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The Association between Serum Lp(a) Concentrations and Angiographically Assessed Coronary Atherosclerosis

Dependence on Serum LDL Levels

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Summary

Lipoprotein(a) concentrations were measured by radial immunodiffusion in a cohort of 40–60 year males who had been classified by coronary angiography as CAD + with 50% stenosis of one or more of the major coronary arteries or CAD − with no signs of coronary lesions. Sample odds ratios were calculated as a measure of association between serum Lp(a) values and the presence of coronary artery disease. An odds ratio of 2.706 ($P < 0.001$) was derived for elevated (≥ 30 mg/dl) Lp(a) levels vs low (< 5 mg/dl) Lp(a) levels indicating a strong association between the presence of coronary artery disease and elevated Lp(a) concentrations. This association was independent of the known risk factors smoking, hypertension and diabetes as well as the serum concentrations of total triglycerides, HDL-cholesterol, α-Lp-cholesterol and pre-β-Lp-cholesterol. In contrast to these variables the association between Lp(a) and coronary artery disease was dependent upon the serum concentrations of LDL-cholesterol, β-Lp-cholesterol and total cholesterol. At concentrations below the respective median for each variable, odds ratios of between 1.42 and 1.67 were calculated whereas at concentrations above the respective medians the odds ratios ranged from 4.50 to 6.33 ($P < 0.001$). Our data, therefore, suggest that increasing LDL concentrations markedly increase the risk of coronary artery disease due to elevated Lp(a) levels.

Key words: *Atherosclerosis – Coronary angiography – Lipoprotein (a) – Low density lipoprotein*

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Introduction

Human lipoprotein (a) is an unusual serum lipoprotein characterised by the presence of a unique glycoprotein(a) linked to apoprotein B-100 by disulfide bridges [1,2]. The glycoprotein(a) is

readily released from the lipoprotein particle by mild reductive cleavage with disulfide reducing agents such as dithiothreitol [3,4]. The reduced lipoprotein obtained free of the protein (a) is virtually identical to LDL in its physicochemical properties and its cellular uptake by the LDL receptor in cultured human fibroblasts [3]. In contrast to its reduced derivative, native Lp(a) is a much poorer ligand for the LDL receptor [3]. Despite the close structural resemblance between LDL and Lp(a), the two lipoproteins appear to be under separate metabolic control. Thus, dietary changes and drugs that alter LDL and apo B-100 levels do not affect Lp(a) [5,6]. Lp(a) is also not derived from normal VLDL and is not converted into other lipoproteins in plasma [7]. However, the (a) antigen has been detected in the VLDL density fraction [5,8] in particular after a fat meal when it was found to be associated with large chylomicron-like particles [9].

Clinical interest in Lp(a) has been stimulated by numerous reports linking elevated serum concentrations with an increased incidence of coronary artery disease [10–14]. Furthermore, the Lp(a) antigen has been detected in arterial lesions in a distribution similar to LDL [8].

Although previous studies have clearly demonstrated a close association between Lp(a) and coronary heart disease, no detailed analyses have been performed on the influence of other risk factors and lipoprotein parameters on this association. We have therefore quantitatively determined serum Lp(a) levels in a cohort of males aged 40–60 years who had been angiographically assessed for coronary artery disease (CAD). A detailed lipoprotein analysis was carried out and the presence of other risk factors was also established.

Materials and Methods

During a period of 12 months Lp(a) concentrations were routinely measured in patients undergoing coronary angiography in the department of cardiology of the University Hospital, Göttingen. Coronary angiography was performed according to [15] in combination with cineangiography. Patients were classified into two groups: CAD +, those patients with at least 50% stenosis of one or more of the coronary arteries; CAD −, those patients with no signs of coronary lesions. Subjects who could not be classified into either of these two categories were excluded from the present study. For the purpose of the present analysis we have considered only results from males aged 40–60 years at the time of angiography. Of the 594 males investigated, 428 could be classified as CAD + and 142 as CAD − according to the above criteria. The remaining 24 subjects were omitted from the analysis. Patient data were also obtained regarding smoking habits and the presence of diabetes or hypertension.

Lipid and lipoprotein analyses

Serum from patients was subject to analyses for lipids and lipoproteins according to the following methods.

Total cholesterol (CHOD-PAP, Boehringer Mannheim) and total triglycerides (Wako chemicals, Neuss) were determined with the aid of enzymatic test kits.

