Prevalence of microalbuminuria, lipoprotein (a) and coronary artery disease in the lipid clinic

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Abstract

***Aims*—To assess the prevalence of microalbuminuria (MA) and elevated serum lipoprotein (a) (Lp (a)) concentration, and their association with coronary artery disease (CAD) and other conventional cardiovascular risk factors in non-diabetic patients attending a lipid clinic.**

***Methods*—Clinical details were obtained from 96 consecutive non-diabetic patients from whom a fasting blood sample was taken to measure serum lipid, lipoprotein, apolipoprotein and plasma glucose, urea, and electrolyte concentrations. The urine albumin/creatinine ratio (U_a/U_c) was estimated from a random clinic sample.**

***Results*—Of the patients, 26% had MA (defined as a U_a/U_c > 2·2 mg/μmol), 38% had an elevated Lp (a) concentration (defined as >0·4 g/l), 36% were hypertensive (blood pressure >160/95) or were taking antihypertensive medication, and 25% had established CAD defined on clinical criteria. In men the U_a/U_c ratio was highly associated with age, plasma low density lipoprotein cholesterol, and triglyceride concentrations. In women there was no association between the U_a/U_c ratio and variables examined. Lp (a) concentration was not associated with variables examined in either sex. In multiple logistic regression analysis adjusted for age and sex, serum Lp (a) concentration, diastolic blood pressure and treatment of hyperlipidaemia were highly associated with CAD. MA was not, however, associated with CAD.**

***Conclusions*—MA is common in a lipid clinic and is more likely to be found among older male patients with hyperlipidaemia. However, in contrast with Lp (a) concentrations, MA is not a risk factor for CAD in this high risk population. Lp (a) concentration may be a useful tool in the lipid clinic, but there does not seem to be a justification for measuring the U_a/U_c ratio, at least in non-diabetic subjects.**

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Hyperlipidaemia is a well recognised risk factor for coronary artery disease (CAD).[1 2] As an elevated cholesterol concentration is a common finding,[3] treatment of hyperlipidaemic patients should aim to optimise available resources by targeting those with the worst cardiovascular prognosis. Over the past decade, the number of lipid clinics has expanded owing to increased awareness of the consequences of hyperlipidaemia and advances in treatment. The identification of high risk patients within this hyperlipidaemic population may potentially be enhanced by screening for additional cardiovascular risk factors such as microalbuminuria[4] and raised lipoprotein (a) (Lp (a)) concentration.[5] Hitherto, however, the prevalence and associations of microalbuminuria and elevated Lp (a) concentration in patients attending a lipid clinic have not been examined.

Several studies have established that in diabetes mellitus microalbuminuria not only predicts the development of nephropathy,[6] but also of CAD.[7–9] Some studies have also suggested that microalbuminuria is associated with CAD in the non-diabetic population.[10–12] The mechanism linking CAD to microalbuminuria is not fully established and it is possible that microalbuminuria represents a nexus for expression of other cardiovascular risk factors such as hyperlipidaemia and impaired glucose intolerance.[11 13–15] Microalbuminuria may also be a marker of vascular dysfunction, reflecting the susceptibility of arterial endothelium to risk factor mediated damage.[4] It may therefore be expected that microalbuminuria will be highly prevalent and independently predictive of CAD in patients attending a lipid clinic.

Another potential risk factor for atherosclerosis is Lp (a), several studies having shown an association between serum Lp (a) concentration and CAD.[16–18] It has been suggested, however, that increased cardiovascular risk associated with Lp (a) may only occur in patients with a high plasma low density lipoprotein (LDL) cholesterol concentration.[5] This observation has been based mainly on the study of patients with familial hypercholesterolaemia[17] but an elevated Lp (a) concentration may also confer additional cardiovascular risk in more common hyperlipidaemias.[19] Elevated serum Lp (a) concentration has also been associated with microalbuminuria.[20 21]

Our study examined patients attending a lipid clinic to determine the prevalence and clinical associations of microalbuminuria and elevated serum Lp (a) concentration. We were also specifically interested in whether these measurements were independent correlates of the presence of CAD in this high risk population.

