

Editorial: Growth Hormone and Cardiovascular Disease: An Area in Rapid Growth

The association between GH and premature cardiovascular disease has been in focus for a considerable amount of time (1, 2). Until recently, however, research in this area were largely confined to epidemiological studies. Before the availability of recombinant GH, the use of GH replacement in GH-deficient subjects was limited primarily to the period of linear growth. This restricted possibilities to study effects of GH replacement in adult GH-deficient subjects. The first placebo-controlled trials of GH replacement in GH-deficient adults were reported about 10 yr ago. Recently, however, this area has received considerable attention. A Medline search for "GH and cardiovascular disease" resulted in 1200 titles, among which about 300 were published since 1995. Studies in both GH-deficient and normal subjects have focused on various aspects of cardiovascular disease, including lipid levels, cardiac function and mass, and, more recently, inflammatory markers. The availability of recombinant GH makes the urgency to study effects of GH more compelling, and an excellent and comprehensive review of the effect of GH replacement in GH-deficient adults was recently published (3).

In 1990, a comprehensive, retrospective study of 333 Swedish patients over 31 yr evaluating mortality in patients with hypopituitarism was reported (2). There was a statistically significant increased mortality in patients with hypopituitarism compared with age- and sex-matched population controls. In addition, death due to cardiovascular disease (myocardial infarction, cardiac failure, cerebrovascular disease, pulmonary embolism, and arterial embolus) was more common among patients than controls. Overall, there was a doubling of mortality due to vascular causes among the patients compared with that of the general population. The authors hypothesized that GH deficiency could account for this increase in mortality (2). Of note, these patients also had lower rates of malignancies, which could argue against an increased mortality due to this cause.

In another retrospective study of 172 patients over 27 yr with complete or partial hypopituitarism, mortality due to all causes was higher than for age- and sex-matched control populations (4). The authors noted an increase in the number of vascular deaths. This did not reach statistical significance, however, possibly due to the lower number of patients in this study, and the authors concluded that the cause of the poor outcome in hypopituitarism may be multifactorial. However, further support for an increased cardiovascular morbidity and mortality in GH deficiency has been provided by other, more recent studies (3). Thus, altogether, available

evidence indicates an association between cardiovascular risk and GH deficiency.

GH has wide-ranging effects, influencing a number of key metabolic processes, body composition, muscle strength, exercise performance, as well as the immune system. All of these factors, alone or in combination, could potentially contribute to the increased cardiovascular morbidity associated with GH deficiency. With the increasing evidence that subjects with insulin resistance are at increased risk for cardiovascular disease, it is of interest that GH deficiency results in a similar phenotype. Thus, GH-deficient adults commonly have more central obesity and increased fasting insulin levels. In several studies using the hyperinsulinemic euglycemic clamp technique, results were indicative of insulin resistance (3, 5). Because GH acts contradictory to insulin in several key metabolic pathways, these findings might be perceived as being opposite to what would be expected. Interestingly, however, during short-term GH administration insulin resistance is further impaired, although long-term studies over 6 months generally report a normalized carbohydrate metabolism (3). It is likely that adaptive mechanisms may modulate a change in response over time. Changes in body composition, mediated by GH, for example, could contribute to these findings. Thus, although the interaction between GH and insulin may be complex, the existence of insulin resistance and its associated phenotype during GH deficiency is well established. It is quite feasible that prolongation of such a state over time could contribute to an increased cardiovascular risk.

A substantial number of studies have addressed plasma lipid levels during both GH deficiency and in response to GH replacement (3). The most common pattern found during GH deficiency is an increase in total and low-density lipoprotein (LDL) cholesterol and apolipoprotein B (apoB) levels, an increase in triglycerides, and a decrease in high-density lipoprotein (HDL) cholesterol levels. In many ways, this profile has the features of combined hyperlipidemia. It is also similar to the lipid profile associated with insulin resistance (where hypertriglyceridemia, low HDL cholesterol, and a qualitative rather than a quantitative change in the LDL fraction with presence of small, dense LDL particles commonly is seen). The quantitative increase in total and LDL cholesterol during GH deficiency might be explained by a decrease in LDL receptor activity, as GH treatment has been found to result in an increase of the receptor activity (6).

In view of the lipid and lipoprotein profile observed during GH deficiency, the decrease in total and LDL cholesterol and apoB levels observed in the majority of studies during administration of GH is compatible with an increase in LDL receptor activity (6). In most studies, GH administration has also been associated with a modest increase in HDL cholesterol, but generally no effects on triglyceride levels have been

Received March 14, 2001. Accepted March 18, 2001.

