Endothelial Function Varies According to Insulin Resistance Disease Type

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OBJECTIVE — We examined the relationship between insulin resistance and vascular function in three insulin-resistant states (type 2 diabetes, non-HIV lipodystrophic diabetes, and nondiabetic polycystic ovary syndrome [PCOS]) and in healthy control subjects.

RESEARCH DESIGN AND METHODS — The population included 12 women with type 2 diabetes, 6 with lipodystrophic diabetes, 10 with PCOS, and 19 healthy female subjects. Metabolic measures included insulin sensitivity by the homeostasis model assessment, lipids, free fatty acids, and adiponectin. High-resolution B-mode ultrasound was used to determine endothelium-dependent and -independent vasodilation.

RESULTS — Type 2 diabetic, liposdystrophic, and PCOS subjects were insulin resistant compared with control subjects ($P = 0.001$). Flow-mediated vasodilation was reduced in diabetic (3.4 ± 1.3%) compared with control (7.3 ± 1.1%) subjects but not in lipodystrophic (7.7 ± 1.2%) or PCOS (9.9 ± 0.7%) subjects ($P = 0.005$). Nitroglycerin-mediated vasodilation was attenuated in both diabetic (15.2 ± 2.0%) and lipodystrophic (16.7 ± 3.6%) subjects compared with healthy control (24.6 ± 2.4%) and PCOS (23.2 ± 1.8%) subjects ($P = 0.019$). Insulin resistance, free fatty acids, adiponectin, or C-reactive protein did not associate with vascular dysfunction.

CONCLUSIONS — Among these different types of patients with insulin resistance, we found abnormal endothelium-dependent vasodilation only in the patients with type 2 diabetes. We postulate that variations in the mechanism of insulin resistance may affect endothelial function differently than glucose homeostasis.

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Insulin resistance, typically defined by impairment of insulin-mediated actions on glucose uptake, affects a wide range of tissues, including adipose tissue, skeletal muscle, and the vascular endothelium. Insulin, via a sequence of intracellular signals, activates endothelial nitric oxide (NO) synthase (1) and increases production of NO. Reductions in the bioavailability of NO are associated with atherogenesis. Impaired insulin action, when assessed by fasting serum insulin levels or the homeostasis model assessment of insulin resistance (HOMA-IR) (2,3), is associated with atherosclerosis and an increased risk of myocardial infarction. Insulin resistance is associated with endothelial dysfunction (4) and may serve as a link between insulin resistance and atherosclerosis.

Insulin resistance, however, is not a single entity and occurs as a consequence of a variety of mechanisms and disparate clinic presentations, unified phenotypically by impaired insulin-mediated glucose uptake. Because the mechanisms of insulin resistance vary in different conditions, its impact on other tissues remains unclear. Determining the effect of various insulin-resistant states on endothelial function may provide insight in NO bioavailability in each disease and contribute to our understanding of a greater prevalence of atherosclerosis in insulin-resistant patients.

Accordingly, we sought to investigate the role of insulin resistance on endothelial function in three distinct populations of insulin-resistant women (polycystic ovary syndrome [PCOS], type 2 diabetes, and lipodystrophic diabetes) compared with healthy subjects. We also measured a marker of inflammation (C-reactive protein [CRP]) and two adipokines (adiponectin and free fatty acids) to determine whether these factors, known to be abnormal in insulin resistance, may serve as mechanism of vascular dysfunction across insulin-resistant states.

RESEARCH DESIGN AND METHODS

— Forty-seven nonsmoking women, including 12 with type 2 diabetes, 10 with PCOS, 6 with non-HIV lipodystrophic diabetes, and 19 healthy control subjects, were recruited through newspaper advertisements and from the Joslin Diabetes Center. All subjects underwent screening of medical history, physical examination, and laboratory analysis, including complete blood count, serum electrolytes, glucose, blood urea nitrogen, and creatinine and total cholesterol and LDL cholesterol. Among the type 2 diabetic, PCOS, and healthy control subjects, those with hypertension, history of tobacco use, LDL or total cholesterol >75th percentile for age and sex, cardiovascular disease, or other significant disease and those who used thiazolidinediones were excluded. Women with PCOS had six or fewer menses per year in addition to hyperandrogenemia defined by either total testosterone >58 ng/dl (2 nmol/l) and/or nonsex hormone–binding globulin-bound testosterone (unbound testosterone) >15 ng/dl (0.5 nmol/l) levels >2 SDs above the mean value that established in reproductively normal women aged 18–40 years in the early follicular phase of the menstrual cycle. Other causes of anovulation and hyperan-

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Abbreviations: CoA, coenzyme A; CRP, reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; PCOS, polycystic ovary syndrome.

