U.K. Prospective Diabetes Study 27

Plasma lipids and lipoproteins at diagnosis of NIDDM by age and sex

U.K. PROSPECTIVE DIABETES STUDY GROUP

OBJECTIVE — To compare fasting plasma lipids and lipoproteins in male and female patients at diagnosis of NIDDM and to examine age and sex differences in lipid concentrations.

RESEARCH DESIGN AND METHODS — Cross-sectional study of fasting plasma total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride in 2,139 male and 1,574 female white patients, aged 25–65 years, at diagnosis of NIDDM.

RESULTS — At diagnosis of NIDDM, the mean age ± SD for men was 52 ± 9 and 53 ± 9 years for women; BMI was 28.3 ± 4.9 and 30.8 ± 6.7 kg/m^2, and fasting plasma glucose was 11.6 ± 3.6 and 12.4 ± 3.8 mmol/l, respectively. The mean total and LDL cholesterol were higher in female than in male NIDDM patients, 5.8 ± 1.2 vs. 5.5 ± 1.1 and 3.9 ± 1.1 vs. 3.6 ± 1.0 mmol/l (both $P < 0.001$), respectively, while triglyceride levels were similar: geometric mean (1 SD interval) for men and women was 1.8 (1.1–3.1) vs. 1.8 (1.1–2.9) mmol/l. HDL cholesterol was higher in female than in male NIDDM patients, 1.09 ± 0.2 vs. 1.01 ± 0.24 mmol/l ($P < 0.001$); the sex differential for HDL cholesterol was 7% in NIDDM patients compared with 22% in the general population. Data analysis by 5-year age bands showed a significant trend toward lower total cholesterol and triglyceride and higher HDL cholesterol in men diagnosed above the age of 50 years. In female NIDDM patients, lipid concentrations increased with age of diagnosis but reached a plateau above the age of 50 years.

CONCLUSIONS — The effect of NIDDM, observed at diagnosis, on plasma lipid and lipoprotein levels is more pronounced in women than in men. This may explain in part why the cardiovascular risk is proportionally higher in female patients.

Cardiovascular disease is more common in NIDDM than in the general population (1) and is the major cause of morbidity and mortality (2,3). Cardiovascular disease is lower in nondiabetic, premenopausal women than men (4); in NIDDM patients the sex differential for this risk is substantially narrowed (1,5,6). The excess relative risk in NIDDM patients compared with nondiabetic patients is not evenly distributed between men and women. Mortality from ischemic heart disease is three to seven times higher in women and two to four times higher in men (1,5–7).

Dyslipidemia may in part account for the excess cardiovascular risk in male and female NIDDM patients (7–9). Several studies have reported plasma lipid levels, including cholesterol subfractions, in male and female patients with NIDDM (10–15), but in most cases the numbers of patients were small and both newly diagnosed and established patients were included.

Our study reports fasting plasma total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride analyzed by 5-year age bands in 3,713 white patients (2,139 men; 1,574 women) entered into the U.K. Prospective Diabetes Study (UKPDS) at diagnosis of NIDDM before the institution of diet therapy. The results were compared with an age-matched, nondiabetic control group from a previously published biochemical evaluation study by the UKPDS consisting of 52 male and 143 female subjects as well as 16,000 male subjects and 10,000 female subjects (non–sex hormone users) of equivalent age from the Lipid Research Clinics Population Prevalence (LRCPP) study in the U.S. (16).

RESEARCH DESIGN AND METHODS

Patients

Ethical approval for the study was obtained from the appropriate committees. Between 1979 and 1991, local general practitioners were asked to refer all newly diagnosed NIDDM patients, aged 25–65 years (inclusive), to one of 23 UKPDS centers. The UKPDS is a randomized clinical trial that aims to determine whether improved glycemic control with intensive therapy reduces morbidity and mortality in NIDDM, and if particular therapies (diet, sulphonylurea, insulin, or metformin) are advantageous. The patients entered the study if fasting plasma glucose was >6 mmol/l on two occasions, unless they had severe vascular disease (more than one major vascular episode, a history of myocardial infarction in the previous year, current angina, or heart failure); accelerated hypertension; proliferative or preproliferative retinopathy; renal failure; other life-threatening diseases such as cancer; an illness requiring systemic steroids; an uncorrected endocrine abnormality; or ketonuria suggestive of type 1 diabetes (17).