Methods

Consecutive patients (n = 106) attending the lipid clinic at St Thomas's Hospital were

Table 1 Clinical and biochemical features of the patients studied

Variable	Men (n=53) Mean (SD)	Women (n=43) Mean (SD)
Age (years)	48·3 (12·3)	58·1 (11·3)
Weight (kg)	77·5 (11·0)	68·0 (12·9)
Height (cm)	173·0 (5·5)	161·8 (6·1)
BMI (kg/m^2)	26·1 (0·4)	26·7 (0·5)
Systolic BP (mmHg)	132·2 (20·6)	140·1 (21·6)
Diastolic BP (mmHg)	82·8 (11·3)	86·7 (9·2)
U_a/U_c (mg/μmol)*	1·14 (0·26,4·89)	1·81 (0·26,12·80)
TC (mmol/l)	6·85 (1·15)	7·51 (1·33)
TG (mmol/l)*	2·58 (0·67,9·94)	1·99 (0·71,5·60)
HDL cholesterol (mmol/l)	1·1 (0·3)	1·4 (0·4)
LDL cholesterol (mmol/l)	4·7 (1·2)	5·3 (1·4)
ApoA1 (g/l)	1·9 (0·3)	2·1 (0·3)
ApoB (g/l)	1·6 (0·4)	1·7 (0·4)
Lp(a) (g/l)*	0·29 (0·06,1·40)	0·34 (0·06,1·99)
Glucose (mmol/l)	5·1 (0·5)	5·1 (0·7)

BMI = body mass index; BP = blood pressure; * geometric mean (95% range).

screened for microalbuminuria. Clinical details were recorded to identify patients with hypertension, macrovascular disease (CAD, peripheral vascular disease or cerebrovascular disease) or diabetes mellitus. Current drug therapy, smoking habits and family history of macrovascular disease were also recorded. Each patient was venesected following a 12 hour fast to determine serum total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL) cholesterol, apolipoprotein A1 (apoA1), apolipoprotein B (apoB), Lp (a), and plasma glucose, urea and electrolyte concentrations. Ten patients were excluded from the study because of diabetes mellitus (defined by the WHO criteria), macroproteinuria, or raised plasma creatinine concentration (>150 μmol/l). This study received ethics committee approval.

ANALYTICAL MEASUREMENTS

A urine albumin/creatinine ratio (U_a/U_c) was determined from analysis of a random urine sample.[10] Urine samples were assayed within five days of collection, having been stored at 4°C prior to analysis. Urine albumin concentration (mg/l) was measured by immunoturbidimetry (Cobas Fara autoanalyser, Roche, Welwyn Garden City, Herts, UK), interassay coefficient of variation (CV) <3·7%. Urine creatinine concentration (μmol/l) was estimated by a modified, end point Jaffé reaction using a Cobas Bio autoanalyser (Roche), CV 2·8%. HDL cholesterol, plasma TC and TG concentrations (mmol/l) were measured by an enzymatic method (Boehringer Mannheim, Sussex, UK) using a Cobas centrifugal analyser (Roche). HDL was separated by precipitation of apoB containing lipoproteins with dextran sulphate/magnesium chloride. LDL cholesterol concentration (mmol/l) was estimated using the Friedewald equation in patients with TG concentrations <4·5 mmol/l. In patients with TG >4·5 mmol/l, cholesterol concentration was measured directly in LDL following preparative ultracentrifugation. ApoA1, apoB and Lp (a) concentrations (g/l) were measured by immunoturbidimetry (Cobas Fara autoanalyser, Roche) using commercially available kits (Immunoturb kit, Immuno, Sevenoaks, UK), CV <2·8%, 2·7% and 2·4% respectively.[22] Plasma glucose (mmol/l) was measured by a glucose oxidase technique (DAX 96, Bayer Diagnostics, Basingstoke, UK), CV 3%.

Table 2 The prevalence of microalbuminuria, raised Lp (a) concentration, dyslipidaemia, hypertension, smokers, drug treatment for hypertension and hyperlipidaemia, and macrovascular disease amongst the patients studied

Variable	Men (n=53) % (n)	Women (n=43) % (n)
Hypertension	28 (15)	47 (20)
Hypercholesterolaemia	94 (50)	98 (42)
Hypertriglyceridaemia	40 (21)	37 (16)
Mixed hyperlipidaemia	38 (20)	35 (15)
Elevated Lp (a) concentration	36 (19)	40 (17)
Microalbuminuria	19 (10)	35 (15)
CAD	32 (17)	16 (7)
Peripheral vascular disease	9 (5)	9 (4)
Cerebrovascular disease	8 (4)	5 (2)
Family history of macrovascular disease	42 (22)	65 (28)
Smokers	19 (10)	12 (5)
Drug treatment for hypertension	23 (12)	35 (15)
Drug treatment for hyperlipidaemia	72 (38)	67 (29)

DEFINITIONS

CAD was defined according to a history of myocardial infarction, coronary artery bypass surgery or the use of anti-anginal medication,[23] or ECG abnormalities at rest or on exercise compatible with CAD.[24] Hypertension was defined as a systolic pressure of >160 mmHg and/or a diastolic pressure >95 mmHg (WHO criteria) and/or a history of hypertension requiring treatment.[25] Microalbuminuria was defined as a U_a/U_c ratio >2·2 mg/μmol (equivalent to an albumin excretion rate >15 g/min)[26] in the absence of macroalbuminuria (Albustix negative). Hyperlipidaemia was defined as total cholesterol concentration >5·2 mmol/l, and/or LDL cholesterol >3·5 mmol/l, and/or triglyceride concentration >2·5 mmol/l.[2] Lp (a) concentration was considered raised if above 0·4 g/l.[17]

