

## Postprandial Hypertriglyceridemia and Insulin Resistance in Normoglycemic First-Degree Relatives of Patients with Type 2 Diabetes

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**Background:** Impaired ability to eliminate lipids in the postprandial state is an atherogenic trait associated with insulin resistance.

**Objective:** To assess insulin sensitivity and postprandial triglyceride metabolism in prediabetic persons.

**Design:** Cross-sectional study.

**Setting:** Sahlgrenska University Hospital, Göteborg, Sweden.

**Participants:** 13 healthy, normotriglyceridemic men with two first-degree relatives with type 2 diabetes and 13 carefully matched controls without known diabetes heredity.

**Measurements:** Oral glucose tolerance test, insulin sensitivity (euglycemic clamp technique), and fasting and postprandial triglyceride levels after a mixed meal.

**Results:** Relatives of persons with type 2 diabetes were insulin resistant but had normal glucose tolerance. They exhibited postprandial hypertriglyceridemia; the 6-hour triglyceride incremental area under the curve was 50% higher than that of the control group ( $P = 0.037$ ).

**Conclusions:** These healthy male first-degree relatives of patients with type 2 diabetes are insulin resistant and exhibit postprandial lipid intolerance despite having normal fasting triglyceride levels. These characteristics, which occur in the absence of glucose intolerance, are associated with an increased risk for macroangiopathy.

Microangiopathy and, in particular, macroangiopathy contribute to excess morbidity and early death in patients with type 2 diabetes (1). At diagnosis, patients with type 2 diabetes have a three- to fourfold greater risk for cardiovascular disease than nondiabetic persons (2, 3); in addition, approximately 40% have evidence of macroangiopathy (4). Therefore, diabetes may be only one of the underlying risk factors for macroangiopathic complications.

Several factors associated with type 2 diabetes can be noted years before diagnosis, including decreased first-phase insulin secretion (5, 6) and an impaired metabolic effect of insulin (insulin resistance) (5, 7–9). Risk factors for macroangiopathy in patients with type 2 diabetes include an elevated fasting triglyceride level; a low high-density lipoprotein (HDL) cholesterol level; and accumulation of small, dense, low-density lipoprotein (LDL) particles, which are atherogenic and easily oxidized (10).

More researchers now recognize that postprandial handling of triglyceride-rich lipoproteins is important for the propensity for atherosclerosis (10–12). Elevated postprandial triglyceride levels have been seen in persons with fasting hypertriglyceridemia (10, 12), persons who smoke (13, 14), and persons with type 2 diabetes (10). Although genetic predisposition for type 2 diabetes is associated with insulin resistance and impaired glucose disposal, fasting lipid levels usually remain normal at this early stage (8, 15). We assessed insulin sensitivity and postprandial triglyceride response in healthy first-degree male relatives of patients with type 2 diabetes and a group of carefully matched controls who had no known genetic predisposition for diabetes.

### Methods

#### Participants

Participants were recruited by advertisements in a local newspaper. Criteria for inclusion in our study were both parents or one parent and a sibling with type 2 diabetes; male sex (to exclude variation in insulin sensitivity during the menstrual cycle); normal glucose tolerance (16); a fasting triglyceride concentration less than 1.7 mmol/L; no evidence of hypertension, endocrine disease, or metabolic disease; and not smoking. The control group con-

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**Table. Metabolic Variables in First-Degree Relatives of Patients with Type 2 Diabetes and in Controls\***

