Papers

Lipid screening in an elderly population: difficulty in interpretation and in detection of occult metabolic disease

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Abstract

Aims—To determine lipid profiles and associations with other metabolic disease in a representative British elderly population.

Methods—Part of a prevalence survey of dementia in all 75+ year olds conducted from the large general practice serving the town and surrounding area of Melton Mowbray, Leicestershire (the M-old study). Patients (n = 224) aged from 75 to 98 years, and representative of the overall population, also provided pre-prandial blood samples on which various age and nutrition related analytes were determined. These included documented medical history, thyroid stimulating hormone (TSH), glucose, immunoglobulins, and lipid profile in plasma.

Results—Cholesterol and lipid variables showed wide scatter, with some negative trends but no significant associations with age for total cholesterol, high density lipoprotein (HDL) cholesterol, the ratio of total to HDL cholesterol or triglycerides. Women had significantly higher concentrations of total and HDL cholesterol at all ages. Serum TSH was above 6.0 mU/l in 10/205 patients, random glucose was above 11.2 mmol/l in nine of 207 patients, borderline dysglobulinaemia was present in four of 210 patients, all without correlation with cholesterol concentrations.

Conclusion—This British data is consistent with an inverse correlation between survival and cholesterol, but wide scatter restricts reliance on single result lipid data in individual patient management. Random lipid screening is also unhelpful, inefficient and without added value in revealing other age related and unrecognised occult metabolic disease.

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Keywords: old age, lipids, lipoproteins, lipid screening, diabetes, thyroid function, immunoglobulins, secondary dyslipoproteinaemia.

Clinical cardiovascular disease is the major cause of death and disability in elderly populations: health checks and patient interest have

increased the extent of lipid screening in the elderly. Most, but not all, studies have shown that associations with lipid profiles still apply, particularly in men,¹⁻⁵ although protocols for lipid screening and benefits of lipid treatment in old age are not defined.^{6,7} Lipaemia can also reveal and be secondary to other metabolic disorders including diabetes,⁸ hypothyroidism⁹ and immunoglobulin disorders expressed grossly as excess or immunosuppression.^{10,11} Cholesterol testing of all age groups in general practice has shown a low yield of such primary disorders,¹² but as these disorders are age related and have potential for treatment, lipid screening of the elderly could acquire further added value if it led to their diagnosis.

There are very little data on lipid profiles in British elderly populations. We have surveyed lipid profiles and some metabolic associations for a sample of a representative British population aged 75 years and over who were registered with a general practice serving the town of Melton Mowbray, Leicestershire, and who had taken part in a total population survey of elderly people.¹³ This is not a management survey, but an attempt to obtain basic information on which future management decisions may be based.

Methods

CLINICAL METHODS: RECRUITMENT AND ASSESSMENT OF SUBJECTS

The study population forms part of a two-stage prevalence survey of dementia conducted from the large general practice (12 doctors) which serves the town and surrounding area of Melton Mowbray, Leicestershire. The first stage of the study consisted of a home interview with all patients registered with the practice and aged 75 years or over on the 31st December 1987. The interview schedule covered the areas of physical health, contact with family and friends and use of services. Full details of the full survey population have already been published.¹³ Melton Mowbray was selected partly because the population was then representative of England and Wales as a whole, in terms of age, sex and social class, and of ethnic distribution with approximately 1% of the population of Polish extraction and no other significant external group. The study was ap-

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proved by the Leicester District ethics committee.

The Mini-Mental State Examination (MMSE) of Folstein¹⁴ in the first stage formed the basis for entry into the second stage of the survey. All those scoring 21 or under (out of a total score of 30) on the MMSE, one in two of those scoring 22 or 23 and one in 10 of the remainder were invited to undergo a full psychiatric assessment using the CAMDEX¹⁵ by a trained clinician. The CAMDEX schedule encompasses items on past medical history, including cardiovascular events of angina or previous myocardial infarction and metabolic disorders such as diabetes. A brief medical examination was also undertaken. Full details of the results of this phase of the survey can be found elsewhere.¹⁶ At the end of the second interview, subjects were asked whether they would give a blood sample: data on those who agreed are presented here.

