A PRODUCT OF FASTING PLASMA GLUCOSE AND FASTING PLASMA INSULIN: SIMPLIFIED AND RELIABLE INDEX OF INSULIN SENSITIVITY

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Although every clinician hopes to diagnose type 2 diabetes in the earliest stages, the United Kingdom Prospective Diabetes Study (UKPDS) revealed that 50% of diabetic complications are present upon the diagnosis of diabetes, even with a fasting plasma glucose (FPG) of 6.1 mM/L.1 This emphasizes the need for diagnosing diabetes in the earliest stages of insulin resistance, before complications such as dyslipidemia and coronary artery disease occur. Diagnosing insulin resistance can be difficult in busy clinical practices. Euglycemic clamp studies, intravenous glucose tolerance tests (IVGTT), the homeostasis model assessment (HOMA), and the quantitative insulin sensitivity check index (QUICKI) were developed to facilitate diagnosis; however, they are impractical for the clinician. Using the insulin-to-glucose ratio has long since proved unreliable. Thus, a simple method to determine insulin resistance is needed.

My colleagues and I conducted 2 studies to determine an insulin sensitivity index (ISI). In the first study, the FPG was multiplied by the fasting plasma insulin (FPI), a common denominator in HOMA and its variations, to determine the ISI in 44 patients with impaired glucose tolerance (IGT), in 53 patients with type 2 diabetes mellitus, and in 41 healthy subjects. The validity and reliability of FPG x FPI was tested by comparison with the ISI, as determined by IVGTT in 26 type 2 diabetic patients, before and after treatment with glyburide or metformin. There were 78 pairs of values. The mean ISI was 100 (±7) in subjects with IGT, 217 (±19) in patients with type 2 diabetes, and 34 (±2) in healthy research subjects (IGT versus normals, P < .001; type 2 diabetes versus normals, P < .0005; and type 2 diabetes versus IGT, P < .001). Linear regression analysis between FPG x FPI and ISI as calculated by IVGTT minimal model showed a highly significant correlation (r = -0.53, P < .00005). We concluded that FPG x FPI could be used to reliably diagnose insulin resistance in clinical practice.

Patients were treated with metformin or glyburide at baseline. After treatment, the product of FPG x FPI decreased in patients who received metformin, indi-
cating the metformin caused some increase in insulin sensitivity but not in those receiving glyburide.

The second study involved administering an oral glucose tolerance test to healthy subjects, to patients with IGT, and to patients with type 2 diabetes. Again, the product of FPG x FPI was lowest in the healthy subjects, higher in patients with IGT, and highest in patients with type 2 diabetes. The difference in glucose tolerance between healthy subjects and patients with IGT is significant.

In summary, linear regression analysis between the FPG x FPI product and the ISI, as calculated by the IVGTT minimal model, showed a highly significant correlation with an r value equal to -0.53. An ISI determined by both the IVGTT and the FPG x FPI product were consistent in the research subjects who were lean, were obese, had IGT, or had type 2 diabetes. Finally, the ISI improved during treatment with metformin but not with glyburide.

Insulin sensitivity indices measured by the product increased progressively in healthy subjects and in patients with IGT. The indices peaked in patients with type 2 diabetes. Using FPG x FPI can provide a clinician with a simple mathematical model to reliably indicate insulin resistance. These results must be validated with glycemic clamp studies, which are the gold standard.

DISCUSSION

QUESTION: How does your method differ from HOMA?

Dr Kabadi: The only difference between this method and HOMA is that other factors must be applied with HOMA. It is not easy to apply those factors in clinical practice, unless HOMA is understood; however, our method can be easily calculated in clinical practice.

Although endocrinologists are more knowledgeable about our method than are primary care physicians or other providers, we wanted to provide a tool everyone could use—to encourage making diagnoses as early as possible, even before the occurrence of postprandial or fasting hyperglycemia.

Dr Hellman: Your slide shows the same common denominator for HOMA and the same arc value (0.5). This only accounts for 25% of the variability between IVGTT and what you have demonstrated. HOMA is not very helpful for individual patients but is useful for examining study populations. Your method will not be too helpful for an individual patient unless different data can be provided. I don't find having an r value helpful. Physicians need to know if patients have normal or abnormal ranges, not if they have diabetes or IGT.

