Hyperlipidemia as a Prognosticator of Abnormal Glucose Tolerance

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INCREASED SERUM cholesterol and triglyceride levels in persons with diabetes compared to age-matched nondiabetic subjects have been reported by Albrink and associates (*1*). Despite a lack of unanimous agreement on criteria for the diagnosis of diabetes mellitus, a diagnosis of overt and clinically manifest diabetes is made primarily by a person's response to the glucose tolerance test (GTT). McDonald and Fisher (*2*) estimated that there are about 1.6 million undetected diabetics in the United States. Identification of these persons is a major and immediate public health responsibility.

The growing recognition of abnormal glucose tolerance as a risk factor predisposing to coronary heart disease is another imperative for a screening device to detect persons with abnormal glucose tolerance. In view of this need, we conducted an exploratory study to determine whether an association exists between lipid levels and response to the glucose tolerance test.

Subjects and Methods

The study group selected consisted of 134 male and female office workers in a New York City insurance company. Their ages ranged from 40 to 65 years. All the subjects routinely received annual medical examinations which included an interim history, physical examination, X-rays of chest and abdomen, electrocardiogram, pulmonary function studies, complete blood count, and serum triglyceride, cholesterol, and blood glucose determinations. Each subject entered the study at the time of his examination.

Based on the medical examination results, the study participants were classified as either "apparently healthy" or "predisposed to diabetes." Criteria for the predisposed-to-diabetes classification were based on one or a combination of the following: a history of diabetes in the immediate family, delivery of high-weight babies (9 pounds or more), and clinical manifestations of heart disease. Classifications of the participants by age groups and sex are shown in table 1. Inclusion of the heart disease criterion was based on two reports (*3*, *4*) which implicated abnormal response to GTT as a pathogenic influence.

At the time of initial examination, each participant was given a 384-calorie breakfast containing a maximum of 17 grams of fat and 41 grams of carbohydrate. This was done to assure that the participants would not eat an inordinately high-fat breakfast, which might have resulted in highly elevated levels of serum triglyceride (*5*, *6*). Blood samples for glucose and lipids were obtained 2 hours after this meal. The subjects were then instructed to consume

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100 grams of carbohydrate in excess of their daily carbohydrate intake for 3 days before the day of the GTT (*7*), which was performed within 1 week after the examination.

For the GTT, after a 14-hour fasting blood sample was drawn, the participant consumed 100 grams of glucose. Then venous blood samples were drawn at ½, 1, 2, and 3 hours for blood glucose determinations. Technicon AutoAnalyzer techniques were used for plasma glucose determinations, which were corrected to whole blood values (*8*). Abnormal glucose tolerance was defined according to the criteria of Fajans and Conn (*9*), the British Diabetic Association (*10*), and the World Health Organization (*11*).

Elevated serum triglyceride was arbitrarily considered to be 160 mg. per 100 ml. or higher while that of serum cholesterol was 260 mg. per 100 ml. (*12*). Briefly, the serum lipid categories are defined as follows.

Category	*Serum triglyceride (mg. per 100 ml.)*	*Serum cholesterol (mg. per 100 ml.)*
1	≥160	≥260
2	≥160	<260
3	<160	≥260
4	<160	<260

Results

By the criteria cited, 63 subjects, mean age 57 years (S.D.=7.03), were apparently healthy and 71 subjects, mean age 57 years (S.D.=6.22), were predisposed to diabetes. Of the 134 subjects, 42 had a positive reaction to the GTT—35 by the criteria of Fajans and Conn and the British Diabetic Association and seven by the criteria of the World Health Organization. The frequency distribution of all 134 participants in relation to serum lipid categories and GTT response is shown in table 2. The findings indicate a relationship between lipid categories and GTT responses for all the participants. The highest percentage of participants with a positive response was seen in lipid category 1.

Table 2. Distribution of 134 study participants in relation to their serum lipid determinations and response to glucose tolerance test

Lipid category [1]	Number GTT positive	Number GTT negative	Total	Percent positive
1	14	17	31	45.2
2	15	26	41	36.6
3	6	15	21	28.6
4	7	34	41	17.1
Total	42	92	134	31.3

[1] See text for lipid category definitions.