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

drogenemia were excluded by appropriate laboratory tests. Patients with lipodystrophic diabetes, because of their rarity, were enrolled despite extant atherosclerosis or risk factors (except for smoking) for atherosclerosis. The lipodystrophic subjects included two with familial partial lipodystrophy, two with Dunnigan's familial partial lipodystrophy, one with familial partial lipodystrophy (mandibuloacral dysplasia variety), and one with acquired lipodystrophy after dermatomyositis. One subject was blind and had renal insufficiency and peripheral arterial disease; this subject died 3 months after the study. One subject had renal insufficiency and died 1 year after the study. One subject had coronary artery disease. Two lipodystrophic subjects were taking ACE inhibitors, and they withheld these medications for 24 h before vascular testing. Diabetes medications were held on the day of study. Other potential subjects taking ACE inhibitors, angiotensin receptor blockers, or statins were excluded. All participants provided written, informed consent. The protocol was approved by the human research committees of the Joslin Diabetes Center and the Brigham and Women's Hospital.

Vascular reactivity studies

All subjects were studied in the morning in the postabsorptive state, fasting after the previous midnight. Cyclooxygenase inhibitors, alcohol, and caffeine were prohibited for 24 h before the study. Subjects were studied in a quiet, temperature-controlled, dimly lit room after resting supine for a minimum of 5 min. High-resolution B-mode ultrasonography of the brachial artery was performed using a Toshiba 270 SSA (Toshiba America Medical Systems, Tustin, CA) ultrasound machine and 7.5-MHz linear array probe. The brachial artery was imaged longitudinally just proximal to the antecubital fossa. Transducer position was adjusted to obtain optimal images of the near and far wall of the intima. Images were simultaneously recorded on super VHS video tape. The video output and electrocardiographic signal of the ultrasound machine were connected to a computer equipped with a Data Translation Frame-Grabber videocard, (Dataviz, Trumbull, CT). The "R" wave on the electrocardiogram served as a trigger to acquire frames at end diastole. After baseline image acquisition, a forearm sphygmomanometric cuff was inflated to suprasystolic pressure (200 mmHg) for 5 min. Upon cuff release, reactive hyperemia causes flow to increase through the brachial artery subserving the forearm. Flow-induced, endothelium-dependent vasodilation of the brachial artery was determined by acquiring images at 1 min after cuff deflation. Flow-mediated vasodilation at this time point is largely endothelium dependent and NO mediated and can be inhibited by administration of the NO synthase antagonist N^G-monomethyl-L-arginine (5). Ten minutes after cuff release, the brachial artery was imaged again to reestablish basal conditions. Then, to determine endothelium-independent vasodilation, subjects received 0.4 mg of nitroglycerin sublingually. The brachial artery was imaged 3 min later. Brachial artery blood flow velocity was determined via time-velocity integral measurement. Nitroglycerin was not administered if the systolic blood pressure was <110 mmHg or if the subject refused nitroglycerin, usually to avoid a severe headache during the second and third visits.

Laboratory analyses

Total, HDL, and LDL cholesterol; triglycerides; and blood glucose levels were measured by standard laboratory techniques. High-sensitivity CRP levels were measured using the Beckman LX-20 (Beckman Coulter, Brea, CA). This assay has been validated against the Dade Behring hsCRP method and has an inter- and intra-assay coefficient of variation (CV) of <8%. Adiponectin levels were measured using a sandwich enzyme-linked immunosorbent assay (Linco Research, St. Charles, MO) and had an inter- and intra-assay CV of <9%. Insulin levels were measured using a two-site immunoassay (Linco Research) with an inter- and intra-assay CV of <11%. Free fatty acids in serum were measured using reagents from Wako Diagnostics. Free fatty acids were measured based on the acylation of coenzyme A (CoA) by the fatty acids in the presence of added acyl-CoA synthetase (Wako Chemicals, Richmond, VA). The acyl-CoA produced is oxidized by added acyl-CoA oxidase generating hydrogen peroxide that is measured spectrophotometrically. The inter- and intra-assay CVs for this assay are between 3 and 7%. The HOMA-IR was calculated as fasting glucose times fasting insulin divided by 22.5 (6).

