Summary of the Thesis
therosclerosis is a major cause of premature cardiovascular morbidity and mortality in the Western World. One of the principal risk factors in atherosclerotic disease is dyslipidemia with a major focus on elevated plasma LDL-cholesterol levels. However, triglyceride-rich particles also possess atherogenic properties and elevated fasting (and postprandial) plasma levels of these particles are therefore associated with an increased cardiovascular morbidity and mortality (Chapter 1.1). Postprandial levels of lipoprotein remnants reflect the composition and quantity of the diet and lipoprotein metabolism itself. Because Western individuals eat at least three times a day, and intrinsic defects in lipoprotein metabolism are frequently present, most of these people are in an accentuated postprandial state during the day. In the recent NCEP ATP III guidelines, the importance to treat high plasma triglyceride-rich particle levels in order to reduce cardiovascular disease was emphasized. It is relevant that cardiovascular mortality is increased in patients with disturbances in the growth hormone (GH) axis/insulin-like growth factor (IGF) system (such as in GH deficiency and acromegaly). GH is secreted from a small gland just down the brain; the pituitary. GH induces IGF and IGF-related proteins principally in the liver, and other functional tissues. Probably, disturbances in the complex GH IGF system are involved in atherogenesis, via changes in lipoprotein metabolism and in endothelial nitric oxide synthesis (Chapter 1.4). The synthesis of nitric oxide by endothelial cells leads to vasodilatation and influence structures in the subendothelial matrix (such as smooth muscle cells). Such an interaction between hormones and/or hormone-like growth factors and the pathophysiology of the cardiovascular system is encapsulated in a recently introduced term, cardiovascular endocrinology.

The presence of increased plasma triglyceride-rich particle levels, and especially of lipoprotein remnants (RLP), has been assessed in several patient groups with an increased risk of cardiovascular disease. In Chapters 1.9 and 1.10, we showed that both fasting and postprandial plasma RLP-C levels were elevated in patients with a primary atherogenic dyslipidemia: heterozygous familial hypercholesterolemia [FH]. In addition, in Chapters 1.5, 1.6, 1.7 and 1.12 in patients with a secondary dyslipidemia: overt acromegaly, and growth hormone deficiency [GHD]) displayed similar increased fasting and postprandial levels, as compared to healthy BMI, age and gender-matched control subjects (Chapter 1.2).

Although plasma RLP levels were elevated in all these patient groups, the origin of these disturbances was detected at different levels; 1. in the postheparin lipoprotein lipase activity (lower in overt acromegaly; Chapter 1.12), 2. in the production of very low-density lipoproteins (increased in GHD and FH; Chapters 1.6, 1.7, and 1.9), 3. in the activity of cholesteryl ester transfer protein (lower in GHD), 4. and in the expression of hepatic LDL-receptors (decreased in FH and GHD; Chapters 1.7 and 1.9).

The atherogenic process consists of several initial steps of which a key feature is endothelial dysfunction. Treatment with recombinant growth hormone (GH) decreases the rise of plasma RLP levels after a fatty meal, and improves endothelial dysfunction in adult-onset GHD (Chapter 1.6). Moreover, such increased postprandial plasma RLP levels induced a pro-inflammatory state, a condition that is associated with premature atherosclerosis (Chapter 1.8). In addition, fasting plasma RLP-C in FH patients are associated with elevated carotid artery intima media thickness, a surrogate marker of atherosclerotic disease (Chapter 1.11). In in-vitro studies, RLP consist mostly of cholesteryl ester and TG, have mostly the size of VLDL-1 (85%), and could be easily oxidized and give rise to formation of macrophage foam cells (Chapter). With these
results, we showed that RLP particles are closely associated to atherogenic processes. In line with this remark, elevated plasma RLP levels make an individual more susceptible to develop premature atherosclerotic disease.

Type 2 diabetes mellitus is generally due to a combination of insulin resistance and impairment in insulin secretion by the pancreatic β-cell. Progression towards type II DM is related to failure of insulin secreting cells to compensate hyperglycaemia. Deterioration of glucose homeostasis, although mostly limited and temporarily, is noted after the start of GH therapy in AGHD patients (as presented in Chapters 1.5, 1.6, 1.7, and 2.4) and more profoundly, in overt acromegaly (Chapters 1.12 and 3.2). Besides a relationship between the GH axis/IGF system and plasma RLP-C levels, a similar relationship (but hitherto only observed in animal studies) is found with glucose homeostasis, and insulin secretion (Chapter 2.1). A central component of the IGF system, IGF-2, was positively related to insulin secretion in healthy adults, independent of IGF-I, IGF BP-3 and BMI (Chapters 2.2 and 2.3). Receptors of IGF-2 are found on the insulin secreting cells in the pancreas, and IGF-2 is a principal factor in the development of mesodermal tissue, such as the pancreas, muscle, liver and the heart. The variability of GH independent plasma IGF-2 levels is mostly genetically determined (66%), and therefore the total capacity of insulin secretion is partly determined in the prenatal period. A decline in insulin secretion is a key symptom in type II diabetes mellitus, as is an increase in glucose synthesis through the gluconeogenic (GNG) pathway. Indeed, we observed a negative correlation between plasma IGF-2 levels and GNG in GHD patients before and during GH therapy, in comparison to age and BMI matched control subjects (Chapter 2.5). Moreover, the degree of decrease in insulin sensitivity (as determined by estimated HOMA index) due to GH therapy is related to baseline plasma IGF-1 level (Chapter 2.4). The increase of GNG during GH therapy has its origin in increased oxidation of the higher circulating free fatty acid levels, that supply energy to the GNG pathway (with pyruvate as a dominant substrate) (Chapter 2.5). The increase in plasma glucose levels is almost completely compensated by higher circulating insulin levels.

In addition to relationships between the IGF system and insulin secretion, GNG and lipoprotein metabolism, cardiomyocytes are highly influenced by the local and systemic GH/IGF system (Chapter 3.1). High plasma levels of IGF-1, but more special GH, were responsible for heart failure due to cardiomyopathy. After strict control of such increased GH levels, the impaired heart function could be progressively restored to normal (Chapter 3.2).

In conclusion, plasma levels of lipoprotein remnants, which are analysed with the immuno-isolation method, are suitable in testing the susceptibility to premature atherosclerotic disease. Moreover, several metabolic (such as lipoprotein remnants and glucose homeostasis) and endothelium-related components that are considered as key factors in atherogenesis are related to disturbances in the GH axis/IGF system.