Variable	Relatives	Controls	Difference (95% CI)	P Value
Oral glucose tolerance test				
Fasting plasma glucose level, mmol/L†	5.3	5.0	0.3 (-0.2 to 0.8)	>0.2
Plasma glucose AUC, mmol/L · min	765	664	100 (-35 to 235)	0.131
Plasma glucose IAUC, mmol/L · min	253	156	97 (-30 to 224)	0.120
Fasting plasma insulin level, pmol/L	45.6	34.2	11.4 (-3.0 to 25.8)	0.104
Plasma insulin level at 120 min, pmol/L	175.8	102.6	73.2 (-16.2 to 162)	0.099
Insulin sensitivity				
Insulin sensitivity index low infusion rate, mg · L/kg lean body mass · min · pmol‡	2.7	4.2	-1.5 (-2.5 to -0.5)	0.006
Insulin sensitivity index high infusion rate, mg · L/kg lean body mass · min · pmol§	2.1	2.8	-0.7 (-1.5 to 0.0)	0.051
Meal tolerance test				
Fasting plasma glucose level, mmol/L†	5.0	4.7	0.3 (0.0 to 0.5)	0.036
Plasma glucose level at 60 min, mmol/L†	6.3	5.5	0.8 (-0.1 to 1.6)	0.039
Plasma glucose AUC, mmol/L · min	1970	1867	103 (-37 to 243)	0.134
Plasma glucose IAUC, mmol/L · min	202	171	31 (-89 to 151)	>0.2
Fasting plasma insulin level, pmol/L	46.2	34.2	12.0 (-3.6 to 27.6)	0.125
Plasma insulin AUC, pmol/L · min	57 204	43 002	14 232 (-6774 to 35 244)	0.166
Plasma insulin IAUC, pmol/L · min	40 632	30 678	9954 (-6342 to 26 250)	>0.2
Fasting serum triglyceride level, mmol/L	1.1	0.9	0.2 (-0.1 to 0.6)	0.196
Serum triglyceride IAUC, mmol/L · min	287	191	95 (7 to 184)	0.037
Fasting plasma free fatty acid level, mmol/L	0.55	0.52	0.03 (-0.16 to 0.22)	>0.2
Plasma free fatty acid level at 60 min, mmol/L	0.29	0.20	0.10 (0.01 to 0.18)	0.030
Fasting serum total cholesterol level, mmol/L	4.9	4.6	0.3 (-0.6 to 1.2)	>0.2
Fasting serum HDL cholesterol level, mmol/L	1.1	1.2	-0.1 (-0.2 to 0.1)	>0.2
Preheparin lipoprotein lipase activity, mU/mL	1.9	2.1	-0.2 (-0.9 to 0.5)	>0.2
Postheparin lipoprotein lipase activity, mU/mL	218	240	-22 (-81 to 37)	>0.2
Hepatic lipase activity, mU/mL	2.4	2.1	0.3 (-0.4 to 1.1)	>0.2
Postheparin hepatic lipase activity, mU/mL	339	306	33 (-96 to 161)	>0.2

\* AUC = area under the curve; HDL = high-density lipoprotein; IAUC = incremental area under the curve.

† To convert mmol/L to mg/dL, divide by 0.00555.

‡ 10 mU/m<sup>2</sup> body surface · min.

§ 60 mU/m<sup>2</sup> body surface · min.

|| To convert mmol/L to mg/dL, divide by 0.02586.

sisted of persons who did not have a known family history of diabetes but fulfilled the remaining criteria. Relatives and controls were pairwise matched for the following variables, expressed as mean ± SD: age (34 ± 5 years compared with 34 ± 4 years), body mass index (24.5 ± 2.4 kg/m<sup>2</sup> compared with 24.6 ± 2.6 kg/m<sup>2</sup>), waist-to-hip ratio (0.89 ± 0.07 compared with 0.88 ± 0.05), and degree of physical activity (as assessed by interview). Thirteen persons who had two first-degree relatives with type 2 diabetes and 13 persons with no known family history of type 2 diabetes were included in the study. All participants gave informed consent, and the protocol was approved by the ethical committee of Göteborg University.

### Oral Glucose Tolerance Test

All participants had a 75-g oral glucose tolerance test.

