# HYPERINSULINEMIA AS AN INDEPENDENT RISK FACTOR FOR ISCHEMIC HEART DISEASE

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**Abstract** *Background.* Prospective studies suggest that hyperinsulinemia may be an important risk factor for ischemic heart disease. However, it has not been determined whether plasma insulin levels are independently related to ischemic heart disease after adjustment for other risk factors, including plasma lipoprotein levels.

*Methods.* In 1985 we collected blood samples from 2103 men from suburbs of Quebec City, Canada, who were 45 to 76 years of age and who did not have ischemic heart disease. A first ischemic event (angina pectoris, acute myocardial infarction, or death from coronary heart disease) occurred in 114 men (case patients) between 1985 and 1990. Each case patient was matched for age, body-mass index, smoking habits, and alcohol consumption with a control selected from among the 1989 men who remained free of ischemic heart disease during follow-up. After excluding men with diabetes, we compared fasting plasma insulin and lipoprotein concentrations at base line in 91 case patients and 105 controls.

*Results.* Fasting insulin concentrations at base line were 18 percent higher in the case patients than in the controls (P<0.001). Logistic-regression analysis showed that the insulin concentration remained associated with ischemic heart disease (odds ratio for ischemic heart disease with each increase of 1 SD in the insulin concentration, 1.7; 95 percent confidence interval, 1.3 to 2.4) after adjustment for systolic blood pressure, use of medications, and family history of ischemic heart disease. Further adjustment by multivariate analysis for plasma triglyceride, apolipoprotein B, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol concentrations did not significantly diminish the association between the insulin concentration and the risk of ischemic heart disease (odds ratio, 1.6; 95 percent confidence interval, 1.1 to 2.3).

*Conclusions.* High fasting insulin concentrations appear to be an independent predictor of ischemic heart disease in men. (N Engl J Med 1996;334:952-7.)
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I NSULIN resistance and hyperinsulinemia are conditions known to be associated with hypertriglyceridemia and low high-density lipoprotein (HDL) cholesterol concentrations.[1,2] Four prospective studies, in which fasting plasma insulin concentrations were used as an index of insulin sensitivity, found that elevated insulin levels are associated with an increased risk of ischemic heart disease in men,[3-6] but this finding has not been confirmed in all studies.[7]

Whether the relation between hyperinsulinemia and ischemic heart disease is independent of related risk factors, such as hypertriglyceridemia, low HDL cholesterol concentrations, and hypertension, is not clear, however. Fontbonne and colleagues[8-10] reported that hyperinsulinemia was not associated with an increased risk of ischemic heart disease unless accompanied by elevated plasma triglyceride concentrations. Results from the Caerphilly prospective study also suggested that the risk associated with hyperinsulinemia was not independent of concomitant variations in triglyceride concentrations.[6] We examined this issue by measuring fasting plasma insulin levels in men with no evidence of ischemic heart disease at study entry, in some of whom ischemic heart disease developed during the subsequent five years. The men with ischemic heart disease were compared with a group of matched controls who remained free of such disease during the same period.

## METHODS

### Study Cohort and Follow-up

The Quebec Cardiovascular Study cohort has been described in detail previously.[11,12] Briefly, 4637 men from 35 to 64 years of age, almost all of French Canadian descent, were recruited in 1973 from seven counties in the Quebec City, Canada, metropolitan area for a study of risk factors for cardiovascular disease, including nonfasting cholesterol concentrations. Men with clinical evidence of ischemic heart disease at entry (n=266) were excluded from further follow-up in the study. Subsequent evaluations were carried out in 1974 and 1975, 1980, and 1985. From 1973 through 1985, 371 men died. In 1985, further evaluation of risk factors, including the fasting lipoprotein–lipid profile, was performed in 2443 (61 percent) of the remaining 4000 men screened in 1973. Among the other 1557 men, 10 percent could not be located in 1985, 19 percent came to the clinic in a nonfasting state, and 71 percent either declined to participate or were evaluated in a nonfasting state at their homes by nurses participating in the project.

