Reduced IGFBP-1 Is Associated With Thickening of the Carotid Wall in Type 2 Diabetes

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OBJECTIVE — The aim of the present study was to assess the role of the insulin-like growth factor (IGF) system and lipids in predicting the carotid intima-media thickness (IMT) in type 2 diabetes.

RESEARCH DESIGN AND METHODS — A total of 239 type 2 diabetic participants in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study (76 women) aged 50–75 years were examined before fenofibrate intervention. Patients underwent carotid ultrasonography for determination of IMT. IGF-I, IGF binding protein 1 (IGFBP-1), IGFBP-3, cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, apolipoprotein B (apoB), lipoprotein(a) (Lp(a)), glucose, HbA_{1c}, and C-peptide were measured in fasting samples. Patients were divided in groups without ($n = 168$) and with ($n = 71$) clinical cardiovascular disease (CVD).

RESULTS — Partial correlations adjusted for age, sex, BMI, and diabetes duration showed an inverse association of IGFBP-1 with C-peptide ($r = -0.24$, $P = 0.018$) and with maximal IMT ($r = -0.42$, $P < 0.001$), whereas IGF I and IGFBP-3 correlated positively with several risk-promoting lipid parameters. In linear regression analysis controlling for age, sex, BMI, diabetes duration, and presence or absence of oral antihyperglycemic or insulin medication, determinants of IMT were age, IGFBP-1, pulse pressure, Lp(a), diabetes duration, and insulin treatment. IGFBP-1 persisted in the model for subjects with CVD.

CONCLUSIONS — In summary, a decrease in IGFBP-1 is a marker of carotid IMT thickening in patients with type 2 diabetes.

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The mortality and morbidity from cardiovascular disease (CVD) is three to four times increased in patients with type 2 diabetes and accounts for ~70% of mortality in this patient group (1). At the time of diabetes diagnosis, many patients already have clinical macrovascular disease. However, to understand the mechanisms in the development of atherosclerosis, it is essential to examine diabetic subjects in whom atherosclerosis is still incipient and nonsymptomatic.

Measurement of carotid intima-media thickness (IMT) using high-resolution B-mode ultrasonography is a noninvasive, well-validated method to assess early CVD (2–4). It shows strong correlations with known risk factors of CVD (5–7) and, more importantly, predicts clinical cardiovascular events such as myocardial infarction and stroke in various patient groups (8,9). In several studies, carotid intima-media is clearly thicker in patients with type 2 diabetes than in age- and sex-matched nondiabetic subjects (10,11). Factors showing consistent correlation with IMT have been age, diabetes, and hypertension. Data on the relationship between different lipid parameters and IMT have been inconsistent (7,11,12).

Insulin resistance is an important feature of type 2 diabetes and has been demonstrated to correlate with IMT in type 2 diabetes in some (13,14) but not in all studies (11). Closely related to insulin resistance, the insulin-like growth factor (IGF) system has been suggested to contribute to atherosclerosis (15–17). IGF-I has insulin-like effects and growth-promoting actions mediated through the IGF-I receptor closely similar to the insulin receptor (18). The main reservoir of IGF-I is in the inactive complex with IGF binding protein 3 (IGFBP-3) (19). IGFBP-1 exhibits diurnal variation, in contrast to the more stable IGFBP-2 and IGFBP-3, and is one of the major regulators of IGF availability in plasma (20). Insulin regulates IGF-I bioavailability by suppressing hepatic IGFBP-1 production, resulting in increased circulating free IGF-I concentration (21). IGFBP-1 is strongly related to insulin sensitivity (21). Growth hormone and/or IGF-I have been demonstrated to contribute to both microvascular and macrovascular complications of diabetes in several studies (reviewed in 22).

In light of these findings, we assessed the potential independent role of IGF-I and IGFBP-1 and IGFBP-3 together with conventional factors like lipid/apoprotein parameters and variables of glycemic con-

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Abbreviations: apoB, apolipoprotein B; CB, carotid bulb; CCA, common carotid artery; CVD, cardiovascular disease; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; FW, far wall; HOMA-IR, homeostasis model assessment of insulin resistance; ICA, internal carotid artery; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; IMT, intima-media thickness; Lp(a), lipoprotein(a); Max IMT, maximal intima-media thickness; OHA, oral antihyperglycemic agents.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

trol as determinants of the carotid IMT of middle-aged and elderly men and women with type 2 diabetes. We were particularly interested in determining whether determinants of IMT are similar in type 2 diabetic patients with and without clinical CVD.