The serum concentrations of Lp(a) were measured by radial immunodiffusion using a commercial kit and standard (Combi RID, Immuno Diagnostika, Heidelberg). The lower limit for this assay was 5 mg/dl Lp(a).

The individual lipoprotein fractions were quantified by both electrophoretic and precipitation procedures.

Electrophoretic quantification

Quantitative lipoprotein electrophoresis (Lipidophor-All-In-System, Immuno Diagnostika, Heidelberg) was performed as previously described [16]. After electrophoretic separation on agarose gels, the lipoproteins were precipitated in the gels and the bands were quantified densitometrically. The densitometric evaluation has been previously standardised [16] in terms of the cholesterol content of the individual lipoprotein-fractions beta (β), pre-beta (pre-β) and alpha (α) by elution of the different bands from the gel and direct measurement of the cholesterol. Thus the terms β-Lp-, pre-β-Lp- and α-Lp-cholesterol in the text refer to the electrophoretically determined parameters. Previous studies [21] have also shown that these values show a high correlation to the classical lipoprotein parameters LDL-, VLDL- and

HDL-cholesterol respectively as estimated by a standard ultracentrifugation procedure.

Precipitation techniques

LDL- and HDL-cholesterol were also measured using commercially available test kits. A precipitation technique based on dextran sulfate (Quantolip-LDL, Immuno Diagnostika, Heidelberg) was used for LDL-cholesterol [17]. Since Lp(a) is also precipitated under these conditions, the cholesterol value obtained includes both LDL- and Lp(a)-cholesterol (LDL/Lp(a)-cholesterol). Taking into account the fact that Lp(a) contains 30% by weight cholesterol, the true LDL-cholesterol was derived by subtracting the corresponding Lp(a) concentration $\times$ 0.3 [14] from the appropriate precipitation value. HDL-cholesterol was determined using a technique based on phosphotungstate/$MgCl_2$ (Boehringer Mannheim). The terms LDL- and HDL-cholesterol in the text therefore refer to the values derived by these precipitation methods.

Analysis

As a measure of association between serum Lp(a) concentrations and coronary artery disease, sample odds ratios were calculated in 2×2 tables as follows.

	'low' Lp(a) < 5 mg/dl	'high' Lp(a) ≥ 30 mg/dl
CAD +	a	b
CAD −	c	d

The sample odds ratio $= \frac{b \times c}{a \times d}$,

where: (a) is the number of subjects who were CAD + and had Lp(a) values below 5 mg/dl;

(b) is the number of subjects who were CAD + and had Lp(a) values of 30 mg/dl or greater;

(c) is the number of subjects who were CAD − and had Lp(a) values below 5 mg/dl;

(d) is the number of subjects who were CAD − and had Lp(a) values of 30 mg/dl or greater.

In this study based on prevalent cases, the sample odds ratio is a consistent estimator of the prevalence odds ratio, provided there are no biases due to the selection of the study subjects. Furthermore, it can be viewed as an estimate of the incidence density ratio (risk) under the simplifying assumptions of [18].

Significance tests were performed using the chi-square test [19]. No effort was made to adjust for the confounding effects of other variables because strong interaction with serum Lp(a) levels was present in the data.

Results

Selected characteristics of the study group are compared in Table 1 to those of a typical collective of male industrial workers [20,21]. The mean age of the study group was slightly higher than that of the industrial collective whereas there was no apparent difference in body weight. As would be expected the patient cohort contained a higher percentage of smokers, hypertensives and diabetics than did the industrial collective. A higher prevalence of hypertensives and diabetics was found in those patients classified as CAD + compared to CAD − whereas no differences in smoking habits were observed. Table 2 summarises the lipid and lipoprotein parameters for the study cohort and the industrial collective. Mean total cholesterol and β-Lp-cholesterol concentrations were notably higher in the study cohort than in the industrial workers. Total triglycerides and pre-β-Lp-cholesterol were also higher in the former group whereas α-Lp-cholesterol concentrations were somewhat lower. After subdivision of the study cohort into CAD + and CAD − the dif-

TABLE 1

SELECTED CHARACTERISTICS OF THE COHORT OF MALES (40–60 YEARS) WHO HAD UNDERGONE CORONARY ANGIOGRAPHY IN COMPARISON TO A LARGE GROUP OF MALE INDUSTRIAL WORKERS (40–60 YEARS)