### Insulin Sensitivity

Insulin sensitivity was measured by using the euglycemic clamp technique and insulin infusion rates of 10 mU/m<sup>2</sup> body surface · min<sup>-1</sup> and 60 mU/m<sup>2</sup> body surface · min<sup>-1</sup>, as described in detail elsewhere (17). Insulin sensitivity was measured by using the rate of glucose infusion during steady-state hyperinsulinemia; this rate is expressed as glucose utilization (mg/kg lean body mass · min<sup>-1</sup>). The insulin sen-

sitivity index represents sensitivity in relation to the prevailing plasma insulin concentration. Lean body mass was calculated from measurements of naturally occurring potassium 40 in a whole-body counter.

### Meal Tolerance Test

The 6-hour postprandial response to a standardized, mixed-meal test was determined as previously described (13) after the participants had fasted overnight. The energy content of the meal was 919 kcal (3.8 MJ); 33 g (14% of energy) were derived from protein, 51 g (49% of energy) were derived from fat, and 83 g (36% of energy) were derived from carbohydrates. The meal contained 30 g of saturated fat, 15 g of monounsaturated fat, and 3 g of polyunsaturated fat. Arterialized venous blood samples were collected from a heated forearm at the times indicated in the **Figure** for assessment of glucose, insulin, free fatty acids, and triglycerides. Postprandial lipoprotein and hepatic lipase activities were determined 6 hours before and 15 minutes after an intravenous injection of heparin, 100 U/kg of body weight (Lövens, Ballerup, Denmark).

### Blood Chemistry

Glucose, insulin, and free fatty acid levels were determined as previously reported (17); other lipid levels were determined with an automated Cobas Mira analyzer (Hoffman-LaRoche, Basel, Switzerland).

land). High-density lipoprotein cholesterol levels were measured by using the phosphotungstic acid-magnesium chloride precipitation method. Lipoprotein and hepatic lipase activities were determined as previously reported (17).

### Statistical Analysis

Data were analyzed as individual values and as the area under the curve above zero or as the incremental area under the curve above baseline. Two-tailed values of statistical significance were evaluated by using the Student paired *t*-test. A *P* value less than 0.050 was considered statistically significant. Correlations were determined by using the Spearman rank test. StatView 4.5 (Abacus Concepts, Inc., Berkeley, California) was used for all statistical calculations.

### Role of the Funding Sources

The funding sources were not involved in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

## Results

The detailed results of the metabolic tests are shown in the **Table**.

### Oral Glucose Tolerance Test

The glucose and insulin concentrations during the oral glucose tolerance test were similar in relatives and controls. All participants had normal glucose tolerance.