RESEARCH DESIGN AND METHODS

Study subjects

Subjects for this study were recruited from participants in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study in Helsinki, Finland. The FIELD Study is a multinational study started in the beginning of 1998 in Australia, New Zealand, and Finland. A total of >9,000 patients with type 2 diabetes were randomly assigned to receive either placebo or micronized fenofibrate (200 mg/day) for 5 years. Subjects with type 2 diabetes aged 50–75 years and with S-cholesterol values 1.0–5.5 mmol/l and either S-triglycerides 1.0–5.0 mmol/l or S-cholesterol/HDL cholesterol ratio >4 were eligible for the study.

In the Helsinki Center, 270 patients were recruited for the FIELD main study. A total of 239 participants (76 women) volunteered for the substudy described herein. In 71 substudy participants, CVD had already been diagnosed (CVD is defined as any of the following: angina pectoris, previous coronary bypass grafting or balloon dilatation, stroke, transient ischemic attack, carotid endarterectomy, claudication, leg amputation, and peripheral arterial reconstruction or balloon dilatation).

All subjects signed informed consent forms. The protocol was approved by the ethical committee of the Helsinki University Central Hospital.

Laboratory analyses

All examinations were performed during the placebo run-in period of the FIELD Study before any fenofibrate intervention. Blood samples were obtained after an overnight fast. Cholesterol and triglyceride levels were measured in serum by automated enzymatic procedures. LDL cholesterol was measured after separating LDL fraction from fresh fasting sera by sequential ultracentrifugation; apolipoprotein B (apoB) level was determined by an immunochemical assay. Lipoprotein(a) (Lp(a)) was measured by turbidimetric immunoassay. P-glucose was measured using the Precision-G device. HbA_{1c} was measured with a DCA 2000 analyzer. Serum free insulin concentrations were determined by double-antibody radioimmunoassay after precipitation with polyethylene glycol. C-peptide was determined by radioimmunoassay.

IGF-I was determined from the serum samples using the DSL-10–5600 Active IGF-I Enzyme-Linked Immuno-Sorbent Assay Kit. The assay uses a modified version of the standard acid-ethanol extraction procedure.

IGFBP-1 concentration was determined by a two-site immunofluorometric assay, as described earlier (23), using two monoclonal antibodies, F34–15C9 and F36–9G3.

The IGFBP-3 against which the monoclonal antibodies were generated was produced by recombinant DNA technology in *Escherichia coli* bacteria (24). The assay uses monoclonal antibody F42–1B6 as the solid-phase antibody and monoclonal antibody F41–5C11 as the Eu-labeled tracer. The assay had no cross-reactions with the other human IGFBPs or IGFs.

Albumin excretion rate was measured from three consequent overnight urinary collections. The median of the three collections was used to determine normoalbuminuria (<20 μg/min), microalbuminuria (20–200 μg/min), or macroalbuminuria (>200 μg/min).

We applied the homeostasis model assessment of insulin resistance (HOMA IR) (25) in subjects without insulin treatment (n = 182) using the following formula: HOMA IR = fasting insulin (mU/ml) × fasting glucose (mmol/l)/22.5.

Carotid sonography

Ultrasound scannings of carotid arteries were performed with a Hewlett Packard Image Point M2410A ultrasound system equipped with a high-frequency 10-MHz linear array transducer. Scannings were videotaped with a Panasonic AG-MD830E PAL S-VHS videocassette recorder. All ultrasound examinations were performed by one physician (E.L.). The ultrasound examination protocol has been described in detail elsewhere (26). In short, longitudinal images were displayed bilaterally for *1*) the distal 1 cm of the common carotid artery (CCA), *2*) the entire carotid bulb (CB), and *3*) the proximal 1 cm of the internal carotid artery (ICA). For the CCA and the CB, three projections (anterolateral, lateral, and posterolateral) were recorded. For the ICA, a single, best-visualized angle was used.

A single reader at Oy Jurilab (Kuopio, Finland), performed the IMT measurements using a personal computer with a video frame grabber interfaced to a Panasonic PAL S-VHS videocassette recorder. Prosound software was used to measure the IMTs at a total of 28 sites. The following variables were derived: mean IMT, maximal IMT, and minimal IMT. All outcome variables were first calculated for each subject.