STATISTICAL ANALYSES

Data were analysed using the SAS statistical package (SAS Institute Inc., Cary, North Carolina, USA). Normally distributed data were expressed as mean (SD). Skewed variables (plasma TG and Lp (a) concentrations and U_a/U_c ratio) were expressed as geometric mean (95% range). Associations between the U_a/U_c ratio, Lp (a) concentration and other variables were examined using Spearman's rank correlation. To determine associates of CAD, univariate associations were examined using logistic analysis adjusted for age and sex. Skewed variables were examined after logarithmic transformation. Stepwise multiple logistic regression analysis, also adjusted for age and sex, was used to assess the relative strength of association with CAD; significance levels for entry and exit were set at 0·10. For continuous risk factors, the standardised relative odds, which indicates the relative change in risk associated with an increase of one standard deviation, is quoted.

Results

The clinical and biochemical features of the patients studied are shown in table 1. Women were older and had higher TC, HDL cho-

Table 3 Association between CAD and variables assessed by univariate logistic analysis, adjusted for age and sex

Risk factor	Odds ratio* (95% confidence interval)	Regression coefficient	Standard error	p value
Total cholesterol	0·54 (0·28, 1·03)	−0·49	0·26	0·06
Systolic BP	0·46 (0·24, 0·85)	−0·04	0·01	0·01
Diastolic BP	0·38 (0·20, 0·74)	−0·09	0·03	0·004
Lp (a)	2·68 (1·41, 5·08)	1·17	0·39	0·003
Drug treatment for hyperlipidaemia†	4·55 (1·35, 27·51)	1·52	0·54	0·02

* Odds ratio associated with an increase of 1 standard deviation.
† Odds ratio associated with taking lipid lowering medication. BP = blood pressure.

Table 4 Association between CAD and variables assessed by stepwise logistic regression analysis, adjusted for age and sex

Risk factor	Odds ratio* (95% confidence interval)	Regression coefficient	Standard error	p value
Lp (a)	2·91 (1·38, 6·13)	1·26	0·45	0·005
Drug treatment for hyperlipidaemia†	11·63 (1·52, 88·89)	2·45	1·04	0·02
Diastolic BP	0·42 (0·21, 0·86)	−0·08	0·03	0·03

* Odds ratio associated with an increase of 1 standard deviation.
† Odds ratio associated with taking lipid lowering medication. BP = blood pressure.

lesterol and Lp (a) concentrations compared with the men. The overall prevalences of microalbuminuria, elevated Lp (a) concentration, hypertension, and CAD were 26%, 38%, 36%, and 25%, respectively (table 2). Although 36% of this population were defined as hypertensive, only 74% of these patients were being treated with anti-hypertensive medication. There was a higher prevalence of hypertension, microalbuminuria and family history of macrovascular disease in women compared with men but fewer women smoked and their prevalence of CAD was lower (16% *v* 32%). In men there were significant associations between the U_a/U_c ratio and age, plasma LDL cholesterol, and TG concentrations ($r=0{\cdot}30$, $p=0{\cdot}02$; $r=-0{\cdot}28$, $p=0{\cdot}04$; and $r=0{\cdot}31$, $p=0{\cdot}03$, respectively). In women no associations were noted between the U_a/U_c ratio and the variables examined. Lp (a) concentration was not associated with variables examined in either sex. In addition, there was no significant difference in these variables when comparing patients with elevated and normal Lp (a) concentrations.

Univariate logistic analysis showed that Lp (a) concentration and treatment of hyperlipidaemia were significantly, positively associated with CAD (table 3). In this population, however, risk of CAD was significantly, inversely associated with TC concentration, and systolic and diastolic blood pressure. Neither the U_a/U_c ratio nor microalbuminuria were significantly associated with CAD ($p=0{\cdot}21$ and $p=0{\cdot}71$, respectively). Multiple logistic regression analysis demonstrated that Lp (a) concentration, diastolic blood pressure and drug treatment for hyperlipidaemia were the factors most strongly associated with CAD (table 4).

Discussion

This is the first study to examine the prevalence and associations of microalbuminuria and elevated Lp (a) concentration in non-diabetic patients attending a lipid clinic. In this cross-sectional study of patients with a clustering of risk factors for CAD, we have shown that microalbuminuria was highly prevalent, but was not associated with CAD. Elevated Lp (a) concentration was also highly prevalent, being present in over one third of the patients but, in contrast to microalbuminuria, was significantly associated with CAD.

