

## INVITED COMMENTARY

**Lipoprotein(a) and growth hormone: is the puzzle solved?**Vincent Mooser and Helen H Hobbs<sup>1</sup>*Department of Internal Medicine, CHUV University Hospital, Lausanne, Switzerland and <sup>1</sup>Departments of Molecular Genetics and Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA**(Correspondence should be addressed to V Mooser, Department of Internal Medicine, CHUV University Hospital, BH-19/135, 1011 CHUV-Lausanne, Switzerland)*

Recombinant human growth hormone (rhGH) is now used routinely in the treatment of congenital and acquired GH deficiency (GHD). Additional indications for long-term administration of rhGH such as osteoporosis and aging have been proposed, but concerns regarding the safety of such prolonged courses of rhGH have been raised. Administration of rhGH is associated with glucose intolerance, higher plasma insulin concentrations and fluid retention. To add to these potential problems is the finding that rhGH may increase plasma concentrations of the atherogenic lipoprotein(a) (Lp(a)) particle (1, 2).

In Caucasians, increased plasma concentrations of Lp(a) are associated with an increased risk of cardiovascular disease (3), but the mechanism by which Lp(a) is atherogenic has not been fully elucidated. Lp(a) is present only in hedgehogs, great apes and humans (4). In humans, plasma concentrations of Lp(a) vary over a 1000-fold range between individuals. Plasma Lp(a) concentrations are primarily determined by sequences at or close to the gene encoding apolipoprotein(a) (apo(a)), a highly polymorphic glycoprotein that is covalently attached to apolipoprotein B-100 (apoB-100) of low-density lipoprotein (LDL) in Lp(a) (5). apo(a) contains variable numbers of a tandemly repeated ~114 amino acid motif called kringle-4. Overall, there is an inverse relationship between the number of kringle-4 repeats encoded by the *apo(a)* gene and the associated plasma Lp(a) concentration (6, 7). Only a restricted number of physiological, pharmacological or environmental factors influence plasma Lp(a) concentrations (8); GH is one of these factors. Over the past 5 years, more than 20 studies, including six placebo-controlled double-blind studies, have examined the effect of the administration of rhGH on plasma Lp(a) concentrations. Most studies show that rhGH administration is associated with a 110–200% increase in plasma Lp(a) concentrations, but in two studies, plasma Lp(a) concentrations remained unchanged after 12 months of rhGH therapy (9, 10). Both of these studies were performed in Japanese children, which may reflect inter-ethnic differences in the effect of rhGH on plasma Lp(a) concentrations.

In this issue of *European Journal of Endocrinology*, Nolte *et al.* (11) report the effect of rhGH administration on plasma Lp(a) concentrations in a randomised,

placebo-controlled, double-blind 12-month study involving 32 adults with GHD. The authors found that rhGH administration induced an ~140% increase in plasma Lp(a) concentrations and an ~14% decrease in LDL-cholesterol concentrations. This well-designed and well-executed study demonstrates once again that administration of rhGH to GHD adults is associated with a significant increase in plasma Lp(a) concentrations.

Should we, as clinicians, be concerned about the Lp(a)-increasing effect of rhGH? The answer to this question is not as straightforward as one might suppose. The increase in plasma Lp(a) concentrations associated with rhGH substitution in GHD patients is modest, especially in relationship to the wide inter-individual variability in plasma Lp(a) concentrations in the general population. A direct relationship exists between plasma LDL-cholesterol concentrations and the incidence of coronary atherosclerosis. In contrast, the atherogenicity of Lp(a) does not appear to be concentration-dependent over the entire range of plasma Lp(a) concentrations. Lp(a) is associated with a significant risk when plasma Lp(a) concentrations are greater than about 20–30 mg/dl (3). If subjects in the study by Nolte's group were classified as having low Lp(a) concentrations (i.e. <20 mg/dl) or high Lp(a) concentrations (>20 mg/dl), only two of 32 subjects treated with rhGH moved from the low- to the high-risk category with treatment.

The Lp(a)-increasing effect of rhGH is coupled with a significant reduction in the plasma LDL-cholesterol concentrations (1, 2, 11). GHD patients tend to have higher plasma LDL-cholesterol concentrations than healthy controls and are at a significantly greater risk of developing cardiovascular events (12), despite their lower plasma Lp(a) concentrations. The beneficial LDL-decreasing effect of rhGH in GHD individuals may counterbalance the potentially detrimental effect of the increase in plasma Lp(a) concentrations. Moreover, in non-GHD subjects, reduction of plasma LDL-cholesterol concentrations using pharmacological agents that do not affect plasma Lp(a) significantly reduces coronary risk (13). Even in individuals with high plasma concentrations of Lp(a), it appears that decreasing plasma LDL-cholesterol concentrations may obviate the atherogenic effects of a high plasma Lp(a) concentration (14).