Statistical methods

Descriptive measures are reported as means ± SD. Experimental measures are reported as means ± SE. Demographic data, arterial diameter, reactive hyperemia, and flow- and nitroglycerin-mediated vasodilation were compared using ANOVA. Post hoc comparisons were made using Dunnett testing with the healthy control group as the referent. Correlation with Spearman's ρ analysis was performed to assess the effects of baseline characteristics and measured parameters on vascular function and insulin resistance. Statistical significance was accepted at the 95% confidence level ($P < 0.05$). All statistics were run on SPSS Base 11.0.04 (SPSS, Chicago, IL).

RESULTS — Baseline characteristics are presented in Table 1. Type 2 diabetic subjects were older than lipodystrophic diabetic, PCOS, and healthy control subjects. A1C was 7.8 ± 1.9% in the subjects with type 2 diabetes and 8.8 ± 2.3% in the subjects with lipodystrophy. Of 12 subjects with type 2 diabetes, glucose lowering was achieved in 7 with a sulfonylurea alone, in 2 with insulin alone, and in 3 with metformin and a sulfonylurea. All lipodystrophic subjects were taking high-dose insulin, and two were taking metformin. Total and LDL cholesterol levels, blood pressure, and BMI did not differ significantly among the groups. HDL cholesterol levels were lower and triglycerides levels were higher in each insulin-resistant group compared with healthy subjects. Insulin resistance, as measured by HOMA-IR, was greater in lipodystrophic (27.6 ± 16.4), PCOS (6.6 ± 1.9), and type 2 diabetic (6.1 ± 1.4) subjects compared with control subjects (2.3 ± 0.4) ($P = 0.001$, by ANOVA). Similarly, insulin levels and glucose levels were higher in the insulin-resistant groups compared with healthy control subjects. The insulin level and HOMA-IR in lipodystrophic subjects were more than twice that of any other group.

Flow-mediated vasodilation was reduced in type 2 diabetic (3.4 ± 1.3%) compared with healthy control (7.3 ± 1.1%) subjects but was unexpectedly preserved in subjects with lipodystrophy (7.7 ± 1.2%) and with PCOS (9.9 ± 0.7%) ($P = 0.005$ by ANOVA; Fig. 1). In post hoc testing, flow-mediated vasodilation was significantly reduced in subjects with type 2 diabetes when compared with healthy subjects ($P = 0.02$). This was not accounted for by differences in baseline arterial diameter. Baseline arterial diameter was similar in each group: 3.11 ± 0.12 mm in healthy control subjects, 3.27 ±

Table 1—*Baseline characteristics*

	Lipodystrophic subjects	PCOS subjects	Type 2 diabetic subjects	Control subjects	*P*
n	6	10	12	19	
Age (years)	47 ± 13	31 ± 6	56 ± 14*	41 ± 11	<0.001
Mean arterial pressure (mmHg)	96 ± 8	94 ± 9	108 ± 13	98 ± 12	>0.2
BMI (kg/m^2)	27 ± 3	30 ± 5	31 ± 7	26 ± 7	>0.2
Total cholesterol (mg/dl)	200 ± 47	192 ± 31	178 ± 37	172 ± 13	>0.2
LDL cholesterol (mg/dl)	101 ± 31	120 ± 26	99 ± 40	98 ± 23	>0.2
HDL cholesterol (mg/dl)	34 ± 8†	37 ± 9†	49 ± 14	61 ± 12	<0.001
Triglycerides (mg/dl)	311 ± 165†	171 ± 72*	153 ± 95	70 ± 39	<0.001
Insulin (μU/ml)	58 ± 85*	28 ± 22	14 ± 12	10 ± 8	0.016
Glucose (mg/dl)	191 ± 113†	88 ± 9	156 ± 68†	88 ± 18	<0.001
HOMA-IR	27.6 ± 16.4†	6.6 ± 1.9*	6.1 ± 1.4*	2.3 ± 0.4	0.001
Adiponectin (μg/ml)	16.1 ± 13.5	8.3 ± 4.2	9.0 ± 3.8	13.4 ± 5.8	0.041
Free fatty acids (mEq/l)	0.15 ± 0.06	0.19 ± 0.05*	0.20 ± 0.07†	0.11 ± 0.05	0.002
CRP (mg/l)	2.25 ± 1.61	1.49 ± 1.12	3.74 ± 4.09	1.54 ± 2.26	>0.2

