Dyslipidemias Among Normoglycemic Members of Familial NIDDM Pedigrees

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OBJECTIVE — To examine the hypothesis that hyperinsulinemia among relatives of NIDDM probands will increase the prevalence of DLPs, we measured insulin levels and examined the frequency of DLPs among NIDDM pedigree members.

RESEARCH DESIGN AND METHODS — We performed 2-h 75-g OGTTs and measured lipid and insulin levels of 287 family members and 86 spouses from 16 large Utah pedigrees ascertained for ≥2 siblings with NIDDM.

RESULTS — One-hour insulin levels were higher among 206 family members with NGT than among 65 NGT spouses (483.3 vs. 361.7 pM, $P = 0.05$). Among the NGT family members, 32% had cholesterol levels at or above the age- and sex-specific 90th percentile level defined by the LRC studies, 33% had HDL levels ≤10th percentile, and 20% had triglyceride levels ≥90th percentile. DLP (any of the three abnormalities) was found among 58% of NGT family members, which was significantly higher than the expected 27% ($P < 0.00001$) and the prevalence among spouses of 45% ($P < 0.05$). By NCEP criteria for hyperlipidemia, 40% of family members met criteria for diet and/or pharmacological therapy.

CONCLUSIONS — Normoglycemic members of NIDDM pedigrees have a high prevalence of DLPs, which approaches the prevalence in patients with NIDDM. Our data suggest that members of NIDDM pedigrees should be screened carefully for lipid abnormalities.

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RECEIVED FOR PUBLICATION 14 JANUARY 1991 AND ACCEPTED IN REVISED FORM 18 JANUARY 1992.

NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; DLP, DYSLIPIDEMIA; LRC, LIPID RESEARCH CLINICS; OGTT, ORAL GLUCOSE TOLERANCE TEST; WHO, WORLD HEALTH ORGANIZATION; NGT, NORMAL GLUCOSE TOLERANCE; HDL, HIGH-DENSITY LIPOPROTEIN; NCEP, NATIONAL CHOLESTEROL EDUCATION PROGRAM; IGT, IMPAIRED GLUCOSE TOLERANCE; BMI, BODY MASS INDEX; LPL, LOW-DENSITY LIPOPROTEIN; OR, ODDS RATIO; CI, CONFIDENCE INTERVAL; ANCOVA, ANALYSIS OF COVARIANCE; CV, COEFFICIENT OF VARIATION.

The association of hyperinsulinemia with dyslipidemias has been noted by several researchers (1–3). Hyperinsulinemia and impaired insulin action appear to be familial and predictive of NIDDM onset (4–12). We recently described hyperinsulinemia among nondiabetic members of 16 large white pedigrees that were ascertained for ≥2 NIDDM siblings compared with spouse control subjects (12). To test the hypothesis that inherited hyperinsulinemia would result in a high prevalence of lipid abnormalities among members of NIDDM pedigrees, we examined triglycerides, total cholesterol, and HDL cholesterol among normoglycemic members of these pedigrees.

RESEARCH DESIGN AND METHODS

— Pedigrees were selected from Utah's white population for ≥2 living available siblings with NIDDM, as described previously (12). Ascertainment was independent of known lipid abnormalities or the presence of coronary artery disease in the family. Diabetic probands, siblings, and offspring of NIDDM probands and siblings were studied. In addition, spouses of diabetic probands and siblings, and some spouses of the offspring, were studied. Table 1 presents characteristics of the pedigrees studied.

Each nondiabetic pedigree member underwent a standard 2-h 75-g OGTT with both fasting and 1-h insulin levels; we also measured height and weight. Individuals who did not meet WHO criteria for diabetes or IGT were considered NGT (13). BMI was calculated as weight/height^2 (kg/m^2), and obesity was defined as BMI >27.8 kg/m^2 for men and >27.3 kg/m^2 for women (14). Glucose levels were measured by standard glucose oxidase assay; insulin levels were measured by double-antibody radioimmunoassay, with an interassay CV of 8.0% at 112.9 μU/ml. Lipid levels were measured using standardized methods in the Cardiovascular Genetics Re-