Should plasma concentrations of Lp(a) be monitored during administration of rhGH in GHD subjects? It seems reasonable to determine plasma Lp(a) concentrations at baseline, as this will assist in the characterization of the cardiovascular risk-factor profile of the subject. However, as there is no evidence suggesting that the modest changes in plasma Lp(a) concentrations during rhGH therapy are grounds for adjusting the doses or discontinuing rhGH, plasma Lp(a) concentrations need not be monitored in GHD subjects. Additional long-term prospective studies are required to determine if the Lp(a)-increasing effect of rhGH treatment has any effect on the development of atherosclerosis in GHD, or in the much larger population of potential non-GHD subjects.

The mechanism by which rhGH administration increases plasma Lp(a) concentrations and yet decreases plasma concentrations of LDL-cholesterol is not understood. The Lp(a)-increasing effect of rhGH does not seem to be mediated by insulin-like growth factor-I (IGF-I), as IGF-I tends to decrease plasma Lp(a) concentrations, at least during short-term administration (15, 16). Apo(a) is synthesized by the liver, but the *cis*-regulatory sequences and the transcription factors that control the *apo(a)* gene expression have not been defined. A significant fraction of the newly synthesized apo(a) protein undergoes endoplasmic reticulum (ER)-associated degradation (A White, personal communication). It appears there is an inverse relationship between the size of the apo(a) glycoprotein and the proportion of apo(a) that is degraded, which may account for the larger molecular weight forms of apo(a) tending to be associated with lower plasma concentrations of Lp(a). After apo(a) is translocated from the ER to the Golgi complex, where additional sugars are added to the protein backbone, the protein is secreted. apo(a) remains bound to the hepatocyte surface and then forms a disulfide linkage with apoB-100 to form Lp(a) (17). The fate of Lp(a) in the circulation is not known. Metabolic turnover studies of Lp(a) before and after rhGH treatment would settle the question as to whether rhGH enhances the synthesis of apo(a) or retards its clearance. GH treatment increases LDL-receptor activity (18) which is likely to be responsible for its LDL-cholesterol decreasing effect. The fact that rhGH administration increases the LDL-receptor activity and yet increases plasma Lp(a) concentrations, provides additional evidence that the LDL-receptor is not the major clearance pathway for Lp(a). Elucidation of the molecular mechanisms by which rhGH increases plasma Lp(a) concentrations may unravel some new targets by which the metabolism of apo(a) could be manipulated.

Finally, the Lp(a)-increasing effect of GH may contribute to inter-ethnic differences in the distribution of plasma Lp(a) concentrations. Median plasma Lp(a) concentrations are two- to threefold higher in individuals of African descent than in either Caucasian or Oriental people (19, 20). Recently, we demonstrated

that plasma Lp(a) concentrations are largely determined by the *apo(a)* gene in African-Americans, just as they are in Caucasians (21), and that plasma Lp(a) concentrations tend to be higher in African-Americans over the entire size spectrum of apo(a) alleles. These data are consistent with the higher plasma concentrations of Lp(a) in African-Americans being due to a common sequence variant in the *apo(a)* gene or a *trans*-acting factor that either upregulates the synthesis of Lp(a) or decreases its degradation. We favor the latter hypothesis, and suggest that GH is such a candidate *trans*-acting factor. Recently, it has been reported that individuals of African descent have higher plasma concentrations of GH (22), but whether this, or other, inter-ethnic differences are responsible for the high plasma Lp(a) concentrations in Africans remains to be established.