LABORATORY METHODS

Venous blood obtained by venepuncture without prolonged use of a tourniquet was collected into heparin tubes for lipid, protein and thyroid assays, and into fluoride tubes for glucose. Samples were pre-prandial but not specifically fasting as this was felt to be a difficult and unreliable restriction for the population involved. Occasional samples were insufficient to allow analysis for all analytes.

Lipid and other laboratory methods were as described for another larger population study,¹⁷ also conducted in part through general practices in Leicestershire, involving the same laboratory and over the same time period. Concentrations of cholesterol and triglycerides in plasma were measured using enzymatic colorimetric methods, as was high density lipoprotein (HDL) cholesterol after heparin-manganese precipitation, all on a Cobas Fara analyser. HDL cholesterol data represent the average of duplicate assays of single samples. Glucose concentrations were measured by an enzymic oxidase method (Technicon). Thyroid status was evaluated by determination of thyroid stimulating hormone (TSH) by a high sensitivity method using time-lapsed immunofluorescence (Delfia). Total protein in plasma was determined by the biuret method, albumin by dye-binding (BCG) and total globulins by subtraction. Performance with all assays was reviewed through national and specialist interest quality assurance schemes.

Apolipoprotein E profiles

The E-4 allele is associated with Alzheimer's disease and inversely with survival. Lipoprotein (a) concentrations—reported to have less clinical impact than in younger populations¹⁸ although lower concentrations could suggest an effect on survival¹⁹—were not investigated.

STATISTICAL METHODS

Differences in lipid concentrations between the sexes after adjustment for age and between age groups after adjustment for sex were assessed by F tests in an analysis of variance. Analysis of the association between lipid profiles and both hyperglycaemia and biochemical thyroid status was by logistic regression with adjustment for age and sex. Significance of the lipid concentrations was assessed by the Wald χ^2 statistic. All analyses were weighted according to the sampling probability between stages 1 and 2 so that results are representative of the total population. This method will slightly deflate standard errors and result in too many variables being considered significant (at a 5% level) in regression models. Where the unweighted and weighted analyses differed, this is indicated in the text.

Results

One thousand, eight hundred and ninety people aged 75 years and over were identified on the age/sex register of the general practice and 1579 were interviewed in the first stage with a refusal rate of 5%.¹³ Of these 1579, 438 completed the CAMDEX assessment forming the second stage of the study. As the CAMDEX group had greater numbers with dementia than in the total population, the demographic characteristics of the group reflected this with more of the very elderly, women and non-community dwellers (table 1). However, after weighting by the sampling procedure for the second stage, there was no evidence that the CAMDEX group were different from the total population on these and other demographic characteristics or physical health. Lipid profiles have also been shown to be unrelated to the development of dementia.⁴

In total, 224 of those completing the CAMDEX assessment agreed to give a blood sample and comprise the present study population. The demographic characteristics of these 224 patients are shown in table 1 and they did not differ significantly from those refusing in these or any other demographic variables or physical or mental health. We believe, therefore, that sampling bias has been addressed and that the survey data are representative of the overall population of Melton Mowbray and thus of England and Wales at that time.

LIPID PROFILES

The samples collected were suitable for determination of total cholesterol (TC) and triglycerides for 59 men and 153 women, with HDL cholesterol and TC:HDL cholesterol ratios for 42 men and 96 women. As blood sampling was not specifically in the fasting state, triglyceride data have not been analysed

Table 1 Demographic characteristics of the total 1988 study population, those subjects assessed by CAMDEX and the subset who agreed to give a blood sample