Of the 7,108 patients referred, 5,102 NIDDM patients were recruited (82% white, 10% Asian, 8% African-Caribbean [18]). At diagnosis of diabetes, 85% of patients had fasting plasma glucose >7.8

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Abbreviations: CDC, Centers for Disease Control; CHD, coronary heart disease; LRCPP, Lipid Research Clinics Population Prevalence; NHANES, National Health and Nutrition Examination Survey; UKPDS, U.K. Prospective Diabetes Study.

Table 1—*Biometric and biochemical variables in fasting patients at diagnosis of NIDDM*

	Men	Women
n	2,139	1,574
Age (years)	52 ± 9	53 ± 9
BMI (kg/m²)	28.3 ± 4.9	30.8 ± 6.7*
Waist-to-hip ratio	0.94 ± 0.06	0.87 ± 0.07*
Fasting plasma glucose (mmol/l)	11.6 ± 3.6	12.4 ± 3.8*
HbA_{1c} (%)	9.0 ± 2.3	9.3 ± 2.2*
Fasting plasma insulin (pmol/l)	95.0 (55.0–164.0)	109.1 (64.6–186.2)*
Systolic blood pressure (mmHg)	134 ± 18	140 ± 20*
Diastolic blood pressure (mmHg)	82 ± 10	84 ± 10*
Smoking (%) (never/ex/current)	21/45/34	44/27/29
Alchohol (%) (none/social/regular)	13/58/29	30/64/6
Exercise (%) (sedentary/moderate/active/fit)	18/32/43/7	21/39/40/1

Data are means ± 1 SD, geometric means (1 SD interval), or proportions; *$P < 0.001$.

mmol/l, and 40% were hypertensive (blood pressure ≥160 and/or ≥90 mmHg or on antihypertensive therapy). As lipids were not measured routinely at the beginning of the study, 3,730 patients of white origin with complete data were available for this study; after excluding 17 patients on lipid-lowering therapy, the analysis was restricted to 2,139 men and 1,574 women. Of the women, 2% were either on the oral contraceptive pill or postmenopausal hormone replacement therapy and were included in the analysis. The data reported in this paper were collected at the initial clinic visit when the diagnosis of diabetes was confirmed.

Measurements

All measurements except glucose were performed in the coordinating laboratory (19). Venous blood was obtained from patients in the sitting position, after fasting from 2200 the previous day. Blood in EDTA vacutainers was centrifuged within 4 h of collection, and plasma was transported, overnight at 4°C, to the coordinating laboratory. Cholesterol was measured by an enzymatic, colorimetric method using Kit C system high-performance CHOD-PAP method with Preciset cholesterol HP standard (Boehringer Mannheim, Lewes, Sussex, U.K.) on a centrifugal analyzer, Cobas FARA (Roche Diagnostica, Welwyn Garden City, Herts, U.K.). HDL cholesterol was measured after precipitation using sodium heparin and manganese II chloride, and LDL cholesterol was measured after precipitation with sodium dodecyl sulphate. Twice the concentration of reagents originally reported (20) was used to ensure complete precipitation of samples. Plasma triglyceride was measured using GPO-PAP kit with Precimat glycerol standard (Boehringer Mannheim, Lewes, E. Sussex, U.K.) on Cobas FARA with no correction for free glycerol (~0.11 mmol/l). HbA1c was measured by high-performance liquid chromatography (HPLC; Biorad Diamat, Automated Glycosylated Hemoglobin Analyzer, Biorad Laboratories, Hemel Hempsted, Herts, U.K.), normal range 4.5–6.2%. Immunoreactive insulin was measured by double-antibody radioimmunoassay (PhRIA100 Pharmacia, Milton Keynes, Bucks, U.K.), with 100% cross-reactivity with intact proinsulin.

Biochemical methods were updated throughout the study when necessary and data realigned to the current method (21). All assays were monitored by QSTAT, an inhouse computer quality assurance program. CVs for total cholesterol, triglyceride, and HbA_{1c} were below 2% and for HDL cholesterol and insulin they were below 6%. The measurements were within the limits for accuracy of the lipid standardization program (22) of the Centers for Disease Control (CDC) and Prevention in Atlanta, GA. The measurements from the UKPDS coordinating laboratory were slightly lower than the CDC reference laboratory in the U.K. (23), −2.5% for total cholesterol, −1.2% for HDL cholesterol, and −3.0% for triglyceride.

