PAPERS AND SHORT REPORTS

Distribution of adipose tissue and risk of cardiovascular disease and death: a 12 year follow up of participants in the population study of women in Gothenburg, Sweden

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Abstract

A longitudinal population study of 1462 women aged 38-60 was carried out in Gothenburg, Sweden, in 1968-9. In univariate analysis the ratio of waist to hip circumference showed a significant positive association with the 12 year incidence of myocardial infarction, angina pectoris, stroke, and death. The association with incidence of myocardial infarction remained in multivariate analysis and was independent of age, body mass index, smoking habit, serum cholesterol concentration, serum triglyceride concentration, and systolic blood pressure.

The relation between the ratio of waist to hip circumference and the end points of myocardial infarction, angina pectoris, stroke, and death was stronger than for any other anthropometric variable studied.

Introduction

The possible relation between obesity and cardiovascular disease has been the subject of great controversy. Interest has been focused mainly on quantity of adipose tissue and less on its distribution. Krotkiewski *et al* showed in a cross sectional study of men and women that cardiovascular risk factors such as hypertension, hypertriglyceridaemia, hyperinsulinaemia, and glucose intolerance were more pronounced in subjects with a masculine type of adipose tissue distribution—that is, in subjects with a high ratio of waist to hip circumference.[1] Similar cross sectional results from Kissebah *et al*,[2] Hartz *et al*,[3] and Szathmary and Holt[4] have recently been published. On the basis of these cross sectional findings we investigated whether the distribution of adipose tissue was important for the incidence of cardiovascular disease in subjects taking part in longitudinal population studies in Gothenburg. As recently reported in this journal, a high ratio of waist to hip circumference was associated with an increased risk of ischaemic heart disease in men during 13 years' follow up[5] despite indices and measures of total obesity having no predictive power. In the present study we examined a representative population sample of women followed up over 12 years.

Subjects and methods

In 1968-9 we studied 1462 women in Gothenburg, Sweden, aged 38, 46, 50, 54, or 60. The systematic sampling method, based on date of birth, and a high participation rate (90·1%) ensured that the participants were a representative cross section of women from the community of the ages studied. Table I shows the numbers of participants in the initial examination. The population sample was followed up on two occasions, in 1974-5 and in 1980-1. Of those participating in 1968-9, 1154 (78·9%) took part in 1980-1. Most of the non-participants were interviewed by telephone or letter concerning their history of angina pectoris, myocardial infarction, or stroke. In this way, information was obtained from a total of 1351 women (97·4%

TABLE I—*Numbers of subjects in each age group participating in the population study of women in Gothenburg*

Year of birth	No (%) of women participating in 1968-9	No (%) of women for whom waist to hip ratio was available
1930	372 (91·4)	353 (86·7)
1922	431 (90·0)	413 (86·2)
1918	398 (91·3)	378 (86·7)
1914	180 (88·7)	180 (88·7)
1908	81 (83·5)	80 (82·5)
Total	1462 (90·1)	1404 (86·6)

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of those participating in 1968-9 still alive in 1980-1). In 1968 a subsample comprising 57 of the randomly selected women was examined in a pilot study as a preparation for the main study. The ratio of waist to hip circumference was not registered in the pilot study and is also missing for one woman aged 60 and is thus missing in 58 (4%) of the women examined (table I). Further details concerning the studies in 1968-9, 1974-5, and 1980-1 have been presented elsewhere.[6-8]

CLINICAL EXAMINATION

In the initial study of 1968-9 blood samples were taken after overnight fasting.[6] Body weight was measured to the nearest 0·1 kg with a balance scale. The women wore only briefs when being weighed. Body height without shoes was measured to the nearest 0·5 cm. Body mass index was calculated as weight/height^2 (kg/m^2). Skinfold thicknesses were measured with a Harpenden caliper (British Indicators, England) to the nearest 0·1 mm on the right side of the subject over the subscapular area and over the triceps muscle. The sum and the ratio (subscapular to triceps thickness) of the thicknesses of the two skinfolds were calculated. Waist circumference was measured to the nearest 1 mm at the level midway between the lower rib margin and the iliac crest using a steel tape measure. Hip circumference was measured with the same steel tape measure to the nearest 1 mm at the widest point between hip and buttock. The circumferences were measured with the subjects standing. All the anthropometric measurements were performed by one observer (ER) only. Blood pressure was measured, with a mercury manometer, in the seated position after about five minutes' rest.[9] Information about smoking habits was obtained via a standardised interview.[9]