Demographic characteristics	Total 1988 study population (n = 1579)	Assessed by CAMDEX (n = 438)	Blood sampled (n = 224)
Age in years (%)			
75-79	760 (48)	148 (34)	71 (32)
80-84	519 (33)	144 (33)	70 (31)
85-89	227 (14)	103 (24)	60 (27)
≥ 90	73 (5)	43 (10)	23 (10)
Sex (%)			
male	541 (34)	119 (27)	64 (29)
female	1038 (66)	319 (73)	160 (31)
Where interviewed (%)			
community	1500 (95)	377 (86)	183 (82)
institution	79 (5)	61 (14)	41 (18)

Table 2 Weighted age and sex specific mean values and standard deviations of total cholesterol (TC), HDL cholesterol, ratio of total to HDL cholesterol (TC:HDL cholesterol) and triglycerides

Lipid	Age group (years)					
	Men			Women		
	75-79	80-84	85+	75-79	80-84	85+
Total cholesterol						
Mean	6.31	6.49	5.57	6.89	6.59	6.70
SD	1.11	1.01	0.83	1.30	1.03	1.20
N*	25	19	15	45	46	62
HDL cholesterol						
Mean	1.23	1.19	1.35	1.34	1.54	1.49
SD	0.31	0.23	0.33	0.27	0.32	0.37
N*	20	12	10	25	30	41
TC:HDL cholesterol ratio						
Mean	5.29	5.45	4.20	4.99	4.33	4.89
SD	1.26	0.94	1.84	1.05	0.98	1.65
N*	20	12	10	25	30	41
Triglycerides						
Mean	2.18	2.08	2.03	2.15	1.68	2.25
SD	1.03	0.87	1.19	1.18	0.61	1.17
N*	25	19	15	45	46	62

* Unweighted.

in detail. Age and sex specific mean values of TC, HDL cholesterol, TC:HDL cholesterol and triglycerides are shown in table 2, weighted to be representative of the total population aged 75 and over. For cholesterol, the highest value was 10.0 mmol/l (394 mg%). Concentrations were above 8 mmol/l (315 mg%) in 17 female and two male participants, aged 75–90 years, including one female known diabetic and one male newly diagnosed as diabetic through hyperglycaemia. Data for cholesterol are shown in figs 1 and 2.

The data are broadly in accord with projections from age/sex related trends previously recorded for a younger UK population, in which the present investigators and laboratory took part.¹⁷ Women had significantly higher concentrations of total (F=11.40, DF=1, p=0.0009) and HDL cholesterol (F=13.74, DF=1, p=0.0003). Trends are discussed: no significant relation between age and levels of any of the lipids was found.

Figure 1 Values for total cholesterol in plasma for 59 men aged 75–91 years. Duplicate data points are not shown.

NON-FASTING GLUCOSE

Glucose concentrations and associated lipid profiles were recorded for 56 men and 151 women. Glucose concentrations greater than 11.2 mmol/l were found in two men and seven women (total nine cases) of whom six were known diabetics. Glucose concentrations in excess of 8.0 mmol/l were found in nine of 56 men, 17/151 women (total 26 cases) of whom nine were known diabetics. Details and clinical status of these 26 cases at the time of testing are shown in table 3.

After adjustment for age and sex, hyperglycaemia (defined as glucose in excess of 8 mmol/l) was significantly associated with decreased total cholesterol (Wald $\chi^2=8.97$, DF=1, p=0.003), decreased HDL cholesterol (Wald $\chi^2=7.46$, DF=1, p=0.006) and increasing triglycerides (Wald $\chi^2=67.65$, DF=1, p<0.0001). In the unweighted analyses only the relation with triglycerides remained significant. Four cases were found with hyperglycaemia and HDL cholesterol below 1.0 mmol/l and all were known diabetics.

THYROID FUNCTION STATUS

As for glucose, the survey provided data on TSH and on lipid profiles, allowing associations both ways to be reviewed. TSH at or in excess of 6.0 mU/l was recorded for 10 (6.8%) of 147 participants, all women, none previously known or suspected to be hypothyroid. Data for TSH and associated lipid profiles and clinical status are shown in table 4 for these 10 women. Biochemical evidence of hypothyroidism was thus a feature of this population. However, after adjustment for age and sex, lipid profiles did not seem to be obviously related to thyroid biochemical status at the time of testing.

