General Introduction
A complex relationship exists between disease of the cardiovascular system and a spectrum of neural and humoral factors. Recently, the modulating role of hormones, such as thyroid hormone (6-9), in the atherosclerotic process has been emphasized. However, several other hormones, in addition to thyroid hormone, may contribute to atherogenesis, thereby constituting a key element in the concept of cardiovascular endocrinology (10). Recently, evidence has been provided to suggest that disturbances of the pituitary growth hormone (GH) axis and its mitogenic partners, including insulin-like growth factor-1 (IGF-1) and IGF-binding proteins (IGFBP), are critical actors in the initiation of atherosclerotic processes (4; 11; 12).

**GH axis/IGF system**

The GH axis originates in the cerebrum with the brain structures, hypothalamus and pituitary, as regulation centers (figure 1). Growth hormone releasing hormone (GHRH) releases, whereas insulin-like growth factor-I (IGF-I) inhibits secretion of GH from the somatotrope cells in the anterior lobe of the pituitary. Recent evidence supports the notion that GH release from the pituitary is controlled not only by GH-RH and Somatostatin from the hypothalamus, but also by GHrelin from the stomach and hypothalamus. GH is secreted from the anterior pituitary in an individual diurnal pattern, with the highest serum peak levels early in the night. In the circulation, GH is mostly bound to GH binding protein (GHBP). Only unbound GH has biological activity. The GH axis is superimposed on the IGF system. The insulin-like growth factors (IGF-I and IGF-II) are important factors in the regulation of somatic growth, cellular proliferation and metabolism. This regulation is modulated further by at least six distinctive insulin-like growth factor binding proteins (IGF BPs) and IGF BP proteases (13). Both IGF-I and IGF-II are synthesized and secreted from the liver and they are mainly bound to the IGF

![Figure 1:](image_url)
BP-3. The total plasma pool of IGF-II is twice that of IGF-I. The synthesis of IGF-I and IGF BP-3, but not IGF-II, is under regulation by GH and environmental factors (e.g. nutritional status) (14). Both IGF-I and IGF-II are products of a single gene, located on the arm of chromosome 12 (IGF-I), and on the short arm of chromosome 11 (IGF-II) (15). In addition, the proportion of variance attributable to genetic effects for the concentration of IGF-I was 38%, IGF-II: 66% and IGF BP-3: 60%. Therefore a substantial genetic contribution is responsible for the interindividual variation of circulating IGF-I, IGF-II, and IGF BP-3 (16).

The availability of biological active (free circulating) IGF-I is determined by its binding on the IGFBP complex, which consist of a 140 kDa, or a smaller 40 kDa IGF-IGF BP complex. Most circulating IGF-I and IGF-II (in an equimolar ratio) is sequestered by IGF BP-3 (38 kDa to 43 kDa, depending upon the number of sites that are glycolsylated), associated with the 80 kDa acid labile subunit (ALS) in a GH-dependent large complex, leading to an increased residence time in plasma (17). The proteolytic enzymes that are bound to the apical side of tissue capillaries break down the large fraction into smaller GH-independent 40 kDa fractions (consisting only of IGF-I and IGF BP-3), that are capable to transfer into extra capillary tissues. This extravasation results in dissociation of IGF-I, and probably of IGF-II, from the 40 kDa complex, thereby enabling its biological activities in local tissues (18). The local level of free exchangeable IGF-1 is of biological importance for its paracrine/autocrine effects, such as cell proliferation, prevention from apoptosis and synthesis of nitric oxide (NO). In addition to the synthesis of IGF-1 in the liver, GH also stimulates IGF-1 expression in other tissues; which has local autocrine and paracrine actions (vide infra).

**GH deficiency**

The GH axis is one of the first hormonal axis that is defective in pituitary disease. Nowadays, the effects of a relative deficiency in GH axis/IGF system on metabolic processes are recognized. A decreased GH secretion, and subsequently, a decreased plasma level of total IGF-1 is observed in ageing and in patients with type 2 diabetes mellitus and/or premature atherosclerosis. In the general population, a low serum total IGF-1 level (without the analysis of GH secretion) gives rise to an increased risk on ischemic heart disease (IHD) (19). In addition, disturbances in the signalling of the GH receptor lead to a GH resistant state (defined as: inappropriately high serum GH with low serum total IGF-1 and IGFBP-3 levels) that is mostly associated with catabolic conditions, such as

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SMR: standard mortality rate; F: female; Male:male

Table 1: Cardiovascular mortality in patients with adult-onset GH deficiency, due to panhypopituitarism
chronic heart failure, progressive cancer or end-stage renal failure (20; 21). Taken together, the term of GHD includes nowadays a broader range of separate insufficiencies or deficiencies in the GH axis/IGF system than a decade ago.

Acromegaly
GH-secreting pituitary adenomas are the most frequent cause of acromegaly. Chronic high circulating GH levels (with plasma GH levels in the range from 5 to 500 ng/mL) result in an increased plasma IGF-I level, which results in several metabolic disturbances, one of which is insulin resistance.