Blood pressure was measured with a Copal UA251 or Takeda UA751 electronic blood pressure machine, or if the patient was obese, with a Hawksley random zero sphygmomanometer. With the patient standing, the waist-to-hip ratio was measured between the abdominal circumference at the level of the umbilicus and the hip circumference at the level of the great trochanters, excluding any abdominal apron. Information about lifestyle was obtained by direct questioning of patients by physicians during visits to the clinical centers about smoking (categorized as current, exsmoker, or nonsmoker), alcohol consumption (none, social, or regular), and exercise (sedentary, moderate, active, or fit).

Statistical analysis

Statistical analyses were carried out using SAS (SAS Institute, Cary, NC) (24). Results for NIDDM patients were expressed as mean (1 SD) for all continuous variables except for triglyceride and insulin, which were presented as geometric mean (1 SD interval). Comparisons of continuous data for male and female NIDDM patients were performed using unpaired Student's *t* tests or the nonparametric equivalent for data that were not normally distributed; χ^2 tests were used for categorical data. The lipid data from the nondiabetic subjects were standardized to the age distribution of the UKPDS patients for comparison. Differences in plasma lipids across age-groups were tested using analysis of variance and in patients >50 years were tested using unpaired Student's *t* test. The relationships of lipids with patient characteristics were examined using univariate analysis and multiple regression models.

RESULTS — At diagnosis of NIDDM, male patients were slightly younger and less obese, with lower fasting plasma glucose, HbA_{1c}, fasting plasma insulin, and blood pressure than female patients; the men smoked more, consumed more alcohol, and took more exercise (Table 1).

Mean fasting plasma total cholesterol, LDL cholesterol, and HDL cholesterol were significantly higher ($P < 0.001$) in female than male NIDDM patients, with a 7% difference in mean HDL cholesterol between male and female NIDDM patients, while triglyceride was similar (Table 2). The sex differences in the lipid profiles remained when the data were adjusted for age, BMI, and fasting plasma glucose.

Table 2 also shows data derived from previously published studies of nondiabetic subjects, both age-matched to UKPDS patients and from the LRCPP study. Although the total cholesterol measurements for LRCPP were within the criteria of the lipid standardization program of the CDC–Atlanta, HDL concentration was measured by heparin manganese precipitation of plasma, and LDL was measured by ultracentrifugation and subtraction of measured HDL. Higher levels of total cholesterol were observed in women than in

Table 2—*Plasma lipids in patients at diagnosis of NIDDM and in nondiabetic subjects*

	Men			Women		
	NIDDM patients*	Nondiabetic subjects (UKPDS)†	Nondiabetic subjects (LRCPP)	NIDDM patients*	Nondiabetic subjects (UKPDS)†	Nondiabetic subjects (LRCPP)
n	2,139	52	16,194	1,574	143	10,694
Total cholesterol (mmol/l)	5.5 ± 1.1	5.27 ± 0.14	5.43	5.8 ± 1.2‡	5.60 ± 0.21	5.59
LDL cholesterol (mmol/l)	3.6 ± 1.0	3.35 ± 0.14	3.67§	3.9 ± 1.1‡	3.47 ± 0.17‖	3.70§
HDL cholesterol (mmol/l)	1.01 ± 0.24	1.11 ± 0.01¶	1.20§	1.09 ± 0.25‡	1.41 ± 0.02‖	1.53§
Triglyceride (mmol/l)	1.8 (1.1–3.1)	1.16 (1.11–1.22)‡	1.35	1.8 (1.1–2.9)	1.07 (1.02–1.12)‖	1.09

Data are means or geometric means (1 SD interval). *± 1 SD; †± 1 SE; ‡$P < 0.001$ compared with male NIDDM patients; §*n* significantly lower for these variables in LRCPP; ‖$P < 0.001$ compared with female NIDDM patients; ¶$P < 0.02$ compared with male NIDDM patients.

men in both nondiabetic and NIDDM populations. LDL cholesterol was higher in female NIDDM patients compared with UKPDS control subjects (where the method of LDL measurement was the same). HDL cholesterol was lower in NIDDM patients than nondiabetic UKPDS control subjects (by 9% in men and 23% in women) and compared with LRCPP normal subjects by 15 and 28%, respectively. Triglyceride levels were 50% higher in NIDDM patients than in nondiabetic UKPDS control subjects.

