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Association between impaired glucose tolerance and circulating concentration of Lp(a) lipoprotein in relation to coronary heart disease

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Abstract

Objective—To examine whether impaired glucose tolerance and raised Lp(a) lipoprotein concentrations are associated in subjects with coronary artery disease.

Design—Study of two subject populations, one with and one without symptomatic coronary artery disease. Case-control analysis of patients with impaired glucose tolerance and normal glucose tolerance performed in each subject population independently.

Setting—A general practice and a hospital ward in Newcastle upon Tyne.

Subjects—517 apparently healthy subjects, 13 with impaired glucose tolerance, and 245 patients who had undergone coronary artery bypass graft surgery 12 months before, 51 with impaired glucose tolerance.

Main outcome measures—Serum Lp(a) lipoprotein concentration, plasma glucose concentration before and after oral challenge with 75 g glucose monohydrate, and Lp(a) lipoprotein isoforms.

Results—In both the asymptomatic subjects and the subjects with coronary artery disease there was no significant difference between subjects with impaired glucose tolerance and subjects with normal glucose tolerance who were matched for age, sex, and body mass index in serum Lp(a) lipoprotein concentrations (geometric mean 61 (geometric SD 4) mg/l v 83 (5) mg/l for asymptomatic subjects, 175 (3) v 197 (2) for subjects with heart disease), nor was there any difference in the proportion of subjects who had Lp(a) lipoprotein concentrations >300 mg/l (31% v 23% for asymptomatic subjects, 37% v 37%

for subjects with heart disease). For both subject groups there was no significant correlation between Lp(a) lipoprotein concentration and plasma glucose concentration after a glucose tolerance test, nor did Lp(a) lipoprotein concentration vary by quintile of glucose concentration after the test. Examination of Lp(a) lipoprotein isoforms in the subjects with coronary artery disease revealed an inverse relation between isoform size and plasma Lp(a) lipoprotein concentration, but there was no evidence that impaired glucose tolerance was associated with particular Lp(a) lipoprotein isoforms.

Conclusion—Raised Lp(a) lipoprotein concentrations are not responsible for the association between impaired glucose tolerance and coronary artery disease.

Introduction

Impaired glucose tolerance has been associated with an approximate doubling in the risk of ischaemic heart disease in studies performed in the United Kingdom.^{1,2} High circulating Lp(a) lipoprotein concentrations have also been associated with an increased risk of ischaemic heart disease.³⁻¹³ A study of people with no evidence of ischaemic heart disease suggested a fivefold increase in the prevalence of raised lipoprotein(a) concentrations (>300 mg/l) in those with impaired glucose tolerance compared with those with normal glucose tolerance.¹⁴ It was proposed that a high concentration of lipoprotein(a) may explain the increased risk of ischaemic heart disease in people with impaired glucose tolerance. To investigate this we examined the relation between glucose tolerance and circulating lipoprotein(a)

concentrations in normal subjects and patients with severe coronary artery disease. We also examined the relation between lipoprotein(a) isoform (a determinant of total concentration¹⁵⁻¹⁸) and impaired glucose tolerance.

Subjects and methods

SUBJECTS

Apparently healthy subjects were recruited from a cohort of 700 people who attended a voluntary health screening programme based at a general practice surgery in Newcastle. The prevalence of cardiovascular risk factors in this cohort were diabetes mellitus 1.4%, hypertension 10%, smoking 15%, and hypercholesterolaemia (>6.5 mmol/l) 27%, similar to previous population studies in Britain.¹⁹⁻²¹ Symptoms of vascular disease (intermittent claudication, previous myocardial infarction, and angina, determined by Rose questionnaire) were present in 4% of the cohort, and the prevalence of electrocardiographic abnormalities compatible with ischaemic heart disease (Minnesota codes 1-1, 1-2, 4-1, 5-1, 8-1, and 8-3) was 3% in a representative sample of 447 subjects.²² Of this cohort, 524 white subjects were selected for study on the basis of the availability of data for both glucose tolerance and Lp(a) lipoprotein concentrations along with freedom from symptoms suggestive of vascular disease (previous myocardial infarction, angina, intermittent claudication, transient ischaemic attacks, previous stroke, congestive cardiac failure).