END POINTS DURING FOLLOW UP

Myocardial infarction—For non-fatal myocardial infarction each participant was asked if she had any history of chest pain, as were most of the non-participants in the follow up studies. Records of all women who were admitted to hospital due to chest pain were studied, and the diagnosis of acute myocardial infarction was defined as the presence of at least two of the following criteria: (1) central chest pain, (2) transient rise of transaminase activities, and (3) typical electrocardiographic changes of recent onset. These criteria have been described in detail elsewhere.[10] Fatal myocardial infarction was accepted if that diagnosis was stated on the death certificate. "Silent" myocardial infarction was defined as electrocardiographic changes interpreted as Minnesota code 1.1[11 12] without a history of myocardial infarction. In our analyses we used the combined incidences of fatal and non-fatal myocardial infarction. The incidence of silent myocardial infarction was added only when indicated in the text.

Angina pectoris—During an interview patients were asked whether they had a history of chest pain. A diagnosis of angina pectoris was accepted when the criteria on the questionnaire proposed by Rose[13] were fulfilled.

Electrocardiographic changes suggesting ischaemic heart disease—Electrocardiography was performed on all participants at rest in 1968-9 and in 1980-1. Minnesota codes 1.1-2, 4.1, 5.1-2 (in the absence of 3.1), 6.1, and 7.1 were defined as electrocardiographic changes suggesting ischaemic heart disease.

Stroke—Stroke was defined as described by Harmsen and Tibblin.[14] If non-fatal, diagnosis at the hospital was required. Stroke was also registered for subjects who showed signs consistent with a recent cerebrovascular accident at postmortem examination and for subjects in whom stroke was recorded as the major cause of death on their death certificate.

Death—Confirmation of whether the women were alive or dead at the end of the 12 years was obtained for 1458 (99·7%) of the initial participants. Death certificates were obtained for all participants who died. Necropsies were performed in five (63%) of patients dying from myocardial infarction and in 27 (40%) of 67 women in whom myocardial infarction had not been diagnosed in the death certificate.

Patients with findings positive for myocardial infarction at the initial examination were excluded when the risk for myocardial infarction as an end point was assessed. Similarly, patients already with findings positive for other end points at the initial examination were excluded in the final calculations for corresponding end points.

STATISTICAL METHODS

Standard methods were used to calculate mean values and standard deviations. Associations between graded or continuous variables were tested by means of Pitman's non-parametric permutation test.[15] In adjusting for confounding variables an extension of Mantel-Haenszel's procedure to permutation test was used.[16] We used the Kaplan-Meier estimate to produce survival curves and the log rank test to test differences between survival curves.[17] The Cox proportional hazard model was used to test differences between survival curves after adjustment for differences in age.[18] Two tailed tests were used, and p values of less than 0·05 were considered to be significant.

Results

Incidence of end points—Of all (1424) women initially free from signs of myocardial infarction on whom we obtained valid follow up data, 23 (1·6%) developed myocardial infarction during the follow up period (eight fatal, 15 non-fatal). Another five women developed silent myocardial infarction during follow up. New symptoms of angina pectoris were recorded in 56 (4·0%) of 1416 women, new signs of electrocardiographic changes suggesting ischaemic heart disease in 73 (6·0%) of 1218 women, and new signs of stroke in 13 (0·9%) of 1426. Altogether 75 women (5·1%) died during the follow up period.

Risk factors—The ratio of waist to hip circumference ranged from 0·59 to 1·00 at the initial examination. Table II shows the mean values for age, systolic blood pressure, serum cholesterol concentration, serum triglyceride concentration, cigarette consumption, body mass index, sum of skinfold thicknesses, and blood glucose concentration in quintiles of the waist to hip ratio. Significant positive associations were found between the waist to hip ratio and all risk variables included in table II. Figure 1 illustrates the positive relation between the waist to hip ratio and age.