	Study cohort			Male industrial workers
	Total	CAD +	CAD −	
n	570	428	142	6410
Mean age (yr)	52.1	52.2	51.7	47.6
Broca index	107.0	106.5	108.3	107.5
% smokers	42.2	42.1	43.0	38.0
% hypertension	26.4	28.3	20.4	11.0
% diabetes	9.4	11.0	4.9	5.5

TABLE 2

MEAN LIPID AND LIPOPROTEIN CONCENTRATIONS FOR THE STUDY COHORT AND THE INDUSTRIAL COLLECTIVE

	MW ± SD (mg/dl)			
	Study cohort			Male industrial workers
	Total	CAD +	CAD −	
Total cholesterol	247 ± 46	250 ± 45	237 ± 48	214 ± 40
Total triglycerides	174 ± 90	179 ± 91	160 ± 84	163 ± 146
β-Lp-cholesterol	179 ± 41	183 ± 41	169 ± 41	144 ± 33
Pre-β-Lp-cholesterol	27 ± 16	28 ± 16	24 ± 14	23 ± 17
α-Lp-cholesterol	41 ± 13	39 ± 12	44 ± 14	48 ± 12
LDL/Lp(a)-cholesterol	178 ± 46	182 ± 45	165 ± 46	–
LDL-cholesterol	172 ± 45	176 ± 44	162 ± 45	–
HDL-cholesterol	41 ± 11	40 ± 10	45 ± 12	46 ± 14

ferences observed above were even more pronounced for the CAD + group compared to the industrial collective. In the case of the CAD − group, the lipid and lipoprotein parameters were generally similar to those of the industrial collective, apart from total cholesterol and β-Lp-cholesterol which were somewhat higher.

Correlation of Lp(a) to other variables

The relationships between Lp(a) and other lipid- and lipoprotein concentrations were investigated for those subjects in the study cohort with Lp(a) concentrations above the lower limit of our assay (≥ 5 mg/dl). A weak but significant correlation was only observed (Table 3) to total cholesterol ($P = 0.005$), pre-β-Lp-cholesterol ($P < 0.001$) and LDL/Lp(a)-cholesterol ($P = 0.008$). Since Lp(a) has pre-β-mobility on electrophoresis the pre-β-cholesterol value will also include Lp(a)-cholesterol, while precipitation with dextran sulfate precipitates both Lp(a) and LDL [17]. After correcting for the coprecipitated Lp(a)-cholesterol, LDL-cholesterol showed no correlation to Lp(a) levels. Correlations were not observed between Lp(a) and total triglycerides, β-Lp-cholesterol, α-Lp-cholesterol, or HDL-cholesterol.

TABLE 3

CORRELATIONS BETWEEN Lp(a) LEVELS (≥ 5 mg/dl) AND OTHER VARIABLES

Variable	*r*	*P*-value
Total cholesterol	0.158	0.005
Total triglycerides	0.059	0.297
β-Lp-cholesterol	0.086	0.127
Pre-β-Lp-cholesterol	0.196	< 0.001
α-Lp-cholesterol	0.060	0.283
LDL/Lp(a)-cholesterol	0.149	0.008
LDL-cholesterol	−0.024	0.665
HDL-cholesterol	0.017	0.768

Distribution of Lp(a) concentrations

The frequency distributions for Lp(a) in our study cohort are highly skewed (Fig. 1), as observed for all other white populations [22]. The distribution of Lp(a) in the CAD + group was shifted to higher values than in the CAD − group. Thus 58% of patients with stenosis had Lp(a) levels of 5 mg/dl or greater while in the case of those patients without stenosis it was only 40%.

Association between Lp(a) and CAD

The prevalence of patients who were CAD + increased with increasing Lp(a) concentrations in our study cohort suggesting a 'dose–response' effect. This is illustrated in Table 4 in which patients were subdivided according to those with Lp(a) concentrations below 5 mg/dl (the lower limit of the assay), those with concentrations between 5 and 29.9 mg/dl and those with concentrations of 30 mg/dl and greater. An odds ratio of

