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Hyperlipoproteinemia of lipoprotein Lp(a)

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ABSTRACT

Lp(a) is a lipoprotein with unknown physiological role. All we know for sure is that individuals with high Lp(a) levels are at an increased atherosclerosis risk. The Lp(a) plasma concentration correlates inversely with the molecular weight of the apo-a isoform; this is valid, however, only in healthy persons belonging to one ethnic group. Diseases, e.g. liver or kidney damage, pregnancy and menopause profoundly alter plasma Lp(a) levels, and it also appears that fertile women have higher levels as compared to men. Many studies of various laboratories demonstrate that plasma Lp(a) concentrations correlate with the incidence of atherosclerosis and myocardial infarction. In the healthy white western population, a threshold level of approx. 25 mg/dl seems to exist below which no increased atherosclerosis risk may be evident. This value certainly has to be adapted for different ethnic groups, as well as for individuals suffering from diseases known to influence Lp(a). Unfortunately we know today only little about the possible therapeutic manipulation of plasma Lp(a) concentrations.

INTRODUCTION

Lipoprotein-a (Lp-a) has been detected in 1963 by Berg [1] Its close relation to LDL has been recognized already at this time, as it was described as a genetic variant of Lp B. Numerous publications of Lp(a) research appeared until today (for reviews see Ref. 2 - 4). After cloning of apo-a and the elucidation of its similarity of the apo-a gene with that of plasminogen [5], a new era of Lp(a) research begun. The interest in Lp(a) is well justified by the fact, that it represents one of the most atherogenic lipoprotein known today. Nevertheless, all the efforts in various laboratories failed to uncover a possible physiological function for this lipoprotein. All what is known today is that individuals with Lp(a) plasma concentrations exceeding 20 - 30 mg/dl are at an 2 - 3 fold risk for atherosclerosis and myocardial infarction (M.I.). An exact figure for a possible threshold value for Lp(a), above which this lipoprotein might be atherogenic cannot be given at present time, because of the difficulties arising in the standardization of Lp(a) measurements.
The quantification of Lp(a) is not a straight forward procedure because of its polymorphic nature: i) Lp(a) consists in its protein moiety of apo B plus the specific antigen (apo-a), the latter being a glycoprotein with variable carbohydrate content; ii) There exist 6 - 10 genetic isoforms of apo-a which exhibit a great variation in the molecular weight ranging from 270 - 1000 kD [6]. iii) Apo-a is composed of a variable number of protein segments which are repeated more than 30 times; these repeats cross react immunochemically with plasminogen, (kringle 4). In spite of all these difficulties it is remarkeable that most of the Lp(a) values published from numerous laboratories using different methodology match each other quite well.

The standardization of Lp(a) measurements in clinical chemistry is currently worked out by many groups. Until firm recommendations may be given it is safe enough to use a commercial standard (e.g. from Immuno AG, Vienna) and express Lp(a) values in mg/ml of Lp(a) lipoprotein mass. There seems to be little difference in the results by either using ELISA, rocket electrophoresis or nephelometry; only radial immuno-diffusion may cause problems because of the large size of the antigen.

Lp(a) as a Risk Indicator for Vascular Diseases

Early reports on the link of increased Lp(a) levels with premature atherosclerosis and MI were published by the group of Dahlen [7]. In their assays based on simple agarose gel electrophoresis, distinctions were only made by the presence or absence of an "extra pre-B-1 band". Those individuals exhibiting this band were called Lp(a)+, and those without the band Lp(a)-. We have re-evaluated this method and compared with our quantitative assays and found out that it had a sensitivity of approx. 25 - 30 mg/dl, i.e. individuals with < 30 mg/dl of Lp(a) were "Lp(a)-". The first quantitative report on the distribution of Lp(a) plasma concentrations among post-M.I. individuals and controls was published by our laboratory in collaboration with the group of Avogaro in Venice [8]. In this study, Lp(a) plasma levels of 76 male post-M.I. patients were measured and compared with that of a control group matched for age and sex. Patients and controls were subdivided into "normolipemics" and hyperlipemics of Fredrickson Types II-IV. The results obtained in that study are shown in Table I.

From this early study we may deduce several rather striking facts:

1) The distribution of Lp(a) plasma concentration is far from normal with median values around 8 - 9 mg/dl.

2) Lp(a) is higher in post-M.I. individuals as compared to a control group. Because of the skew frequency distribution, simple statistics may not be applied to calculate cut-off values. Although it appears that the atherosclerosis risk increases with increasing Lp(a) concentrations, a simple formula considering this observation cannot be calculated. But from this and some consecutive studies we may deduce that Lp(a) levels < 20 - 25 mg/dl may be harmless.