Baseline anthropometric variables and end points—As age is an important confounding factor, being associated both with the ratio of waist to hip circumference and with most of the end points studied, age was considered in all our calculations. Table III shows the age specific p values for the non-parametric correlations[15] between different anthropometric variables and incidence of the end points of myocardial infarction, angina pectoris, electrocardiographic changes suggesting ischaemic heart disease, stroke, and death. Significant risk factors for myocardial infarction according to this correlation analysis

TABLE II—*Mean (SD) of variables measured in 1462 women in 1968-9 in relation to quintiles of the ratio of waist to hip circumference*

Quintiles of the waist to hip ratio	Variables							
	Age (years)	Systolic blood pressure (mm Hg)	Serum cholesterol (mmol/l)	Serum triglyceride (mmol/l)	No (%) of smokers	Body mass index (kg/m^2)	Sum of skinfold thicknesses (mm)	Blood glucose (mmol/l)
I	44·9 (6·1)	130 (19)	6·70 (0·98)	1·04 (0·39)	89 (31·3)	22·5 (2·7)	29·4 (9·0)	4·02 (0·62)
II	45·8 (5·8)	128 (19)	6·64 (1·00)	1·10 (0·39)	122 (43·7)	23·0 (3·2)	31·2 (10·4)	3·99 (0·69)
III	46·8 (6·0)	132 (20)	6·84 (1·15)	1·15 (0·45)	112 (40·0)	23·3 (3·1)	32·6 (10·0)	4·11 (0·80)
IV	47·9 (5·8)	135 (21)	6·93 (1·07)	1·30 (0·54)	130 (46·3)	24·6 (3·6)	35·8 (12·1)	4·12 (0·68)
V	49·1 (6·6)	142 (27)	7·16 (1·65)	1·55 (0·89)	118 (42·3)	27·0 (4·2)	43·4 (13·8)	4·41 (1·37)
Total	46·8 (6·2)	133 (22)	6·86 (1·21)	1·22 (0·60)	571 (40·7)	24·1 (3·8)	34·5 (12·2)	4·14 (0·88)
p*	<0·001	<0·001	<0·01	<0·001	<0·001	<0·001	<0·001	<0·001

* Age specific p values.
Conversion: SI to traditional units—Cholesterol: 1 mmol/l ≈ 39 mg/100 ml. Triglyceride: 1 mmol/l ≈ 88·6 mg/100 ml. Glucose: 1 mmol/l ≈ 18 mg/100 ml.

TABLE III—*p values for age specific correlation between anthropometric variables and specified end points*

Variables	End points				
	Myocardial infarction	Angina pectoris	Electrocardiographic changes suggesting ischaemic heart disease	Stroke	Death
Body weight	0·109	0·472	0·311	0·549	0·935
Body mass index	0·017*	0·116	0·043*	0·388	0·771
Subscapular skinfold	0·026*	0·265	0·208	0·275	0·523
Triceps skinfold	0·247	0·54	0·946	0·681	0·386†
Sum of skinfolds	0·049*	0·307	0·4	0·373	0·965
Ratio of subscapular to triceps skinfold	0·106	0·442	0·074	0·079	0·046*
Waist circumference	0·005*	0·048*	0·14	0·093	0·099
Hip circumference	0·345	0·442	0·646	0·968	0·762†
Ratio of waist to hip circumference	0·0006*	0·02*	0·096*	0·017*	0·006*

* $p < 0·05$.
† Negative correlation.

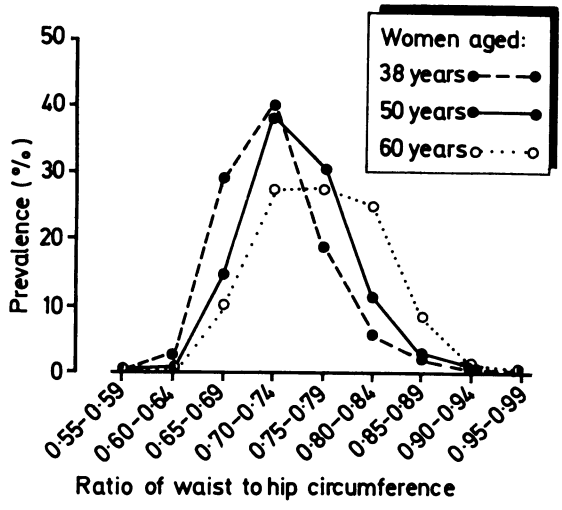

FIG 1—Initial percentage distribution of ratio of waist to hip circumference among women aged 38, 50, or 60 in 1968-9.