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## References

- Olivecrona H, Ericsson S, Berglund L & Angelin B. Increased concentrations of serum lipoprotein(a) in response to growth hormone treatment. *British Medical Journal* 1993 **306** 1726–1727.
- Oscarsson J, Ottosson M, Wiklund O, Marin P, Vikman-Adolfsson K, Björntorp P & Edén S. Low dose continuously infused growth hormone results in increased lipoprotein(a) and decreased low density lipoprotein cholesterol concentrations in middle-aged men. *Clinical Endocrinology* 1994 **41** 109–116.
- Bostom AG, Cupples LA, Jenner JL, Ordovas JM, Semal LJ, Wilson PWF, Schaefer EJ & Castelli WP. Elevated plasma lipoprotein(a) and coronary heart disease in men aged 55 years and younger. A prospective study. *Journal of the American Medical Association* 1996 **276** 544–548.
- Utermann G. The mysteries of lipoprotein(a). *Science* 1989 **246** 904–910.
- Boerwinkle E, Leffert CC, Lin J, Lackner C, Chiesa G & Hobbs HH. Apolipoprotein(a) gene accounts for greater than 90% of the variation in plasma lipoprotein(a) concentrations. *Journal of Clinical Investigation* 1992 **90** 52–60.
- Utermann GH, Menzel HJ, Kraft HG, Duba HC, Kemmler HG & Seitz C. Lp(a) glycoprotein phenotypes. Inheritance and relation to Lp(a)-lipoprotein concentrations in plasma. *Journal of Clinical Investigation* 1987 **80** 458–465.
- Mooser V, Mancini FP, Bopp S, Pethö-Schramm A, Guerra R, Boerwinkle E, Muller HR & Hobbs HH. Sequence polymorphisms in the apo(a) gene associated with specific levels of Lp(a) in plasma. *Human Molecular Genetics* 1995 **4** 173–181.
- Berglund L. Diet and drug therapy for lipoprotein(a). *Current Opinion in Lipidology* 1995 **6** 48–56.
- Hassan HMS, Kohno H, Kuromaru R, Honda S & Ueda K. Lipoprotein(a) changes during growth hormone treatment. *Clinical Endocrinology* 1995 **43** 655.
- Hassan HMS, Kohno H, Kuromaru R, Honda S & Ueda K. Body composition, atherogenic risk factors and apolipoproteins following growth hormone treatment. *Acta Paediatrica* 1996 **85** 899–901.
- Nolte W, Rädisch C, Armstrong VW, Hüfner M & von zur Mühlen A. The effect of recombinant human GH replacement

- therapy on lipoprotein(a) and other lipid parameters in adults with acquired GH deficiency: results of a double-blind and placebo-controlled trial. *European Journal of Endocrinology* 1997 **137** 459–466.
- 12 Rosen T & Bengtsson BA. Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet* 1990 **336** 285–288.
  - 13 Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW *et al.* Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *New England Journal of Medicine* 1995 **333** 1301–1307.
  - 14 Maher VM, Brown BG, Marcovina SM, Hillger LA, Zhao XQ & Albers JJ. Effects of lowering elevated LDL cholesterol on cardiovascular risk of lipoprotein(a). *Journal of the American Medical Association* 1995 **274** 1771–1774.
  - 15 Oscarsson J, Lundstam U, Gustafsson G, Wilton P, Edén S & Wiklund O. Recombinant human insulin-like growth factor-I decreases serum lipoprotein(a) concentrations in normal adult men. *Clinical Endocrinology* 1995 **42** 673–676.
  - 16 Zenobi PD, Holzmann P, Glatz Y, Riesen WF & Froesch ER. Improvement of lipid profile in Type 2 (non-insulin-dependent) diabetes mellitus by insulin-like growth factor I. *Diabetologia* 1993 **36** 465–469.
  - 17 White AL & Lanford RE. Cell surface assembly of lipoprotein(a) in primary cultures of baboon hepatocytes. *Journal of Biochemical Chemistry* 1994 **269** 28716–28723.
  - 18 Rudling M, Olivecrona H, Eggersten G & Angelin B. Regulation of rat hepatic low density lipoprotein receptors. *In vivo* stimulation by growth hormone is not mediated by insulin-like growth factor I. *Journal of Clinical Investigation* 1996 **97** 292–299.
  - 19 Marcovina SM, Albers JJ, Wijsman, Zhang Y, Chapman NH & Kennedy H. Differences in Lp(a) concentrations and apo(a) polymorphs between Black and White populations. *Journal of Lipid Research* 1996 **37** 2569–2585.
  - 20 Gaw A, Boerwinkle E, Cohen JC & Hobbs HH. Comparative analysis of the *apo(a)* gene, apo(a) glycoprotein and plasma concentrations of Lp(a) in three ethnic groups. *Journal of Clinical Investigation* 1994 **93** 2526–2534.
  - 21 Mooser V, Sheer DC, Marcovina SM, Wang J, Guerra R, Cohen J & Hobbs HH. The apo(a) gene is the major determinant of variation in plasma Lp(a) levels in African-Americans. *American Journal of Human Genetics* 1997 (In Press).
  - 22 Wright NM, Renault J, Willi S, Veldhuis JD, Pandey JP, Gordon L, Key LL & Bell NH. Greater secretion of growth hormone in Black than in White men: possible factor in greater bone mineral density – a clinical research center study. *Journal of Clinical Endocrinology and Metabolism* 1995 **80** 2291–2297.
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