Table 1—*Characteristics of pedigrees under study*

Diagnoses of family members and spouses				Characteristics of NGT family members and spouses				
	NIDDM				Mean age	Mean BMI	DLP‡	
Family	(n)*	IGT (n)†	NGT (n)	Men (n)	(yr)	(kg/m^2)	n	%
1	4	3	14	7	33.0	26.7	10	77
2	5	0	14	10	31.1	23.9	11	79
4	4	0	13	8	33.9	26.1	7	58
7	3	2	20	6	38.0	25.8	10	52
8	3	0	11	4	39.1	25.4	2	18
9	2	7	10	3	32.6	27.1	4	40
10	2	2	12	7	26.8	27.0	10	83
11	3	0	13	5	34.8	28.7	9	75
13	4	2	8	3	42.4	28.5	3	43
14	2	1	10	1	39.2	24.2	10	100
15	3	4	15	6	34.7	25.6	5	36
16	3	0	17	12	34.7	32.5	15	88
17	5	1	23	12	34.8	23.9	10	43
18	2	2	8	3	38.6	26.1	3	38
19	3	0	8	2	34.1	24.4	2	25
20	4	1	10	7	31.5	27.4	4	40
Total	53	25	206	96	34.8	26.4	115	58
Spouses§	9	13	65	30	53.3	26.9	27	45

*Includes both known and newly diagnosed NIDDM.
†WHO criteria used for diagnosis.
‡Any of three lipid abnormalities (cholesterol, triglycerides, or HDL); expected value is 27%. Numbers may not total because of missing values for some variables.
§Unrelated individuals married into above families.

search Laboratory (15–17). The Utah laboratory has been standardized to the Northwest LRC and to the Centers for Disease Control.

The published age- and sex-specific average lipid levels of the LRC prevalence study of 48,482 people were used to identify study subjects with total cholesterol and triglyceride levels ≥90th percentile or HDL ≤10th percentile (18). Williams et al. (19) observed that normotensive spouses of individuals in Utah pedigrees studied for early coronary heart disease, stroke, or hypertension have a distribution of lipid abnormalities similar to the LRC data. DLP was defined as having any of three lipid abnormalities (cholesterol or triglyceride ≥90th percentile or HDL ≤10th percentile).

We also used criteria for hyperlipidemia as defined by the NCEP (20), in order to compare our results with those reported previously for NIDDM and non-NIDDM individuals (21,22). Those meeting criteria for dietary and/or pharmacological intervention include individuals with LDL cholesterol >4.14 mM (160 mg/dl) or LDL >3.38 (130 mg/dl) if coronary artery disease or two or more risk factors are present. Risk factors include male sex, cigarette smoking, hypertension, diabetes, severe obesity (>30% overweight), HDL cholesterol <0.91 mM (35 mg/dl), and a family history of coronary heart disease. In this study, family history of heart disease was not available, and severe obesity was defined as BMI >30 kg/m^2. In addition, we did not have information on cerebrovascular or peripheral vascular diseases.

Data analysis

Family members with NGT were compared with NGT spouses. ANCOVA with the SAS (SAS Institute, Cary, NC) general linear model procedure was used to adjust continuous variables for age, sex, and BMI. Categorical outcomes were analyzed with Mantel-Haenszel χ^2 statistic and logistic regression (23). In addition, we compared the number of family members and spouses with a lipid abnormality to the expected number with the binomial distribution (24). The expected proportion is 10% for individual lipids and 27% for any of three lipids [100–(90%)^3]. Because the three lipid levels are not independent, the estimate of 27% for any of the three abnormalities is actually higher than the true expected value, and thus is a conservative estimate because our hypothesis is that the prevalence will be >27%.

Because the analyses involved families, the assumption that each individual is an independent observation may not be correct. To address this problem, the family members were categorized by sibship and a random member of each sibship was selected and compared with the spouses. Thus, the family-member group consisted mostly of second- and third-degree relatives, in which family correlations are much less important. In addition, we used a logistic regression program that controlled for within-pedigree intraclass correlations of the dependent variable to confirm statistical relationships detected in the SAS analyses (25).

RESULTS— The characteristics of the 16 pedigrees are shown in Table 1. This study focuses on lipid results for the 206 spouses and 65 family members with normal OGTTs (Table 2). Detailed information on analyses of insulin levels has been presented elsewhere (12). As reported previously, stimulated insulin levels were higher among family members

Table 2—*Insulin and lipid abnormalities in normal OGTTs spouses and family members*