The mean of maximal IMT (Max IMT) measurements over 28 sites was chosen for the primary outcome variable. Secondary outcome variables were *1*) the average of mean IMT (Mean IMT), *2*) average of mean far wall (FW), *3*) the mean of maximum for CCA, *4*) the mean of maximum for CB, and *5*) the mean of maximum for ICA. The ultrasound examination was performed for 236 study subjects.

The intra-observer repeatability for Max IMT was 0.994 (SE 0.0152). The intra-reader repeatability for Max IMT was 0.996 (SE 0.0082).

Statistical methods

Parameters with skewed distributions were log-transformed for statistical analysis. Pearson and partial Pearson correlation coefficients and one-way ANOVA were used to demonstrate relationships between variables.

Linear regression analysis was performed for the whole study cohort and for subgroups with or without CVD to explain variation in Max IMT. To control for age, sex, diabetes duration, BMI, oral antihyperglycemic agents (OHA), and insulin treatment, these parameters where entered in the regression analyses in step 1. Parameters with even a weak correlation ($r > 0.200$) with Max IMT, but independent from each other, were entered in step 2. Parameters were removed until the best-fitting model was achieved. All statistical analyses were performed with SPSS for Windows software (version 9; SPSS, Chicago, IL).

RESULTS

Subject characteristics

The characteristics of the study subjects are shown in Table 1. The mode of diabe-

Table 1—*Characteristics of the study subjects*

	No CVD	With CVD	*P*
Age (years)	60.8 ± 6.5	63.2 ± 6.5	0.009
N (men/women)	168 (111/57)	71 (52/19)	—
BMI (kg/m^2)	30.4 ± 5.4	31.0 ± 5.6	NS
Waist-to-hip ratio	0.93 ± 0.07	0.94 ± 0.07	NS
Triglycerides (mmol/l)	1.8 ± 0.8	1.8 ± 0.8	NS
Cholesterol (mmol/l)	5.0 ± 0.7	5.1 ± 0.7	NS
LDL cholesterol (mmol/l)	3.1 ± 0.7	3.3 ± 0.6	NS
HDL cholesterol (mmol/l)	1.2 ± 0.3	1.1 ± 0.3	NS
ApoB (mg/dl)	101 ± 23	104 ± 25	NS
Lp(a) (mg/l)	136 ± 15	179 ± 32	NS
IGF-I (nmol/l)	142 ± 65	150 ± 62	NS
IGFBP-1 (μg/l)	85.7 ± 75	87.1 ± 71	NS
IGFBP-3 (μg/l)	4,463 ± 1,623	4,720 ± 1,559	NS
Fasting P-glucose (mmol/l)	7.9 ± 2.3	8.0 ± 1.7	NS
HbA_{1c} (%, normal range 4–6)	7.3 ± 1.3	7.5 ± 1.4	NS
C-peptide (nmol/l)	1.0 ± 0.8	1.2 ± 1.1	NS
Microalbuminuria or macroalbuminuria	12%	43%	<0.001

Data are means ± SD or %. Group 1: subjects without clinical CVD. Group 2: subjects with clinical CVD: history of coronary artery disease, transient ischemic attack, stroke, claudication, or leg amputation.

tes treatment was diet only in 34 (14%), OHA in 149 (62%), insulin only in 11 (5%), and a combination of OHA and insulin in 45 (19%) subjects.

We divided the subjects in two groups according to the presence of clinical CVD (defined in RESEARCH DESIGN AND METHODS). These groups were very similar, except that those with CVD were slightly older ($P = 0.009$) and had somewhat longer diabetes duration (8.7 vs. 7.3 years, NS). The proportion of women was 27% in subjects with CVD and 34% in subjects without CVD. The difference in smoking habits was not significant (data not shown). A history of arterial hypertension was present in 61% of subjects without CVD and 62% of subjects with CVD. Mean blood pressure values for the groups were 144/88 and 146/86 mmHg, accordingly.

The concentrations of IGF-I, IGFBP-1, and IGFBP-3 did not significantly differ between the two groups. Glycemic control was comparable (mean HbA_{1c} 7.3 vs. 7.5%) in both groups. The lipid and apoprotein values were comparable in the two groups. As expected, albuminuria was more common in those with CVD. IGFBP-1 concentration increased with age ($r = 0.217$, $P = 0.001$) and correlated inversely with BMI ($r = -0.386$, $P < 0.001$) and waist circumference ($r = 0.438$, $P < 0.001$), whereas IGF I and IGFBP-3 did not correlate with these parameters. Neither IGF-I, IGFBP-1, nor IGFBP-3 correlated with pulse pressure or albuminuria.