Subjects with ischaemic heart disease came from a series of 353 consecutive patients who underwent elective coronary artery bypass graft surgery between October 1988 and December 1989. In the first post-operative year 27 of these patients died. Metabolic follow up was obtained for 270 of the remaining patients, of whom seven were not white. Glucose tolerance and Lp(a) lipoprotein concentration were therefore measured for 263 patients at 12 months after their surgery. For case-control analysis subjects with and without impaired glucose tolerance were matched for age (to within five years), sex, and body mass index (weight (kg)/(height (m))²) (to within 1 kg/m²). Among the patients with coronary artery disease a 1:1 match was found for 51 patients with impaired glucose tolerance. Among the asymptomatic subjects, each person with impaired glucose tolerance was matched with two normal controls.

BIOCHEMICAL TESTS

Venous blood samples were taken for various analyses from the subjects after they had fasted overnight for 10-12 hours. The subjects were given a drink containing 75 g glucose monohydrate, and another blood sample was taken two hours later

to measure glucose concentration. Venous plasma glucose concentrations were measured by an automated glucose oxidase assay (interassay coefficient of variation 1-3%). The results of the glucose tolerance tests were classified according to the criteria of the World Health Organisation.²³ Serum for Lp(a) lipoprotein assay was frozen at -70°C for later enzyme linked immunosorbent assay (ELISA: Biopool, Umea, Sweden) with a between batch coefficient of variation of 3-8%. The lower limit of detection was 10 mg/l, which is the maximum cross reactivity between the polyclonal antihuman Lp(a) lipoprotein antibody used and plasminogen at a concentration of 200 mg/l. The performance of this antibody against the various isoforms of Lp(a) lipoprotein is known to be satisfactory.²⁴ Lp(a) lipoprotein isoforms were demonstrated by immunoblotting after separation with sodium dodecyl sulphate polyacrylamide gel electrophoresis under reducing conditions.²⁴ Appropriate reference samples of known pure Lp(a) lipoprotein isoform classes were used. Standard enzymatic methods were used to measure serum concentrations of cholesterol (cholesterol oxidase, interassay coefficient of variation 1.5-2.2%) and triglycerides (lipase-glycerol kinase, interassay coefficient of variation 3.0%). High density lipoprotein cholesterol was isolated from EDTA plasma after precipitation of apolipoprotein B with heparin and manganese and was assayed with the cholesterol oxidase method (interassay coefficient of variation 3.6%).

STATISTICAL ANALYSIS

The results for triglyceride and Lp(a) lipoprotein concentrations underwent log transformation before analysis so that they were normally distributed. These concentrations are presented as geometric mean (geometric SD). For other measures mean (SD) are presented. Differences between subjects with impaired and normal glucose tolerance matched 1:1 were analysed either with unpaired Student's *t* tests or, for case-control analyses, paired *t* tests; analysis of variance was used for cases and controls matched 1:2. Pearson correlation coefficients were used to analyse linear associations. The distribution of Lp(a) lipoprotein isoforms in different subject groups was compared by χ^2 analysis. The effect of isoform size on Lp(a) lipoprotein concentration was analysed by Kruskal-Wallis test. The power of the present study to show an effect of impaired glucose tolerance on Lp(a) lipoprotein concentration of the magnitude suggested by Davies *et al*⁴ was greater than 95% in the patients with coronary artery disease. In the asymptomatic subjects power was well in excess of 80% to detect a fivefold higher prevalence of high Lp(a) lipoprotein concentrations (>300 mg/l) in subjects with impaired glucose tolerance compared with controls.

Results

Table I shows the characteristics of the subjects selected for study and those of the cohorts from which they were recruited. Of the 524 asymptomatic, apparently normal subjects initially chosen, five had diabetes mellitus and were not considered further. Of the 263 subjects with coronary artery disease initially selected, 18 had diabetic tolerance tests and were not considered further. The values given for the subjects with heart disease are from preoperative measurements taken before the subjects underwent coronary artery bypass surgery. The subjects studied were representative of their respective cohorts.