In 1990 and 1991, all participants were contacted by mail and invited to answer a short, standardized questionnaire covering smoking habits, use of medication, history of cardiovascular disease, and diabetes mellitus. For those who reported such diseases and those who had died, all hospital charts were reviewed. For those who reported exertional angina and who were not hospitalized, a study cardiologist obtained the history to ascertain the characteristics of the angina. Telephone calls were made to participants who did not answer a second letter or, if this was unsuccessful, to a close family member.

Data on mortality were obtained for 99 percent of the entire cohort and data on morbidity for 96 percent. Analyses performed with the 1973 data revealed that the age distribution of the 2443 participants tested in 1985 was representative of the 1973 cohort and that there was no significant difference in mortality due to ischemic heart disease between the 2443 participants and the 1557 nonparticipants. Men who had ischemic heart disease in 1985 (n=253) were excluded; a complete risk-factor profile was obtained for 2103 of the men who were free of ischemic heart disease in 1985.[12]

### Definition of Events

Criteria for the diagnosis of a first ischemic event included exertional angina, coronary insufficiency,[13] nonfatal myocardial infarction, and death from coronary disease,[14] as previously described.[11,12] Confirmation of myocardial infarction required diagnostic electrocar-

diographic changes or two of the three following criteria: the presence of symptoms, elevations in cardiac-enzyme levels, or ischemic electrocardiographic changes. The diagnosis of exertional angina was based on typical symptoms of retrosternal squeezing or pressure-type discomfort occurring on exertion and relieved by rest, nitroglycerin, or both. Coronary insufficiency was defined as typical retrosternal chest pain lasting at least 15 minutes and associated with transient ischemic changes on the electrocardiogram (Minnesota code 5-1 or 5-2), but without elevation in the level of creatine kinase. All electrocardiograms were interpreted by the same cardiologist, who was unaware of the participants' risk profile. Criteria for classifying a death as due to coronary disease included confirmation of the diagnosis on the death certificate or an autopsy report confirming the presence of coronary disease and the absence of noncardiac disease that could explain death. Myocardial infarction was considered fatal if death occurred within four weeks after the event or if myocardial infarction was diagnosed at autopsy. Myocardial infarction and death related to ischemic heart disease were confirmed by data from the Provincial Death Registry. Informed consent was obtained from the subjects to review the relevant hospital files. Autopsies were performed in about a third of the patients who died.

### Evaluation of Risk Factors

In 1985, data on demographic and lifestyle variables, medical history, and medication use were obtained by means of a standardized questionnaire administered by trained nurses and further reviewed by a physician. Each subject's weight and height were recorded. Resting blood pressure was measured after a five-minute rest with the patient sitting up; phase I and phase V of the Korotkoff sounds were used to measure systolic and diastolic blood pressure, respectively. The mean of two blood-pressure measurements obtained five minutes apart was used in the analyses. Information compiled from the questionnaire included family and personal history of diabetes, smoking habits, alcohol consumption, and use of medications. The use of hypolipidemic drugs was not very common in 1985; about 1 percent of the cohort received such therapy. The men in whom ischemic heart disease developed during follow-up were more likely than those who remained free of ischemic heart disease to use beta-blockers (11 percent vs. 6.5 percent) and diuretics (7.5 percent vs. 2.8 percent). Alcohol intake was computed from the number of ounces of each type of beverage (beer, wine, or spirits) consumed per week and then standardized as an absolute quantity of alcohol (1 oz = 22.5 g).[15] Men were classified as having a family history of ischemic heart disease if they had at least one parent or sibling with a history of ischemic heart disease.

### Matching Procedures

Of the initial sample of 2103 men who were free of clinical signs of ischemic heart disease in 1985, ischemic heart disease developed in 114 during five years of follow-up, which ended in September 1990.[12] Each subject with confirmed ischemic heart disease (case patient) was matched with a control subject selected from among the 1989 men who had no clinical evidence of ischemic heart disease during follow-up. Subjects were matched on the basis of age, cigarette smoking, body-mass index (the weight in kilograms divided by the square of the height in meters), and weekly alcohol intake. The mean differences in matched case–control pairs were 0.6 year for age, 0.2 for body-mass index, and 0.2 oz (4.5 g) per week for alcohol intake. The mean difference within pairs of cigarette smokers was 0.3 cigarette per day; all nonsmokers were matched with nonsmokers. Eight men were excluded from the analysis either because they had such high values for the number of cigarettes smoked per day that no matched control was available or because they had missing values for the insulin concentration. Men who reported having diabetes mellitus or who were receiving hypoglycemic therapy at the base-line evaluation (15 case patients and 1 control) were also excluded.