TABLE IV—*Age standardised incidence (%) over 12 years of specified end points by centiles of the ratio of waist to hip circumference*

Centiles of the waist to hip ratio	End points		
	Myocardial infarction	Stroke	Death
0-10	0	0	2·9
0-20	0·4	0·4	3·2
21-40	0·4	0·7	5·4
41-60	2·4	0·4	3·9
61-80	2·4	1·1	6·5
81-90	2·2	0	3·6
91-95	2·9	1·5	2·9
96-100	5·9	4·4	15·5

were body mass index, subscapular skinfold thickness, sum of two skinfold thicknesses, waist circumference, and waist to hip ratio. Angina pectoris was related to waist circumference and to waist to hip ratio. Electrocardiographic changes suggesting ischaemic heart disease were related to body mass index. Stroke was associated only with the ratio of waist to hip circumference, and death from any cause was correlated with this ratio as well as with the skinfold ratio. The waist to hip ratio seemed to be stronger and more consistently correlated with the end points than were indices of general obesity (body mass index, sum of skinfolds). Table IV presents the 12 year age specific incidences of myocardial infarction, stroke, and death by centiles of the waist to hip ratio. The risk ratio between the highest quintile and the lowest quintile was 8·2 for myocardial infarction, 3·8 for stroke, and 2·0 for death from any cause. When comparing women in the top 5% of the distribution with those in the lowest quintile the risk ratios were 14·8, 11·0, and 4·8 for the three end points, respectively. Among the 140 (10%) women with the lowest ratio of waist to hip circumference not a single woman developed myocardial infarction or stroke. To illustrate the relation between the ratio of waist to hip circumference and end points in another way we studied the highest and the lowest age specific quintiles of the waist to hip ratio in a life table analysis. Figure 2 shows the probability of avoiding myocardial infarction and death during the 12 year follow up for the highest and lowest quintiles of the waist to hip ratio. Significant differences were observed with both myocardial infarction ($p = 0·01$) and death ($p = 0·0003$).

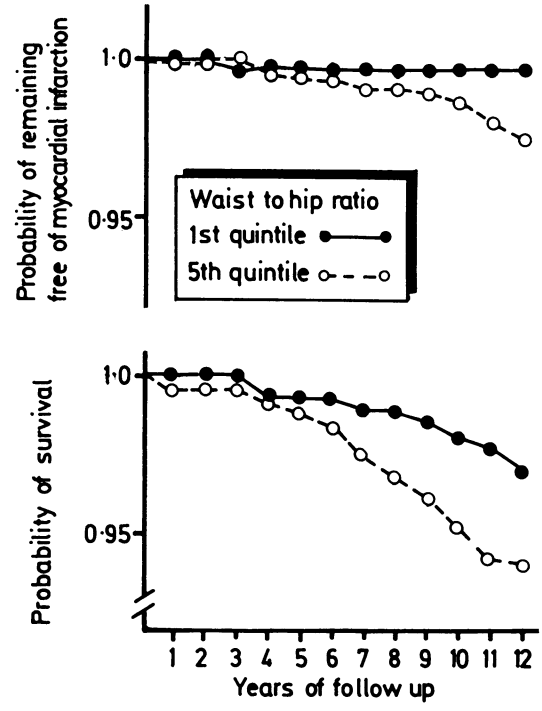

FIG 2—Probability of remaining free of myocardial infarction and of dying of any cause for every year of a 12 year follow up by highest and lowest quintiles of ratio of waist to hip circumference at entry.

TABLE V—*p values for correlation between waist to hip ratio and specified end points when selected traditional risk factors were taken into account as background variables in a non-parametric permutation test*

Background variables	End points				
	Myocardial infarction	Angina pectoris	Electrocardiographic changes suggesting ischaemic heart disease	Stroke	Death
Age (years)	0·0006*	0·02*	0·096	0·017*	0·006*
Age (years) and body mass index (kg/m²)	0·01*	0·056	0·258	0·011*	0·004*
Age (years), body mass index (kg/m²), and No of cigarettes consumed	0·008*	0·123	0·228	0·044*	0·019*
Age (years), body mass index (kg/m²), and triglycerides (mmol/l)	0·045*	0·11	0·22	0·065	0·068
Age (years), body mass index (kg/m²), and cholesterol (mmol/l)	0·009*	0·056	0·199	0·006*	0·002*
Age (years), body mass index (kg/m²), and systolic blood pressure (mm Hg)	0·016*	0·046*	0·356	0·008*	0·015*

* $p < 0·05$.