Accelerated atherosclerotic disease
AGHD
In several retrospective studies, cardiovascular mortality in AGHD is increased in comparison with a matched healthy population. The first report by Rosén and Bengsston showed an increased cardiovascular mortality in subjects with panhypopituitarism substituted with adrenal, gonadal and thyroid hormones, as compared to an age- and gender-matched control population (standard mortality rate, 1.8) (22). Subsequent reports have confirmed this observation (23-28)(Table 1).

No long term effects of GH therapy on the vascular mortality are known at present, although short term analysis of GH intervention in AGHD patients shows a decrease in the increased cardiovascular mortality. However, long term randomised follow-up GH intervention trials will definitively answer whether GH treatment in AGHD patients will result in reduction of cardiovascular mortality.

Acromegaly
Intriguingly, increased mortality from cardiovascular disease is observed in acromegaly. Although cardiomyopathy is presented as a major cause of death, atherosclerotic disease is equally reported as an underlying cause in acromegaly.

In general, the relationship between mortality due to cardiovascular diseases and disturbances in the GH axis/IGF system is best represented by a U-curve: revealing an increased mortality in both GH deficiency and in GH excess.

Lipoprotein metabolism
Disturbances in the GH axis/IGF system coincides with abnormalities in lipoprotein metabolism. Lipoproteins which originates from the intestine or liver, are major carriers for lipids in the circulation. Dietary fatty acids are absorbed in the small intestine, packaged into chylomicrons and secreted into the circulation via the lymphatic system (exogenous lipid pathway). Chylomicrons display a size of 0.1 to 1.0 µM, and a chemical composition in weight percentage of TG 87%, cholesterol 3%, phospholipids 9% and proteins 2%. The major structural protein of chylomicrons is apolipoprotein B-48. In the circulation, chylomicrons are enriched with apo E which facilitate receptor-mediated uptake in the liver.

The liver secretes very low density lipoproteins (VLDL) that possess apo B-100 as their major structural protein. This pathway is called the endogenous lipid pathway. Major functional apolipoproteins are apo C-I, apo C-II, apo C-III and apo E. VLDL particles have a size between 300 and 800 Å, and chemical composition expressed as weight percentage consists of: TG 50-60%, cholesterol 17%, phospholipids 19% and proteins 10%. This pathway is called endogenous lipid pathway.

In the circulation, both chylomicrons- and VLDL-triglycerides are hydrolysed by lipoprotein lipase (LPL) via a so-called common saturable pathway (29). This enzyme is attached to the luminal side of the endothelium. Lipolysis is catalysed by apo C-II, and inhibited by apo C-III. The lipid particle which remains after lipolysis and intravascular remodelling by hepatic lipase and CETP,
is called a remnant particle. Apo B-48 containing remnant particles are preferentially taken up by apo B-48 receptors at the hepatic surface (30), whereas apo B-100 containing particles may either be taken up via the LDL-receptor by hepatocytes or be further processed into smaller lipid particles, such as intermediate density lipoprotein (IDL) and low density lipoproteins (LDL) that are more enriched in cholesteryl-esters by cholesteryl-ester transfer protein (CETP) (31).

High density lipoprotein (HDL) with apo AI as principal protein, removes cholesterol from the peripheral cells. HDL cholesterol is esterified by lecithin: cholesteryl acyltransferase (LCAT), forming cholesteryl esters (CE). This HDL-CE is returned to the liver by: 1. transfer of CE from HDL to triglyceride-rich particles by CETP (as apo B-48 and apo B-100) or 2. by selective uptake by scavenger receptor B1 (32).

Catabolic lipid pathways are mediated through receptors that are expressed at the hepatic surface. apo B-48 lipid particles are taken up by LDL-receptors, apo B-48 receptors and LRP (LDL-receptor related protein) receptors (33). The LDL-receptor expression is dependent upon intracellular cholesterol content; the more cholesterol in the hepatocyte, the less expression of LDL-receptors. No relation is found between intracellular cholesterol content and hepatic LRP expression. Apo E facilitates particle uptake by the LDL receptor.