### Laboratory Analyses

After the subjects had fasted for 12 hours, blood samples were obtained from an antecubital vein while the subjects were sitting. A tourniquet was used but released before the withdrawal of blood into Vacutainer tubes (Becton Dickinson, Mountain View, Calif.) containing EDTA. Plasma was separated from blood cells by centrifugation and immediately used for measurement of lipids and apolipoprotein B. Aliquots of fasting plasma were frozen at the time of collection for the subsequent assessment of insulin levels. Plasma cholesterol and triglyceride concentrations were determined with an AutoAnalyzer II (Technicon Instruments, Tarrytown, N.Y.), as previously described.[16] HDL cholesterol was measured in the supernatant after precipitation of apolipoprotein B–containing lipoproteins with heparin–manganese chloride.[17] Low-density lipoprotein (LDL) cholesterol concentrations were estimated with the equation of Friedewald et al.[18] for men with triglyceride concentrations below 400 mg per deciliter (4.5 mmol per liter). Plasma apolipoprotein B concentrations were measured by the rocket-immunoelectrophoresis method of Laurell,[19] as described previously.[16] Serum standards for the apolipoprotein assay were prepared in our laboratory and calibrated against serum samples from the Centers for Disease Control and Prevention. The standards were lyophilized and stored at −85°C until use. Peak heights between 15 and 35 mm yielded linear and reliable results. The coefficients of variation for cholesterol, HDL cholesterol, triglyceride, and apolipoprotein measurements were all less than 3 percent.

Fasting insulin concentrations were measured with a commercial double-antibody radioimmunoassay (human-insulin–specific radioimmunoassay method, LINCO Research, St. Louis). In this assay insulin shows little cross-reactivity (<0.2 percent) with human proinsulin.[20] The coefficients of variation were 3.5 percent for lower insulin concentrations (8 to 25 $\mu$U per milliliter [50 to 150 pmol per liter]), and 5.2 percent for higher concentrations (33 to 83 $\mu$U per milliliter [200 to 500 pmol per liter]).

### Statistical Analysis

Student's t-tests were used to compare mean values at base line in men in whom ischemic heart disease developed with those in the men who remained free of such disease during the five-year follow-up. Differences in frequency were tested by chi-square analysis. Associations among variables were assessed with the Pearson and Spearman correlation coefficients for parametric and nonparametric variables, respectively. Preliminary analyses showed that the relation between metabolic risk factors and ischemic heart disease was linear across their distribution. Logistic-regression analyses were therefore performed with plasma lipid, lipoprotein, and apolipoprotein concentrations included as continuous variables.

Odds ratios for ischemic heart disease were computed as the change in the risk of disease associated with an increase of 1 SD in the concentration of the substance in question, according to unconditional logistic-regression analysis. Odds were adjusted for the confounding effects of systolic blood pressure, use of medications, and family history of ischemic heart disease.

The study design eliminated the association between age, smoking, obesity, and alcohol intake, on the one hand, and the risk of ischemic heart disease, on the other. Inclusion of these variables in the logistic models had no effect on the estimates of the association between other risk factors and ischemic heart disease. In addition, the use of conditional logistic regression, which takes into consideration the potentially confounding effects of the variables used to match case patients and controls, yielded results that were essentially the same as those of the unconditional regression analyses (data not shown).

For these reasons, variables used in the matching procedure were not included in the analyses. Multiplicative terms of interaction were also used to assess the potential interactions between fasting insulin concentrations and lipid, lipoprotein, and apolipoprotein concentrations in relation to the risk of ischemic heart disease. All statistical tests were performed with the SAS software package (SAS Institute, Cary, N.C.).