Analysis of fasting plasma lipid levels in 5-year age bands showed a significant trend toward lower total cholesterol and triglyceride, and higher HDL cholesterol in male NIDDM patients after the age of 50 years (Table 3). In female patients, there was a statistically significant trend to higher levels of all lipids with increasing age, which reached a plateau after the age of 50 (Table 4). Exclusion of patients on drugs known to affect lipids (i.e., contraceptive pills, hormone replacement therapy, β-blockers, and thiazide diuretics) did not affect the concentrations of lipids and lipoproteins analyzed by sex and age.

In a univariate analysis, total cholesterol, LDL cholesterol, and triglyceride correlated significantly ($P < 0.001$) with fasting plasma glucose (Spearman's rank correlation coefficients 0.16, 0.12, and 0.17, respectively) and HbA1c (0.15, 0.13, and 0.08). HDL cholesterol correlated with fasting plasma glucose in male patients only ($rs = 0.07$, $P < 0.001$). Similarly for blood pressure, there were significant correlation coefficients between 0.06 and 0.14 ($P < 0.001$). Plasma triglyceride was also positively associated with BMI and fasting insulin, 0.25 and 0.29, respectively, and HDL negatively associated with these variables (all $P < 0.001$).

Stepwise multivariate regression analysis explained <3% of the total variance for the relationship of lipids and lipoproteins with age, BMI, blood pressure, fasting plasma glucose, fasting plasma insulin, and lifestyle variables such as alcohol consumption, exercise, and smoking at diagnosis of NIDDM. After adjustment for obesity, glycemia, and insulinemia, the effect of age remained for total cholesterol in both male and female patients, although the significance of the effect of age on HDL cholesterol in male patients was diminished ($P = 0.09$).

The associations with lifestyle variables indicated that in NIDDM patients consuming moderate or large amounts of alcohol (compared to minimal or no consumption), there was a 5% increase in HDL cholesterol ($P < 0.001$ for men, $P < 0.05$ for women), and an ~8% increase in triglyceride. NIDDM patients who smoked had lower HDL cholesterol by 8% ($P < 0.001$) than those who had never smoked.

CONCLUSIONS — Cardiovascular disease is the major cause of death for NIDDM patients in the UKPDS in the 9 years after diagnosis of diabetes (25), and the standardized mortality ratio is significantly higher for female than for male patients (2.4 vs. 1.6 [26]). The mortality is therefore about twice that of the general population with female patients being particularly at risk, compared with nondiabetic subjects.

Previous studies have reported inconsistent results for plasma lipids and lipoproteins in male and female NIDDM patients (10–15), which may be explained by small sample size and the heterogeneous nature of the diabetic population studied. The largest study was based on the National Health and Nutrition Examination Survey (NHANES) II, a population-based study in U.S., and comprised over 600 white NIDDM patients (11); only three studies (12–14) have reported data for newly diagnosed, untreated patients. Our study has provided a unique opportunity to assess

Table 3—*Plasma lipids in male type 2 diabetic patients by age*

Age range (years)	<40	40 to ≤45	45 to ≤50	50 to ≤55	55 to ≤60	60 to ≤65	*P* value
n	229	210	299	444	498	459	—
Total cholesterol (mmol/l)	5.4 ± 1.3	5.7 ± 1.2	5.6 ± 1.2	5.5 ± 1.0	5.4 ± 1.1	5.4 ± 1.0	<0.01
LDL cholesterol (mmol/l)	3.4 ± 1.1	3.8 ± 1.1	3.6 ± 1.1	3.6 ± 1.0	3.6 ± 1.0	3.5 ± 1.0	NS
HDL cholesterol (mmol/l)	0.99 ± 0.28	1.01 ± 0.22	0.97 ± 0.20	1.01 ± 0.22	1.03 ± 0.25	1.04 ± 0.26	<0.001
Triglyceride (mmol/l)	2.1 (1.1–4.1)	2.0 (1.1–3.7)	2.0 (1.2–3.5)	1.8 (1.1–3.0)	1.7 (1.0–2.9)	1.6 (1.0–2.6)	<0.001

Data are means ± 1 SD or geometric means (1 SD interval).