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noted (3). However, the small number of subjects in most studies might present a problem, as variation in triglyceride levels between individuals is usually higher than for any of the cholesterol parameters. Nevertheless, because triglyceride and HDL cholesterol levels are inversely correlated based on their close metabolic relationship, it should be noted that triglyceride levels were not affected in the majority of studies where HDL cholesterol levels increased. This might suggest that GH could affect these parameters in different ways. The lack of triglyceride increase would seem to be in apparent contradiction to the stimulation of adipose tissue lipolysis during the initial phase of GH replacement therapy. An increased lipolysis in the adipose tissue results in an increased flow of free fatty acids to the liver, which could be expected to result in an increase in triglyceride biosynthesis, lipoprotein formation, and very low density lipoprotein (VLDL) secretion. As discussed above, this pattern would more likely contribute to hypertriglyceridemia and low HDL cholesterol, which are not commonly found during GH replacement. Interestingly, in a mechanistic study, using stable isotope technique, an increased VLDL apoB secretion was, indeed, observed in response to GH replacement therapy, but in parallel an increase in VLDL apoB clearance was also found (7). Thus, the lack of change in VLDL apoB, and likely the lack of overall triglyceride changes, was a result of two opposing mechanisms: increased secretion and increased clearance of VLDL. VLDL particle properties also changed during GH replacement therapy with a relative increase in triglyceride and apoB, leading to a relative increase of the larger VLDL subfraction. It is possible that an increase in LDL receptor activity could contribute also to a faster direct clearance of such large, triglyceride-rich VLDL particles.

In addition to the effects on lipoprotein metabolism, additional mechanisms for the action of GH are possible, including effects on the regulation of fat oxidation and glucose utilization. At present, our knowledge of the hepatic regulation of fatty acid oxidation in relation to the precursor role of fatty acids in formation of triglyceride for storage and/or secretion is limited. The promising findings with a decrease in insulin resistance during administration of thiazolidinediones, peroxisome proliferator-activated receptor γ agonists, could suggest that processes involved in fatty acid metabolism might impact on insulin resistance. While there currently are no data regarding GH and fatty acid oxidation, one could speculate that GH could impact also on such processes.

A somewhat unexpected finding during GH replacement has been a consistently observed increase in lipoprotein (a) [Lp(a)], an independent cardiovascular risk factor (8). Plasma levels of Lp(a) are, to a major extent, determined genetically. Although the lipid portion of Lp(a) closely resembles LDL, the metabolism of Lp(a) and LDL are different, as LDL receptors do not seem to be of major importance for clearance of Lp(a). Lp(a) levels are largely stable within individuals, and the Lp(a) raising effect of GH is, therefore, clearly of interest from a mechanistic viewpoint. So far, the underlying mechanisms have not been clarified (9). Because the magnitude of the increase in Lp(a) is modest, however, it is likely that a possible increase in cardiovascular risk associated with GH replacement therapy would be limited. Furthermore, the

beneficial effects of GH replacement therapy on other lipoprotein fractions likely outweigh an increase in Lp(a).

It is increasingly clear that markers of inflammation are associated with the development of atherosclerosis in the vessel wall. Interestingly, in a recent study, GH was implicated in decreasing inflammatory markers such as C-reactive protein and interleukin 6 (10). However, an increase in C-reactive protein levels is also associated with obesity and an increase in body mass index. The complex association between inflammatory markers, obesity, and cardiovascular disease has made it difficult to dissect cause-effect relationships, and notably GH affects several of these parameters. It has been suggested that a low-level chronic inflammatory state might induce insulin resistance and endothelial dysfunction, although the opposite mechanism also is possible. Because GH shares molecular pathways with a number of cytokines, it is possible that GH may modulate the inflammatory response. All in all, the etiology of increased cardiovascular risk in GH-deficient patients is likely multifactorial, with the potential effect of GH on inflammatory markers being an intriguing possibility that warrants further study.