Data are means ± SD. *$P < 0.05$ vs. control subjects; †$P < 0.01$.

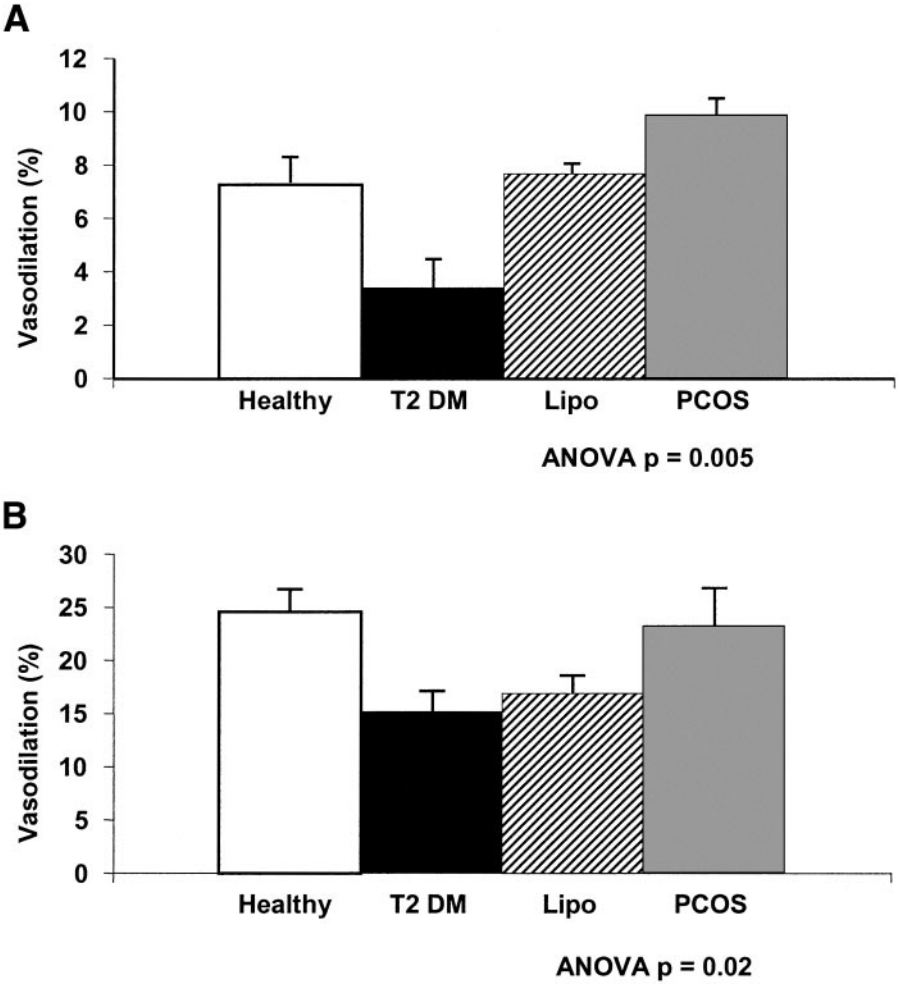

Figure 1—*Vascular function.* A*: The mean percent increase in brachial artery size 1 min after cuff release compared with baseline is illustrated.* B*: The mean percent increase in brachial artery size 3 min after sublingual nitroglycerin administration compared with baseline is illustrated. Lipo, lipodystrophic; T2 DM, type 2 diabetic.*

0.14 mm in type 2 diabetic subjects, 3.20 ± 0.15 mm in PCOS subjects, and 3.31 ± 0.29 mm in lipodystrophic subjects ($P > 0.2$).