Figure 2 Values for total cholesterol in plasma for 153 women aged 75–98 years. Duplicate data points are not shown.

Table 3 Hyperglycaemia and associated dyslipoproteinaemia

Participant	Glucose (mmol/l)	Cholesterol (mmol/l)	Triglycerides (mmol/l)	HDL cholesterol (mmol/l)	Status before test
LF M76	20.0	4.5	1.9	0.99	Known diabetic
MF M84	18.5	6.4	3.8	—	Unknown
VB F84	16.8	6.7	2.4	—	Not diabetic
AW F80	16.8	4.3	3.0	0.66	Known diabetic
FL F85	15.8	6.0	4.0	0.90	Known diabetic
IW F77	15.3	6.5	5.4	1.00	Not diabetic
JM F83	13.1	9.5	3.2	1.20	Known diabetic
HH F78	13.1	7.1	1.2	1.54	Known diabetic
DE F82	11.3	5.8	1.2	—	Known diabetic
AM F76	10.8	6.9	2.3	1.43	Not diabetic
WT M80	10.7	6.2	1.1	1.55	Known diabetic
CW M85	10.7	6.0	4.5	0.93	Known diabetic
MS F85	10.2	6.4	4.7	1.33	Known diabetic
RG M88	10.2	4.2	2.0	1.59	Not diabetic
HT F76	9.6	6.1	3.2	—	Not diabetic
AC M86	9.5	5.4	1.9	1.99	Not diabetic
MS F82	9.4	4.6	1.0	1.40	Not diabetic
— M80	9.3	6.6	1.6	—	Not diabetic
— M82	9.2	6.6	1.2	—	Not diabetic
RS F87	9.0	5.7	4.8	—	Not diabetic
EC F85	8.8	10.0	6.0	1.05	Not diabetic
MC F79	8.8	7.6	3.8	1.02	Not diabetic
— F75	8.6	5.7	1.8	—	Known diabetic
— F87	8.2	7.9	3.1	1.26	Not diabetic
EB F89	8.2	6.0	2.8	—	Not diabetic
JP M89	8.1	5.3	1.2	1.50	Not diabetic

PLASMA PROTEINS

Dysglobulinaemia defined as concentrations at or marginally beyond the reference range of 20–40 g/l was present in one of 58 men and three of 152 women tested. Details with associated lipid profiles are shown in table 5. Dyslipoproteinaemia as hypercholesterolaemia was associated with borderline dysglobulinaemia in one participant only, who also had known diabetes mellitus (fasting blood glucose 13.1 mmol/l).

OTHER CARDIOVASCULAR STATUS AT ENTRY

Myocardial infarction or angina

This was recorded for only six male and eight female participants at entry. Three of the six men had known hypertension, one of whom was also a known diabetic. Three of the eight women had known hypertension, one of whom had a documented stroke, and one further case was then newly diagnosed as diabetic.

Stroke

Stroke was recorded for one male and for 20 female participants, of whom 10 were known hypertensive, two were known hypertensive/diabetic and two were known diabetic. Of the two women with myocardial infarction and stroke, one was a known diabetic, one a known hypertensive.

Hypertension

This was documented at entry for 12 men and 44 women, a total of 56 participants. Standard medication when used at that time was thiazide diuretics or beta blockers, agents with potential to distort lipid profiles. Concentrations of TC were therefore reviewed in comparison with age/sex quintiles for the overall group of participants as follows:

- age 75–80 years: men (n=8) with a mean TC of 5.6 mmol/l which is on the mean of the trend line for age; women (n=21) with a mean TC of 6.95 mmol/l, 0.4 mmol/l above trend line for age;
- age 81–85 years: women (n=14) with a mean TC of 6.4 mmol/l, 0.05 mmol/l below the trend line for age;
- age 86–90 years: women (n=7) with a mean TC of 6.4 mmol/l, 0.1 mmol/l above the trend line for age. (Data on males above 80 years of age is not listed as these groups were restricted to one to three participants only.)