Apart from effects on carbohydrate and lipid metabolism, GH has consistently been found to affect parameters of cardiac function. Several studies have addressed cardiac function during GH replacement as well as assessed cardiac function parameters in GH-deficient patients compared with healthy controls (3). The studies indicate that GH deficiency was associated with a reduced left ventricular mass and an impaired systolic function. During GH replacement therapy, results suggest an increase in left ventricular mass, as well as in stroke volume and cardiac output (3). The degree of increase in ventricular mass during GH administration was in one study similar to the increase in skeletal muscle mass, compatible with a general anabolic effect of GH (11). Are there any potential drawbacks regarding cardiac function with GH administration? Results from patients with acromegaly suggest that caution should be exercised, because these patients have an increased incidence of left ventricular hypertrophy, hypertension, cardiac failure, and cardiovascular death (1). The underlying mechanisms are likely multifold, as GH in addition to its anabolic effects on muscle tissue also has an antinatriuretic effect, which could lead to an increased plasma volume and overload, that secondarily could affect cardiac function. Altogether, these results could be taken as evidence that either too much or too little GH results in cardiac function parameters associated with cardiovascular risk. It is important to keep in mind, however, that GH has many different actions and that most studies, to date, have been based on a limited number of patients. Thus, our experience is limited, and in the future, larger, more detailed studies with mechanistic approaches are needed.

An example of a comprehensive study of cardiovascular risk factors during GH replacement is published in this issue of the journal. In this study, Colao *et al.* (12) prospectively addressed lipid and lipoprotein levels, fibrinogen levels as well as parameters of cardiac function in 20 patients with GH deficiency during GH replacement therapy over the course of 12 months. Of the patients studied, 10 had childhood-onset and 10 adult-onset hypopituitary states. An additional feature of this study was the inclusion of age- and sex-matched

normals. As the number of both controls and patients were limited, however, comparisons between groups should be interpreted with caution. All patients (except three with idiopathic childhood-onset GH deficiency) had been treated with surgical removal of functioning or nonfunctioning pituitary adenomas and craniopharyngiomas. The authors demonstrated lower levels of insulin-like growth factor I (IGF-I) and HDL cholesterol and higher total cholesterol, triglycerides, and fibrinogen levels in patients than controls. For cardiac function parameters, left ventricular mass index, left ventricular ejection fraction at rest and exercise, peak ejection rate, exercise duration, and exercise capacity were lower in patients than in controls.

After 12 months of treatment with GH, starting at 10 $\mu\text{g}/\text{kg}\cdot\text{day}$ and titrated for the IGF-I concentration, levels of lipids, IGF-I, fibrinogen, and a number of cardiac factors were reevaluated. The results corroborate the body of data on the topic with increases observed in IGF-I and decreases in total and LDL cholesterol, triglycerides, and fibrinogen levels. The authors also found a modest, but significant increase in HDL cholesterol levels. In addition, the left ventricular mass index, left ventricular ejection fraction at peak exercise, exercise duration, and exercise capacity were all increased. These results were consistent in both childhood-onset and adult-onset GH deficiency, although adult-onset patients had somewhat more pronounced changes in cardiac function parameters at study entry.

The authors conclude that although there were improvements in lipids, fibrinogen, and systolic function, the changes were still abnormal compared with age- and sex-matched controls. Thus, a longer period of GH treatment may be necessary to fully normalize the pattern. Overall, the study verifies previous findings regarding lipoprotein and cardiac function parameters during GH replacement therapy. The results also suggest that the more pronounced changes in cardiac function parameters in adult-onset compared with childhood-onset GH-deficient patients at baseline could be due to longer exposure to GH deficiency, as the childhood-onset patients were treated with GH during their developmental period. Thus, the magnitude of changes in cardiac function parameters is likely dependent on the duration of GH deficiency.

It is now well established that adult patients with hypopituitarism have a decreased life expectancy and a higher cardiovascular mortality even with thyroid, adrenal, and gonadal hormone replacement. This indicates that sustained GH replacement therapy to GH-deficient subjects even after cessation of linear growth may be beneficial from a cardiovascular risk point of view. This raises the question of which patients should receive GH replacement therapy. GH secretion varies with age, gender, and body mass index. Such factors may impact both on decisions to administer GH as

well on the response to treatment. Additional studies are needed to assess the role of GH treatment in partially GH-deficient patients. The dose to be chosen also comes into question, and currently used GH doses are largely lower than in years past. Earlier studies have reported high rates of adverse effects with IGF-I levels exceeding age- and sex-matched controls. In view of the recent increase in the availability of recombinant GH and the notion that GH may be used as an antiaging compound, the yin-yang situation regarding GH and cardiovascular disease should be kept in mind. There is good evidence that GH deficiency as well as GH excess results in an increased cardiovascular risk. Because the effect of excess GH is laden with its own burden, continued critical assessment of optimal dosing becomes increasingly important with the widening use of GH therapy. Longer, prospective studies are, therefore, needed to assess the long-term risk for cardiovascular disease in GH-treated patients.

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