NOTE: $X^2_3=7.29$; $0.050<P<0.072$.

As shown in table 3, the percentages of apparently healthy participants with positive GTT responses indicate a similar trend between serum lipid characteristics among apparently healthy subjects as shown for all the subjects in table 2. However, the striking difference in the apparently healthy group when compared to the total group was the much higher percentage with a positive response to GTT in category 1 (62.5 percent) than in categories 2 (22.2 percent), 3 (18.2 percent), and 4 (5.6 percent).

The distribution of 71 prediabetic participants by serum lipid characteristics and re-

Table 1. Characteristics of 134 study participants

Age group (years)	Men				Women				
	Number	Apparently healthy	FH [1]	CD [2]	Number	Apparently healthy	FH [1]	CD [2]	OB [3]
40–45	10	5	4	2	3	2	1	------	------
46–50	9	5	4	2	4	1	2	------	2
51–55	6	2	2	4	4	1	1	1	2
56–60	27	13	9	14	17	5	4	7	5
61–65	40	25	9	12	14	4	5	5	7
Total	92	50	28	34	42	13	13	13	16

[1] Family history of diabetes.
[2] Clinical manifestation of heart disease.
[3] Delivery of high-weight babies 9 pounds or more.

NOTE: Numbers may not total the number of subjects in each age group because some persons had more than 1 classification criterion.

sponse to the GTT (table 4) reveals that in all lipid categories 25 percent or more had a positive response—47.8 percent were in category 2, 40 percent in category 3, 26.7 percent in category 1, and 26.1 percent in category 4.

The results of the GTT in relation to serum lipid categories of 17 predisposed-to-diabetes participants who had documented signs and symptoms of cardiovascular disease are shown in table 5. A trend was evident only in category 4, where no positive GTT responses occurred; however, there were only two participants in this category.

For the 54 predisposed-to-diabetes subjects without cardiovascular disease (table 6), the characteristic distribution of those with positive GTT response in each lipid category was essentially the same as for the entire group of 71 prediabetic subjects.

The numbers of subjects with positive GTT response in each group and lipid category in relation to their 2-hour postprandial blood sugar levels are shown in table 7. A greater number of subjects had normal postprandial blood sugar levels (<110 mg.) than elevated postprandial levels (≧110 mg.). A relatively greater number were in lipid category 1.

Of the total 134 participants, 12 were overweight (>120 percent of ideal weight) according to the method of relative weight determination. Six of the 12 had a positive response to the GTT and six a negative response.

Table 3. Distribution of 63 apparently healthy participants in relation to their serum lipid determinations and response to glucose tolerance test

Lipid category [1]	Number GTT positive	Number GTT negative	Total	Percent positive
1	10	6	16	62.5
2	4	14	18	22.2
3	2	9	11	18.2
4	1	17	18	5.6
Total	17	46	63	27.0

[1] See text for lipid category definitions.
NOTE: $X_3^2=15.28$; $0.001<P<0.002$.

Table 4. Distribution of 71 predisposed-to-diabetes participants in relation to their serum lipid determinations and response to glucose tolerance test

Lipid category [1]	Number GTT positive	Number GTT negative	Total	Percent positive
1	4	11	15	26.7
2	11	12	23	47.8
3	4	6	10	40.0
4	6	17	23	26.1
Total	25	46	71	35.2

[1] See text for lipid category definitions.
NOTE: $X_3^2=3.05$; $0.261<P<0.392$.

Table 5. Distribution of 17 predisposed-to-diabetes participants with cardiovascular disease in relation to their serum lipid determinations and glucose tolerance test

Lipid category [1]	Number of subjects	GTT positive	
		Number	Percent
1	4	2	50
2	8	4	50
3	3	1	33.3
4	2	0	0
Total	17	7	41

[1] See text for lipid category definitions.