MULTIVARIATE ANALYSES

Because of the strong associations found not only between the ratio of waist to hip circumference and the degree of obesity but also between this ratio and other traditional risk factors for cardiovascular disease, multivariate analyses were performed to assess the independent association between waist to hip ratio and the studied end points. Table V shows the association between the waist to hip ratio and the end points myocardial infarction, angina pectoris, electrocardiographic changes suggesting ischaemic heart disease, stroke, and death when age, body mass index, and other selected traditional risk factors for cardiovascular disease were taken into account as background variables in a non-parametric permutation test. For myocardial infarction, stroke, and death the waist to hip ratio remained a significant risk factor when age plus body mass index were accounted for. The ratio of waist to hip circumference correlated significantly with myocardial infarction when, in addition to age and body mass index, either smoking habit, triglyceride concentration, cholesterol concentration, or systolic blood pressure was considered as a confounder. When women with silent myocardial infarction were included the p values were about the same for all end points studied as when not included.

When the combined influence of the waist to hip ratio and the body mass index were studied (table VI) there was a tendency for an increased risk of myocardial infarction and death with increasing waist to hip ratio in all tertiles of body mass index. One exception to this tendency was the high risk of death (7·6%) in the lowest tertile of both the waist to hip ratio and body mass index.

TABLE VI—*Percentage probabilities of myocardial infarction and death from any cause in relation to tertiles of body mass index and ratio of waist to hip circumference*

Tertiles of waist to hip ratio	Tertiles of body mass index		
	I	II	III
	Myocardial infarction		
I	0·9	0	0
II	1·1	0·9	1·5
III	3·8	0	3·5
	Death		
I	7·6	2·5	1
II	4·7	4·7	4·7
III	7	5·2	6·3

Discussion

The relation between obesity and cardiovascular disease has been much discussed during the past decades.[19 20] Many reports from insurance companies, based on observations since the beginning of this century, have shown a significant relation as reviewed in a previous report.[20] This report also dealt with prospective studies that were not able to show any association between obesity and cardiovascular disease. In a recent report from the Framingham study, however, obesity was found to be a risk factor for cardiovascular disease independently of age, systolic blood pressure, serum cholesterol concentration, cigarette smoking, and glucose intolerance.[21] A relation between obesity and cardiovascular disease was also observed in a Norwegian longitudinal study of 1 700 000 subjects.[22]

In the studies showing a relation between obesity and cardiovascular disease a long observation period (10-26 years) has been required to prove the association. One possible reason for this might be that only a subgroup of the obese population is associated with an increased risk. If so, a long observation period would be expected before the subgroup had any impact on the risk for all obese subjects.

Our cross sectional results indicated that subjects with a typically masculine distribution of adipose tissue (high waist to hip ratio) might constitute such a subgroup.[1] The finding that a high ratio of waist to hip circumference was associated with cardiovascular risk factors in both sexes prompted us to investigate if this ratio had a predictive power in population studies going on in Gothenburg. In a follow up study of men in Gothenburg there was no association between degree of obesity measured as body mass index or as the sum of three skinfold thicknesses on one hand and incidence of myocardial infarction or death on the other but the ratio of waist to hip circumference was found to be related to incidence of cardiovascular disease and death even when the possible confounding effect of body mass index and sum of three skinfold thicknesses were taken into consideration.[5] We therefore investigated whether a masculine distribution of adipose tissue increased the risk in women also. The present report strongly suggests that this is in fact the case. Although general indices of obesity, such as body mass index or sum of skinfold thicknesses, predicted myocardial infarction in women, the waist to hip ratio was a much stronger predictor in this respect. Unlike body mass index and sum of skinfold thicknesses, the ratio also predicted angina pectoris, stroke, and total mortality with convincing levels of significance. Most of these predictions were independent of age, body mass index, and either systolic blood pressure, serum cholesterol concentration, or smoking habit. The addition of serum triglyceride concentration as a background variable to age and body mass index removed the correlation between the ratio of waist to hip circumference and all end points except for myocardial infarction. When using several background variables the Pitman permutation test loses power, and we must be cautious about conclusions concerning the disappearance of significances observed when triglyceride concentration was included as a background variable.

Interpreting the associations found in terms of causality is difficult, but the high and independent relations observed in this study speak in favour of a causal relation. Similar results with a high correlation between the distribution of adipose tissue and cardiovascular disease were also observed in men in Gothenburg.[5] Both studies were prospective with high participation rates and with participants who were representative of the general population. The consistent results in the two studies is another indication of a causal relation. Furthermore, there might be pathophysiological mechanisms that could in part explain a causal relation. An increased abdominal distribution per se of fat could be one possible explanation as discussed in previous reports.[1 5 19] Alternative or contributing explanations could hypothetically be that certain sex hormones or other internal or external factors might both determine the distribution of adipose tissue and influence the risk of cardiovascular disease.

