Fasting Insulin Levels as a Measure of Insulin Resistance in American Blacks

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ABSTRACT

Insulin resistance is a common finding in diabetes mellitus and may serve as a measure of efficacy of therapies (exercise, exogenous insulin, sulfonylureas, and PPAR gamma agonists) for diabetes mellitus and as a possible marker for risk of developing type 2 diabetes mellitus.

The purpose of our study was to compare 1 measure of insulin resistance, the QUICKI method, which is a calculation of the inverse of the sum of the log of fasting serum glucose plus the log of fasting insulin level, with the observational measure of fasting serum insulin levels.

We studied 79 African American and Caribbean black patients in an inner-city hospital-based internal medicine practice, 37 subjects had type 2 diabetes mellitus and 42 subjects served as controls.

We found that most controls fell within manufacturer's proposed reference range for fasting insulin levels. However, about 5% were appreciably above the range, suggesting insulin resistance, despite euglycemia. Among our diabetics there were 2 subpopulations, those with elevated fasting insulin levels and those with normal or deficient insulin levels. Only about 30% had elevated fasting insulin levels by immunoassay, suggesting insulin resistance; however, by the QUICKI method, 54% showed insulin resistance. These findings suggest that QUICKI might be more sensitive measure of insulin resistance, while elevated fasting insulin levels may be more specific.

INTRODUCTION

Type 2 diabetes mellitus is a common disease affecting over 18 million people in the United States. The cause is unknown but recent evidence suggests that in a group of patients, resistance to the effects of insulin in target organs leads to glucose intolerance and ultimately to frank diabetes mellitus. Insulin resistance has been shown to

Table 1. Characteristics of Subject Groups*

	Controls	Diabetics	*t* test
Mean Age (years)	60.14	62.73	*P*=0.36
Mean Height (inches)	65.45	66.41	*P*=0.21
Mean Weight (pounds)	206.8	204.1	*P*=0.70
% Over Ideal Body Weight	62.6	50.1	*P*=0.25

*There is no significant difference between the groups.

correlate with obesity, in persons with diabetes as well as in those who do not have diabetes.[1,2] The prevalence of such insulin resistance has yet to be determined in various ethnic groups. Many studies have pointed to resistance to insulin effects as a cause of diabetes and dyslipidemia in minorities, particularly blacks and Hispanics.[3] Such insulin resistance has been associated with obesity in these populations. The aim of this study was to determine the prevalence of insulin resistance among a sample of African Americans and Caribbean blacks.

Various methodologies have been used to show insulin resistance. The hyperinsulinemic euglycemic glucose clamp technique is the "gold standard" for quantifying insulin sensitivity. However, this method is cumbersome to perform.[4] Other methods include frequently sampled intravenous glucose tolerance test (FSIVGTT) and the homeostasis model (HOMA), which are both also cumbersome and not well suited to clinical practice. Recently the QUICKI (Quantitative Insulin sensitivity Check Index) method has been used to quantitate insulin sensitivity/ resistance, requiring only fasting glucose and insulin levels. The QUICKI method is a calculation of the inverse of the sum of the log of fasting serum glucose plus the log of fasting insulin level. However, this method works best in persons without diabetes, and caution must be used interpreting results in persons with type 2 diabetes.[4] Laakso has suggested that fasting insulin levels alone may be used to determine insulin resistance.[5] However, he cautioned that care must be taken in interpreting results in persons with diabetes on medication. Intuitively, once a normal range for insulin levels is determined, readings above this range must suggest insulin resistance of some etiology. An exception to this would be the rare, autonomously secreting, insulinoma. Conversely, non-elevated fasting insulin levels may suggest normal response to insulin, or, in persons with type 2 diabetes, may suggest inadequate secretion due to beta cell dysfunction or beta cell exhaustion in the presence of insulin resistance.