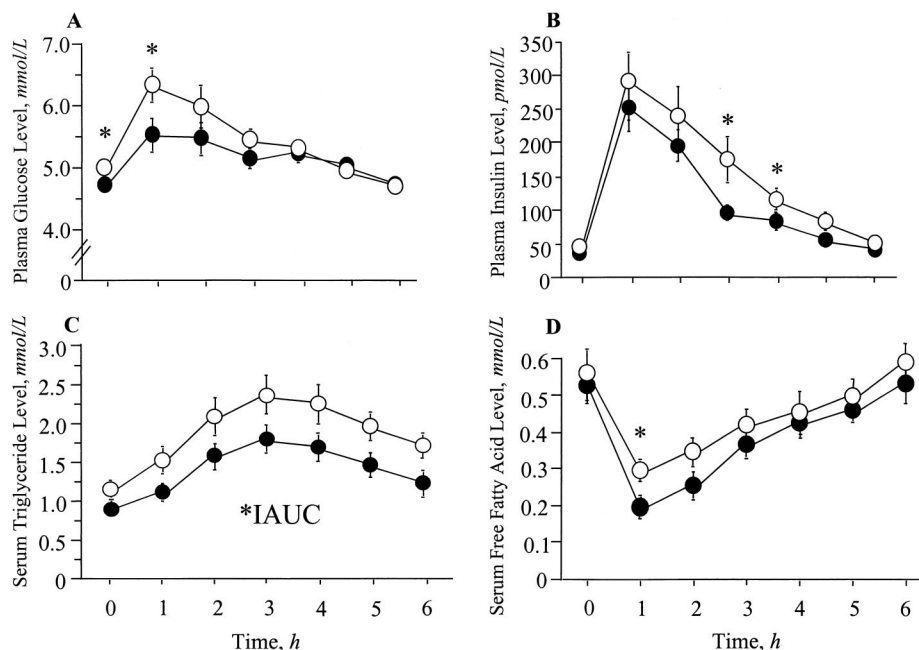
### Insulin Sensitivity

At the low insulin infusion rate, relatives had lower insulin sensitivity than controls when the euglycemic clamp was used ( $P = 0.006$ ). The difference at the high insulin infusion rate, however, was of borderline significance ( $P = 0.051$ ).

### Meal Tolerance Test

Glucose concentrations before the meal ( $P = 0.036$ ) and 1 hour after the meal ( $P = 0.039$ ) were slightly but significantly higher in relatives than in controls (**Figure, part A**). Relatives had higher postprandial insulin levels 3 and 4 hours after the meal (**Figure, part B**). However, because of the variations, differences in the total 6-hour area under the curve and the incremental area under the curve for glucose and insulin during the meal tolerance test were not statistically significant (**Table**).

Fasting triglyceride concentrations before the meal tolerance test were similar in relatives and controls (**Table**). However, the postprandial response, expressed as the 6-hour incremental area under the curve for triglycerides, was significantly increased by 50% in relatives ( $P = 0.037$ ) (**Figure, part C**).



**Figure.** Metabolic variables during a meal tolerance test in 13 first-degree relatives of patients with type 2 diabetes (white circles) and 13 controls (black circles). **A.** Mean glucose level. **B.** Mean insulin level. **C.** Mean triglyceride level. **D.** Mean free fatty acid level. Asterisks signify that a *P* value less than 0.05 was used for comparisons. Vertical bars represent standard error. To convert plasma glucose values to mg/dL, divide by 0.05555. IAUC = incremental area under the curve.

Relatives and controls had similar fasting concentrations before the meal; however, free fatty acid levels were 50% higher in relatives 1 hour after the meal ( $P = 0.030$ ) (Figure, part D). Fasting total cholesterol levels and HDL cholesterol levels did not differ significantly between the groups. Basal and heparin-released plasma lipase activities, assessed in 11 matched participants, were also similar (Table).

Insulin sensitivity was significantly and negatively correlated to the fasting triglyceride concentrations ( $r_s = -0.52$  [95% CI,  $-0.76$  to  $-0.15$ ];  $P = 0.011$ ) and the postprandial triglyceride response ( $r_s = -0.46$  [95% CI,  $-0.72$  to  $-0.07$ ];  $P = 0.026$ ). The fasting HDL cholesterol levels were also negatively correlated to the fasting triglyceride concentrations ( $r_s = -0.60$  [95% CI,  $-0.80$  to  $-0.28$ ];  $P = 0.003$ ) and the postprandial triglyceride response ( $r_s = -0.44$  [95% CI,  $-0.71$  to  $-0.07$ ];  $P = 0.027$ ).

## Discussion

In our study, male normoglycemic first-degree relatives of patients with type 2 diabetes exhibited an increased postprandial triglyceride response to a mixed meal, despite having normal fasting triglyceride levels. Because the relatives were carefully matched to the control group for potential confounding factors, such as sex, age, body mass index, and waist-to-hip ratio, the data suggest that the differences in postprandial triglyceride metabolism were caused by an inherited defect. This defect is probably linked to insulin resistance in the relatives. An increased and prolonged postprandial triglyceride response represents an atherogenic profile that is therefore present long before fasting hypertriglyceridemia or glucose intolerance becomes evident. As insulin resistance becomes exacerbated and free fatty acid levels become elevated by obesity (7), smoking (17), or an inherent progression to impaired glucose tolerance, the dyslipidemic features of the insulin resistance syndrome (that is, elevated fasting triglyceride levels and decreased HDL cholesterol levels) are consistently seen. The relation between postprandial lipid intolerance and fasting hypertriglyceridemia is well established (10, 12).