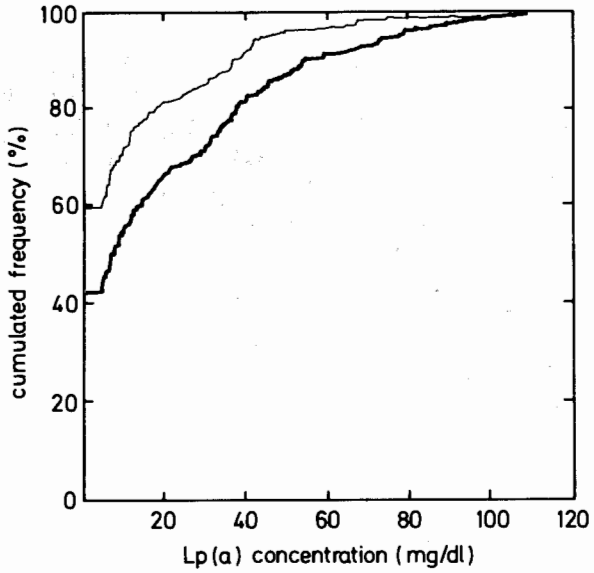

Fig. 1. Frequency distributions of serum Lp(a) concentrations in (———) CAD+ patients and (– – – –) CAD− patients.

2.706 ($P < 0.001$) was derived for Lp(a) values greater than 30 mg/dl versus levels smaller than 5 mg/dl. There is therefore a strong association between the presence of coronary artery disease and elevated Lp(a) concentrations in our study cohort.

Influence of other variables on the association

In order to take into account the effects of known or suspected risk factors of CAD, the LP(a)–CAD relationship was examined in various strata of the study population. For this purpose the odds ratios were determined for high (≥ 30 mg/dl) and low (< 5 mg/dl) values of Lp(a) after subdivision of the collective as shown in Table 5.

TABLE 4

PREVALENCE OF CAD+ AFTER STRATIFICATION ACCORDING TO Lp(a) LEVELS

Lp(a) (mg/dl)	n		Prevalence
	CAD+	CAD−	
< 5	181	85	0.68
5–29.9	126	36	0.78
≥ 30	121	21	0.85

TABLE 5

INFLUENCE OF OTHER VARIABLES ON THE ASSOCIATION BETWEEN Lp(a) AND CAD AS ESTIMATED BY THE ODDS RATIO FOR HIGH (≥ 30 mg/dl) AND LOW (< 5 mg/dl) Lp(a) LEVELS

Stratified according to	Odds ratio	
	≤ Median	> Median
Total cholesterol	1.56	4.50
Total triglycerides	2.89	2.66
β-Lp-cholesterol	1.56	6.33
LDL/Lp(a)-cholesterol	1.42	5.23
LDL-cholesterol	1.67	6.00
Pre-β-Lp-cholesterol	2.84	2.48
α-Lp-cholesterol	2.80	2.78
HDL-cholesterol	2.96	2.72
	Yes	No
Smoker	2.24	2.20
Hypertension	2.59	2.16
Diabetes	–	2.14

When subdivision was performed according to the median of either total triglycerides, pre-β-Lp-cholesterol, α-Lp-cholesterol or HDL-cholesterol then there were no differences in the values of the odds ratios whether derived above or below the respective medians. The values obtained were all similar to that of 2.706 for the whole collective. Similar results were found on dividing the cohort into smokers/non-smokers and hypertensive/normotensive. In the case of diabetes, the odds ratio of 2.14 for non-diabetics was also fairly close to that of the total collective. Because of the small number of diabetics in the cohort, a reliable odds ratio could not be derived for this subgroup. The association between Lp(a) and coronary artery disease is therefore independent of the above variables.

In contrast to the previous subdivisions, when the medians for total cholesterol, β-Lp-cholesterol, LDL/Lp(a)-cholesterol or LDL-cholesterol were chosen as the dividing limits then the odds ratios obtained above and below the respective medians were markedly different. The values ranged between 4.50 and 6.33 above the medians whereas the corresponding values below the medians were all lower than 2. The odds ratios above the median were all highly significant ($P < 0.001$) showing a strong association to coronary artery disease. On

the other hand, the associations did not reach statistical significance for the subgroups below the medians.

The possibility that the stronger association between elevated Lp(a) levels and coronary artery disease at values of total cholesterol, β-Lp-, LDL/Lp(a)-, and LDL-cholesterol greater than the respective medians may have been due to the fact that these sub-groups contained patients with excessively high Lp(a) concentrations was also examined. The results are presented in Table 6 as means for the Lp(a) concentrations greater than 30 mg/dl stratified according to the corresponding medians. As can be seen there appear to be no major differences in the Lp(a) levels of the patients in the different sub-groups.