Thus for patients with known hypertension, TC concentrations were broadly in line with the age/sex trends of the overall population from which they were drawn.

Hormone replacement therapy was not a characteristic of the female participants.

Table 4 Thyroid status and associated dyslipoproteinaemia

Participant	TSH (mU/l)	Cholesterol (mmol/l)	Triglycerides (mmol/l)	HDL cholesterol (mmol/l)
NT F76	61.0	6.8	2.4	1.27
MM F81	29.0	6.3	1.0	1.85
AF F86	21.3	8.2	1.6	—
HS F85	16.9	6.4	1.4	1.55
GL F83	13.7	6.8	2.0	1.56
DD F83	9.7	5.5	1.0	—
AR F92	9.6	5.1	1.0	1.79
FS F87	8.4	6.4	2.3	—
EA F83	6.3	7.9	2.3	—
IW F77	6.0	6.5	5.4	1.00

Table 5 Dysglobulinaemia and associated dyslipoproteinaemia

Participant	Globulins (g/l)	Cholesterol (mmol/l)	Triglycerides (mmol/l)	HDL cholesterol (mmol/l)
JB F79	44	6.6	1.2	1.44
JE F84	40	5.1	0.9	2.3
LF M76	42	4.5	1.9	0.99*
JM F83	19	9.5	3.2	1.2*

* Known diabetic.

Discussion

Our objective was to enlarge the data available on lipoprotein profiles and their metabolic associations in a British geriatric population,

an essential pre-requisite to any considerations of management. From our study, total lipid concentrations showed wide scatter with "pudding" graphs as reported in other vertical surveys of elderly populations.¹⁷ Concentrations of TC for men and women in the 75+ age group were slightly below the age/sex related trends recorded in a large national multicentre study of adults over the age range 21–59 years, to which we contributed, over an overlapping time period.¹⁷ This overall relation was also reported in one previous British study extending into old age,²⁰ although Pocock and Seed²¹ noted that TC concentrations recorded in 4376 men and women aged 65–74 years showed an increase of 0.16–0.17 mmol/l at one year. Inversion of the relation between cholesterol and age at extremes of life as here was reported in surveys in North America and apparently represents both selection with earlier death at higher values, lipid profiles in the elderly having some associations with later outcome as in earlier life, and some natural fall with age.^{1–4 7 22 23}

Considering undetected hyperglycaemia and diabetes, levels of glucose concentrations above 8.0 mmol/l were found in nine of 56 men, and 17/155 women (total of 26 cases, 12.3%) of whom nine were known diabetics. Glucose concentrations above 11.2 mmol/l were found in two men, and seven women (total nine cases) of whom six were known diabetics. Triglyceride data are not well defined as noted above, but concentrations were higher in the hyperglycaemic group than in the overall population. There was no consistent difference between concentrations of total and HDL cholesterol for hyperglycaemic and other participants, but the four cases with hyperglycaemia and HDL cholesterol below 1.0 mmol/l were known diabetics. Concentrations of TC were not significantly different between groups and wide inter-individual variation was evident for all lipid markers. (Concentrations of glycosylated haemoglobin were not measured: these can correlate with concentrations of cholesterol in both normal and known diabetic populations.²⁴) With data on both lipid profiles and concentrations of glucose, relations in either direction can be reviewed. For hyperglycaemic individuals identified in our survey, there were no close associations between lipid profiles and overall glucose status: lipoprotein profiles and particularly cholesterol concentrations were not obviously associated with or a marker for random sample hyperglycaemia.