No intervention study has yet shown that a changed distribution of fat will reduce cardiovascular morbidity or total mortality; such a finding would be stronger proof of a causal relation. Our findings suggest that studies of reduction of body weight and concomitantly of the ratio of waist to hip circumference in subjects in whom this index is increased are urgently needed. The effect of such intervention should be studied with respect to risks for cardiovascular disease.

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Long term follow up of untreated primary hyperparathyroidism

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Abstract

Fourteen patients with primary hyperparathyroidism and whose initial serum calcium concentrations were 2·75 mmol/l (11·0 mg/100 ml) or more were followed up for five to 23 years without operative treatment. One had osteitis fibrosa when seen and died with a fibrosarcoma 22 years later. The remaining 13 patients, who were followed up for a mean of 10 years, came to little obvious harm from not being operated on. Their serum calcium concentrations did not rise and there was no evidence of progressive renal impairment. In four patients who presented originally with renal calculi there were three further episodes of renal colic in 54 patient years of follow up.

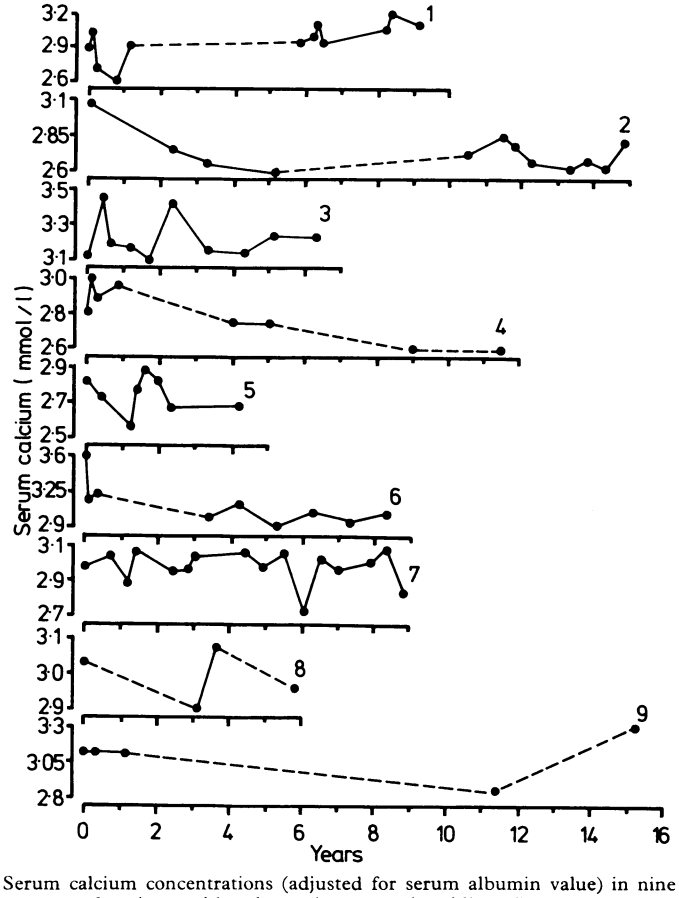
Conservative management of primary hyperparathyroidism is not an unreasonable option, and patients who do not have symptoms need not necessarily be pressed to accept surgery.

Introduction

Primary hyperparathyroidism is increasingly recognised as a common disorder, particularly in older women. Many patients are symptom free; the classic symptoms of bone disorders, renal stones, or abdominal pain are uncommon.[1] In the past it was usual to advise an exploration for all patients with primary hyperparathyroidism to prevent an "inevitable" decline in renal function.[2-4] Now, however, it is clear that progressive renal impairment seldom occurs in mild primary hyperparathyroidism[5] and, since exploration of the parathyroids has a small morbidity and mortality,[6-9] more and more patients are being treated conservatively.[10-12]

Some workers think that most patients should be treated surgically. The reasons given are that they may not appreciate that they really have symptoms, that there is a risk of acute hypercalcaemia, that progressive osteopenia may occur, that medical follow up is expensive, and that if surgery is deferred the patient may be unfit for operation when indications for surgery do appear.[1 9 13-16]

While these arguments continue in respect of patients with mild hypercalcaemia, most physicians advise an early parathyroid exploration for all, or almost all, patients with more severe hypercalcaemia. We describe a series of patients with hyperparathyroidism and serum calcium values of 2·75 mmol/l



Serum calcium concentrations (adjusted for serum albumin value) in nine unoperated patients with primary hyperparathyroidism. For case 2 results of only first 15 years shown; table gives final figures after 23 years.

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