In order to determine whether the association of Lp(a) to coronary artery disease was simply due to its contribution to the total pool of potentially atherogenic cholesterol or whether additional factors were involved, we compared the mean LDL/Lp(a)-cholesterol concentrations in the different sub-groups. In the case of those patients with low Lp(a) levels (< 5 mg/dl) the mean LDL/Lp(a) concentration was 226 mg/dl, a value very similar to that of 227 mg/dl for those patients with high Lp(a) levels (≥ 30 mg/dl).

TABLE 6

MEAN VALUES FOR THOSE Lp(a) CONCENTRATIONS ≥ 30 mg/dl STRATIFIED ACCORDING TO TOTAL CHOLESTEROL, β-Lp-CHOLESTEROL, LDL/Lp(a)-CHOLESTEROL AND LDL-CHOLESTEROL CONCENTRATIONS

Stratified according to		Lp(a) concentration (mg/dl) mean ± SD
Total cholesterol	≤ 245 mg/dl	50.1 ± 19.1
Total cholesterol	> 245 mg/dl	54.4 ± 21.1
β-Lp-cholesterol	≤ 179 mg/dl	53.9 ± 21.4
β-Lp-cholesterol	> 179 mg/dl	52.4 ± 20.3
LDL/Lp(a)-cholesterol	≤ 178 mg/dl	51.2 ± 21.0
LDL/Lp(a)-cholesterol	> 178 mg/dl	53.4 ± 20.1
LDL-cholesterol	≤ 172 mg/dl	52.7 ± 21.3
LDL-cholesterol	> 172 mg/dl	52.3 ± 19.4

Discussion

Due to the nature of the study design, our cohort is highly selected. This is reflected in the higher prevalence of smokers, hypertensives and diabetics in the angiographically assessed patients than would be expected in a typical population of German middle aged males. In contrast to earlier studies from our laboratory [20,21] the patients total cholesterol and in particular the β-Lp-cholesterol values were also considered in the decision as to whether to perform angiography. Thus in comparison to the previous results the means for total cholesterol and β-Lp-cholesterol in the CAD − patients were somewhat higher than those of the normal controls indicating that some selection bias had occurred. They were still, however, clearly lower than the corresponding means for the CAD + patients.

In the case of Lp(a), several lines of evidence support the assumption that subjects were selected for the study independent of Lp(a) concentrations. (1) The Lp(a) concentrations of the patients were unknown to the cardiologists who performed the coronary angiography. (2) Lp(a) appears to be under separate metabolic control from VLDL and LDL [7,11] and serum concentrations are unaffected by diet and drug regimens that affect LDL. (3) Serum levels of Lp(a) have generally been shown to be independent of most other variables associated with coronary heart disease. In our study we only observed a weak correlation of Lp(a) to total cholesterol, pre-β-lp-cholesterol and LDL/Lp(a)-cholesterol. In the case of the latter two parameters, the weak correlations are readily explained by the fact that Lp(a)-cholesterol is included in these variables. The weak correlation to total cholesterol may reflect the small contribution of Lp(a)-cholesterol to this value. While some previous studies [5,23] have also found a correlation between these two parameters, others [22] have reported no relationship. There may be a weak relationship between apo-B concentrations and Lp(a) levels in normolipidemics [22], but this does not seem to hold in collectives with a wider range of lipid concentrations [5]. Of other risk factors associated with coronary heart disease there is some evidence that elevated Lp(a) values are associated with smoking [12,22], but this could not

be confirmed in other studies [24,25]. There is therefore no unanimous evidence from the literature linking Lp(a) to any of the variables involved in coronary heart disease. We conclude that the selection of patients into our study cohort did not operate differently at different Lp(a) values, whereas it is evident from the high prevalence of CAD + patients that the selection probabilities depend on CAD status. Thus, the sample odds ratio rather than the prevalence ratio is an estimate without selection bias.