The idea that atherosclerosis is linked to postprandial lipid metabolism was introduced by Zilverman (11) approximately 20 years ago. Postprandial lipemia consists of a heterogeneous group of triglyceride-rich particles of different compositions and origins. It is not yet clear which lipoprotein particle or particles are related to the type of postprandial hyperlipidemia that is the major risk factor for coronary artery disease. However, evidence is accumulating that small chylomicrons; remnants of very-

low-density lipoprotein (VLDL) particles; and easily oxidized small dense LDL particles are atherogenic (10, 12). In addition, in our study, postprandial triglyceride levels were negatively correlated with HDL cholesterol levels.

The 50% increase in postprandial triglyceride concentrations in first-degree relatives of patients with type 2 diabetes was not associated with significant differences in the capacity to metabolize triglycerides (preheparin or postheparin lipoprotein lipase activity). This finding does not completely exclude a lipolytic defect. However, we propose that an impaired postprandial suppression by insulin of hepatic release of endogenous very-low-density lipoprotein (VLDL) triglycerides—which has recently been documented in patients with type 2 diabetes (18)—may be the most likely reason for lipid intolerance in the relatives. It has recently been shown that activation of PI3-kinase, a key enzyme for initiating insulin action, is necessary for suppression of the release of endogenous VLDL triglycerides (19). An impaired cellular activation of PI3-kinase by insulin has also been found in patients with type 2 diabetes (20).

In our study, male normotriglyceridemic first-degree relatives of patients with type 2 diabetes exhibited postprandial hypertriglyceridemia after a mixed meal; this finding suggests an inherited defect in postprandial triglyceride metabolism. This lipid intolerance is probably related to insulin resistance and an impaired postprandial—and insulin-mediated—suppression of the hepatic release of endogenous VLDL triglycerides. These factors are associated with an increased risk for cardiovascular disease. Persons with a family history of type 2 diabetes should be examined not only for risk for diabetes but also for other risk factors for cardiovascular disease. The diagnostic procedure used to identify postprandial lipid intolerance needs to be simplified. Future studies should include female relatives of patients with type 2 diabetes.