IGF I, IGFBP-1, and IGFBP-3 concentrations were dependent on the mode of treatment. Mean values for subjects with diet treatment, OHA, combination of OHA and insulin, and only insulin treatment for IGF-I were 157, 145, 137, and 116 nmol/l, correspondingly. For IGFBP-1, the corresponding mean concentrations were 49, 85, 95, and 168 μg/l, and for IGFBP-3, the mean concentrations were 4,529, 4,594, 4,526, and 3,888 μg/l. The difference between sexes was significant for IGFBP-1 and IGFBP-3 concentrations (data not shown). When considering the presence of components of the metabolic syndrome—long waist circumference, hypertriglyceridemia, low HDL cholesterol, high blood pressure, diabetes—as defined by the third Adult Treatment Panel (27), the concentration of IGFBP-1 decreased steadily with increasing prevalence of these components, from a mean of 144 μg/l in patients with only diabetes to 54 μg/l in patients with all five components ($P < 0.001$).

Relationship between clinical and biochemical characteristics and IMT

The Max IMT was significantly thicker in men than in women (1.32 vs. 1.24 mm, $P = 0.038$). In patients with CVD, Max IMT was significantly thicker than in those without clinical CVD (mean of Max IMT 1.39 vs. 1.30 mm; $F = 7.62$, $P = 0.006$). Similar significant differences were noted for Mean IMT (1.10 vs. 1.03 mm; $F = 7.98$, $P = 0.005$), FW IMT (1.11 vs. 1.03 mm; $F = 7.50$, $P = 0.007$), and CCA IMT (1.26 vs. 1.16 mm; $F = 12.1$, $P = 0.001$). Age, systolic blood pressure, and pulse pressure were strongly correlated with Max IMT in both groups (r values between 0.254 and 0.418, P values between <0.001 and 0.034). The duration of diabetes correlated with Max IMT in subjects with CVD ($r = 0.358$, $P = 0.002$). Measures of glucose metabolism—C-peptide, P-glucose, or HbA_{1c}—did not correlate with Max IMT. Overnight urinary collection was received from 232 subjects; of these, 193 were normoalbuminuric, 34 had microalbuminuria, and 5 had macroalbuminuria. The presence of microalbuminuria or macroalbuminuria was strongly associated with Max IMT ($P = 0.001$).

We also calculated HOMA IR for the subjects without insulin treatment ($n = 182$). IGFBP-1 and HOMA IR were strongly inversely correlated ($r = -0.437$, $P < 0.001$). This correlation remained highly significant, even when adjusted for age, sex, BMI, and diabetes duration ($r = -0.304$, $P < 0.001$). HOMA IR was, however, not correlated to IMT (data not shown).

Partial correlation analysis for the entire group, adjusted for age, sex, BMI, and diabetes duration, revealed a significant inverse correlation between IGFBP-1 and Max IMT ($r = -0.241$, $P = 0.018$) and IGFBP-1 and C-peptide ($r = -0.415$, $P = 0.000$). Correlations between IGFBP-1 and the other IMT values were also significant, except for ICA IMT (mean IMT $r = -0.571$, $P = 0.001$; CCA IMT $r = -0.442$, $P = 0.014$; CB IMT $r = -0.590$, $P = 0.001$; and FW IMT $r = -0.571$, $P = 0.001$). Because the type of treatment influenced the IGF system in our study, as also reported earlier (28), we repeated this analysis including also presence of oral or insulin medication. The relationship between IGFBP-1 and Max IMT remained significant in the entire study group ($r = -0.135$, $P = 0.041$) and in the subgroup with CVD ($r = -0.258$, $P = 0.038$).

In the group with clinical CVD, when controlling for age, sex, BMI, and diabetes duration, the parameters significantly associated with IMT in order of importance

Table 2—*Partial Pearson correlation of Max IMT with selected variables*

	No CVD		With CVD	
	r	*P*	*r*	*P*
Glucose*	0.000	0.998	0.197	0.296
HbA_{1c}	−0.081	0.532	0.252	0.179
C-peptide*	0.055	0.669	0.062	0.745
Pulse pressure	0.184	0.153	0.367	0.046
Total cholesterol	0.020	0.876	0.444	0.014
Triglycerides*	−0.199	0.122	0.281	0.132
HDL cholesterol*	0.041	0.749	−0.150	0.430
LDL cholesterol	0.071	0.584	0.491	0.006
ApoB*	0.042	0.748	0.542	0.002
Lp(a)*	0.283	0.026	0.034	0.859
IGF-I*	0.123	0.338	0.047	0.804
IGFBP-1*	−0.153	0.235	−0.614	0.000
IGFBP-3	0.003	0.982	0.147	0.439