ASYMPTOMATIC SUBJECTS

Of the 519 subjects studied, 15 showed impaired glucose tolerance and 13 of these were matched with

TABLE I—Characteristics of the subjects studied and of the cohorts from which they were recruited. Values are means (standard deviations) unless stated otherwise

	Asymptomatic subjects		Subjects with coronary artery disease	
	Whole cohort (n=700)	Selected subjects (n=519)	Whole cohort (n=353)	Selected subjects (n=245)
No of men:No of women	357:343	266:253	298:55	211:34
Age (years)	46 (10)	46 (10)	57 (8)	56 (8)
Body mass index (kg/m ²)	25.0 (3.7)	24.9 (3.6)	25.7 (2.8)	25.6 (2.9)
Blood pressure (mm Hg):				
Systolic	121 (17)	122 (17)	127 (18)	127 (18)
Diastolic	77 (10)	77 (10)	76 (10)	76 (10)
Serum concentrations (mmol/l):				
Total cholesterol	5.8 (1.2)	5.9 (1.3)	6.5 (1.3)	6.5 (1.4)
Triglyceride*	1.21 (0.95)	1.23 (1.18)	1.58 (1.26)	1.56 (1.41)
Plasma concentrations (mmol/l):				
High density lipoprotein cholesterol	1.42 (0.37)	1.43 (0.37)	1.01 (0.27)	1.01 (0.26)
Fasting glucose	5.2 (0.8)	5.1 (0.8)	5.4 (1.5)	5.2 (0.8)
Glucose after glucose tolerance test	4.8 (1.0)	4.9 (1.2)		

*Expressed as geometric mean (geometric SD).

26 subjects with normal glucose tolerance (table II). The subjects with impaired glucose tolerance were significantly older than the 504 subjects with normal glucose tolerance and had higher body mass index, systolic and diastolic blood pressures, and serum triglyceride concentration. There was, however, no significant difference in the serum concentrations of Lp(a) lipoprotein, the proportion of subjects with high Lp(a) lipoprotein concentrations (> 300 mg/l), and the concentrations of serum cholesterol and plasma high density lipoprotein cholesterol. There was no difference between the subjects with impaired glucose tolerance and their matched controls except for plasma glucose concentrations.

In the group as a whole there was no significant

TABLE II—Characteristics of asymptomatic subjects with normal and impaired glucose tolerance. Values are means (standard deviations) unless stated otherwise

	Subjects with normal glucose tolerance (n=504)	Subjects with impaired glucose tolerance (n=13)	Matched subjects with normal glucose tolerance (n=26)†
No of men:No of women	257:247	9:4	18:8
Age (years)	46 (11.2)*	54 (8.2)	54 (7.3)
Body mass index (kg/m ²)	24.9 (4.5)**	26.2 (5.1)	25.0 (2.6)
Blood pressure (mm Hg):			
Systolic	121 (17)*	134 (22)	128 (21)
Diastolic	77 (10)**	83 (8)	81 (11)
Serum Lp(a) lipoprotein (mg/l)‡	83 (4)	61 (4)	83 (5)
No (%) of subjects with Lp(a) lipoprotein concentration > 300 mg/l	116 (23)	4 (31)	6 (23)
Serum concentrations (mmol/l):			
Total cholesterol	5.90 (1.30)	6.63 (1.40)	6.00 (1.50)
Triglyceride‡	1.22 (1.20)***	1.40 (1.58)	1.34 (1.45)
Plasma concentrations (mmol/l):			
High density lipoprotein cholesterol	1.43 (0.37)	1.40 (0.69)	1.39 (0.48)
Fasting glucose	5.1 (0.6)***	5.7 (0.7)	5.3 (0.5)***
Glucose after glucose tolerance test	4.7 (1.2)***	8.8 (0.4)	4.8 (0.3)***

Significance of difference from value of subjects with impaired glucose tolerance: *p<0.05, **p<0.01, ***p<0.001.

†See text for details.

‡Expressed as geometric mean (geometric SD).

TABLE III—Characteristics of subjects with coronary artery disease with normal and impaired glucose tolerance. Values are means (standard deviations) unless stated otherwise