Nitroglycerin-mediated vasodilation was reduced in both type 2 diabetic (15.2 ± 2.0%) and lipodystrophic (16.7 ± 3.6%) subjects compared with healthy control (24.6 ± 2.4%) and PCOS (20.7 ± 2.8%) subjects ($P = 0.02$, by ANOVA; Fig. 2). In post hoc testing, nitroglycerin-mediated vasodilation was significantly reduced in subjects with type 2 diabetes ($P = 0.02$) and trended toward attenuation in lipodystrophic subjects ($P = 0.09$) when compared with healthy subjects. Six subjects did not receive nitroglycerin. One PCOS and three healthy control subjects had systolic blood pressure below our cutoff level of 110 mm/Hg, whereas two subjects with type 2 diabetes refused.

Free fatty acids were significantly higher in each insulin-resistant group compared with healthy subjects ($P = 0.004$, by ANOVA; Table 1). Adiponectin levels were significantly lower in the type 2 diabetic and PCOS groups compared with healthy control ($P = 0.04$, by ANOVA) and lipodystrophic subjects. CRP was not significantly different among the four groups ($P > 0.2$, by ANOVA).

Insulin resistance, whether measured by HOMA-IR or fasting insulin level, correlated inversely with HDL and adiponectin levels and directly with triglycerides levels and BMI (Table 2). Free fatty acid levels correlated indirectly with HDL ($r = -0.31$, $P = 0.04$) and directly with triglycerides levels ($r = 0.39$, $P = 0.008$).

Table 2—*Insulin resistance correlations*

	HOMA correlation coefficient	Spearman's ρ (*P*)	Insulin correlation coefficient	Spearman's ρ (*P*)
Age	0.06	>0.2	0.06	>0.2
BMI	0.49	0.005	0.46	0.006
Total cholesterol	0.2	>0.2	0.23	>0.2
LDL cholesterol	0.23	>0.2	0.28	>0.2
HDL cholesterol	−0.55	0.001	−0.53	0.001
Triglycerides	0.46	0.001	0.36	0.014
Flow-mediated vasodilation	−0.18	>0.2	−0.05	>0.2
Nitroglycerin-mediated vasodilation	−0.06	>0.2	0.18	>0.2
Adiponectin	−0.53	0.001	−0.47	0.001
Free fatty acids	0.17	>0.2	0.01	>0.2
CRP	0.26	0.13	0.11	>0.2

Markers of insulin sensitivity, BMI, CRP, or adipokines did not correlate with endothelium-dependent or -independent vasodilation. Glucose levels correlated inversely with endothelium-independent ($r = -0.46$, $P = 0.009$) but not -dependent vasodilation.

CONCLUSIONS — In this investigation, we evaluated vascular function in subjects with different types of insulin resistance, including those with type 2 diabetes, lipodystrophic diabetes, and PCOS, and compared those patients with healthy control subjects. Insulin resistance, as determined by HOMA-IR, was more profound in each insulin-resistant group compared with control subjects. Despite the presence of insulin resistance, endothelium-dependent vasodilation was reduced only in subjects with type 2 diabetes. Endothelial function was preserved in subjects with lipodystrophic diabetes and with PCOS. Our results do not support a direct relationship between insulin resistance and endothelial function across a spectrum of insulin-resistant states. This was surprising because worsening insulin resistance is broadly associated with increases in atherosclerosis across these same disease states, from least in PCOS to most in lipodystrophic diabetes (7–9). Phenotypic variations in insulin-affected tissues suggest that the mechanism of insulin resistance, instead of the severity of either insulin resistance or glucose disturbance, may be relevant to understanding the specific effect of these disease states on vascular function.

In type 2 diabetes, serine phosphorylation of the insulin receptor substrate attenuates normal activation of phosphatidylinositol 3-kinase and AKT attenuating endothelial NO synthase activity (10). The molecular basis for defects in insulin signaling differs in lipodystrophy and PCOS compared with type 2 diabetes. For example, lamin or peroxisome proliferator–activated receptor-γ mutations in some forms of lipodystrophy, but not common type 2 diabetes or PCOS, suggest a different origin for the resistance to insulin action (11). Differing responses to leptin administration (12), peroxisome proliferator–activated receptor-γ therapy (13), and variations in insulin-mediated free fatty acid and ketone body suppression (14,15) further indicate that lipodystrophy causes insulin resistance differently than type 2 diabetes.

