Increased incidence of coronary disease in people with impaired glucose tolerance: link with increased lipoprotein(a) concentrations?

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Plasma concentrations of lipoprotein(a) (Lp(a)), a variant of low density lipoprotein, are determined largely genetically.¹ A recent review described Lp(a) as "emerging as a major determinant of coronary heart disease."² Impaired glucose tolerance affects around 10% of the population and is associated with an increased likelihood of developing both non-insulin dependent diabetes and coronary artery disease.² In non-insulin dependent diabetes most of the excess mortality is due to deaths from coronary heart disease, but the reasons are unclear. Associated hypertension, dyslipoproteinaemia, and the recognition of their association with hyperinsulinaemia in "syndrome X" are possible explanations.³ As impaired glucose tolerance often precedes non-insulin dependent diabetes we decided to look at concentrations of Lp(a) in these subjects.

Patients, methods, and results

Subjects were identified during a screening programme for diabetes mellitus, in which registered patients aged 45-70 from a local general practice were invited to attend fasting for a 75 g oral glucose tolerance test. Glucose tolerance was classified according to the World Health Organisation's 1985 criteria. Thirty six subjects with impaired glucose tolerance were matched with 36 normal subjects for age (± 3 years), sex, and body mass index (± 2 (weight in kg over square of height in m)). All matched pairs were selected from the same screened population.

Fasting samples were separated within two hours and stored at -70°C . Samples were sent for Lp(a) assay after matching. Lp(a) concentration was measured by Rocket electrophoresis (Immuno; Vienna), the coefficient of variation being 6%. The lower detection limit of the assay was 50 mg/l, values below this being recorded as zero. Serum cholesterol and triglyceride concentrations were determined by an enzymatic method (Boehringer Mannheim, Germany). High density lipoprotein cholesterol concentration was determined by an enzymatic method after precipitation with heparin and manganese (Boehringer Mannheim). Low density lipoprotein cholesterol concentration was calculated by Friedewald's formula. Clinical details included body mass index, waist to hip ratio, previous history of hypertension and ischaemic heart disease, and current medication. Blood pressure was measured twice after 30 minutes' rest. A 12 lead electrocardiogram was recorded. All subjects with a history of ischaemic heart disease or an abnormal electrocardiogram were excluded.

Lp(a) has a skewed distribution of values. As the median for normal subjects lies below the detection limit of the assay the 75th centile is given and the Wilcoxon signed rank test used to compare the groups. For normally distributed data means and standard deviations (SD) are presented and compared by using a paired *t* test. For triglyceride concentrations medians (ranges) are given. *p* Values of <0.05 were considered significant. The proportions of the groups having an Lp(a) concentration above 300 mg/l were compared by χ^2 test with Yates's correction. The 95% con-

fidence interval for difference in proportions is given.

Normal controls and subjects with impaired glucose tolerance did not differ significantly in age (59.3 (7.9) *v* 59.0 (7.2) years), body mass index (26.6 (3.3) *v* 27.0 (3.4)), waist to hip ratio (0.88 (0.08) *v* 0.89 (0.08)), or systolic (144.7 (18.3) *v* 151.8 (16.9) mm Hg) or diastolic blood pressure (85.1 (9.9) *v* 89.5 (10.2) mm Hg). The 75th centile for Lp(a) concentrations was significantly higher in subjects with impaired glucose tolerance than in the controls (310 (0-1320) *v* 110 (0-650) mg/l; *p* <0.03) (figure). Nine of the 36 subjects with impaired glucose tolerance had Lp(a) values above 300 mg/l compared with two of the normal controls ($\chi^2=5.3$; difference in proportions=0.19 (95% confidence interval 0.003 to 0.35); *p* <0.03). There were no significant differences between controls and subjects with impaired glucose tolerance in total cholesterol concentration (6.0 (0.98) *v* 6.4 (0.96) mmol/l), high density lipoprotein cholesterol concentration (1.4 (0.4) *v* 1.4 (0.36) mmol/l), or low density lipoprotein cholesterol concentration (3.8 (0.9) *v* 4.0 (0.91) mmol/l). Triglyceride concentration was significantly higher in the subjects with impaired glucose tolerance than in controls (1.8 (0.7-6.0) *v* 1.4 (0.3-2.8) mmol/l; *p* <0.001).