## RESULTS

In the overall sample of 2103 men who were free of ischemic heart disease at study entry, the prevalence of diabetes mellitus was higher among the men in whom ischemic heart disease subsequently developed than among those who remained free of ischemic heart disease (16 percent vs. 4 percent, P<0.001). After the

exclusion of patients with diabetes from the matched analysis, the 91 nondiabetic men in whom ischemic heart disease developed also had higher base-line plasma total cholesterol, LDL cholesterol, triglyceride, and apolipoprotein B concentrations than the 105 matched controls who remained free of disease (Table 1). A significant difference in the insulin concentration in fasting subjects was observed between case patients and controls. Men in whom ischemic heart disease developed had baseline insulin levels while fasting that were 18 percent higher than those of men who had no ischemic heart disease ($P<0.001$). The ratio of total cholesterol to HDL cholesterol was also markedly higher (18 percent higher) among the men who subsequently had ischemic heart disease.

We investigated the association between the insulin concentration and the risk of ischemic heart disease, both before and after adjustment for plasma lipid and apolipoprotein concentrations, using multiple logistic-regression analysis (Table 2). Higher plasma concentrations of insulin were associated with a significant increase in the risk of ischemic heart disease (odds ratio for ischemic heart disease with each increase of 1 SD in the insulin concentration, 1.7; 95 percent confidence interval, 1.3 to 2.4); this association was independent of systolic blood pressure, medication use, and family history

Table 2. Relation between Insulin Concentrations at Base Line in Fasting Subjects and the Subsequent Development of Ischemic Heart Disease, before and after Adjustment for Plasma Lipid and Apolipoprotein B Levels, from Seven Models in the Multivariate Logistic Analysis.*

| VARIABLE | MODEL 1 | MODEL 2 | MODEL 3 | MODEL 4 | MODEL 5 | MODEL 6 | MODEL 7 |
|---|---|---|---|---|---|---|---|
| Insulin | | | | | | | |
| β | 0.31 | 0.34 | 0.28 | 0.29 | 0.30 | 0.26 | 0.30 |
| Odds ratio | 1.7† | 1.9† | 1.7‡ | 1.7‡ | 1.7‡ | 1.6§ | 1.6‡ |
| 95% CI | 1.3–2.4 | 1.3–2.6 | 1.2–2.3 | 1.2–2.3 | 1.2–2.4 | 1.1–2.3 | 1.1–2.3 |
| LDL cholesterol | | | | | | | |
| β | | 0.35 | | | | | |
| Odds ratio | | 1.9† | | | | | |
| 95% CI | | 1.3–2.7 | | | | | |
| Triglycerides | | | | | | | |
| β | | | 0.17 | | | | 0.02 |
| Odds ratio | | | 1.4¶ | | | | 1.0 |
| 95% CI | | | 1.0–1.9 | | | | 0.7–1.5 |
| HDL cholesterol | | | | | | | |
| β | | | | −0.07 | | | 0.02 |
| Odds ratio | | | | 0.88 | | | 1.0 |
| 95% CI | | | | 0.65–1.2 | | | 0.7–1.5 |
| Apolipoprotein B | | | | | | | |
| β | | | | | 0.37 | | 0.36 |
| Odds ratio | | | | | 1.9† | | 1.9‖ |
| 95% CI | | | | | 1.4–2.8 | | 1.3–2.9 |
| Total:HDL cholesterol ratio | | | | | | | |
| β | | | | | | 0.26 | |
| Odds ratio | | | | | | 1.6** | |
| 95% CI | | | | | | 1.2–2.2 | |

*Odds ratios are expressed as the increase in the risk of ischemic heart disease for every increase of 1 SD in the variable in question. β denotes the standardized estimate, which is the parameter estimate of each variable in the multivariate logistic models, and CI denotes confidence interval. All seven models included the following covariates: systolic blood pressure, family history of ischemic heart disease (presence or absence), and use of beta-blockers or diuretics at base line (yes or no). The study design eliminated the potentially confounding effects of age, smoking, body-mass index, and alcohol consumption on the risk of ischemic heart disease. Only the variables included in each model are shown.