In confirmation of the results of Frick et al. [12] we found a significant association between the presence of coronary artery disease as assessed by coronary angiography and elevated Lp(a) levels. Over 60% of our CAD − patients had Lp(a) values below 5 mg/dl while only 42% of CAD + patients fell into this category. The 95th percentile cut-off for the former group was 42 mg/dl whereas for the CAD + group it was much higher at 75 mg/dl. Previous investigations have, however, not performed any detailed analyses on the influence of other variables on the association between Lp(a) and coronary artery disease. In our cohort we found that the risk factors smoking, diabetes and hypertension as well as total triglycerides, pre-β-Lp-cholesterol and HDL/α-cholesterol had no influence on the association between Lp(a) and coronary artery disease. However, when the study cohort was stratified according to either total cholesterol or β-Lp-/LDL-cholesterol a strong interaction was observed. At total cholesterol or β-Lp-/LDL-cholesterol concentrations lower than the respective median for the cohort, only a weak association that did not reach statistical significance occurred, whereas at concentrations higher than the respective median a strong highly significant ($P < 0.001$) association was found. The same phenomenon was seen when other arbitrary limits were chosen for the stratification. When stratified according to the 33rd and 66th percentile cut-offs for LDL-cholesterol (154 and 190 mg/dl) then the odds ratios for the association of elevated Lp(a) levels to coronary artery disease in the lower, middle and upper thirds of the frequency distribution were 1.47 ($P > 0.1$), 3.86 ($P < 0.01$), and 4.73 ($P < 0.005$) respectively. The corresponding values for β-Lp-cholesterol (162, 193 mg/dl) were 1.64 ($P > 0.1$), 2.68 ($P < 0.05$) and 4.57 ($P < 0.005$) and for total cholesterol (229, 265 mg/dl) 1.83 ($P > 0.1$), 2.64 ($P < 0.06$) and 3.97 ($P < 0.005$). If our patients were drawn from a static population with mean duration of illnes being independent of Lp(a) values, the calculated sample odds ratio would estimate the incidence density ratio [18]. Under these conditions it would appear that increasing LDL concentrations markedly increase the risk of coronary artery disease due to elevated Lp(a) levels. Guyton et al. [22] recently reported Lp(a) levels to be higher in a normolipidemic black population than in a corresponding white population despite the fact that the former do not experience greatly increased atherosclerosis and mortality. Interestingly LDL-cholesterol levels (adjusted for Lp(a) levels) in male blacks were 16% lower than in the male whites. Our results suggest one possible reason for the lack of atherogenicity of Lp(a) in the black population might be correspondingly low LDL-cholesterol levels. It does not of course rule out the possibility that other genetic factors may protect against the atherogenicity of Lp(a). Kostner et al. [14] assessed the association of elevated Lp(a) levels with myocardial infarction after subdivision of their study and control groups according to the different lipoprotein phenotypes. Irrespective of the phenotype, elevated Lp(a) levels were more frequent in myocardial infarction survivors than in controls even in the case of normolipemics. A cholesterol value of 260 mg/dl was chosen as the upper limit for the latter sub-group. From our own data it can be seen that there is still a significant association between Lp(a) and coronary artery disease at total cholesterol values below 265 mg/dl. In a Japanese study [26], however, elevated Lp(a) levels were found to be associated with coronary artery disease (myocardial infarction or angina pectoris) even at total cholesterol levels below 230 mg/dl when compared to a control group whereas we only observed a weak association at cholesterol levels below 229 mg/dl that did not reach statistical significance.

The mechanism by which Lp(a) exerts a possible atherogenic effect is still speculative. Lp(a) is not simply contributing to the vascular pool of potentially atherogenic LDL-cholesterol since patients with low (< 5 mg/dl) and high (≥ 30 mg/dl) Lp(a) concentrations had similar mean LDL/

Lp(a)-cholesterol concentrations. Although Lp(a) can apparently be cleared by the LDL-receptor pathway [3,7], it is a much poorer ligand for the receptor than LDL itself [3]. Therefore, at high concentrations of LDL a greater proportion of Lp(a) may be cleared by receptor-independent and potentially more atherogenic pathways than at low LDL concentrations.

Taking a threshold value of 30 mg/dl for Lp(a) Kostner et al. [14] estimated the relative risk for myocardial infarction in normolipidemic patients to be 1.75. The corresponding value for our study cohort comparing patients with Lp(a) levels greater than 30 mg/dl to those with values below this level was higher at 2.27, presumably due to the fact that hyperlipidemics were included in this evaluation. In a further study in which a less sensitive test for Lp(a) was employed, the presence or absence of a sinking pre-β band on electrophoresis, Rhoads et al. [13] estimated a relative risk for coronary heart disease based on prevalence cases to be 1.7 in men with a definite pre-β band and 1.4 in those with a trace pre-β band. Taken together these findings would suggest that considering the frequency of coronary heart disease in the general population, the coronary risk due to Lp(a) may be considerable. Furthermore, this risk is accentuated at elevated LDL concentrations.

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