Hypothyroidism can be associated with hypercholesterolaemia through impairment of receptor based clearance or of hepatobiliary metabolism.^{9 25} Most patients with mild sub-clinical hypothyroidism have lipoprotein profiles similar to those of normal controls and replacement is not recommended.²⁶ Associations between hypercholesterolaemia and asymptomatic hypothyroidism have been noted in some, but not all, surveys in the general population, but they are a feature of referrals to a lipid clinic. Thus, Ball *et al*⁹ found that 9.6% of a mixed group of adults below age 70 years of age contributing to a nutritional survey

with concentrations of plasma cholesterol above 7 mmol/l had raised TSH above 6 mU/l and asymptomatic but biochemically definite or compensated hypothyroidism, not found in any participant with cholesterol below 4.1 mmol/l. Similar results were reported for a hyperlipidaemic adult population in Glasgow,²⁷ and in new referrals to a lipid clinic,^{28–30} all over a wide age range. The criteria for selection are important. Our population was selected by age and not by hypercholesterolaemia, and with data on both lipid and thyroid status any relations can be reviewed from both perspectives. From table 4 it is clear that the lipid profile alone, and particularly raised total or HDL cholesterol, or both, was not a strong marker in individuals for any degree of unrecognised hypothyroidism.

Lipoprotein lipase activity can be directly or indirectly impaired in the presence of excess of immunoglobulins, with specific interactions with various components of the clearance pathway for triglyceride-rich lipoproteins.^{10 11} But dyslipoproteinaemic individuals in our population were not readily identified by association with dysglobulinaemia defined either through borderline values or deficiency with the potential to indicate immunosuppression.

Lipid profiles in the elderly are of special interest because of the burden of atherosclerotic disease expressed by our ageing population.¹ Other markers of risk also apply and identification of diabetes and hypertension in particular as in our study may alert to that risk status independent of any association with lipid profiles. There are no clinical trial data on the benefits of lipid management in the elderly.³¹ Calculations of risk status and potential benefit can be made for the elderly but they are theoretical and unweighted for short life expectancy.³² At present, profiles have no clearly defined role in general clinical management, with or without active cardiovascular disease, except that falling concentrations of cholesterol can alert to malignancy.³³ This may turn out to be the final position but the issue deserves further attention: the clinical consequences of atherosclerosis should not be seen as acceptable, perhaps even normal in the elderly as other active treatment—for example, by coronary surgery in selected cases can have clear benefits including enhanced longevity beyond that of their host general population.^{34 35} As clinical outcome after surgery for mixed age groups is related to lipid variables,^{36 37} a key issue for the elderly may be to survive long enough to derive any benefit from medical intervention. Recent trials of the clinical benefits of modifying lipid profiles in middle aged men in secondary prevention,³⁸ and in both men and women in primary prevention,³⁹ have been encouraging for that age range, and also suggest that benefits may arise in less than one year. Considerations of toxicity in the elderly have also been reassuring⁴⁰ and support extension of secondary prevention into older age groups, particularly if lead times for benefit are short. Haemostatic variables also need further evaluation as in the elderly they can be adverse, are related to lipid profiles, and in other groups

have been shown to respond rapidly to lipid intervention.^{41,42} But the main difficulties in defining clinical significance of lipid profiles in old age are that reference populations can show wide scatter as here, that reference "normal" ranges defined through population surveys with or without reference to clinical events differ from and cannot be simply extrapolated from those recorded for younger, generally much younger, age groups, and that values can differ greatly on repeat testing,⁴³ compromising both confidence in a result and the range against which it is assessed. Difficulties of interpretation could perhaps be sidlined by replacement with selective and multifactorial screening programmes in early and middle age, with more secure associations with outcome and reduced interest in obtaining new data in later life.⁶ Apart from malignancy, this awkward variability may involve other general metabolic disorders,^{33,44} including asymptomatic hypothyroidism, diabetes and paraproteinaemia, and perhaps also antihypertensive medication, although for TC this was not a strong feature at recruitment with our survey. From our survey, associations with these age related and expected features of the study population did not significantly contribute to the wide scatter of lipid profiles seen and the consequent difficulties in their interpretation. Their identification does not strengthen arguments for and give added value to untargeted lipid screening in the elderly.

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