†$P<0.001$.     ‡$P=0.002$.     §$P=0.006$.
¶$P=0.05$.     ‖$P=0.001$.     **$P=0.004$.

of ischemic heart disease. The odds ratio for ischemic heart disease in patients with higher insulin concentrations after fasting was essentially unchanged when the variables used in matching (age, body-mass index, smoking status, and alcohol consumption) were included in the logistic model (odds ratio, 2.1; 95 percent confidence interval, 1.4 to 3.0). Further adjustment for the potentially confounding effects of the triglyceride, LDL cholesterol, HDL cholesterol, and apolipoprotein B concentrations (models 2 through 6 in Table 2) did not substantially weaken the relation between insulin and the risk of ischemic heart disease. Accordingly, the association between the concentrations of LDL cholesterol, triglycerides, and apolipoprotein B and the total:HDL cholesterol ratio, on the one hand, and the risk of ischemic heart disease, on the other, remained significant after adjustment for insulin levels. Finally, the relation between plasma insulin concentrations and the risk of ischemic heart disease was not altered significantly when the additive contribution of the triglyceride, HDL cholesterol, and apolipoprotein B concentrations to risk was accounted for (model 7); this finding suggests that the increased risk of ischemic heart disease associated with hyperinsulinemia was at least partly independent of variations in plasma lipoprotein concentrations.

The potential interaction between hyperinsulinemia and plasma lipoproteins was tested by subdividing the sample into thirds according to insulin concentration and either low or high triglyceride levels, apolipopro-

Table 1. Base-Line Characteristics of 91 Men with Clinical Manifestations of Ischemic Heart Disease (Case Patients) and 105 Matched Controls from the Quebec Cardiovascular Study.*

| CHARACTERISTIC† | CONTROLS (N = 105) | CASE PATIENTS (N = 91) | % DIFFERENCE‡ | P VALUE |
|---|---|---|---|---|
| Age (yr) | 58.9±6.9 | 59.2±7.7 | — | — |
| Body-mass index | 26.5±3.8 | 26.2±3.8 | — | — |
| Smokers at base line (%) | 41 | 41 | — | — |
| Alcohol (oz/wk) | 5.3±8.1 | 5.1±7.8 | — | — |
| Systolic blood pressure (mm Hg) | 133±18 | 136±16 | — | 0.3 |
| Cholesterol (mmol/liter) | 5.5±0.9 | 6.1±1.1 | 11 | <0.001 |
| Triglycerides (mmol/liter) | 1.74±0.67 | 2.03±0.77 | 17 | 0.006 |
| HDL cholesterol (mmol/liter) | 1.02±0.25 | 0.96±0.22 | −6 | 0.07 |
| Apolipoprotein B (mg/dl) | 113±27 | 132±33 | 17 | <0.001 |
| Total:HDL cholesterol ratio | 5.7±1.6 | 6.7±2.0 | 18 | <0.001 |
| Fasting insulin (pmol/liter) | 78.2±28.8 | 92.1±27.5 | 18 | <0.001 |

*Plus−minus values are means ±SD. The variables used in matching case patients and controls were age, body-mass index, smoking status, and alcohol consumption.

