Is Atherosclerosis in Diabetes and Impaired Fasting Glucose Driven by Elevated LDL Cholesterol or by Decreased HDL Cholesterol?

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OBJECTIVE — To evaluate the atherogenicity of lipids in coronary patients with normal fasting glucose (NFG), impaired fasting glucose (IFG), and type 2 diabetes.

RESEARCH DESIGN AND METHODS — Serum lipid values, the presence of angiographic coronary artery disease (CAD) at baseline, and the incidence of vascular events over 2.3 years were recorded in 750 consecutive patients undergoing coronary angiography.

RESULTS — Triglycerides significantly (P < 0.001) increased and HDL cholesterol (P < 0.001) as well as LDL particle diameter (P < 0.001) significantly decreased from subjects with NFG < 5.6 mmol/l (n = 272) over patients with IFG ≥ 5.6 mmol/l (n = 314) to patients with type 2 diabetes (n = 164). Factor analysis revealed two factors in the lipid profiles of our patients: triglycerides, HDL cholesterol, apolipoprotein A1, and LDL particle diameter loaded high on an HDL-related factor, and total cholesterol, LDL cholesterol, and apolipoprotein B loaded high on an LDL-related factor. In patients with type 2 diabetes, the HDL-related factor (odds ratio 0.708 [0.506–0.990]; P = 0.044), but not the LDL-related factor (0.921 [0.677–1.251]; P = 0.597), was associated with significant coronary stenoses ≥ 50%. Consistently, in the prospective study, the HDL-related factor (0.708 [0.506–0.990]; P = 0.044), but not the LDL-related factor (1.362 [0.985–1.883]; P = 0.061), proved significantly predictive for vascular events in patients with type 2 diabetes.

CONCLUSIONS — The low HDL cholesterol/high triglyceride pattern is associated with the degree of hyperglycemia. In coronary patients with type 2 diabetes, this pattern correlates with the prevalence of CAD and significantly predicts the incidence of vascular events.

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Epidemiologic data from the Framingham Study (1) and the Multiple Risk Factor Intervention Trial (2) indicate that the risk for cardiovascular death is increased two- to threefold in type 2 diabetic individuals. Moreover, after a first myocardial infarction, cardiovascular morbidity and mortality are increased in patients with diabetes compared with nondiabetic patients (3). In the U.K. Prospective Diabetes Study, protocols targeted to optimize glycemic (4) or blood pressure control (5) failed to significantly reduce the incidence of myocardial infarction. Therefore, and because in the U.K. Prospective Diabetes Study plasma levels of LDL cholesterol and low levels of HDL cholesterol were strong predictors of myocardial infarction (6), the main interest for risk intervention now focuses on lipids. However, it is still not clear which lipoprotein abnormality predominantly endangers diabetic patients.

Typically, patients with type 2 diabetes are characterized by hypertriglyceridemia and low HDL cholesterol levels (7), whereas levels of LDL cholesterol have been reported to be normal (7), higher (8) or lower (9) than those in nondiabetic control subjects. Moreover, compositional changes of lipoproteins have been demonstrated: both LDL and HDL are smaller and denser than average (10). Finally, diabetic patients exhibit alterations in postprandial lipid transport (10).

Both strategies to lower LDL cholesterol (9,11,12) and efforts to increase HDL cholesterol (13–15) proved beneficial in diabetic patients. However, because no study directly compared LDL lowering to HDL raising, interventional data are not valid to discern the lipoprotein abnormalities that are central for atherogenesis.

Whereas observational data predominantly come from patients in early diabetic states (6), no data exist for a later stage when many diabetic patients are already affected by coronary artery disease (CAD) and thus face a large absolute mortality risk, the prediction of which is of paramount clinical importance.

It is thus important to study diabetic individuals with a very high absolute risk for cardiovascular events. In such a population, it should be possible to find an association of the most important risk factors with the prevalence of atherosclerosis (by angiography) and with the short-term
incidence of cardiovascular events (by a prospective study). We therefore investigated a large cohort of angiographed patients with normal fasting glucose (NFG) or impaired fasting glucose (IFG) or with type 2 diabetes and tried to answer three questions: which lipid risk factor(s) 1) distinguish diabetic individuals from those with impaired and with normal fasting glucose, 2) are associated with coronary atherosclerosis, and, most importantly, 3) are predictive of future vascular events.

