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Insulin Resistance in Idiopathic Dilated Cardiomyopathy

A Possible Etiologic Link

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OBJECTIVES This study was designed to quantify the prevalence of abnormal glucose tolerance and insulin resistance in patients with idiopathic dilated cardiomyopathy (IDCM).

BACKGROUND Insulin resistance is an independent risk factor for mortality in patients with heart failure (HF) and is a known risk factor for ischemic cardiomyopathy. Though potential physiologic links between insulin resistance and HF have been hypothesized, the relationship between insulin resistance and IDCM remains unclear.

METHODS A total of 230 consecutive patients from a university HF clinic were screened for IDCM, the absence of diabetes mellitus, and the lack of significant co-morbid conditions. Oral glucose tolerance tests were performed in the 43 patients with IDCM who met these criteria, and their plasma glucose and insulin responses were compared with those of 40 healthy volunteers, matched for age, gender, and body mass index.

RESULTS Plasma glucose responses were higher during the oral glucose tolerance tests in patients with IDCM ($p < 0.01$), associated with significantly higher plasma insulin concentrations following the oral glucose challenge ($p < 0.01$). In addition, abnormalities of glucose tolerance were significantly ($p < 0.05$) more common in patients with IDCM (49% vs. 23%).

CONCLUSIONS Insulin resistance and abnormal glucose tolerance are more prevalent in patients with IDCM and represent potentially reversible metabolic derangements in these individuals. (J Am Coll Cardiol 2004;44:78–81) © 2004 by the American College of Cardiology Foundation

Resistance to insulin-mediated glucose disposal and compensatory hyperinsulinemia predicts the development of type 2 diabetes mellitus in individuals with normal glucose tolerance (1–6). However, the ability of insulin-resistant individuals to maintain glucose homeostasis by secreting large amounts of insulin is not an unqualified victory, and it is now clear that insulin resistance represents the central component of a common syndrome that links major cardiovascular disease risk factors (1,2,7,8).

Vascular disease severe enough to cause ischemic cardiomyopathy is commonly associated with diabetes mellitus, and a causal link is now well established (9). However, many patients develop heart failure (HF) without manifest diabetes or vascular disease, and these patients are often classified as having "non-ischemic cardiomyopathy" or "idiopathic dilated cardiomyopathy" (IDCM). Included in this group are patients who may have been diagnosed with "diabetic cardiomyopathy" (9–14). The possibility that insulin resistance, in the absence of frank hyperglycemia, can be a contributing factor to the development of IDCM has not been carefully evaluated. The current study was initiated to address this issue and represents an effort to test the hypothesis that minor degrees of glucose intolerance and insulin resistance are more prevalent in patients with IDCM in the absence of manifest diabetes. Confirmation of this formulation would provide insight into the pathophysiology of IDCM and serve as a basis for new approaches to its treatment.

METHODS

The records of 230 consecutive medically stable outpatients from the Stanford University Heart Failure Clinic were reviewed, the majority of whom had been referred for consideration of cardiac transplantation. A total of 104 patients were diagnosed with IDCM on the basis of left ventricular systolic dysfunction (left ventricular ejection fraction ≤30%) in the absence of coronary artery disease (CAD) either on angiography or in the patients' history. Of these, 20 patients (19%) had been diagnosed with type 2 diabetes and were excluded from further study. Patients were excluded if they had significant renal (serum creatinine >1.9 mg/dl), hepatic, pituitary, or adrenal disease. Patients were also excluded if they had another known cause for their HF (valvular disease, anthracycline-associated, familial, congenital, or alcohol/drug abuse). All patients were New York Heart Association functional class II or III.

The remaining 69 patients were contacted, and 43 volunteered for this study. In addition, data from 40 healthy individuals who had volunteered during the same time span for unrelated studies of insulin resistance were used for comparison. The demographic characteristics of the two experimental groups are given in Table 1, and they are

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Abbreviations and Acronyms

BMI = body mass index
CAD = coronary artery disease
CHF = congestive heart failure
HF = heart failure
IDCM = idiopathic dilated cardiomyopathy
IFG = impaired fasting glucose
IGT = impaired glucose tolerance
pDM = provisional diagnosis of diabetes mellitus

similar in terms of age, gender distribution, body mass index (BMI), and fasting plasma glucose concentrations. The study group had a large standard deviation for BMI, largely attributable to one patient with a BMI of 52.5 kg/m^2. All testing was performed in the Stanford University General Clinical Research Center after informed consent in accordance with the Investigational Review Board and Human Subjects Use Committee.

An oral glucose tolerance test was performed on all 83 participants in the morning after an overnight fast of 10 to 12 h. Blood was taken before and 30, 60, 120, and 180 min after a 75 g oral glucose challenge, plasma separated, and stored at −80°C until measurements were made of plasma glucose and insulin concentrations as described previously (15).