Using the finding of elevated fasting insulin levels as representing insulin resistance, we determined the prevalence of insulin resistance in diabetic and non-diabetic African Americans and Caribbean blacks seen in the primary care internal medicine clinic at University Hospital, University of Medicine and Dentistry of New Jersey, Newark, NJ.

MATERIALS AND METHODS

Sera from 37 patients with type 2 diabetes and 42 non-diabetic controls were analyzed for fasting insulin, C peptide and glucose levels. Height, weight, age, gender and medication were recorded for all subjects. Fasting insulin and C peptide levels were determined using a

Table 2. Laboratory Findings for Subject Groups

	Controls	Diabetics	*t* test
Fasting Glucose	94.4	158.3	0.00000015
Insulin	15.8	29.1	0.0038
C peptide	3.7	3.8	0.90
QUICKI	0.328	0.294	0.00015

chemiluminescent immunoassay on the Immulite (DPC, Los Angeles, Calif). Fasting glucose levels were determined using CX3 chemistry analyzer (Beckman Corp, Brea, Calif).

Ideal body weight (IBW) was calculated based on 100 pounds for women 5 foot height, plus 5 pounds for each inch above 60 inches. For men, 106 pounds was considered IBW at 5 foot height; 6 pounds were added for each inch above 60 inches. IBW was subtracted from the patient's actual weight and the difference was divided by IBW to determine the percent exceeding IBW. Statistical analysis was performed using the two-tailed *t*-test.

RESULTS

The mean age, height and weight of the 2 groups are shown in Table 1. Interestingly, the average weight of the controls was higher than that of diabetic patients, although this was not statistically significant. Similarly, the percentage above ideal body weight was slightly higher among the non-diabetic controls (62.6% vs. 50.1%, P=0.25). The proposed reference interval for normal fasting insulin levels was 6 to 27 µIU/mL and for C'-peptide 0.9 to 4 ng/mL. The mean insulin level for controls was 15.8 µIU/mL. Two samples were considered outliers with fasting insulin levels of 33.6 and 52.4; the revised mean fasting insulin level was 14.50 µIU/mL, with standard deviation of 6.96. In the remaining 40 controls, fasting insulin values ranged from 1.9 to 29.6 µIU/mL. The mean C'-peptide level for all 42 control subjects was 3.7 ng/mL. Among the diabetics, the mean fasting insulin level was elevated at 29.1 µIU/mL and mean C'-peptide was 3.8 ng/mL. Mean fasting glucose levels were 94.4 mg/dL for controls and 158.3 mg/dL for diabetics. The differences in mean fasting insulin and mean fasting glucose levels between controls and diabetics were highly significant: P<0.005 and P<0.0000005, respectively, while the difference in C'-peptide levels was not statistically significant.

The percentage of subjects with elevated insulin levels, ie, greater than 27 µIU/mL, was 9.5% (4/42) among the controls and 29.7% (11/37) for diabetic patients. In order to see whether exogenous insulin administration had any effect on our results, we looked at those patients who were receiving insulin therapy. Eleven diabetic subjects were receiving exogenous insulin therapy. Interestingly, 8 of the 11 subjects (72.7%) had elevated insulin levels, while only 3 patients receiving insulin had fasting serum insulin levels within the normal range. The mean fasting glucose for those patients with elevated insulin levels while receiving exogenous insulin was 150 mg/dL while the mean fasting glucose level for those with normal insulin levels while on insulin therapy was 134 mg/dL. This finding indicates that in many patients receiving insulin therapy, higher blood insulin levels do not correlate with lower glucose levels. A likely explanation is some form of insulin resistance.