†The body-mass index is calculated as the weight in kilograms divided by the square of the height in meters. To convert alcohol values to grams, multiply by 22.5. To convert cholesterol values to milligrams per deciliter, divide by 0.02586. To convert triglyceride values to milligrams per deciliter, divide by 0.01129. To convert values for insulin to microunits per milliliter, divide by 6.
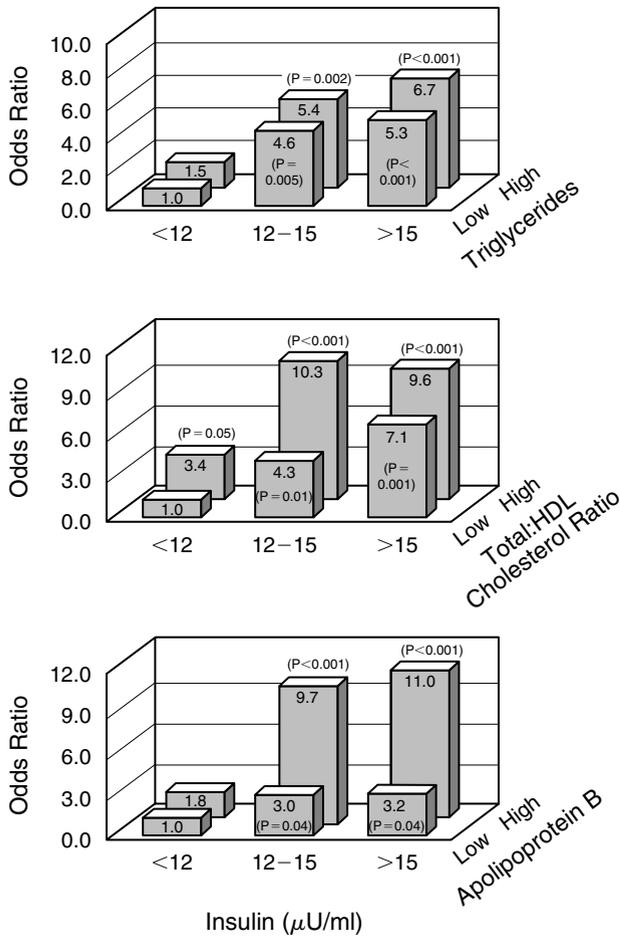
‡Case patients as compared with controls.

Figure 1. Odds Ratios for Ischemic Heart Disease According to Plasma Insulin and Triglyceride Concentrations, Total:HDL Cholesterol Ratios, and Apolipoprotein B Concentrations.

Insulin was measured after subjects had fasted for 12 hours. The median triglyceride concentration (150 mg per deciliter [1.7 mmol per liter]), total:HDL cholesterol ratio (6.0), and apolipoprotein B concentration (119 mg per deciliter) were used to define men with either low levels (below the 50th percentile) or high levels (at or above the 50th percentile) for these variables. The results of tests for multiplicative interactions did not reach significance at the 0.05 level for any of the combinations. P values are for comparisons with the reference group, which was assigned an odds ratio of 1.0. To convert values for insulin to picomoles per liter, multiply by 6.

tein B levels, and total:HDL cholesterol ratios. The results, presented in Figure 1, indicate that the risk of ischemic heart disease associated with hyperinsulinemia did not appear to be further increased in the presence of elevated triglyceride levels (odds ratios for insulin concentrations >15 μU per milliliter [>92 pmol per liter], 5.3 in men with triglyceride concentrations below the 50th percentile and 6.7 in men with concentrations at or above the 50th percentile, as compared with the reference group; P<0.001]). Among men with an elevated total:HDL cholesterol ratio (i.e., one at or above the 50th percentile), those with high or intermediate insulin concentrations (≥12 μU per milliliter) had the greatest increase in risk. Furthermore, men with high plasma insulin concentrations but with a total:HDL cho-

lesterol ratio below 6 (the 50th percentile) were also at greater risk for ischemic heart disease than men in the lowest third of the sample with respect to insulin (odds ratio, 7.1; P=0.001). Elevated plasma insulin concentrations were also associated with an increased risk of ischemic heart disease among men with low apolipoprotein B concentrations (odds ratio, 3.2; P=0.04). However, the most substantial increase in the risk of ischemic heart disease was observed among men with elevated concentrations of both insulin and apolipoprotein B (odds ratio, 11.0; P<0.001). Although a test for multiplicative interaction between apolipoprotein B and insulin did not indicate significance (P=0.2), the absolute effect of hyperinsulinemia on ischemic heart disease appeared to depend largely on the apolipoprotein B concentration.

Although statistically significant, the associations between plasma insulin concentrations in fasting subjects and body-mass index (r=0.41, P<0.001), triglyceride concentrations (r=0.23, P=0.001), apolipoprotein B concentrations (r=0.16, P=0.02), HDL cholesterol concentrations (r=−0.28, P<0.001) and the total:HDL cholesterol ratio (r=0.25, P<0.001) were of only moderate magnitude; these findings therefore provide further support for the concept that the risk of ischemic heart disease associated with hyperinsulinemia appears to be largely independent of variations in plasma lipoprotein concentrations. No association was found between plasma insulin concentrations and systolic or diastolic blood pressure.