Dr Kabadi: I think your comment is valid. That's the reason why our study group said that we need to validate our model further with the glycemic clamp studies; but I think the numbers can be determined by dividing them into 3 boxes, or even into a fourth box, i.e., type 1 diabetics who probably have the highest insulin sensitivity. Most of them will have a product that is almost zero because their insulin level is undetectable.

Dr Hellman: In one of your earlier diagrams, your product did not correlate as well for relatively low degrees of insulin resistance. The product of FPG x FPI appears to be less sensitive in patients with lower degrees of insulin resistance.

There are 2 additional points: First, one barrier for the clinician is whether the insulin assay you used is comparable to the insulin assay other physicians have used. A great problem in clinical practice is the lack of insulin standardization among the assays, which is one reason the data are not directly comparable.

Also, some investigators have studied larger populations than those in your study and have not found the same correlations as yours. As you broaden your study population, there will be many subsets of patients in whom your formula does not pertain. The formula, for example, may be more accurate for males than for females, since women are more likely to have disproportionately higher postchallenge glucose and insulin values. Nevertheless, it is relevant to use some measure of insulin resistance. Are our assays sufficiently comparable? If an insulin assay is used in clinical practice, it should be well validated and correlate closely with other well-studied assays. Otherwise, results will be misleading.

COMMENTARY

Dr Richard Hellman

Recently published data have clearly shown that the HOMA and related measurements of insulin sen-
sitivity that use only fasting insulin and glucose provide an imperfect measure of insulin sensitivity; at best the correlation coefficient (r) is 0.6.\textsuperscript{2,3} Postchallenge glucose and insulin data can be used in a variety of formulae, whether with the trapezoidal rule to calculate the total integrated insulin response or the multiplicative formula of Matsuda and DeFronzo,\textsuperscript{2} to provide a value for insulin sensitivity that correlates with glucose clamp values with an r of 0.73 to 0.79. In other words, postchallenge data provide a better measure of insulin sensitivity than do fasting data alone. Some investigators believe this is because the fasting insulin and glucose data offer a reliable measure of hepatic insulin sensitivity, while the postchallenge insulin and glucose data are a reliable measure of muscle insulin sensitivity, which can vary up to 10-fold in some individuals.

Methods using HOMA or QUICKI indices, which are based on fasting insulin and glucose, are useful but can be misleading. Using a validated formula that employs both fasting and postchallenge glucose data derived from an oral glucose challenge test would be a better choice. A research procedure that directly measures insulin sensitivity by glucose and insulin clamp studies is still the best method. Physicians must understand that careful insulin sensitivity analyses might reveal a significant decrease in insulin sensitivity, that is, an increase in insulin resistance, in patients who do not yet have IGT. According to Abbasi and Reaven and others, these patients may be at increased risk for cardiovascular complications associated with metabolic or insulin resistance syndrome.\textsuperscript{3} All the caveats notwithstanding, we must find better ways to assess insulin sensitivity and put them into clinical practice.

REFERENCES


**Clozapine-induced Diabetes Mellitus and Diabetic Ketoacidosis**

Based on a Presentation by Anca Avram, M D

Clozapine-induced diabetes mellitus and diabetic ketoacidosis (DKA) is an interesting phenomenon that has been reported with increased frequency since 1994. Clozapine belongs to the class of atypical antipsychotics, which also includes olanzapine, risperidone, and quetiapine. Clozapine was introduced in the United States in 1989 and was considered a breakthrough in psychiatric treatment, because it was the only medication effective for the negative symptoms of schizophrenia, such as social withdrawal and flat affect. Clozapine also had fewer extrapyramidal adverse effects and less dyskinesia, as compared with classical agents like phenothiazine and haloperidol.

The enthusiasm for treatment with clozapine has been counterbalanced by the occurrence of serious adverse effects such as life-threatening agranulocytosis (which occurs in 1% of patients), hypotension, weight gain, and, more recently, hyperglycemia. Clozapine is a dopamine receptor antagonist with low affinity for D2 receptors in the brain and this may be the reason it has fewer adverse extrapyramidal effects.