Glucose homeostasis
Glucose is a major substrate for metabolic fuel. Some tissues and cells are completely dependent on glucose (e.g. erythrocytes and brain) for their energy metabolism. Plasma glucose levels are therefore strictly controlled by several hormones. Dietary glucose is absorbed by enterocytes and delivered to insulin-sensitive tissues, such as liver and skeletal muscles for storage of glucose in the form of glycogen (glycogenolysis). In the fasting and postabsorptive period, glucose is released by degradation of stored glycogen (glycogenolysis), and by gluconeogenesis. Glycogen stores are limited (150 g in the liver, and 300 g in skeletal muscles). The glycogene stores in skeletal muscles are direct sources for energy substrate (e.g. during exercise). Regulation of the glycogenolysis metabolism is reciprocal and depends upon two key enzymes: glycogen phosphorlyase (glycogenolysis) and glycogene synthase (glycogenogenesis). These enzymes are activated by phosphorylation that is itself regulated by hormones (such as adrenalin, insulin and glucagon). Due to limited stores of glycogen, gluconeogenesis (GNG) will contribute most to the circulating glucose after 24 to 36 hours of fasting. The process of GNG takes place for 80% in the liver, and 20% in the kidney. After a 10 day period of fasting, both kidney and liver contribute equally through GNG to the amount of circulating glucose. For GNG, the precursors are pyruvate and lactate (a total contribution of 35%) that are derived from the red blood cell and skeletal muscle, alanine (a total contribution of 35%) that is derived from skeletal muscle, and glycerol (a total contribution of 8%) that is derived from adipose tissue. Entry in the GNG pathway is at three levels: 1. through pyruvate (lactate and alanine), 2. through phosphoenolpyruvate (glutamate) and 3. through dihydroxyacetone phosphate (glycerol). Its regulation occurs at different levels in the GNG pathway, that depends mostly upon glucagon, the substrate availability (alanine), the NADH/NAD+ balance and the level of available ATP. Fatty acids degradation provides additional components, such as acetyl-Co A and NADH/NAD+, that facilitates GNG. Under physiological conditions, catabolism of amino acids from the skeletal muscle to supply substrate for GNG is quantitatively not important. However, in pathological conditions, the release of alanine by skeletal muscle, as a precursor for GNG, results in an increase in GNG (through pyruvate), but also of an increase of urea synthesis through glutamate (Felig Cycle). Consequently,
increased plasma glutamate levels are found. All steps that limit the availability of glucose for degradation (glycolysis) are related to the biological action of insulin. Insulin resistance may be a manifestation of a defect in glucose transport (GLUT4; in muscle and adipose tissue), in decreased expression of enzymes required in the glycolytic cascade (ie hexokinase, glucokinase, fosfokinase I, pyruvate dehydrogenase) or further downstream in the glycolytic pathway. In general, progressive hyperglycemia, or finally type 2 diabetes mellitus, is due to combination of peripheral insulin resistance and impairment in insulin secretion by the insulin-secreting β-cells in the pancreas (34). The function of insulin secreting beta cells is under influence of the different receptors that are involved in the action of insulin and the IGF system. The capacity to compensate for hyperglycemia is related to the maximal insulin secretion. Indeed, in type 2 DM patients who are unable to compensate for hyperglycemia, a decrease in β-cell mass, due to increased apoptosis of insulin secreting cells, was detected (35). Local growth factors, such as IGF-I and IGF-II, control apoptosis (in case of IGF-I), and increase β-cell growth (in case of IGF-I and IGF-II). Receptors for IGF-I and IGF-II are present in the pancreas. Knock-out mice for the IGF-I receptor in the pancreas cell showed an absent first phase and a blunted second phase insulin secretion response (36). IGF-II is a part of the glucose sensitising mechanism in the pancreas that forms an autoregulatory loop to control the definite insulin secretion; insulin secretion is known to adapt to systemic needs for insulin, and in systemic insulin profiles mostly reflect peripheral sensitivity to insulin action in man (37).

**GH/IGF and myocardial adaptation**

Both GH and IGF-I have trophic effects on cardiac muscle. Receptors for GH and IGF-I are found on the surface of cardiomyocytes, but also in the endothelium of the coronary artery. The expression of the IGF-I receptor in cardiomyocytes is facilitated by GH. An increase of systemic GH, due to hormonal substitution in AGHD or in excess in acromegaly, give rise to vasodilation of arteries, with a decrease in cardiac afterload. The ejection fraction of the left ventricle increases after start of GH therapy in AGHD. In excessive amounts of systemic GH, a decreased after load increases heart frequency to maintain constant heart minute volumes, and subsequently the work load of the heart increase. Such long-term periods definitely result in diastolic dysfunction, with a decrease in left ventricular function.

In situations of an increased work or stress load, the heart is in adaptation. During adaptation, cardiomyocytes express more local tissue IGF-I. The expression of local IGF-I is under influence of the GH axis that determine the level of IGF-I receptors on the cardiomyocyte. The exact pathway that regulates the local expression of IGF-I in tissue is not elucidated yet. Downregulation of the expression of IGF-I with a subsequent rise in angiotensin-II gives maladaptation with heart failure. Therefore, IGF-I has trophic effects, controls apoptosis and hypertrophy of cardiomyocytes. Hypertrophic adaptations of the heart muscle are also found in cardiomyopathy, that most frequently results from ischemic heart disease (38). Indeed, although results are not yet conclusive, intervention with GH in patients with ischemic heart disease gives rise to an increase in ejection force of the left ventricle, and GH substitution may therefore be beneficial in this kind of patients (39).