Adjusted for age, sex, BMI, and duration of diabetes. *Log-transformed to achieve normal distribution.

were IGFBP-1, apoB, LDL cholesterol, total cholesterol, and pulse pressure (Table 2). In subjects without CVD, IGFBP-3 correlated inversely with Max IMT ($r = -0.168$, $P = 0.032$), but this correlation disappeared after adjustment for age, sex, BMI, and diabetes duration. Lp(a) was the only parameter significantly associated with IMT in patients without CVD.

To further characterize the role of the IGF system, we calculated the correlations between IGF parameters and different parameters of glucose and lipid metabolism (Table 3). IGF-I and IGFBP-3 were significantly correlated with LDL cholesterol and Lp(a). In addition, IGFBP-3 correlated significantly with total cholesterol and apoB. There was no significant association between IGFBP-1 and any of the lipoprotein parameters. There was a strong inverse relationship between IGFBP-1 and C-peptide. Parameters of glycemic control did not correlate with the concentrations of IGF-I, IGFBP-1, and IGFBP-3.

Linear regression analyses

To establish independent determinants of Max IMT, we performed a linear regression analysis controlled for age, sex, BMI, presence or absence of OHA or insulin medication, and diabetes duration initially for the entire study group. In the final model that explained 28.3% of variation of Max IMT (adjusted multiple $R^2 = 0.283$), the most important determinants were age (standardized coefficient $\beta = 341$, $P < 0.001$), IGFBP-1 (−0.209, $P = 0.017$), pulse pressure (0.216, $P = 0.023$), and Lp(a) (0.185, $P = 0.032$). Also, diabetes duration and insulin treatment remained in this model but did not reach statistical significance alone.

Similarly adjusted linear regression analyses were also performed for both subgroups. The model for subjects without CVD explained 34.8% of variation in Max IMT. The main determinants were age (standardized coefficient $\beta = 0.429$, $P < 0.001$) and albuminuria (0.323, $P = 0.002$). The other determinants remaining in the model, but not individually significant, were Lp(a), insulin treatment, diabetes duration, and smoking, in order of importance.

In the model for subjects with CVD, of the included parameters (age, sex, diabetes duration, BMI, OHA, insulin treatment, apoB, HbA_{1c}, albuminuria, IGFBP-1), only age (standardized coefficient $\beta = 0.351$, $P = 0.003$), DM duration (0.246, $P = 0.034$), IGFBP-1 (−0.183, $P = 0.092$), and sex (−0.162, P 0.138) remained in the model. This model explained 23.6% of Max IMT variation in subjects with CVD.

CONCLUSIONS — The novel finding of this study is that a decrease of IGFBP-1 is an important marker of carotid IMT in patients with type 2 diabetes. This association was independent of lipid metabolism, because IGFBP-1 concentration did not correlate with any of the investigated lipid or apoprotein parameters. IGFBP-1 correlated with all the IMT parameters except ICA IMT.

This study confirmed the previous results that age, diabetes duration, and blood pressure are important determinants of carotid IMT in type 2 diabetes. The presence of albuminuria was strongly related to IMT in accordance with previous studies (6). The duration of diabetes correlated significantly with carotid IMT likewise in previous studies (29). The correlation between Max IMT and diabetes duration was significant in subjects with CVD, and in subjects without CVD, there was a clear trend for similar association.

Total, LDL, and HDL cholesterol have failed to correlate with IMT in patients with type 2 diabetes in several studies (30), although these factors generally correlate with IMT in subjects without diabetes. This probably reflects the epiphenomenon that diabetes itself is a very strong CVD risk factor. In our study, total and LDL cholesterol were associated with IMT only in patients with clinical CVD but not in the group without CVD. After adjustment for age, sex, diabetes du-

Table 3—*Partial correlation between IGF-I, IGFBP-1, IGFBP-3, and glucose and lipid metabolism*