Clozapine has a high affinity for D4 receptors and is a central serotoninergic receptor agonist, which leads to increased appetite and subsequent weight gain. Clozapine is the first-line medication for psychotic patients with Parkinson's disease and is the medication of choice for refractory schizophrenia after failure of 2 previous medications.

**Case Study**

A 33-year-old white male came to our outpatient clinic with nausea, vomiting, weakness, and abdominal pain. His medical history was significant for paranoid schizophrenia, gastritis, and chronic low back pain. His family history was negative for type 1 or type 2 diabetes mellitus; his medications included clozapine (50 mg bid) for the past 8 months, sertraline, naproxen, and trihexyphenidyl.

The patient was in moderate to severe distress. He was hypotensive and tachycardic and, because of his poor clinical condition, required admission to the hospital. The admission laboratory data indicate severe hyperglycemia, metabolic acidosis, ketonuria, and a glycated hemoglobin (A1c) of 14%.
The diagnosis of DKA was obvious. The patient received an insulin infusion and, after stabilization, was discharged from the hospital with a prescription for insulin 70/30 (a total dose of 65 U/d). In the subsequent weeks, the patient experienced multiple episodes of hypoglycemia; therefore, his dose of insulin 70/30 was reduced. The insulin was discontinued 59 days after admission for DKA, and the patient has remained euglycemic for a 2-year period.

**Commentary and Treatment**

At the beginning of clozapine treatment, the patient was overweight with a body mass index (BMI) that placed him in Class I obesity, according to the National Institutes of Health guidelines. During the 6 months he was on clozapine therapy, the patient gained 14 kg and reached a maximal BMI of 37.2. In the next 2 months, he lost 20 kg and finally presented with DKA, which developed after a prolonged period of hyperglycemia. The acute weight loss, characteristic of uncontrolled hyperglycemia, preceded the development of DKA by 2 months. His A1c level of 14% indicated a long period of hyperglycemia.

There have been multiple reports of new-onset, symptomatic diabetes mellitus and DKA in people treated with clozapine. Koller et al. conducted an epidemiologic study examining spontaneous adverse events occurring in patients treated with clozapine. The data were extracted from the Med-Watch Surveillance Program from January 1990 through February 2001, and the cases were pulled from published cases of diabetes mellitus and DKA.

A total of 384 Med-Watch Surveillance Program reports were examined; of these, new-onset diabetes occurred in 242 cases. Exacerbation of pre-existing diabetes mellitus occurred in 54 cases, DKA in 80 cases, and deaths resulting from the acute hyperglycemic episodes in 25 cases. There were also 46 cases of improved glycemic control after discontinuation or dose reduction of clozapine. The hyperglycemia had a variable clinical presentation, ranging in severity from mild glucose intolerance to DKA and hyperosmolar nonketotic coma. The mean age of presentation was 40 years. Most cases occurred within 6 months of initiation of clozapine therapy. The large number with reports of temporal association to initiation of clozapine treatment, the young age of the patients, and the prompt reversibility of hyperglycemia on clozapine discontinuation in some patients all suggest a causal relationship between clozapine and diabetes.

To understand the mechanism of clozapine-induced hyperglycemia, oral glucose tolerance tests were performed on our patient. At 60 days and at 320 days after presentation with DKA, the results indicate the patient was euglycemic and continued to maintain his euglycemia. His glucose and insulin levels were well within the normal range.

We also examined markers for pancreatic autoimmunity on 2 separate occasions: on initial admission with DKA and at 320 days post-DKA. The markers were negative, thus ruling out type 1 diabetes mellitus. An intravenous glucose tolerance test (IVGTT) was performed to assess his beta-cell function. He did have a first-phase insulin response.

All these studies were done after the patient was discharged from the hospital and after clozapine therapy was discontinued. This patient refused rechallenge, and all these studies were conducted while he was in the basal state, i.e., after return to euglycemia and after discontinuation of clozapine therapy.

We also assessed his insulin secretion and insulin sensitivity using the Bergman Minimal Model Method. Surprisingly, the patient's glucose disappearance constant placed him in the diabetic glucose tolerance range. His glucose tolerance constant was definitely less than 1.