The prevalence of microalbuminuria in the present study was higher than in non-diabetic populations reported previously.[10 11 27 28] In addition, our findings differ from studies of non-diabetic subjects randomly selected from the community, where microalbuminuria was found to be associated with CAD.[10–12] It is likely that this disparity in findings between the present and other studies is due mainly to differences in patient characteristics. In our study, there was a higher prevalence of hypertension compared with other unselected, non-diabetic populations[10 11] and this risk factor for CAD is independently associated with microalbuminuria in diabetic[7–9] and non-diabetic[10–12] subjects. In addition, there was selection bias as our patients were referred to a clinic because of established or high risk of CAD because of dyslipidaemia and other cardiovascular risk factors. The contrasting findings may also be due to different techniques used to measure urine albumin concentration or the different thresholds used to define microalbuminuria.

Several studies have shown an association between Lp (a) concentration, myocardial infarction[16 17] or the extent of CAD assessed angiographically.[18] However, whether Lp (a) is an independent risk factor for CAD, or is atherogenic only in the presence of raised LDL cholesterol remains unclear.[5] The suggestion that cardiovascular risk from elevated Lp (a) concentration is greatest when LDL cholesterol concentration is raised, is derived predominantly from studies of familial hypercholesterolaemia[17] although this may apply to other hyperlipidaemic conditions.[19] Our study examined a heterogenous group of hyperlipidaemic patients and provides further evidence that Lp (a) concentration is an independent risk factor for CAD. Although two thirds of the patients studied were taking cholesterol lowering medication, none of these

drugs have been consistently shown to lower serum Lp (a) concentration.[5]

Lp (a) possesses both thrombogenic and atherogenic properties which may mediate the increased cardiovascular risk associated with this lipoprotein. Given the sequence homology of apo (a) with plasminogen,[29] Lp (a) reduces fibrinolysis by inhibiting the binding of plasminogen to its receptor site.[30] Lp (a) is also found in high concentrations within atherosclerotic plaques[31] and it has been proposed that oxidation of the lipid component of Lp (a) could result in foam cell development, as seen with oxidised LDL.[5] In other studies where microalbuminuria was associated with CAD, the mechanism linking these two variables has not been fully established. Possible mediators of atherogenesis include disorders of lipid metabolism[11 13–15] and vascular endothelial dysfunction[32] which may be related to changes in the quality of the endothelial extracellular matrix.[4]

One possible shortcoming of our study is the definition of microalbuminuria based on the measurement of an U_a/U_c ratio in a single random urine sample, as used by others.[10] It has been shown, however, that the U_a/U_c ratio estimated from a single random urine sample correlates closely with albumin excretion rate in a 24 hour or overnight sample,[33] and in non-insulin dependent diabetic patients is of value in identifying patients with an increased risk of mortality or progression to nephropathy.[34] It is also possible that error occurred in measurement of Lp (a) concentration as analysis by immunoturbidimetry has been criticised for having low specificity for larger apo (a) isoforms.[35] More recently, we have demonstrated that estimation of Lp (a) concentration by immunoturbidimetry using a highly specific polyclonal antibody is highly correlated with a slight positive bias, when compared with measurement of Lp (a) by a standard enzyme linked immunosorbent assay method.[19] We also acknowledge that diagnosis of CAD based upon clinical and electrocardiographic evidence is relatively insensitive and that angiographic correlations may have proved more informative; evidence from previous studies[18] suggests that these measurements would improve the statistical significance of the correlation with Lp (a) concentration.

Some caution is required in interpreting results from our cross-sectional study of a highly selected population. This high risk population was studied for practical reasons as patients attending a lipid clinic are likely to have a great impact on available hospital resources. The absence of significant association between microalbuminuria and CAD in our hyperlipidaemic population may be due to overrepresentation of conventional cardiovascular risk factors such as dyslipidaemia, smoking and hypertension. The association between conventional risk factors and CAD is difficult to assess in the present population, however, as our patients were already receiving treatment aimed at reducing cardiovascular risk. This would explain why an increased risk of CAD was associated with lower cholesterol concentration and blood pressure; patients who were initially hypertensive, hypercholesterolaemic, who presented with established CAD, or were at high risk of atherosclerosis, were more likely to receive aggressive lipid lowering or anti-hypertensive treatment.

In conclusion, elevated Lp (a) concentration, but not microalbuminuria, was associated with CAD in patients attending a lipid clinic. We suggest that measurement of Lp (a) concentration, but not the U_a/U_c ratio, may be useful in assessing and targeting treatment in this high risk population. In order to confirm our findings, however, longitudinal studies examining the relation among the U_a/U_c ratio, Lp (a) concentration and the development of CAD are required. Moreover, interventional studies are needed to determine whether decreasing Lp (a) concentration reduces the risk of CAD. As there are currently no potent Lp (a) lowering agents available, more aggressive intervention of other treatable cardiovascular risk factors may be warranted.

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