum* 1999; 42(1):17-24.
- (82) Lohmander LS, Felson DT. Defining the role of molecular markers to monitor disease, intervention, and cartilage breakdown in osteoarthritis. *J Rheumatol* 1997; 24(4):782-785.
- (83) Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthritis. *Ann Rheum Dis* 1957; 16(4):494-502.
- (84) Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. *Osteoarthritis Cartilage* 2007; 15 Suppl A:A1-56.
- (85) Chipman JJ, Attanasio AF, Birkett MA, Bates PC, Webb S, Lamberts SW. The safety profile of GH replacement therapy in adults. *Clin Endocrinol (Oxf)* 1997; 46(4):473-481.
- (86) Barkan A. Acromegalic arthropathy and sleep apnea. *J Endocrinol* 1997; 155 Suppl 1:S41-S44.
- (87) Barkan AL. Acromegalic arthropathy. *Pituitary* 2001; 4(4):263-264.
- (88) Bluestone R, Bywaters EG, Hartog M, Holt PJ, Hyde S. Acromegalic arthropathy. *Ann Rheum Dis* 1971; 30(3):243-258.
- (89) Dons RF, Rosselet P, Pastakia B, Doppman J, Gorden P. Arthropathy in acromegalic patients before and after treatment: a long-term follow-up study. *Clin Endocrinol (Oxf)* 1988; 28(5):515-524.
- (90) Alexander L, Appleton D, Hall R, Ross WM, Wilkinson R. Epidemiology of acromegaly in the Newcastle region. *Clin Endocrinol (Oxf)* 1980; 12(1):71-79.

- (91) Rajasoorya C, Holdaway IM, Wrightson P, Scott DJ, Ibbertson HK. Determinants of clinical outcome and survival in acromegaly. *Clin Endocrinol (Oxf)* 1994; 41(1):95-102.
- (92) Wassenaar MJ, Biermasz NR, van DN, van der Klaauw AA, Pereira AM, Roelfsema F *et al.* **High prevalence of arthropathy, according to the definitions of radiological and clinical osteoarthritis, in patients with long-term cure of acromegaly: a case-control study.** *Eur J Endocrinol* 2009; 160(3):357-365.
- (93) Hua SC, Yan YH, Chang TC. Associations of remission status and lanreotide treatment with quality of life in patients with treated acromegaly. *Eur J Endocrinol* 2006; 155(6):831-837.
- (94) Kauppinen-Makelin R, Sane T, Sintonen H, Markkanen H, Valimaki MJ, Loyttyniemi E *et al.* **Quality of life in treated patients with acromegaly.** *J Clin Endocrinol Metab* 2006; 91(10):3891-3896.
- (95) Trepp R, Everts R, Stettler C, Fischli S, Allemann S, Webb SM *et al.* **Assessment of quality of life in patients with uncontrolled vs. controlled acromegaly using the Acromegaly Quality of Life Questionnaire (AcroQoL).** *Clin Endocrinol (Oxf)* 2005; 63(1):103-110.
- (96) Webb SM, Badia X, Surinach NL. Validity and clinical applicability of the acromegaly quality of life questionnaire, AcroQoL: a 6-month prospective study. *Eur J Endocrinol* 2006; 155(2):269-277.
- (97) Rowles SV, Prieto L, Badia X, Shalet SM, Webb SM, Trainer PJ. **Quality of life (QOL) in patients with acromegaly is severely impaired: use of a novel measure of QOL: acromegaly quality of life questionnaire.** *J Clin Endocrinol Metab* 2005; 90(6):3337-3341.
- (98) Biermasz NR, van Thiel SW, Pereira AM, Hoftijzer HC, van Hemert AM, Smit JW *et al.* **Decreased quality of life in patients with acromegaly despite long-term cure of growth hormone excess.** *J Clin Endocrinol Metab* 2004; 89(11):5369-5376.
- (99) Neggers SJ, van Aken MO, de Herder WW, Feelders RA, Janssen JA, Badia X *et al.* **Quality of life in acromegalic patients during long-term somatostatin analog treatment with and without pegvisomant.** *J Clin Endocrinol Metab* 2008; 93(10):3853-3859.
- (100) Paisley AN, Rowles SV, Roberts ME, Webb SM, Badia X, Prieto L *et al.* **Treatment of acromegaly improves quality of life, measured by AcroQoL.** *Clin Endocrinol (Oxf)* 2007; 67(3):358-362.
- (101) Biermasz NR, Pereira AM, Smit JW, Romijn JA, Roelfsema F. **Morbidity after long-term remission for acromegaly: persisting joint-related complaints cause reduced quality of life.** *J Clin Endocrinol Metab* 2005; 90(5):2731-2739.
- (102) Aloia JF, Petrak Z, Ellis K, Cohn SH. **Body composition and skeletal metabolism following pituitary irradiation in acromegaly.** *Am J Med* 1976; 61(1):59-63.
- (103) Halse J, Melsen F, Mosekilde L. **Iliac crest bone mass and remodelling in acromegaly.** *Acta Endocrinol (Copenh)* 1981; 97(1):18-22.
- (104) Ezzat S, Melmed S, Endres D, Eyre DR, Singer FR. **Biochemical assessment of bone formation and resorption in acromegaly.** *J Clin Endocrinol Metab* 1993; 76(6):1452-1457.
- (105) Ho PJ, Fig LM, Barkan AL, Shapiro B. **Bone mineral density of the axial skeleton in acromegaly.** *J Nucl Med* 1992; 33(9):1608-1612.
- (106) Kaji H, Sugimoto T, Nakaoka D, Okimura Y, Kaji H, Abe H *et al.* **Bone metabolism and body composition in Japanese patients with active acromegaly.** *Clin Endocrinol (Oxf)* 2001; 55(2):175-181.

- (107) Biermasz NR, Hamdy NA, Pereira AM, Romijn JA, Roelfsema F. Long-term maintenance of the anabolic effects of GH on the skeleton in successfully treated patients with acromegaly. *Eur J Endocrinol* 2005; 152(1):53-60.
- (108) Munson KD, Hensien MA, Jacob LN, Robinson AM, Liston WA. Diverticulitis. A comprehensive follow-up. *Dis Colon Rectum* 1996; 39(3):318-322.
- (109) Stollman NH, Raskin JB. Diverticular disease of the colon. *J Clin Gastroenterol* 1999; 29(3):241-252.
- (110) Suster SM, Ronnen M, Bubis JJ. Diverticulosis coli in association with Marfan's syndrome. *Arch Intern Med* 1984; 144(1):203.
- (111) Clunie GJ, Mason JM. Visceral diverticula and the Marfan syndrome. *Br J Surg* 1962; 50:51-52.
- (112) van Karnebeek CD, Naeff MS, Mulder BJ, Hennekam RC, Offringa M. Natural history of cardiovascular manifestations in Marfan syndrome. *Arch Dis Child* 2001; 84(2):129-137.
- (113) van der Klaauw AA, Bax JJ, Smit JW, Holman ER, Delgado V, Bleeker GB *et al.* Increased aortic root diameters in patients with acromegaly. *Eur J Endocrinol* 2008; 159(2):97-103.
- (114) Thompson BJ, Shang CA, Waters MJ. Identification of genes induced by growth hormone in rat liver using cDNA arrays. *Endocrinology* 2000; 141(11):4321-4324.