Serum Lp(a) concentrations in normal controls and subjects with impaired glucose tolerance. Bars are 75th centiles. Dashed line is detection limit of assay

Comment

Six per cent of the normal population have Lp(a) concentrations above 300 mg/l.⁴ In vitro studies show that at this concentration plasminogen binding is reduced by 20%, resulting in a procoagulant state, which is thought to be the reason for the doubled risk of coronary artery disease which is seen.⁵ We have shown that in subjects with impaired glucose tolerance there is a fivefold increase in the proportion who have Lp(a) concentrations above 300 mg/l. The reason why people with impaired glucose tolerance develop coronary artery disease is not fully understood, and therefore clear preventive strategies are difficult to implement. Our finding of increased Lp(a) concen-

trations in such subjects raises the need for further studies and highlights a possible area of intervention.

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Effects of long term octreotide on gall stone formation and gall bladder function

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Gall stones seem to be a complication of prolonged treatment of acromegaly with the long acting somatostatin analogue octreotide (Sandostatin).¹⁻³ To get further information on the risk of cholelithiasis we conducted a study in patients with and without acromegaly having octreotide in a therapeutic trial. We also evaluated the effect on fasting gall bladder volume and the potential reversibility of gall stones on withdrawing octreotide.

Patients, methods, and results

We studied 15 subjects with active acromegaly (11 men, four women; mean age 50) and 10 non-acromegalic subjects with obstructive sleep apnoea (all men; mean age 51). All subjects gave written informed consent. The data in nine of the acromegalic subjects have been reported.¹ All 15 acromegalic subjects were treated for a median of 12 months (range 4-32 months) with variable doses of octreotide ranging from 100 to 500 µg thrice daily subcutaneously. All 10 subjects with sleep apnoea received 100 µg twice daily for two to three months. The results of the sleep study will be reported separately. All subjects had ultrasound examination before beginning octreotide. Seven subjects who formed new gall stones with octreotide were withdrawn from treatment and studied further. At all examinations fasting gall bladder volumes were estimated by the ellipsoid method,⁴ studies during treatment being performed two hours after the morning injection of octreotide. The presence or absence of gall stones and the gall bladder volume were determined by one of us (GB-W) in a blinded manner. Data are presented as means and standard error of mean (SEM). Paired and unpaired *t* tests were performed as appropriate.

Gall stones formed in six of the 15 subjects with acromegaly and two of the 10 with sleep apnoea. The combined incidence was therefore 32% (eight of 25 subjects). There was no significant difference in incidence of gall stones between the two groups (χ^2 analysis). All gall stones were very small (1-2 mm) or small (2-5 mm) and varied in number from a few to the gall bladder being packed with calculi. In seven subjects with new gall stones who were studied up to eight months after withdrawal of octreotide gall stones completely resolved or substantially decreased in number in all but one. In five subjects who had studies available three months after withdrawal gall stone resolution had occurred in only two.

Fasting gall bladder volume was significantly increased during treatment with octreotide. In acromegalic subjects fasting volume increased nearly three-

Top: Fasting gall bladder volume two hours after octreotide injection in 13 acromegalic subjects both before and during octreotide treatment and after withdrawal of treatment in seven subjects. Bottom: Fasting gall bladder volume in nine sleep apnoea subjects both before and during octreotide treatment

fold, from 27 (SEM 3) ml to 71 (8) ml ($p=0.0002$). (figure), and in sleep apnoea subjects there was also a significant increase, from 30 (4) ml to 50 (6) ml ($p=0.0006$) (figure). The baseline and treatment fasting gall bladder volumes were not significantly different between the two groups. There was no significant difference in mean fasting gall bladder volume between subjects who developed gall stones and those who did not. A subgroup of seven acromegalic subjects had studies performed before, during, and after withdrawal of treatment. Fasting gall bladder volume was similarly increased during treatment (27 (3) ml to 63 (7) ml) and reversed to normal after treatment withdrawal (25 (4) ml) (figure).

Comment

This study confirms our observation that long term octreotide increases the risk of cholelithiasis in acromegalic subjects¹ and shows that this risk extends to a non-acromegalic population, with an overall incidence of 32% (eight to 25 subjects), implying a generalised lithogenic risk with octreotide use. Our study design did not allow us to determine whether dose and duration of treatment were important determinants of gall stone formation.

Impaired gall bladder motility and subsequent bile