## DISCUSSION

Our results agree with those of previous prospective investigations, which have found that a high plasma insulin concentration in fasting subjects is associated with an increased incidence of ischemic heart disease in nondiabetic men.[2-6] The mechanisms responsible for this association, however, remain speculative. It had been suggested that the risk associated with hyperinsulinemia was largely explained by the lipid abnormalities that are common among men with elevated insulin concentrations.[6,8-10,21,22] Although we found significant associations between insulin levels in fasting subjects and lipoprotein concentrations, further analyses revealed that the risk of ischemic heart disease related to hyperinsulinemia was largely independent of the concomitant dyslipidemic state. A synergistic effect was noted, however, since the combination of hyperinsulinemia and elevated apolipoprotein B concentrations or an increased total:HDL cholesterol ratio substantially increased the risk of ischemic heart disease in men who had both these metabolic alterations.

These results support the notion that hyperinsulinemia may increase the risk of ischemic heart disease through alterations in metabolic processes other than the related dyslipidemia. In this regard, it has been reported that plasma concentrations of plasminogen-activator inhibitor type 1 are increased in patients with hyperinsulinemic insulin resistance,[23] an alteration that may impair fibrinolysis and increase susceptibility to

thrombosis in men with hyperinsulinemia. Furthermore, the concomitant elevation of blood pressure may also be a contributing factor,[24] although the association between hyperinsulinemia and ischemic heart disease in our study was unchanged by adjustment for blood pressure.

On the other hand, it has been suggested that hyperinsulinemia in persons without diabetes may be a marker for a cluster of metabolic abnormalities, including hypertension, dyslipidemia, impaired fibrinolysis, and impaired insulin-mediated glucose uptake.[1] The concept of the insulin-resistance syndrome has evolved considerably since its introduction by Reaven in 1988,[1] and it has been suggested that visceral obesity may also be a common component of the cluster of metabolic abnormalities found in insulin-resistant subjects.[25,26] We have shown that persons in whom overweight is characterized by the accumulation of only small amounts of visceral adipose tissue, as measured by computed tomography, did not differ substantially from normal-weight controls in terms of risk factors for cardiovascular disease.[27-29] Overweight patients in whom there was a large amount of visceral adipose tissue were, on the other hand, characterized by a cluster of metabolic disturbances that included glucose intolerance, hyperinsulinemia, hypertriglyceridemia, elevated apolipoprotein B concentrations, abnormally low HDL cholesterol concentrations, and an elevated total:HDL cholesterol ratio.[27,29] Analyses of the Paris Prospective Study cohort suggested that the abdomen-to-thigh ratio, a crude anthropometric estimate of upper-body fat, was an independent predictor of the risk of death from ischemic heart disease, whereas the insulin concentration in fasting subjects was no longer independently associated with ischemic heart disease after this variable was controlled for.[30] Although additional work is clearly warranted to clarify this issue, the results of our study suggest that the relation of hyperinsulinemia to ischemic heart disease may be largely independent of alterations in body weight, blood pressure, and plasma lipoprotein concentrations.

The presence of hyperinsulinemia in fasting subjects may therefore serve as a crude but clinically relevant marker for other metabolic and hemostatic disturbances — namely, visceral obesity, a procoagulant state, and alterations in growth factor levels — all of which are associated with an increased risk of ischemic heart disease.[31] However, laboratory standardization of insulin measurements remains a problem, and there is currently no universally accepted criterion for hyperinsulinemia in the fasting state. We believe that it is relevant to raise this issue, since we used a radioimmunoassay that did not cross-react with pro-insulin[32]; this was not the case in previous prospective studies, in which insulin could not be identified as an independent predictor of ischemic heart disease after adjustment for other risk factors. Since an insulin-resistant, hyperinsulinemic state increases the risk of type II diabetes mellitus,[33] our results also support the notion that maintaining an adequate level of insulin sensitivity and low plasma insulin

concentrations through proper diet and exercise habits not only may be of value in preventing type II diabetes, but also may reduce the risk of heart disease.

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