Pituitary growth hormone is a potent metabolic hormone introduced into clinical practice by Raben in 1958\[1\]. In the following years, pituitary extracted growth hormone has been used exclusively to stimulate linear growth of growth hormone deficient children\[2\]. The biosynthesis of recombinant human growth hormone (hGH) in 1985 made this hormone available in unlimited amounts and enabled the initiation of clinical trials in conditions other than growth hormone deficiency, such as short children with normal growth hormone secretion, osteoporosis, ageing etc.\[3\]. The findings that growth hormone deficient patients have a small sized heart\[4\] and an impaired cardiac output and that hGH administration to such patients increased the thickness of the cardiac muscle and normalized cardiac performance\[5\], as well as the common knowledge of cardiomegaly in acromegaly\[6\], led to the use of growth hormone in experimental heart disease in animals. Duerr et al.\[7\] and Yang et al.\[8\] reported that insulin-like growth factor-I (IGF-I) and growth hormone, respectively, improved cardiac function in experimental heart failure. Fazio et al.\[9\] followed by treating patients with dilated cardiomyopathy with hGH. These authors reported significant improvement in the left ventricular ejection fraction and an increase in left ventricular muscle mass during 3 months of hGH treatment. All the above findings will undoubtedly lead to an extended use of growth hormone in cardiac diseases.

The increasing use of hGH since 1985 to adult growth hormone deficient patients as well as elderly subjects\[10\], has shown that adults are more sensitive to this hormone than children and their need for replacement is approximately one third the dose administered to children to stimulate\[11\]. If higher doses were used, water and electrolyte retention was registered causing oedema and arthralgia\[11\] presenting an overload to the heart.

Reacting to the report by Fazio et al.\[9\], Turner and Wass\[12\] drew attention to the fact that the pharmacological use of hGH to adults may increase the risk of insulin resistance and colon cancer and enhance mortality from cardiovascular and respiratory disease, to which Frustaci et al.\[13\] added the possibility of arrhythmia.

In addition to its biological effects on protein metabolism, including muscle mass and function, as well as nervous tissue, which are mediated by IGF-I, growth hormone acts on the carbohydrate and lipid metabolism. In relation to the latter, recent studies from different countries have shown undesirable effects on lipoprotein(a) (Lp(a)), a recognized independent risk factor for cardiovascular disease\[14–16\].

Lipoprotein(a) is an LDL-like lipoprotein with an additional apo(a) molecule for each given Lp(a) particle. As it also contains apo B it binds the LDL receptor. The gene for apolipoprotein(a) [apo(a)], the component of Lp(a) that distinguishes it from LDL, has 80% homology with the plasminogen gene. Thus, it has been postulated that the atherogenicity of Lp(a) could be mediated via both the LDL-like mechanism, i.e. abnormal accumulation in the extracellular matrix of the arterial wall, as well as the plasminogen-like character, i.e. inhibition of fibrinolysis by competition with plasminogen binding to fibrin\[14\]. Harpel et al.\[17\] found that degradation of a fibrin clot unmasks sites which bind with apo(a); the same sites would associate Lp(a) with a blood clot at a stage when the clot begins to dissolve. Lipoprotein(a) may also enter blood vessels in macrophages and transform these cells into non-active ‘foam cells’\[14\].

The individual levels of circulating Lp(a) are strongly determined by genetic factors\[18\]. It has been established that variable numbers of K ringle IV-like repeats manifested as apo(a) size isoforms could contribute to 40 to 60% of the genetic variance. Other DNA variants at the apo(a) gene including 5’ flanking are thought to be responsible for the rest. Studies have further shown that Lp(a) levels in offspring closely resemble those of parental levels and are strongly associated with parental and grandparental histories of premature coronary artery disease\[18\]. The levels of Lp(a) are mostly expressed at birth and reach adult levels by the first year of life. A person’s Lp(a) levels are remarkably stable throughout their lifetime\[14\]; however, serum Lp(a) can change during
certain diseases such as chronic renal failure\textsuperscript{[15]}. Insulin treatment of patients with non-insulin dependent diabetes (NIDDM) increased Lp(a)\textsuperscript{[19]}, whereas oestrogens reduced the levels by 10\% in menopausal women\textsuperscript{[20]}. Recently, several authors reported that short- or long-term administration of hGH significantly increased the serum Lp(a) levels both in adults and in children. Eden et al.\textsuperscript{[21]} treated nine adult patients (one woman and eight men) after pituitary tumour operation with hGH and observed marked increases of serum Lp(a) during treatment. Oscarsson et al.\textsuperscript{[22]} treated eight middle-aged overweight men by continuous subcutaneous infusions of hGH for 14 days and found a 42\% increase in serum Lp(a). Olivecrona et al.\textsuperscript{[23]} treating 11 male adults with osteoporosis by hGH for 7 days registered a 10\% increase in Lp(a). We treated three groups of patients with hGH for 1 year\textsuperscript{[24,25]} (seven young adults with growth hormone deficiency; seven girls with Turner syndrome; 15 short children with chronic renal failure) and, in addition seven prepubertal boys with short stature by the growth hormone secreagogue, hexarelin\textsuperscript{[24]}, and found in all four groups serum Lp(a) increases of 67–100\% above pretreatment levels; in some patients the serum levels passed the accepted risk level for cardiovascular disease of 300 mg. l\textsuperscript{-1}. Garry et al.\textsuperscript{[26]} treated 21 growth hormone deficient adults for 3 years and registered a rise in serum Lp(a) in some of the patients. Two recent additional reports on hGH treatment of eight children with idiopathic short stature\textsuperscript{[27]} and eight children with chronic renal insufficiency\textsuperscript{[28]} also describe a rise in serum Lp(a), whereas treatment of patients with acromegaly by octreotide significantly reduced serum growth hormone as well as apolipoprotein(a), a regulator of Lp(a)\textsuperscript{[29]}. The unanimous findings in the papers reviewed above that hGH treatment raises serum Lp(a) in both children and adults sometimes to critical levels, can indicate that the use of hGH in patients with cardiovascular disease or subjects at risk of these diseases, should be viewed with caution. A series of recommendations seem indicated: (a) serum Lp(a) should be monitored during hGH treatment; (b) consideration should be given to discontinue hGH treatment once levels of serum Lp(a) reach 300 mg. l\textsuperscript{-1}, the accepted risk level; (c) children and adults with a genetic predisposition to cardiovascular disease (familial history, hyperlipidemias) may have to be excluded from trials with hGH and IGF-I be used instead (see below).

There is also good news: both Oscarsson et al.\textsuperscript{[30]} and our group\textsuperscript{[31]} found that treatment with IGF-I significantly reduced the serum Lp(a) levels. Insulin-like growth factor-I is the effector hormone of hGH regarding protein metabolism, renotropic effect and bone metabolism and could therefore replace hGH in future cardiologic indications. Furthermore, IGF-I has been found beneficial in the treatment of NIDDM and IDDM in patients of young and adult age\textsuperscript{[32,33]} by reducing insulin secretion\textsuperscript{[34]} and improving glucose utilization. As cardiovascular risk is increased by hyperinsulinemia\textsuperscript{[34]} these patients would have a double benefit by IGF-I treatment applied by a single injection a day in adjusted doses\textsuperscript{[35]}.

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