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## References

1. Tuomilehto J, Rastenyte D. Epidemiology of macrovascular disease and hypertension in diabetes mellitus. In: Alberti KG, DeFronzo RA, Zimmet P, eds. International Textbook of Diabetes Mellitus. 2d ed. Chichester: J Wiley; 1997: 1559-83.
2. Fontbonne A, Eschwege E, Cambien F, Richard JL, Ducimetiere P, Thibault N, et al. Hypertriglyceridaemia as a risk factor of coronary heart disease mortality in subjects with impaired glucose tolerance or diabetes. Results from the 11-year follow-up of the Paris Prospective Study. *Diabetologia*. 1989;32:300-4.
3. Uusitupa MI, Niskanen LK, Siitonen O, Voutilainen E, Pyorala K. Ten-year cardiovascular mortality in relation to risk factors and abnormalities in lipoprotein composition in type 2 (non-insulin-dependent) diabetic and non-diabetic subjects. *Diabetologia*. 1993;36:1175-84.
4. Laakso M, Barrett-Connor E. Asymptomatic hyperglycemia is associated with lipid and lipoprotein changes favoring atherosclerosis. *Arteriosclerosis*. 1989;9:665-72.
5. Vaag A, Henriksen EJ, Madsbad S, Holm N, Beck-Nielsen H. Insulin secretion, insulin action, and hepatic glucose production in identical twins discordant for non-insulin-dependent diabetes mellitus. *J Clin Invest*. 1995; 95:690-8.
6. Pimenta W, Korytkowski M, Mitrakou A, Jenssen T, Yki-Järvinen H, Evron W, et al. Pancreatic beta-cell dysfunction as the primary genetic lesion in NIDDM. Evidence from studies in normal glucose-tolerant individuals with a first-degree NIDDM relative. *JAMA*. 1995;273:1855-61.
7. Lillioja S, Mott DM, Howard BV, Bennett PH, Yki-Järvinen H, Freymond D, et al. Impaired glucose tolerance as a disorder of insulin action. Longitudinal and cross-sectional studies in Pima Indians. *N Engl J Med*. 1988; 318:1217-25.
8. Eriksson J, Franssila-Kallunki A, Ekstrand A, Saloranta C, Widen E, Schalin C, et al. Early metabolic defects in persons at increased risk for non-insulin-dependent diabetes mellitus. *N Engl J Med*. 1989;321:337-43.
9. Martin BC, Warram JH, Krolewski AS, Bergman RN, Soeldner JS, Kahn CR. Role of glucose and insulin resistance in development of type 2 diabetes mellitus: results of a 25-year follow-up study. *Lancet*. 1992;340:925-9.
10. Syväne M, Taskinen MR. Lipids and lipoproteins as coronary risk factors in non-insulin-dependent diabetes mellitus. *Lancet*. 1997;350(Suppl 1):S120-3.
11. Zilversmit DB. Atherogenesis: a postprandial phenomenon. *Circulation*. 1979;60:473-85.
12. Patsch JR. Triglyceride-rich lipoproteins and atherosclerosis. *Atherosclerosis*. 1994;110(Suppl 3):S23-6.
13. Axelsen M, Eliasson B, Joheim E, Lenner RA, Taskinen MR, Smith U. Lipid intolerance in smokers. *J Intern Med*. 1995;237:449-55.
14. Eliasson B, Mero N, Taskinen MR, Smith U. The insulin resistance syndrome and postprandial lipid intolerance in smokers. *Atherosclerosis*. 1997; 129:79-88.
15. Perseghin G, Ghosh S, Gerow K, Shulman GI. Metabolic defects in lean nondiabetic offspring of NIDDM parents: a cross-sectional study. *Diabetes*. 1997;46:1001-9.
16. World Health Organization. Food and Agriculture Organization of the United Nations. Diabetes Mellitus: Report of a WHO Study Group. Technical Report Series No. 727. Geneva: WHO; 1985.
17. Eliasson B, Attvall S, Taskinen MR, Smith U. The insulin resistance syndrome in smokers is related to smoking habits. *Arterioscler Thromb*. 1994; 14:1946-50.
18. Malmström R, Packard CJ, Caslake M, Bedford D, Stewart P, Yki-Järvinen H, et al. Defective regulation of triglyceride metabolism by insulin in the liver in NIDDM. *Diabetologia*. 1997;40:454-62.
19. Phung TL, Roncone A, Jensen KL, Sparks CE, Sparks JD. Phosphoinositide 3-kinase activity is necessary for insulin-dependent inhibition of apolipoprotein B secretion by rat hepatocytes and localizes to the endoplasmic reticulum. *J Biol Chem*. 1997;272:30693-702.
20. Rondinone CM, Wang LM, Lönnroth P, Wesslau C, Pierce JH, Smith U. Insulin receptor substrate (IRS) 1 is reduced and IRS-2 is the main docking protein for phosphatidylinositol 3-kinase in adipocytes from subjects with non-insulin-dependent diabetes mellitus. *Proc Natl Acad Sci U S A*. 1997;94: 4171-5.

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My stars alive, what may be going on even in my very own heart is enough to scare me to death. Which is what that psychiatrist was trying to tell me about that time. That it's what's down inside that you don't ever let out that is important, and we need to bring it up and face it and even talk to somebody about it. What he meant was me bring it up and talk to him about it and me pay him to listen. I'll tell you right now, I never went to him but once. It makes me mad as all get-out to go to a doctor anytime what's too busy to talk to me or worse yet acts like he's not interested in what I have got to say.

Ferrol Sams  
*The Widows Mite and Other Stories*  
Atlanta: Peachtree Publishers; 1987:3

Submitted by:  
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