	Subjects with normal glucose tolerance (n=194)	Subjects with impaired glucose tolerance (n=51)	Matched subjects with normal glucose tolerance (n=51)†
No of men:No of women	167:27	44:7	44:7
Age (years)	57 (7.7)	58 (6.9)	58 (7.1)
Body mass index (kg/m ²)	25.4 (2.6)	26.1 (3.0)	24.7 (2.8)*
Blood pressure (mm Hg):			
Systolic	124 (17)**	130 (18)	120 (25)**
Diastolic	75 (9)	78 (11)	73 (11)*
Serum Lp(a) lipoprotein (mg/l)‡	182 (4)	175 (3)	197 (2)
No (%) of subjects with Lp(a) lipoprotein concentration > 300 mg/l	70 (36)	19 (37)	19 (37)
Serum concentrations (mmol/l):			
Total cholesterol	5.90 (0.50)	6.21 (0.55)	5.80 (0.36)
Triglyceride‡	1.50 (1.35)*	1.78 (1.58)	1.41 (1.58)*
Plasma concentrations (mmol/l):			
High density lipoprotein cholesterol	1.20 (0.71)	1.14 (0.36)	1.27 (0.36)*
Fasting glucose	5.1 (0.5)***	5.6 (0.4)	5.1 (0.4)***
Glucose after glucose tolerance test	5.8 (1.1)***	8.9 (0.4)	5.9 (0.4)***

Significance of difference from value of subjects with impaired glucose tolerance: *p<0.05, **p<0.02, ***p<0.001.

†See text for details.

‡Expressed as geometric mean (geometric SD).

TABLE IV—Distribution of isoforms of Lp(a) lipoprotein among 51 subjects with coronary artery disease and impaired glucose tolerance and 51 matched subjects with coronary artery disease and normal glucose tolerance

Isoform class*	Subjects with normal glucose tolerance		Subjects with impaired glucose tolerance	
	No (%) of each isoform detected	Lp(a) lipoprotein concentration (mg/l)†	No (%) of each isoform detected	Lp(a) lipoprotein concentration (mg/l)†
Null	4 (5)	24 (6)	2 (3)	9
<0.35	1 (1)	148	2 (3)	91
0.4	5 (7)	89 (6)	7 (11)	85 (6)
0.5	19 (26)	98 (9)	16 (24)	174 (6)
0.6	12 (16)	155 (6)	14 (21)	138 (12)
0.7	13 (16)	240 (6)	8 (12)	229 (9)
0.8	7 (10)	209 (9)	10 (15)	589 (6)
0.9	7 (10)	398 (3)	5 (8)	214 (12)
1.0	2 (3)	513	2 (3)	479
1.1	3 (4)	457	0	
>1.15	1 (1)	631	0	

*Expressed as relative mobility of apolipoprotein(a) compared with apolipoprotein B100.

†Expressed as geometric mean (geometric SD).

correlation between the log of the circulating Lp(a) lipoprotein concentration and the plasma glucose concentration two hours after oral challenge with glucose (log Lp(a) lipoprotein concentration=0.008 plasma glucose concentration+1.87, $r^2=0.001$, $p=0.56$). There was, however, a significant positive correlation between glucose tolerance and serum triglyceride concentration (log triglyceride concentration=0.027 plasma glucose concentration -0.04, $r^2=0.061$, $p<0.0001$) and a significant negative correlation between glucose tolerance and high density lipoprotein cholesterol concentration (concentration=-0.025 plasma glucose concentration+1.54, $r^2=0.017$, $p<0.01$). Concentrations of Lp(a) lipoprotein were no different in the subjects in the lowest quintile of plasma glucose concentration after oral glucose challenge (mean (SD) log Lp(a) lipoprotein concentration 85 (5)) compared with subjects in the highest quintile of plasma glucose concentration (log Lp(a) lipoprotein concentration 74 (8)).

SUBJECTS WITH CORONARY ARTERY DISEASE

Table III shows the characteristics of the subjects with heart disease 12 months after they had undergone coronary artery bypass surgery. Of the 245 subjects studied, 51 had impaired glucose tolerance and were matched with 51 subjects with normal glucose tolerance. The subjects with impaired glucose tolerance had significantly higher serum triglyceride concentration than the 194 subjects with normal glucose tolerance and the 51 matched controls. They also had significantly higher body mass index, higher total serum cholesterol concentration, and lower concentrations of high density lipoprotein cholesterol than the 51 matched controls. There was, however, no significant difference in the Lp(a) lipoprotein concentration and proportion of subjects with high Lp(a) lipoprotein concentrations (>300 mg/l). Body mass index did not correlate significantly with Lp(a) lipoprotein concentration ($r=-0.136$, $r^2=0.019$, $p=0.345$).