	IGF-I		IGFBP-1		IGFBP-3	
	r	*P*	*r*	*P*	*r*	*P*
Triglycerides*	−0.032	0.758	−0.055	0.592	0.058	0.574
Cholesterol	0.099	0.338	−0.072	0.486	0.254	0.013
LDL cholesterol	0.226	0.027	−0.130	0.206	0.292	0.004
HDL cholesterol*	−0.140	0.174	0.084	0.417	−0.020	0.849
ApoB*	0.150	0.146	−0.197	0.054	0.234	0.022
Lp(a)*	0.204	0.047	−0.076	0.463	0.235	0.021
Glucose*	−0.142	0.169	0.158	0.123	0.045	0.661
HbA_{1c}	−0.171	0.096	−0.041	0.694	−0.050	0.628
C-peptide*	0.071	0.494	−0.415	0.000	−0.080	0.438

Adjusted for age, BMI, and duration of diabetes. *Log-transformed to achieve normal distribution.

ration, and BMI, the typical features of diabetic dyslipidemia, elevated triglycerides, and low HDL cholesterol were not associated with IMT in either of the groups.

The inclusion criteria of the FIELD Study excluded subjects with high serum cholesterol levels (>5.5 mmol/l), aiming to have a typical diabetic dyslipidemia. The lipid values in our cohort are slightly better than baseline values in the U.K. Prospective Diabetes Study (UKPDS) and Diabetes Atherosclerosis Intervention Study (DAIS) (31,32). Therefore, the power of lipoproteins as determinants of IMT may be underestimated. However, both apoB and LDL cholesterol correlated with IMT in subjects with clinical CVD. Interestingly, Lp(a) correlated significantly with Max IMT. The association of Lp(a) and IMT has been detected previously in various patient groups (7,33). In the 117 Japanese type 2 diabetes subjects (7), serum Lp(a) level correlated significantly with carotid IMT and plaque count; in addition, IMT and Lp(a) were significantly associated with presence of cerebrovascular disease but not coronary heart disease.

Reduced IGFBP-1 concentration was one of the main determinants of IMT in the linear models adjusted for age, sex, BMI, and diabetes duration. IGFBP-1 levels have been reported to be higher in patients with type 2 diabetes (34) and lower in subjects with impaired glucose tolerance compared with healthy subjects (35). IGFBP-1 fluctuates rapidly in human plasma due to insulin-regulated (attenuated) IGFBP-1 transcription (18). The inverse relationship of IGFBP-1 with insulin resistance, cardiovascular risk factors, and morbidity has been almost uniformly detected in previous studies.

IGFBP-1 levels have correlated negatively with cardiovascular risk factors such as low HDL cholesterol, triglycerides, hypertension, insulin, proinsulin, BMI, and waist-to-hip ratio both in type 2 diabetic and healthy subjects (15,21,35) and positively with insulin sensitivity (21,35). The lack of significant correlations between IGFBP-1 and individual cardiovascular risk factors in our study may be due to the rather small size of the study cohort. However, when the risk factors were clustered into metabolic syndrome, the association became significant. Likewise, in earlier studies (21,35), we found an inverse association between HOMA IR and IGFBP-1 and between C-peptide and IGFBP-1, indicating that a low IGFBP-1 concentration is a marker of insulin resistance. Therefore, the inverse relationship of IGFBP-1 with carotid IMT may not be due to a direct contribution by IGFBP-1 to the thickening of the carotid wall but may be an epiphenomenon of insulin resistance.

We found that IGF-I and IGFBP-3 correlated positively with LDL cholesterol and Lp(a) after controlling for age, sex, BMI, and diabetes duration. IGFBP-3 also correlated with total cholesterol and apoB. In our study, however, IGF-I and IGFBP-3 did not correlate with either carotid IMT or the presence of CVD.

In growth hormone–deficient adults, IGF-I concentrations have been reported to be inversely correlated with carotid IMT; moreover, IMT thickening was reversible and could be corrected by growth hormone substitution (36). These data suggest a beneficial effect of IGF-I on the vasculature. In contrast, the correction of growth hormone overproduction in acromegalic patients also resulted in reversion of IMT thickening (37). Therefore, the influence of the IGF-system on atherosclerosis is complex and may be substantially modulated by the metabolic state.

In summary, the inverse relationship of IGFBP-1 with IMT reinforces the role of IGFBP-1 as a marker of insulin resistance and cardiovascular risk in patients with type 2 diabetes. The associations of IGF-I and IGFBP-3 with dyslipidemia support the hypothesis that an activated growth hormone–IGF axis might be one of the factors behind the increased risk of CVD in the metabolic syndrome.

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