Discussion and Conclusions

Prevalence of a given disease is obviously influenced by the criteria used for its diagnosis. In our study, if 2-hour postprandial blood sugar levels alone were used as the criteria for administration of a GTT, 25 of the 42 subjects who had abnormal glucose tolerance would not have been included in this study (table 7).

Abnormal levels of serum triglyceride and serum cholesterol have a prognostic potential for positive GTT response in apparently healthy and prediabetic subjects (table 2). This is particularly true in the response of the apparently healthy subjects with hypercholesterolemia and hypertriglyceridemia (table 3).

In our limited series of 17 subjects with cardiovascular disease, a positive correlation appeared to exist between elevated lipid categories and abnormal glucose tolerance. These results agree with those of Reaven (*13*) and Tzagournis (*14*) and their associates.

In contrast, the magnitude of abnormal glucose tolerance in the prediabetic subjects was as

great in lipid category 1 (hypertriglyceridemia and hypercholesterolemia) as in lipid category 4 (normal serum triglyceride and cholesterol levels). Categories 2 and 3 showed a slight increase in positive GTT response.

The association between serum triglyceride and serum cholesterol levels and abnormal glucose tolerance may suggest a common metabolic variance responsible both for hypertriglyceridemia and hypercholesterolemia which may also be related to abnormal glucose tolerance.

The results of this exploratory study suggest that in addition to the prediabetic population, people aged 40 years or over with a serum triglyceride ≧160 mg. per 100 ml. in conjunction with a serum cholesterol ≧260 mg. per 100 ml. with or without the presence of hyperglycemia should be viewed as diabetic "suspects," and an oral GTT should be administered. Hopefully, this concept will effectively aid in screening and identifying an additional population at risk for diabetes.

Summary

In an exploratory study to determine whether an association exists between lipid levels and response to the glucose tolerance test, 134 men and women, aged 40–65 years, were classified as either "apparently healthy" or "predisposed to diabetes," based on results of medical examinations. They were then categorized further according to serum lipid levels. All the subjects were given a glucose tolerance test.

Seventeen of 63 apparently healthy and 25 of 71 predisposed-to-diabetes subjects had an abnormal glucose tolerance response. Within the lipid categories (defined as combinations of high and low serum triglyceride and serum cholesterol) in the predisposed-to-diabetes group, the glucose positive subjects ranged from 26 to 48 percent. Among the apparently healthy group this range was 5 percent (in the low serum triglyceride and low serum cholesterol category) to 62 percent (in the high serum triglyceride and high serum cholesterol category).

The results indicate that increased levels of serum triglyceride (≧160 mg. per 100 ml.) in conjunction with increased levels of serum cholesterol (≧260 mg. per 100 ml.) in apparently healthy mature people have a prognostic potential for a positive glucose tolerance response.

Table 6. Distribution of 54 predisposed-to-diabetes participants without cardiovascular disease in relation to their serum lipid determinations and glucose tolerance test

Lipid category [1]	Number of subjects	GTT positive	
		Number	Percent
1	11	2	18. 2
2	15	7	46. 7
3	7	3	42. 9
4	21	6	28. 6
Total	54	18	33. 3

[1] See text for lipid category definitions.

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Table 7. Distribution of glucose positive participants in each group according to their 2-hour postprandial blood sugar levels

Lipid category [1]	Apparently healthy		Predisposed to diabetes		Total
	≧110 mg. per 100 ml.	<110 mg. per 100 ml.	≧100 mg. per 100 ml.	<110 mg. per 100 ml.	
1	3	7	2	2	14
2	2	2	5	6	15
3	0	2	2	2	6
4	0	1	3	3	7
Total	5	12	12	13	42

[1] See text for lipid category definitions.

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Tearsheet Requests

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Second Company Licensed for Rubella Vaccine

The Philips Roxane Laboratories of Columbus, Ohio, is the second pharmaceutical company to be licensed to distribute rubella vaccine in the United States. The Roxane Laboratories was licensed on December 2, 1969, and the other company, Merck, Sharp, & Dohme, received its license in June 1969. These two companies have indicated that their combined production had reached about 4 million doses a month by January 1, 1970.