In the group as a whole there was no correlation between Lp(a) lipoprotein concentration and glucose tolerance (log Lp(a) lipoprotein concentration=0.003 plasma glucose concentration after oral challenge+2.27, $r^2=0.00$, $p=0.86$). In contrast there were significant correlations between glucose tolerance and triglyceride concentration (log triglyceride concentration=0.014 plasma glucose concentration+0.10, $r^2=0.045$, $p<0.0005$) and high density lipoprotein cholesterol concentration (concentration=-0.017 plasma glucose concentration+1.3, $r^2=0.022$, $p<0.02$). Concentrations of Lp(a) lipoprotein were no different in subjects in the lowest quintile of plasma glucose concentration after oral challenge (geometric mean (geometric SD) Lp(a) lipoprotein concentration 158 (13) mg/l) compared with subjects in the highest quintile of plasma glucose concentration (Lp(a) lipoprotein concentration 166 (11) mg/l).

LIPOPROTEIN ISOFORMS

Isoforms of Lp(a) lipoprotein were examined in the 51 subjects with heart disease who had impaired glucose tolerance and their 51 matched controls. Apart from a few subjects who had no detectable circulating isoforms ("null" phenotypes) the subjects had one or two circulating isoforms in the blood. There was no difference between the subjects with impaired glucose tolerance and their matched controls in the proportion of null, single, and double band phenotypes (single bands 71% v 57%, χ^2 test $p=0.13$). Table IV shows the distribution of isoforms. Impaired glucose tolerance was not associated with an increased proportion of small or large molecular mass isoforms, but Lp(a) lipoprotein concentration increased with relative mobility of isoform both in subjects with impaired

glucose tolerance ($p < 0.05$, Kruskal-Wallis test) and those with normal glucose tolerance ($p < 0.01$).

Discussion

A raised Lp(a) lipoprotein concentration is associated with coronary artery disease,^{3,13} and impaired glucose tolerance has also been shown to be predictive of coronary heart disease in some studies¹² but not in others.^{25,26} A link has been suggested between impaired glucose tolerance and an increased circulating Lp(a) lipoprotein concentration.¹⁴ Our results do not support this report even though the asymptomatic subjects in our study were similar to those described in the earlier study (which also excluded patients with coronary artery disease). Our group of patients with coronary artery disease showed a high prevalence of impaired glucose tolerance. Our assay for Lp(a) lipoprotein was sensitive, and only 5% of results (3% of those from the patients with coronary artery disease and 8% of those from asymptomatic subjects) were below the assay's limit of detection so that real effects would not have been missed. Our results showed no relation between glucose tolerance and Lp(a) lipoprotein concentrations either in the subjects as a whole or when the subjects with impaired glucose tolerance were compared with matched individuals with normal glucose tolerance. Impaired glucose tolerance was not associated with an increase in the proportion of subjects with high Lp(a) lipoprotein concentrations (> 300 mg/l). We found no evidence of either a graded continuous effect or a threshold effect of glucose concentration after the glucose tolerance test on Lp(a) lipoprotein concentrations in either group. There were, however, significant correlations between glucose concentration after the glucose tolerance test and log triglyceride concentration and high density lipoprotein cholesterol concentration. The differences between subjects with impaired and normal glucose tolerance in their blood pressure and lipid profile were consistent with previous reports.²⁷⁻³² It is therefore unlikely that a real association between glucose tolerance and Lp(a) lipoprotein was missed because the populations we studied were not representative.

A genetic association between impaired glucose tolerance and diabetes mellitus in families in which non-insulin dependent diabetes mellitus occurs is well known.³³⁻³⁶ If there was a genetic association between

impaired glucose tolerance, high Lp(a) lipoprotein concentrations, and coronary artery disease it should have been revealed by examination of the patients with coronary artery disease (all of whom were unrelated). In this group we compared concentration and isoform of Lp(a) lipoprotein (isotype reflecting genotype) between the subjects with impaired glucose tolerance and those with normal glucose tolerance. The expected inverse relation between isoform size and Lp(a) lipoprotein concentration was found in both the subjects with impaired glucose tolerance and those with normal glucose tolerance. Both subgroups showed similar distributions of isoforms with no difference in the proportion of patients who had higher mobility (smaller size and higher concentration) isoforms. A specific association between impaired glucose tolerance and particular Lp(a) lipoprotein isoforms (and hence genotypes) is thus excluded.