**RESEARCH DESIGN AND METHODS** — Between September 1999 and October 2000, we enrolled 750 consecutive Caucasian patients who were referred to coronary angiography for the evaluation of either suspected or established CAD solely on the basis of the clinical indication made by the referring physicians. The recruitment period of exactly 1 year was chosen to exclude seasonal bias on risk factors and disease presentation.

At baseline, height and weight as well as waist and hip circumferences were recorded, information on conventional coronary risk factors (history of smoking, hypertension, established diabetes, and a family history of atherosclerotic disease) was obtained by a standardized interview, and systolic/diastolic blood pressure was measured by the Riva-Rocci method under resting conditions in a sitting position at the day of hospital admission.

Patients were categorized into subgroups with NFG <5.6 mmol/l (n = 272), with IFG ≥5.6 and ≤6.9 mmol/l (n = 314), or with type 2 diabetes (n = 164), which was defined according to World Health Organization criteria (16). Among the 164 patients with type 2 diabetes, 70 were not receiving any antidiabetic medication, and 57, 53, 40, and 2 were receiving, alone or in combination, sulfonylurea, biguanides, insulin, and α-glucosidase inhibitors, respectively.

Coronary angiography was performed at baseline using the Judkins technique as described previously (17,18).

**Prospective study**

After a mean (±SD) period of 2.3 ± 0.4 years, the 750 patients underwent a follow-up investigation. Fatal and nonfatal cardiovascular end points were recorded, encompassing coronary death (fatal myocardial infarction, sudden cardiac death, mortality from congestive heart failure due to CAD), fatal ischemic stroke, nonfatal myocardial infarction, nonfatal stroke, and the need for coronary artery bypass grafting, percutaneous coronary intervention, or noncoronary revascularization.

Time and causes of death were regularly obtained from a national survey (Statistik Austria, Vienna, Austria) or from hospital records. Among survivors, myocardial infarction was diagnosed in the presence of at least two of three criteria: 1) standard electrocardiographic criteria, 2) ischemic cardiac pain, and 3) creatinine kinase isoenzyme MB activity of at least twice the upper limit of normal. Stroke was defined as a neurological deficit lasting longer than 48 h with a confirmative computer tomography or magnetic resonance image. Angioplasty and vascular surgery were considered as end points unless they were planned as a consequence of the baseline angiography and therefore were not "future" events. The Ethics Committee of the University of Innsbruck approved the present study, and all participants gave written informed consent.

**Analytical procedures**

Laboratory analyses were performed from venous fasting plasma as described previously (17). LDL cholesterol was measured directly with QuantiopLDL (Immuno). The LDL peak particle diameter was measured by PAGE (Labomed, Germany). GHb was determined by high-performance liquid chromatography on a Menarini-Arkay KDK HA 8140 (Japan), and glucose levels were measured enzymatically from venous fluoride plasma by the hexokinase method (Roche) on a Hitachi 717 or 911. Serum insulin was measured by an enzyme immunoassay on an AIA 1200 ( Tosoh). As a measure of insulin resistance (19), we used the homeostasis model assessment, which has been shown to be a reliable estimate of insulin resistance both among nondiabetic patients and patients with type 2 diabetes (20).

**Statistical analysis**

Differences in baseline demographic and clinical characteristics between NFG, IFG, and type 2 diabetes were assessed with the Mantel-Haenszel χ² test for trend for categorical variables and ordered Jonckheere-Terpstra test for continuous variables. Factor analysis by the method of principal components was applied to extract initial factors from the lipid profiles of our patients. Only factors with an eigenvalue >1 were retained in the analysis. The initial factors were subjected to Varimax rotation to facilitate their interpretation and then were introduced as continuous variables in further cross-sectional and prospective analyses. To evaluate the association of risk factors with the presence of significant stenoses and their predictive power for the incidence of vascular events, we applied multivariate logistic regression analysis and Cox regression analysis, respectively. For these analyses, continuous variables were z-transformed and standardized adjusted ORs were calculated, indicating the change of relative odds associated with a 1-unit change of the z-transformed variable, i.e., with 1 SD of the original variable. Significance was defined as a two-tailed P value <0.05. All statistical analysis was performed with the software package SPSS 12.0 for Windows.