Previous investigations by Dunaif and colleagues (16,17) have demonstrated increased insulin receptor serine phosphorylation and decreased insulin receptor substrate-1 tyrosine phosphorylation in obese women with PCOS. Several studies, including ours, demonstrate preserved endothelial function in women with PCOS who are either nonobese or without morbid obesity (18,19), but this remains controversial (20–22). The presence of obesity may contribute importantly to the attenuation in vascular function in this condition. Although overweight, our cohort of PCOS was less obese than those with attenuated vascular function (22), and endothelial function was similarly preserved in lean women with PCOS (18,19). Supporting the concept of an effect of obesity on vascular function, Baron and colleagues (4,23) found that insulin-mediated increases in leg blood flow and skeletal muscle glucose uptake were reduced in obese subjects and those with type 2 diabetes. Escobar-Morreale et al. (24) found no difference in plasma inflammatory maker concentrations of CRP, interleukin-6, tumor necrosis factor α, soluble type 2 tumor necrosis factor receptor, and soluble intercellular cell adhesion molecule-1 in 35 PCOS and 28 healthy subjects paired for BMI, prevalence of obesity, and smoking. Thus, in the absence of morbid obesity, vascular function remains preserved despite evidence of insulin resistance in PCOS.

Potential mediators of endothelial dysfunction in insulin resistance

Hyperglycemia. We tested several established mediators of vascular dysfunction in insulin-resistant states, including glycemia, adipokines, and inflammation, to determine whether one consistently modulated vascular function. We have previously demonstrated that hyperglycemia impairs endothelial function in healthy humans (25,26). Endothelium-dependent vasodilation correlates with glycemia in healthy subjects, subjects with impaired fasting glucose, and subjects with type 2 diabetes (27,28). Improvements in glycemia in subjects with type 2 diabetes improve endothelial function (29). Despite this evidence, in our cohort, the lipodystrophic subjects had the highest fasting glucose and yet had normal endothelium-dependent vasodilation. An expected trend was noted in the correlation between glucose levels and endothelium-dependent vasodilation when only diabetic and healthy control subjects were examined (data not shown), but this only supports the lack of a relationship across insulin-resistant states.

Adipokines. Adiponectin expression in our cohort was lower in type 2 diabetic and PCOS subjects when compared with healthy subjects. However, adiponectin levels were not decreased in the lipodystrophic subjects. Adiponectin levels in the lipodystrophic subjects were similar to

the data of Haque et al. (30) in patients with familial partial lipodystrophy, which were relatively preserved in comparison to patients with congenital generalized lipoatrophy, which were not represented in our cohort. Additionally, although we did find the expected strong association between adiponectin and HDL, we did not find an association between adiponectin and endothelium-dependent vasodilation across the range of healthy and insulin-resistant subjects. This is consistent with our observations regarding adiponectin in offspring of patients with type 2 diabetes (31). Other investigators have reported associations between adiponectin and vascular function, but a review of the literature reveals an inconsistent link between adipocyte products and vascular function. Adioponectin has been correlated to reactive hyperemia in healthy Japanese subjects (32); to nitroglycerin-mediated, endothelium-independent, but not -dependent, vasodilation in healthy Spanish subjects (33); and weakly with endothelium-dependent vasodilation ($r < 0.3$) in a large sample of type 2 diabetic and healthy control subjects in Hong Kong (34).

Likewise, there was no correlation between free fatty acids and endothelium-dependent vaosodilation in our subjects. However, as expected free fatty acid levels were increased in each insulin-resistant state compared with healthy control subjects; yet, the extent of insulin resistance did not correlate with free fatty acid levels. Also, triglycerides were directly associated and HDL was inversely associated with insulin resistance. Similarly, across a population of healthy control subjects, type 2 diabetic subjects without microalbumineria, and type 2 diabetic subjects with albumineria, free fatty acid levels did not associate with endothelium-dependent vasodilation (35). Moreover, Ballotshafer et al. (36) demonstrated no association between ambient free fatty acid levels and flow-mediated vasodilation in first-degree relatives of patients with type 2 diabetes. Thus, abnormalities in these adipocyte factors in insulin resistance do not independently mediate vascular dysfunction across a range of insulin-resistant states.