	Spouses	Family members	P
Demographics			
N	65	206	—
Age (yr)*	53.3 ± 13.3	34.8 ± 10.6	—
BMI (kg/m^2)*	26.9 ± 4.33	26.4 ± 5.75	—
Men, n (%)	30 (46.2)	96 (46.6)	—
Obese, n (%)	26 (40.6)	64 (31.1)	—
Mean 1-h insulin†	361.7	483.3	0.05
Percentiles of lipid levels‡			
Cholesterol ≥90th %			
Obese	20.8 (5/24)	43.6§ (27/62)	0.33
Nonobese	28.6§ (10/35)	27.3§ (38/139)	0.47
Triglyceride ≥90th %			
Obese	20.8 (5/24)	37.1§ (23/62)	0.24
Nonobese	8.6 (3/35)	12.2 (17/139)	0.87
HDL ≤10th %			
Obese	29.2§ (7/24)	45.9§ (28/61)	0.21
Nonobese	28.6§ (10/35)	26.7§ (36/135)	0.99
Any DLP¶			
Obese	45.8§ (11/24)	69.4§ (43/62)	0.09
Nonobese	45.7§ (16/35)	52.2§ (72/138)	0.20

*Values are means ± SD.

†Insulin adjusted for age, sex, and BMI with ANCOVA; $P = 0.05$, spouses vs. family members.

‡Lipid values presented as percentage and $n \geq$ 90th percentile of age–sex-specific values from the LRC prevalence study (≤10th percentile for HDL). In parentheses are number affected over total in that category. Numbers may not total because of missing variables in some categories.

§Greater than expected proportion at $P < 0.05$ using binomial distribution, with expected prevalences of 0.10 for cholesterol, triglyceride, and HDL, and 0.27 for any DLP.

¶Any of three lipid abnormalities (cholesterol, triglycerides, or HDL); expected value is 27%. Using logistic regression to compare spouses and family members or 2.1, 95% CI 1.0–4.4).

P values, spouses vs. family members (based on logistic regression controlling age, sex, BMI).

than among spouses. Only one individual who reported using an anticholesterol medication is included.

The prevalences of lipid abnormalities, as defined by the age- and sex-specific values of the LRC, were found at higher than expected levels among family members. Among NGT family members, 32% had cholesterol levels at or above the age- and sex-specific 90th percentile level, 33% had HDL levels ≤10th percentile, and 20% had triglyceride levels ≥90th percentile. DLP (any of the three abnormalities) was found among 58% of NGT family members, which was significantly higher than the expected 27% ($P < 0.00001$).

Family members also had a higher prevalence of DLP than did spouses. Among NGT spouses, 45% had DLP ($P = 0.044$, family members vs. spouses). Differences between family members and spouses were most evident among the obese group. Among family members, 69.4% of the obese group and 52.2% of the nonobese group had DLP; among spouses, 45.8% of the obese and 45.7% of the nonobese had DLP. Controlling for age, sex, and BMI with logistic regression, the OR comparing family members with spouses for prevalence of DLP was 2.1 (95% CI 1.0–4.4).

To examine the hypothesis that the high prevalence of DLP was mediated through hyperinsulinemia, we compared family members and spouses, controlling 1-h insulin level. The difference between family members and spouses was decreased (OR, 1.8, 95% CI 0.8–4.0, $P = 0.14$), indicating that at least some of the increased prevalence of DLP among family members can be attributed to higher insulin levels.

Using criteria of the NCEP, 40% of family members met criteria for dietary and/or pharmacological therapy. Because we did not have data on family history of coronary heart disease, this estimate is conservative. Only 23% of hyperlipidemic family members were aware of their diagnosis. In comparison, Stern et al. (21) reported that 24% of non-Hispanic nondiabetic individuals and 43% of non-Hispanic NIDDM individuals met NCEP criteria for hyperlipidemia; of these, only 20 and 25%, respectively, were aware of their diagnosis (21). Harris (22) reports that ~32% of NGT individuals and 70% of NIDDM individuals meet NCEP criteria for initiation of dietary/and or pharmacological intervention. In our data, the prevalence of hyperlipidemia with NCEP criteria did not differ between family members and spouses when we controlled for age, sex, and BMI.

Lipid abnormalities were found in normoglycemic members of all 16 pedigrees (Table 1). The percentage with lipid abnormalities ranged from 18 to 100%. The increased prevalence of lipid abnormalities did not result from multiple affected members of only a few pedigrees. None of the pedigrees met criteria for familial hypercholesterolemia; 5 met criteria for familial combined hyperlipidemia (26). In addition, differences in DLP prevalence between men and women were not evident.

Among family members, there were 84 sibships. A random member of each sibship was selected to determine whether the increased prevalence of DLPs could be attributed to familial correlations. Among this group, findings were virtually identical to those from the entire sample: 33% had cholesterol levels at or above the age- and sex-specific 90th percentile levels; 37% had HDL levels ≤10th percentile, and 21% had triglyc-

eride levels ≥90th percentile. The presence of any DLP (any of the three abnormalities) was found among 61%, and the differences between spouses and family members remained statistically significant ($P = 0.013$, controlling age, sex, and BMI). Controlling for intraclass correlations within pedigree did not change the findings.