The QUICKI method for determining insulin resistance calculates the inverse of the sum of the log of the insulin level plus the log of the glucose

level: 1/(log insulin level +log glucose level). Using the QUICKI calculation, the mean value for controls was 0.328 and for diabetic patients, the mean value was 0.294, $P<0.0002$. Among our controls, 9 of the 42 subjects (21%) had QUICKI values below an arbitrary cut-off value of 0.30 (see Discussion), while 20 of the 37 diabetic patients (54%) had QUICKI values below this cut-off. All individuals with elevated fasting insulin fell below this cut-off value. Five controls and 9 diabetic patients with insulin resistance evaluated by the QUICKI method had insulin levels within the reference range. Hence, it seems that QUICKI may be a more sensitive method for detecting insulin resistance (using our arbitrary cut-off), while elevated fasting insulin levels may be more specific for insulin resistance in the setting of diabetes.

DISCUSSION

Approximately 5% of our controls had appreciably elevated fasting insulin levels. Many studies have pointed to resistance to insulin effects as a cause of diabetes and dyslipidemia in minorities, particularly in blacks and Hispanics.[3] Such insulin resistance has been associated with obesity in these populations. Whether such insulin resistance is genetic and present in persons without diabetes is currently under intensive investigation. Type 2 diabetes appears heterogeneous in etiology. In some patients, there is a defect in insulin secretion by the beta cells, as in secondary diabetes due to cystic fibrosis and in diabetes secondary to hemochromatosis. About 1% of diabetic patients have been shown to have hemochromatosis.[6] However, we have previously found that the C282Y mutation in HLA-H/HFE (the hemochromatosis gene) was rare among African Americans.[7] In other diabetics there is hyperglycemia due to glucokinase deficiency. Polymorphisms in the insulin receptor substrate-1 (IRS-1) and IRS-2[8] and the common genetic variant PPARg Pro12Ala[9] may play a role. Polymorphisms in the variable number of tandem repeats (VNTR) in the insulin gene may affect insulin levels and is currently being analyzed by us to rule out a role for VNTR size in elevated insulin levels among our subjects.

Insulin resistance determination by the homeostasis model (HOMA) and QUICKI methods works well in non-diabetic patients, but caveats in diabetic patients exist. In their article introducing the QUICKI method[4], the authors did not select a cut-off point defining insulin resistance, but rather portrayed a continuum of insulin sensitivity. However, their data suggest an arbitrary cut-off of 0.30 may be informative, if not entirely accurate. In their study, all diabetics had QUICKI values less than 0.33, with subject groups having mean QUICKI values of 0.382, 0.331, and 0.304 for non-obese non-diabetics, obese non-diabetics, and diabetics, respectively.[4] Our data support a cut-off of 0.30 for insulin resistance, wherein (54%) of our diabetic patients and 21% of our controls have QUICKI values less than 0.30. All subjects who were receiving exogenous insulin had QUICKI values below 0.30 except the 2 lowest fasting insulin levels (5.5 and 11.0 μIU/mL). In contrast to the patients with insulin resistance, 18% (2 of 11) of patients on insulin were highly sensitive to insulin, and exogenous insulin was likely needed to accommodate insulin deficiency or defective secretion. The fact that these 2 individuals had QUICKI values above 0.30, demonstrates the sensitivity of QUICKI to insulin levels, irrespective of glycemic control. However, in diabetic patients, hyperglycemia alone can account for the low QUICKI values, even in the presence of deficient insulin levels.

On the other hand, patients receiving insulin-sensitizing agents, such as

PPARg agonists, fasting insulin levels may not be sensitive enough to detect underlying insulin resistance, in as much as the mechanism of the therapy is to correct the underlying defect. Physicians are at times tempted to blame patients for non-compliance when prescribed therapies seem to fail to achieve target glucose and glycated hemoglobin levels. Data from our patients who received exogenous insulin demonstrated that they were compliant with their insulin therapy. Furthermore, lack of absorption of insulin from subcutaneous injection sites was not a major factor contributing to poor glycemic control. Rather, our findings suggest that in these patients, elevated serum fasting insulin levels reflect insulin resistance. Our data supports a proposal that fasting serum insulin determinations may be useful in identifying insulin resistance in some diabetics, and that insulin-sensitizing agents may be appropriate first line therapy in these individuals.

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