Abnormalities of glucose tolerance were defined by the following criteria of the American Diabetes Association (16): impaired fasting glucose (IFG) as a fasting plasma glucose concentration between 110 and 125 mg/dl, impaired glucose tolerance (IGT) as a plasma glucose concentration between 140 and 199 mg/dl 120 min after the oral glucose challenge, and a provisional diagnosis of diabetes mellitus (pDM) as a fasting plasma glucose concentration >125 mg/dl or ≥200 mg/dl 120 min after the oral glucose challenge.

The total integrated glucose and insulin responses during the oral glucose tolerance test were calculated by the trapezoidal method, and the two groups were compared by Student *t* test. The Student *t* test was also used to compare the baseline clinical characteristics of the two groups; the prevalence of states of glucose intolerance in the two groups was compared by chi-square analysis.

RESULTS

Figure 1 illustrates the plasma glucose and insulin responses of the two experimental groups before and after the oral glucose challenge. The results in the top panel show that

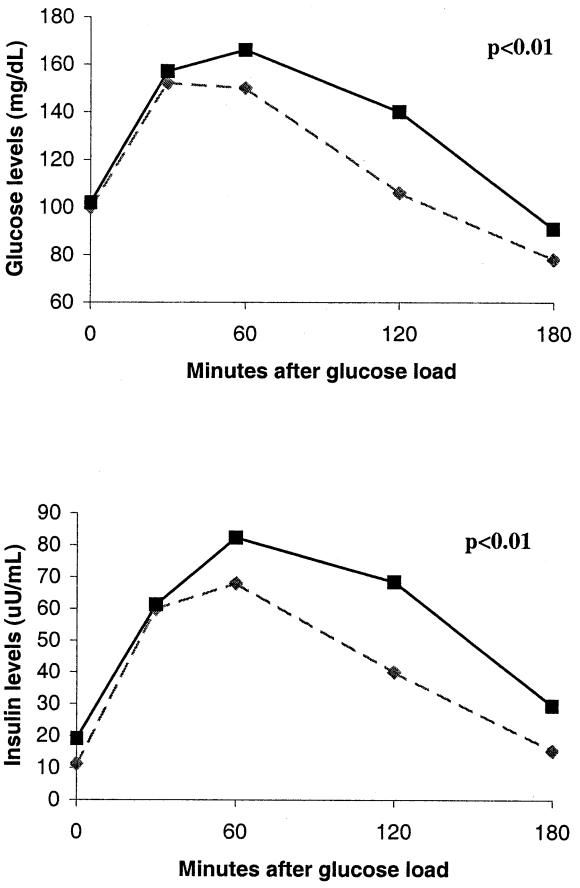

Figure 1. Glucose and insulin versus time after oral glucose tolerance test for study population and controls. **Diamonds** = controls; **squares** = study population.

plasma glucose concentrations after the oral glucose load were significantly higher in the patients with IDCM ($p < 0.01$). Although the fasting plasma glucose concentrations of the two groups did not differ, both the plasma glucose concentration 120 min after the oral glucose challenge and the total integrated glucose response (413 mg/dl per 180 min vs. 359 mg/dl per 180 min, $p < 0.01$) were significantly greater in those with IDCM.

The two groups were even more dissimilar in measurements of insulin, with the total integrated insulin response (172 μU/ml per 180 min vs. 131 μU/ml per 180 min, $p < 0.01$) and the plasma insulin concentration before and 120 min after the oral glucose challenge all being significantly higher in patients with IDCM (Fig. 1).

In addition to having higher plasma glucose concentrations in response to the oral glucose challenge, the preva-

Table 1. Baseline Characteristics of the Two Groups

	IDCM (n = 43)	Controls (n = 40)	p value
Age (yrs)	50 ± 12 (21–75)	50 ± 11 (19–67)	NS
Gender (M/F)	28/15	26/14	NS
BMI (kg/m^2)	29.6 ± 6.8 (21.3–52.5)	29.3 ± 4.6 (18.7–37.2)	NS
Fasting glucose (mg/dl)	105 ± 17 (82–176)	100 ± 10 (81–124)	NS

BMI = body mass index; IDCM = idiopathic dilated cardiomyopathy; NS = not significant.

Table 2. Glucose Tolerance Status of the Two Experimental Groups ($p < 0.05$)

	Normal	IFG	IGT	pDM	% Abnormal
IDCM	22	3	12	6	49% (21/43)
Control	29	8	3	0	28% (11/40)

IDCM = idiopathic dilated cardiomyopathy; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; pDM = provisional diagnosis of diabetes mellitus.

lence of clinical states of glucose intolerance was greater in the patients with IDCM. This comparison is shown in Table 2, where 21 of the 43 patients with IDCM (49%) had some degree of glucose intolerance as indicated by the diagnosis of IFG (n = 3), IGT (n = 12), or pDM (n = 6). By comparison, only 28% of the non-CHF control patients had evidence of glucose intolerance ($p < 0.05$). The prevalence of glucose intolerance was not only increased in patients with IDCM, but the abnormalities present were of greater magnitude; 18 of the 21 patients with IDCM with abnormalities of glucose tolerance had either IGT or pDM, whereas evidence of glucose intolerance in 8 of the 11 control subjects was limited to IFG.