Additionally, we calculated his early-phase insulin response index, which is obtained by a summation of insulin at 1-minute and 3-minute intervals during the IVGTT. The result was compared to the early-phase insulin response index in 200 healthy control subjects. Our patient had a first-phase response, albeit a suboptimal insulin response, that placed him in the 10% index of the healthy population.

At 8 months after DKA, we performed a euglycemic hyperinsulinemic clamp, the standard criterion for assessing peripheral insulin resistance. This patient failed to suppress hepatic glucose production, both at low clamp and at high clamp; therefore, his glucose disposal rate was diminished both at low clamp and at high clamp. His high-clamp glucose disposal rate was 55% of normal.

**Conclusion**

Clozapine induces a state of glucose intolerance resulting from preexisting defects in insulin secretion.
and insulin action. With the administration of clozapine therapy, these patients fail to mount an appropriate increase in insulin secretion to overcome the degree of insulin resistance. Persistent hyperglycemia leads to glucose toxicity, resulting in further suppression of insulin secretion, and to decreased peripheral insulin sensitivity. The severe synergy of these combined defects in insulin secretion and insulin sensitivity lead to glucose intolerance, clinically manifested as a spectrum ranging from impaired glucose tolerance to DKA and hyperglycemic/hyperosmolar nonketotic coma.

We, therefore, recommend that clinicians monitor fasting glucose levels at the beginning and throughout the course of clozapine therapy. At the onset of clozapine therapy, in patients with previously well-controlled diabetes mellitus, we recommend monitoring for deterioration of glucose control as well as educating patients and caregivers about the symptoms of uncontrolled diabetes mellitus.

**DISCUSSION**

**Dr Hellman:** Reports in the literature indicate that the diagnosis of DKA is delayed in people who are psychotic or have psychotic symptoms. You stated that the literature reported nearly a 30% death rate from DKA in this patient population. This is extremely high. Would you please comment on that?

**Dr Avram:** Many of these patients were in psychiatric hospitals because of agitation or other severe psychotic symptoms; however, the patient described in this case was living at home with his mother. The physicians in the psychiatric hospitals did not expect to find, and therefore did not look for, DKA in patients with no known history of diabetes. Consequently, the clinicians did not suspect the diagnosis and probably did not test for the presence of DKA, explaining the high mortality rate and making our recommendation even more valuable. We should be aware of and screen for the occurrence of hyperglycemia in patients taking clozapine.

**QUESTION:** Is this problem associated only with clozapine, or does it extend to olanzapine or other medications in the same class?

**Dr Avram:** There have been numerous reports of hyperglycemia and DKA occurring in patients taking olanzapine and, recently, risperidone. The problem is not limited to a direct toxic effect on the beta-cell; rather there may be a complex interaction with some preexisting defect in a select population. Not all patients with type 2 diabetes who were started on clozapine developed this complication.

** QUESTION:** Has this patient remained euglycemic in follow-up?

**Dr Avram:** Yes, he has.

** QUESTION:** So, this patient's long-term prognosis is a function of his underlying dysmetabolic syndrome. Does this event have any implications in terms of his developing diabetes in the future?

**Dr Avram:** As long as this patient has subclinical defects that remain balanced in the absence of clozapine, he should have no further problems. He must maintain adequate nutrition and not gain weight. We do not know if he has a predisposition for diabetes.

We have obtained multiple subsequent fasting glucose and insulin levels. After nearly 3 years, this patient not only has fasting glucose levels in the normal range but also insulin values around 7 to 9 µU/mL. Although the last oral glucose tolerance test was obtained 320 days after the DKA, fasting insulin and glucose levels were unambiguously normal.

**Dr Hellman:** Much of the earlier literature has stressed that people gained weight first and then developed diabetes; however, it is clear that this does not fully explain the condition of patients in these cases.

**Dr Avram:** Henderson and colleagues conducted a 5-year prospective study involving 82 patients who were treated with clozapine. They found a high inci-
idence (nearly 36.6%) of new-onset diabetes mellitus. Patients experienced an average weight gain of 1.16 pounds per month, but the weight gain alone was not a significant risk factor for developing diabetes mellitus.

Dr Hellman: We hope the increased use of endocrinologists as consultants in psychiatric facilities will prevent patients from becoming as ill as this patient.

REFERENCES