Table 4—*Plasma lipids in female type 2 diabetic patients by age*

Age range (years)	<40	40 to ≤45	45 to ≤50	50 to ≤55	55 to ≤60	60 to ≤65	*P* value
n	147	111	226	303	362	425	—
Total cholesterol (mmol/l)	5.3 ± 1.1	5.4 ± 1.0	5.7 ± 1.1	6.0 ± 1.2	6.0 ± 1.2	6.0 ± 1.2	<0.001
LDL cholesterol (mmol/l)	3.5 ± 1.0	3.6 ± 1.0	3.8 ± 1.1	4.1 ± 1.2	4.1 ± 1.2	4.0 ± 1.1	<0.001
HDL cholesterol (mmol/l)	1.05 ± 0.24	1.07 ± 0.27	1.08 ± 0.23	1.11 ± 0.28	1.11 ± 0.25	1.10 ± 0.24	<0.05
Triglyceride (mmol/l)	1.7 (0.9–3.0)	1.7 (1.0–2.8)	1.8 (1.1–2.9)	1.9 (1.1–3.0)	1.8 (1.1–2.8)	1.9 (1.2–2.9)	<0.01

Data are means ± 1 SD or geometric means (1 SD interval).

plasma lipid and lipoprotein levels at diagnosis of NIDDM in a cohort of over 3,700 newly diagnosed white NIDDM patients.

As in the general population, our study showed that female NIDDM patients had significantly higher plasma total and LDL cholesterol concentrations than male patients, with these levels being slightly higher than those in the general population. Triglyceride concentrations were similar in male and female NIDDM patients and were higher than in nondiabetic subjects. In females at diagnosis of diabetes, the normally higher cardioprotective levels of HDL cholesterol were not present. The HDL cholesterol levels in female NIDDM patients were only slightly higher than in male patients. The sex difference in HDL cholesterol concentrations was 7% for NIDDM patients compared with the age-standardized difference among 4,075 normal subjects in the LRCPP study of 22% (16). In a previous biochemical evaluation of nondiabetic subjects and newly diagnosed NIDDM patients studied in fewer numbers over a short period of time, sex differences in HDL cholesterol were 11% in NIDDM patients and 22% in nondiabetic subjects (19). Similar findings for plasma lipids and lipoproteins were found in the white population studied in NHANES II.

Investigation of lipid levels at the different ages of diagnosis showed a decrease in dyslipidemia in male NIDDM patients diagnosed above age 50 years; this may be due in part to a survivor effect of healthy individuals but may also be explained by the recruitment of a healthy cohort, since patients with evidence of severe cardiovascular disease were excluded from the trial. A similar decrease in dyslipidemia was seen for men in the nondiabetic population of the LRCPP study (16) with higher HDL cholesterol above age 55 years and lower total cholesterol and triglyceride above age 70 years. In female NIDDM patients, lipid levels were higher as the age at diagnosis increased up to age 50 years, after which the levels reached a plateau. In the LRCPP study, this plateau in HDL cholesterol and total cholesterol was seen 5–10 years later than in female NIDDM patients.

The recognized clustering of cardiovascular risk factors associated with lipidemia, such as hyperglycemia, raised blood pressure, obesity, and hyperinsulinemia, was observed in these NIDDM patients. Lifestyle factors, such as alcohol intake, cigarette smoking, and physical exercise, known to affect plasma lipid levels in the nondiabetic population (27), were also evident in the NIDDM population, although the increase in HDL cholesterol with alcohol consumption was less marked. The association of smoking with raised triglyceride and lowered HDL cholesterol in the NIDDM population (results not shown) could explain the higher cardiovascular risk in smokers with NIDDM (7,8). The higher plasma triglyceride levels in younger male NIDDM patients may be related to the increased smoking and alcohol consumption in this age-group.

One of the main differences in plasma lipids in NIDDM was the lower HDL cholesterol found in female patients at diagnosis, a decrease of ~0.3 mmol/l compared with the nondiabetic population age-matched to the UKPDS. In an analysis of four prospective American studies, it was calculated that a 0.026 mmol/l increment in HDL cholesterol was equivalent to a coronary heart disease (CHD) risk decrement of 3.2% (28). The HDL-mediated excess CHD risk for female NIDDM patients may therefore be in the order of 30% or more. The compositional abnormalities of the lipoprotein particles, glycation, formation of advanced glycosylation end products, or oxidation will substantially increase further this risk (29).

In summary, our results showed conclusively that the dyslipidemia observed at diagnosis of NIDDM was more pronounced in women than in men, which may explain why the cardiovascular risk associated with NIDDM is proportionally higher in female patients.

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