DISCUSSION

The results of this study provide strong evidence that glucose intolerance is a common characteristic of patients with IDCM. At the simplest level, plasma glucose concentrations were significantly higher in response to the oral glucose challenge in patients with IDCM. In addition, ~20% of the patients with IDCM who met all the other inclusion criteria for this study were excluded because they had already been diagnosed as having type 2 diabetes. Finally, approximately half of the individuals with IDCM who were enrolled in the study were shown to have either IFG, IGT, or pDM by the criteria of the American Diabetes Association (16), a significantly greater prevalence than was seen in the control population.

Parenthetically, it should be remembered that although the two groups were not different in terms of age, gender, and BMI, the control group was not a random selection of the population at large, but individuals who had volunteered for studies of insulin resistance. Thus, it is highly likely that the control group was enriched with individuals who considered themselves to be at increased risk to be insulin resistant. Although the study group also consisted of volunteers, most of the consecutive patients from our HF clinic who were eligible entered the study. Consequently, the approximate doubling of states of glucose intolerance in patients with IDCM was, if anything, an underestimate of the magnitude of abnormalities of glucose tolerance present in these patients.

Some patients in the study population were receiving medications that could alter insulin sensitivity, though most of these medications (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, carvedilol, and statins) actually improve insulin sensitivity (17–22).

In addition to being glucose intolerant, patients with IDCM were hyperinsulinemic. Although we did not quantify insulin-mediated glucose disposal in this study, the combination of glucose intolerance and hyperinsulinemia strongly suggests that patients with IDCM were also insulin resistant (1,2). More specifically, we have shown in a recent study of 490 individuals that the total integrated insulin response to a 75 g oral glucose load was highly correlated ($r = 0.8$) with a specific measure of insulin-mediated glucose disposal (15) and was a better predictor than either the fasting insulin concentration or the homeostatic model assessment ($r = 0.6$). Consequently, we feel safe in concluding that the prevalence of insulin resistance, compensatory hyperinsulinemia, and glucose intolerance is significantly increased in patients with IDCM.

Although the prevalence of glucose intolerance was increased in patients with IDCM, the patients were not frankly hyperglycemic, and the fasting plasma glucose concentrations of the two groups were not significantly different. Given the mild degree of plasma glucose elevations in patients with IDCM, the notion that the cardiomyopathy resulted from an untoward effect of hyperglycemia per se (as opposed to insulin resistance itself) can be questioned. Indeed, the fact that insulin resistance (1,2) and day-long hyperinsulinemia (23) are present in the majority of patients with type 2 diabetes raises the possibility that IDCM and diabetic cardiomyopathy share a common pathogenesis, related in some manner to insulin resistance/hyperinsulinemia.

The possibility that insulin resistance and compensatory hyperinsulinemia may play a casual role in the development of IDCM and diabetic cardiomyopathy has important clinical implications. In patients with diabetes, improved glycemic control, which decreases insulin resistance (24), can prevent the development of systolic dysfunction (25). Insulin resistance may predate the development of HF by 20 years or more (26). Treatment of impaired glucose metabolism has been shown to actually reverse systolic dysfunction in animal models (27). Furthermore, recent preliminary investigations by our group have demonstrated that HF patients with insulin resistance or frank diabetes may represent a subgroup of patients who are more likely to have greater response to beta-adrenergic blockade than those with normal insulin and glucose metabolism, regardless of the etiology of their HF.

On the other hand, it could be argued that HF leads to insulin resistance, rather than vice versa. Swan et al. demonstrated that patients with HF with and without CAD were found to be insulin resistant compared with non-HF controls (28). Notably, only the presence of HF (regardless of CAD status) was found to be independently predictive of insulin resistance, despite the fact that patients with CAD tended to be more insulin resistant than those without CAD. In a longitudinal study of patients with HF secondary to valvular disease, Paolisso et al. (29) extensively evaluated the relationship between HF and insulin resistance. These investigators demonstrated that increasing

severity of insulin resistance was related to worsened HF and decreased survival time. Importantly, this link between insulin resistance and worsened survival was independent of other measured variables, including peak oxygen consumption. Although these results provide further evidence of an association between HF and insulin resistance, the causal nature of the relationship remains elusive and will remain so until appropriate clinical studies are performed.

In conclusion, the results presented provide substantial evidence that the prevalences of insulin resistance, glucose intolerance, and hyperinsulinemia are increased in patients with IDCM. Because insulin resistance represents a potentially reversible metabolic derangement, its identification may hold potential importance in the treatment of HF, either to better guide therapy or to aim for disease stabilization or regression.

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