**RESULTS**

Factor analysis

By the factor analysis, we extracted two factors from the lipid profiles of our patients. Factor 1 explained 39.1% and factor 2 explained an additional 38.3% of the variance in the lipid variables measured. Correlation coefficients for the correlation between factor 1 and triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol, apolipoprotein A1, apolipoprotein B, and LDL peak particle diameter were 0.29, 0.96, 0.91, 0.18, 0.24, 0.90, and −0.08, respectively. For factor 2, the respective correlation coefficients were −0.69, 0.12, 0.15, 0.90, 0.77, −0.23, and 0.84. Thus, total cholesterol, LDL cholesterol, and apolipoprotein B loaded high on factor 1, which therefore weights LDL; triglycerides, HDL cholesterol, apolipoprotein A1, and LDL peak particle diameter loaded high on factor 2, which thus weights HDL.

Pattern of dyslipidemia in diabetic and nondiabetic coronary patients

Table 1 summarizes the demographic and lipid characteristics of our patients. The percentage of patients receiving lipid-lowering drugs increased from patients...
with NFG (27.6%) over patients with IFG (34.4%; \( P < 0.001 \)) to patients with type 2 diabetes (41.5%; \( P = 0.011 \)). For all 750 patients, triglycerides steadily increased (\( P < 0.001 \)) as well as the LDL peak particle diameter (\( P < 0.001 \)) steadily and significantly decreased from patients with NFG, over patients with IFG, to patients with type 2 diabetes. Table 1 and Fig. 1 present the data separately for patients on and off lipid-lowering drugs.

### Table 1—Baseline and lipid characteristics for patients with NFG, IFG, or type 2 diabetes

<table>
<thead>
<tr>
<th>Patients not receiving lipid-lowering drugs</th>
<th>Patients receiving lipid-lowering drugs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFG†</td>
<td>IFG‡</td>
</tr>
<tr>
<td>( n )</td>
<td>197</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61 ± 11</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>60.9</td>
</tr>
<tr>
<td>Significant coronary stenosis ≥50%</td>
<td>48.2</td>
</tr>
<tr>
<td>Any lesion of the coronary arteries (%)</td>
<td>72.1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>38.6</td>
</tr>
<tr>
<td>Smoking history</td>
<td>50.8</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/l)</td>
<td>5.1 ± 0.3</td>
</tr>
<tr>
<td>GLb (%)</td>
<td>5.6 ± 0.5</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.74 ± 1.12</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.56 ± 0.93</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.80 ± 1.06</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>3.55 ± 0.93</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.35 ± 0.39</td>
</tr>
<tr>
<td>Apolipoprotein B (g/l)</td>
<td>1.14 ± 0.24</td>
</tr>
<tr>
<td>Apolipoprotein A1 (g/l)</td>
<td>1.51 ± 0.30</td>
</tr>
<tr>
<td>LDL peak particle diameter (Å)</td>
<td>260 ± 5</td>
</tr>
<tr>
<td>Factor 1</td>
<td>0.10 ± 0.1</td>
</tr>
<tr>
<td>Factor 2</td>
<td>0.31 ± 0.95</td>
</tr>
</tbody>
</table>

*From the 251 patients on lipid-lowering drugs, 229 were receiving statins, 16 were receiving fibrates, and 6 were receiving a combined therapy with statins and fibrates. No other lipid-lowering medication was taken. †NFG < 5.6 mmol/l. ‡IFG ≥ 5.6 mmol/l. HOMA-IR, homeostasis model assessment for insulin resistance.

#### Relation between the prevalence of coronary atherosclerosis and metabolic characteristics

Overall, the prevalence of significant stenoses (i.e., narrowings ≥50%) increased significantly (\( P \) for trend = 0.003) from patients with NFG (55.5%) over patients with IFG (60.8%) to patients with type 2 diabetes (69.5%). For the total study cohort, HDL cholesterol (OR 0.629 [0.527−0.759]; \( P < 0.001 \)), apolipoprotein A1 (0.628 [0.528−0.747]; \( P < 0.001 \)), and LDL peak particle diameter (0.782 [0.662−0.923]; \( P = 0.004 \)) were associated with the presence of significant stenoses in logistic regression analysis adjusting for age, sex, and use of lipid-lowering medication. Total cholesterol (1.024 [0.874−1.199]; \( P = 0.770 \)), LDL cholesterol (1.037 [0.887−1.214]; \( P = 0.647 \)), and apolipoprotein B (1.154 [0.987−1.350]; \( P = 0.072 \)) in contrast were not associated with the presence of significant stenoses in coronary angiography.