CONCLUSIONS— To our knowledge, this study is the first to report lipid values for a large number of normoglycemic white members of NIDDM families. We found that 58% of the family members had either cholesterol or triglycerides >90th percentile for their age and sex or HDL <10th percentile. Using the NCEP criteria, 40% met criteria for hyperlipidemia requiring initiation of dietary and/or pharmacological intervention; the prevalence approaches that reported by Stern et al. (21) for individuals who have already developed NIDDM. The NCEP criteria are age dependent, making comparisons with other studies difficult; however, the finding that ≥40% of these relatively young family members (mean age 34.8 yr) meet NCEP criteria for hyperlipidemia has important clinical implications. We also found, as did Stern et al., that a large percentage are unaware of their diagnosis.

Although many researchers have described lipid abnormalities among individuals with NIDDM (22,27,28), only a few have examined lipid levels among unaffected relatives (7,8), and none have examined extended families with multiple affected members. The treatment of lipid disorders in individuals with NIDDM has received increased attention (22,29). Our findings indicate that relatives of individuals with NIDDM also should be screened carefully for lipid disorders. Previously, we reported that only 2.6% of the same family members were newly diagnosed with NIDDM and only 7.7% with IGT (12). Thus, screening individuals with a family history of NIDDM for DLPs may be even more appropriate than screening for NIDDM.

Although no previous studies of lipid abnormalities with large NIDDM pedigrees have been conducted, others have found evidence for DLPs among relatives of NIDDM individuals. In their studies Haffner et al. (6,7) observed that Mexican Americans with a parental history of diabetes had higher insulin levels, higher blood pressures, and more abnormal lipid values than those without a parental history. Laws et al. (8) examined 35 nondiabetic subjects and found higher triglyceride and VLDL levels among those having at least one first-degree relative with diabetes.

Our finding that DLPs are increased in a group at high risk to develop NIDDM is consistent with previous findings. McPhillips et al. (30) reported that, among an older population, the baseline prevalence of hypertension and DLPs was higher among individuals who eventually developed IGT and NIDDM than among those who remained normoglycemic. Haffner et al. (9) found that nondiabetic Mexican Americans who eventually developed NIDDM over an 8-yr follow-up had higher levels of cholesterol, triglycerides, fasting glucose, fasting insulin, BMI, and blood pressure at baseline, and lower levels of HDL. The differences between those developing diabetes and those not developing the disease disappeared when they controlled for baseline fasting insulin levels.

We found higher 1-h insulin levels among family members than among spouses, and the differences in the prevalence of DLP between spouses and family members decreased when controlling for 1-h insulin levels. The decrease in the difference when controlling for insulin levels is consistent with the findings of Haffner et al. (9) and indicates that the increased prevalence of cardiovascular risk factors among individuals who eventually develop NIDDM may be mediated through hyperinsulinemia (31).

Although family members had higher prevalence of DLPs than spouses, spouses also had higher than expected prevalence of DLPs. Both assortive mating and common environment are explanations: Spouses would be expected to be similar to their mates for environmental factors that modify the risks of both NIDDM and DLP, including obesity, diet, and physical activity. However, because spouses share a common environment, they are a conservative control group; the use of spousal control subjects biases against finding a significant difference. We did find significant differences between spouses and family members; however, further work is needed to investigate the complex interactions between genetics and environment in the etiology of hyperinsulinemia, DLPs, and NIDDM in high-risk families.

Acknowledgments— Pedigree ascertainment and sampling was supported by National Institutes of Health Grant DK-39311 to S.C.E. (Diabetes Research and Education Foundation) and by Public Health Services Research Grant M01-RR-00064 from the Division of Research Resources. S.C.E. is supported by the Research Service of the Veterans Affairs Medical Center. National Institutes of Health Grants HL-24855 and HL-21088 to R.R.W. supported M.C.S., L.L.W., computer support for data analysis, and measurement of lipids in the study subjects.

We thank the American Diabetes Association, Utah affiliate, and colleagues for assistance in patient recruitment, and Dorothy Hudman, administrator of the Cardiovascular Genetics Research Clinic.

This paper was presented in abstract form at the annual meeting of the American Diabetes Association, Atlanta, Georgia, 16–19 June 1990.

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