Spearheading the Department of Health, Education, and Welfare's "Stop Rubella" program is the National Communicable Disease Center of the Health Services and Mental Health Administration, Atlanta, Ga. The national goal is the immunization of 40–60 million children 1 year of age to puberty.

A recent survey shows that rubella control activity is underway in nearly every State and in many communities across the nation. Many State, local, and private agencies are expected to contribute support to the Department's "Stop Rubella" campaign.

In New York City, for example, a program in 1,284 schools attempted to immunize 500,000 children before the Christmas holidays. In Washington, D.C., more than 100,000 children from kindergarten through sixth grade have already received the vaccine. Other States with active rubella control programs include Iowa, Arkansas, Oklahoma, Louisiana, California, and Alaska.

Education Notes

Master of Public Health in Health Planning and International Health Problems. The University of Michigan School of Public Health is offering a graduate program leading to the degree of master of public health in health planning or international health problems or both.

The program of study approaches the problems of health planning in a systematic manner, emphasizing the interrelationships between health and environment, urban problems, and public policy. The curriculum includes courses in environmental, mental, and community health; concepts and methods of public health; economics, public policy, and urban-regional analyses; planning and quantitative methods for policy analysis; and other courses offered by related departments and schools of the university. Students may elect a specialization in international health planning, focusing on control of communicable diseases, epidemiology, population planning, industrial health, and planning for economic and social development.

Applicants holding a bachelor's degree with a background in social science and a high standing in their class will be given preference. Familiarity with statistics is essential. Students with no background in statistics will be required to remedy deficiencies.

Public Health Service traineeships are available to accepted applicants. Awards provide full payment of tuition, travel allowances, and annual living allowance of $3,000–$7,000 plus $500 for each dependent. Other scholarship aid may be available for those who do not receive traineeships.

Additional information is available from the Program in Health Planning, School of Public Health, University of Michigan, Ann Arbor, Mich. 48104.

Fellowships in Medical Care Organization. The University of Michigan School of Public Health is offering fellowships for 1- and 2-year programs of study which prepare students for administrative positions at the policy level in public and private medical care programs, health insurance plans, and other agencies concerned with the provision and financing of personal health services.

The 1-year program is intended for persons with an advanced degree or appropriate related work experience. The 2-year program is intended for those with only a bachelor's degree. Both programs lead to the degree of master of public health. The programs are designed to provide students with an understanding of the principles of the social science disciplines as they relate to the functioning of the medical care system; a working knowledge of community organization, administrative practice, and organizational behavior; and a thorough knowledge of the organization of medical care in the United States.

Stipends are $2,400–$3,600, depending on academic background, plus an additional $500 for each dependent and full tuition.

For application or further information write to Eugene Feingold, Department of Medical Care Organization, Room 3547, School of Public Health, University of Michigan, Ann Arbor, Mich. 48104.

Summer Session of Statistics in the Health Sciences. The 12th annual summer session of statistics in the health sciences will be held at the University of Washington, June 22–July 31, 1970.

The eight to 12 courses to be offered will cover such topics as elementary, intermediate, and advanced biostatistics, demographic methods in public health, statistical methods in epidemiology, sampling techniques, bioassay, statistical genetics, multivariate methods, and stochastic processes.

These courses are designed to be of interest to statisticians and epidemiologists from local, State, and Federal agencies; graduate students in statistics and the health sciences; professional workers in health sciences from health agencies, the pharmaceutical industry, and departments of research and medical records in hospitals; senior public health personnel; research workers in epidemiology and the medical sciences; teachers of public health statistics; persons interested in research design, sampling theory, demography, management of records, vital statistics, bioassay, and statistical applications in genetics, sociology, psychology, and pharmacology.

This program is made available by funds from the Bureau of Health Professions, Education, and Manpower Training and from the National Center for Health Statistics, Public Health Service.

Additional information is available from the Division of Biostatistics (SSS), Department of Preventive Medicine, University of Washington, Seattle, Wash. 98105.