**Figure 1**—Lipid parameters in patients with NFG < 5.6 mmol/l, in patients with IFG ≥ 5.6 mmol/l, and in patients with type 2 diabetes (T2DM) (from left to right, respectively). □, patients not receiving lipid-lowering drugs; ■, patients receiving lipid-lowering medication. The bars denote SDs. PPD, peak particle diameter.
phy. Consistently, factor 2, but not factor 1, was associated with significant coronary stenoses (Fig. 2A), with standardized adjusted ORs of 0.651 (0.545–0.777; P < 0.001) and 1.040 (0.889–1.216; P = 0.623), respectively. Most importantly, only factor 2 (0.648 [0.464–0.904]; P < 0.001) and its constituents HDL cholesterol (0.508 [0.347–0.742]; P < 0.001) and apolipoprotein A1 (0.539 [0.371–0.782]; P = 0.001) were significantly associated with coronary stenoses in the subgroup of patients with type 2 diabetes, but not factor 1 (0.921 [0.677–1.251]; P = 0.597) or its constituents.

**Prospective study**

During a mean (± SD) follow-up time of 2.3 ± 0.4 years, we recorded 95 vascular end points (encompassing coronary death [n = 26], fatal ischemic stroke [n = 3], nonfatal myocardial infarction [n = 10], nonfatal stroke [n = 10], coronary artery bypass grafting [n = 15], percutaneous coronary intervention [n = 14], and vascular surgery at the carotid or peripheral arteries [n = 17]). The overall incidence of vascular end points increased from 9.2% in patients with NFG over 12.1% in patients with IFG to 19.5% in patients with type 2 diabetes (P for trend = 0.007). After adjusting for age, sex, and use of lipid-lowering medication, type 2 diabetes was a strong predictor of vascular events in our population of coronary patients (1.839 [1.201–2.817]; P = 0.005). Also, factor 2 (0.757 [0.606–0.944]; P = 0.014) and, from the individual lipid parameters, triglycerides (1.172 [1.002–1.370]; P = 0.048) and LDL peak particle diameter (0.783 [0.628–0.976]; P = 0.029) were significantly predictive for vascular events. In contrast, neither factor 1 (1.104 [0.898–1.357]; P = 0.347) nor any of its constituents (total cholesterol, LDL cholesterol, apolipoprotein B) were significantly associated with the incidence of vascular events. Importantly, factor 2 was a significant predictor of vascular events in the subgroup of patients with type 2 diabetes (0.708 [0.506–0.990]; P = 0.044). Like for the total cohort, factor 1 was not significantly associated with vascular events in the patients with type 2 diabetes (1.362 [0.985–1.883]; P = 0.061).

**CONCLUSIONS** — From our lipid data, a consistent picture arises. The major driving force for coronary atherosclerosis in patients with type 2 diabetes appears to reside in the lipid triad of low HDL, high triglycerides, and small dense LDL. We could demonstrate that this triad was 1) significantly associated with the categories of glycemia, 2) significantly associated with the angiographically defined prevalence of coronary atherosclerosis, and 3) significantly predictive for the incidence of clinical events of atherosclerosis. These data were obtained by the use of three novel approaches: factor analysis, the new classification of IFG by the American Diabetes Association, and a prospective study in angiographically characterized patients.

To characterize clusters of correlated parameters in the lipid profiles of our patients, we performed factor analysis. This is a mathematical technique by which a larger number of correlated variables can be reduced to a fewer “factors” that represent distinct attributes that account for a large proportion of the variance in the original variables. We could identify two factors: an LDL-related factor that weights total cholesterol, LDL cholesterol, apolipoprotein B and an HDL-related factor that (inversely) weights the severity of diabetic dyslipidemia.

The HDL-related factor, but not the LDL-related factor, was correlated to the
glycemic status. These results may suggest a possible mechanism for dyslipidemia: resistance to the antilipolytic effect of insulin leads to an exaggerated flux of free fatty acids into the liver (21). The increased supply of these molecules to the liver together with a resistance of the hepatic VLDL secretion to the inhibitory effects of insulin (22) ensue in hypertriglyceridemia. Via neutral lipid transfer, triglycerides enter LDL and HDL particles and are eventually removed from these particles by hepatic lipase, giving rise to both smaller LDL (small dense LDL) and smaller HDL, predominantly HDL₃ (23,24).