We conclude that, while both impaired glucose tolerance and increased concentrations of Lp(a) lipoprotein are associated with coronary artery disease, increased Lp(a) lipoprotein concentrations are not responsible for the association between impaired glucose tolerance and coronary artery disease.

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Clinical implications

- High serum concentrations of Lp(a) lipoprotein and impaired glucose tolerance are both associated with coronary artery disease
- It has been suggested that the association between impaired glucose tolerance and coronary artery disease may be caused by the raised Lp(a) lipoprotein concentrations
- In this study of two groups, one of apparently healthy subjects and one of subjects with coronary artery disease, high Lp(a) lipoprotein concentrations and impaired glucose tolerance were associated with coronary artery disease
- Neither group, however, showed a significant correlation between Lp(a) concentration and glucose tolerance, nor was there an association between impaired glucose tolerance and particular isoforms of Lp(a) lipoprotein
- Raised Lp(a) lipoprotein concentrations are not responsible for the association between impaired glucose tolerance and coronary artery disease

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Measuring the impact of menopausal symptoms on quality of life

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Abstract

Objective—To examine the impact of menopausal symptoms on the overall quality of life of women.

Design—Data collection with a questionnaire administered by an interviewer, incorporating two different quality of life measurement techniques (time trade off and rating scale).

Setting—Specialist menopause clinic and two general practices in Oxford.

Subjects—63 women aged 45-60 years recruited opportunistically during a clinic or appointment with a general practitioner; no exclusion criteria.

Results—Subjects gave very low quality of life ratings for health states with menopausal symptoms. The time trade off method of measuring preferences for these health states (on a scale from 0 to 1, where preference for full health is given as 1) yielded utility values of 0.64 for severe menopausal symptoms and 0.85 for mild symptoms. The rating scale measurement technique yielded even lower values: utilities of 0.30 and 0.65 were obtained for severe and mild symptoms respectively. Kappa scores indicated that the two methods produced results that were poorly related but not contradictory. Comparison of quality of life ratings before and after treatment with hormone replacement therapy showed significant improvements: with the rating scale measurement technique mean increases in utility values after the relief of severe and mild menopausal symptoms were 0.56 and 0.18 respectively.

Conclusions—Quality of life may be severely compromised in women with menopausal symptoms, and perceived improvements in quality of life in users of hormone replacement therapy seem to be substantial. This emphasises the need to include quality of life measurements when assessing outcomes of hormone replacement therapy. Several limitations may exist with widely applied measurement techniques, calling for the development of appropriate and well validated instruments for measuring quality of life associated with reduced health states.

Introduction

In recent years there has been much interest in hormone replacement therapy and the overall balance

of benefits and risks.¹⁻³ One benefit of hormone replacement therapy is its proved effect in alleviating menopausal symptoms⁴⁻⁹—symptoms which persist for more than one year in over 80% of menopausal women.¹⁰ Few attempts have been made to measure the impact of menopausal symptoms on quality of life or changes in quality of life resulting from use of hormone replacement therapy. In a cost effectiveness study of hormone replacement therapy carried out in the United States, adjustments for quality of life were based on the authors' own judgments rather than on evidence.¹¹ Here we report some fieldwork to assess the impact of menopausal symptoms on quality of life, involving a questionnaire based interview of 63 women aged between 45 and 60. The objective was to derive a quantitative measure of the value or "utility" placed by women on quality of life states associated with menopausal symptoms. The fieldwork was undertaken as part of a cost effectiveness study in which the outcome of hormone replacement therapy was expressed in terms of quality adjusted life years, or QALYs, an outcome measure which strives to combine the change in quality of life associated with an intervention with the change in life expectancy.

Methods

Several methods exist to measure quality of life.¹²⁻¹⁴ We decided to use two valuation methods and to compare the results obtained from each. Firstly, subjects were given descriptions of menopausal symptoms and shown a simple visual numerical scale of 0 to 10 with defined end points of death and normal health. They were asked to pick a point on the scale that reflected the quality of life associated with the health state in question. We will refer to this as the rating scale method.

Secondly, subjects were given the same descriptions of menopausal symptoms and invited to enter a procedure for the valuation of health states known as the time trade off method, again supported by a visual illustration. This method has been applied widely in the United States for the evaluation of health states.¹² It has been argued that this method has advantages in terms of ease of application and consistency of result,^{15,16} especially where the disease under investigation is chronic or does not involve life threatening

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