Inflammation. Inflammation has been demonstrated to associate with endothelial dysfunction in healthy subjects and patients with coronary artery disease (37,38). Moreover, when inflammation is induced by vaccination, endothelial function is depressed and blocking the increase in inflammatory cytokines prevents endothelial dysfunction (39,40). Despite this relationship between inflammation and endothelial function in nondiabetic populations, several studies have demonstrated that CRP does not correlate with vascular function in diabetic subjects (41–43). Similarly, in our cohort, CRP levels did not vary significantly across our insulin-resistant populations and did not correlate with endothelial function. CRP, as one marker of inflammation, however, may not represent all inflammatory markers.

Vascular smooth muscle dysfunction. The response to nitroglycerin was attenuated in subjects with type 2 diabetes and lipodystrophic diabetes. We have previously reported an impaired response to nitroglycerin in subjects with type 2 diabetes (44), but this is the first report of a similar finding in subjects with lipodystrophic diabetes. Markers of insulin resistance, adipokines, and inflammation did not associate with vascular smooth muscle function. Glucose levels correlated inversely with smooth muscle function. The attenuation in endothelium-independent vasodilation may relate to chronic hyperglycemia as reflected in attenuation of nitroglycerin-mediated vasodilation in diabetes (44,45). Despite the attenuation in endothelium-independent vasodilation in the subjects with lipodystrophic diabetes, flow-mediated, endothelium-dependent vasodilation was preserved. These results suggest that endothelial vasodilator production was sufficient to maintain endothelium-dependent vasodilation despite attenuations in vascular smooth muscle function.

Limitations

In this investigation of vascular function in insulin resistance, HOMA-IR was used to approximate insulin resistance. This measure, in large part, reflects the relationship between insulin production and hepatic glucose output and is reported to correlate well with dynamic measures of insulin resistance, such as a euglycemic clamp or the minimal model (46). However, HOMA-IR may underestimate the severity of insulin resistance in subjects with long-standing type 2 diabetes because of an inability to make insulin. It is unlikely that insulin resistance in type 2 diabetic subjects would approach the same severity in subjects with lipodystrophy. Lipodystrophic subjects were the most insulin resistant and had preserved endothelial function unlinking a direct relationship between the two parameters.

In studying these populations, the number of subjects with lipodystrophy was small compared with the other groups because of their rarity in the population. Moreover, two of the subjects were taking ACE inhibitors, which may improve endothelial function, whereas three had microvascular disease or atherosclerosis, which should worsen it. Although these study conditions were imperfect, the similarity of vascular function within subjects with lipodystrophy and between them and healthy control subjects suggests that our observations are valid and not likely to be altered if a greater number of lipodystrophic patients were included.

Age varied significantly among the groups. Several investigations have noted that older subjects have attenuated endothelial function compared with younger control subjects (47–50). Despite this difference, in this study, endothelial function remained significantly different among the groups after controlling for age.

Conclusions

How, then, do we explain our findings? Our measure of insulin resistance is strongly correlated with impairment of insulin-mediated skeletal muscle glucose uptake. Although there is a link between the skeletal muscle defect and vascular defect in obesity/diabetes, different vascular insulin-signaling disturbances are likely operational in the other insulin-resistant states. Insulin levels in the lipodystrophic diabetic subjects were markedly higher than every other group, possibly stimulating endothelial NO synthase enough to overcome the disturbances in vascular smooth muscle function demonstrated in our cohort.

Thus, the effects of insulin resistance on vascular function vary according to origin of impaired insulin signaling. Lipodystrophic and PCOS patients have normal endothelial function, indicative of preserved endothelial insulin signaling, despite impaired glucose handling. Abnormal endothelium-dependent vasodilation in subjects with type 2 diabetes suggests that attenuated endothelial activation of phosphatidylinositol 3-kinase and Akt importantly affects endothelial function in this insulin-resistant disorder. Mechanisms of insulin resistance that are associated with an increased risk of atherosclerosis

require better characterization to explain the variations in bioavailability of NO and risk of atherosclerosis.

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