Of note, this is the first report on lipid values in patients with IFG according to the new definition recently put forth by the American Diabetes Association (25). Both among patients on and, even more importantly, among those off lipid-lowering drugs, triglycerides gradually increased and HDL cholesterol as well as LDL particle size gradually decreased from patients with NFG over those with IFG to those with type 2 diabetes. In parallel, homeostasis model assessment insulin resistance increased with worsening glycemic state. These results reflect the pathophysiological interrelation of insulin resistance, impairment of glucose homoeostasis, and diabetic dyslipidemia. Similar associations of diabetic dyslipidemia with glycemia have been reported earlier using the old cutoff value of 6.1 mmol/l for IFG (26).

The prevalence of significant stenoses at baseline gradually increased from NFG over IFG to type 2 diabetes, as did the incidence of vascular events. These data are in line with data from the Third National Health and Nutrition Examination (26) that indicate an increased cardiovascular risk for patients with IFG. We now present the first report on the prevalence of angiographic CAD in patients with IFG. Also, our study is the first investigation providing data on the incidence of vascular events among angiographically characterized patients with IFG.

The HDL-related factor, an estimate for the severity of diabetic dyslipidemia, was significantly associated with the presence of significant coronary stenoses among patients with NFG, IFG, and type 2 diabetes. This finding is well in line with reports from earlier studies not considering diabetes (17,18,27–29). In these investigations, HDL cholesterol and related lipoproteins as in our investigation were significantly associated with angiographic CAD. However, there are hardly any published data on the impact of lipids and lipoproteins on angiographic CAD in patients with diabetes (30).

In the prospective part of our study, the HDL-related factor was significantly predictive for the incidence of vascular events. The increased risk associated with a low HDL-related factor was carried predominantly by patients with diabetes. This is in line with observations from the Veterans Affairs HDL Intervention Trial where the beneficial effect of gemfibrozil was more pronounced in patients with diabetes (13). Earlier prospective studies have demonstrated that HDL cholesterol (6,31) and triglycerides (6,32) as well as triglyceride-rich particles (31,32) are significant predictors of cardiovascular events among patients with diabetes. Very recently, an inverse association between serum HDL cholesterol and mortality was demonstrated in a cohort of Brazilian type 2 diabetic patients (33). In contrast to these investigations, we enrolled patients characterized by coronary angiography. Our data indicate that in this high-risk setting, diabetic dyslipidemia significantly predicts cardiovascular events in as short a follow-up time as 2.3 years and therefore emphasize the key role of diabetic dyslipidemia in cardiovascular disease among patients with type 2 diabetes.

In contrast to the HDL-related factor, the LDL-related factor was neither significantly associated with glycemia nor with the presence of significant stenoses nor with the incidence of vascular events. A large body of evidence has established total and LDL cholesterol as important cardiovascular risk factors, in particular among patients with diabetes (2,6,34). However, in parallel to the results of our prospective study, no significant associations between high total or LDL cholesterol and the presence of CAD have been found in cross-sectional angiographic investigations (27,28,35). Among our coronary patients, 31.3% were on statins. Drug-induced lowering of LDL cholesterol may have contributed to the lack of an association between LDL cholesterol and cardiovascular disease in the present investigation. Further, from our investigation on 750 patients over 2.3 years, we cannot exclude that with the greater statistical power of a larger study or a longer duration of follow-up a significant association between LDL cholesterol and vascular events could be demonstrable in diabetic coronary patients. However, our data suggest that in today’s setting of effective LDL cholesterol lowering with statins, HDL cholesterol, triglycerides, and LDL particle diameter are the predominant lipid risk factors determining the fate of coronary patients with diabetes.

Our investigation is characterized by the limitations and strengths of studies enrolling patients undergoing coronary angiography. This is a selected population of high-risk patients; our results therefore are not necessarily applicable to low-risk individuals. However, the cohort we chose to investigate allowed us to study the impact of lipids both on the presence of angiographic CAD and on the incidence of vascular events.

Our data suggest that, in the era of successful statin treatment of elevated LDL cholesterol, specific treatment of diabetic dyslipidemia is most promising to further reduce cardiovascular events among patients with diabetes. With well-tolerated extended-release formulations of niacin, it is now possible to effectively improve the typical pattern of lipid abnormalities observed in patients with type 2 diabetes (36). Moreover, inhibition of cholesterol ester transfer protein activity with torcetrapib has recently been shown to increase HDL cholesterol by as much as 106% (37). Clinical end point trials are now warranted to investigate the efficacy and safety of such drugs in addition to statin treatment to reduce cardiovascular events in patients with diabetes.

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Lipid risk factors in diabetes and IFG

References


34. Howard BV, Robbins DC, Sievers ML, Lee

