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Mini Review

The I0*G60, a New Kid on the Block

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Abstract

In this Minireview we describe how, in the process of finding the appropriate diagnostic cutoffs for several traditional biochemical predictors of insulin resistance, we found that the product of the fasting insulin value (I0) times the glucose value at 60 min of the OGTT (G60) predicted insulin resistance. Moreover, it did so more efficiently than the traditional predictors of insulin resistance (HOMA, the QUICKI, and the ISI-OL). The new predictor was labelled as the I0*G60. Its area under the ROC curve against the Steady State Plasma Glucose (SSPG) value of the Pancreatic Suppression Test was 0.867, higher than the respective value of the ISI-OL (0.835), the best performing of the traditional biochemical predictors of insulin resistance. The sensitivity rose from 0.811 (ISI-OL) to 0.865 (I0*G60). The cutoff for the new predictor suggesting insulin resistance was > 428.2 mMol/L*pMol/L (> 1,110 mg/dL*mU/L). The ROC Curve analysis-defined cutoff against the SSPG of the traditional predictors improved notoriously the sensitivity of these tests when compared with the commonly used cutoffs. The HOMA and the QUICKI had similar diagnostic performances. The ISI-OL and the I0*G60 had a strong non-linear mathematical relationship (r > 0.9). A simple OGTT with 3 glucose values (0-60-120 min) and a single insulin value (0 min) would allow the proper categorization of a patient, both in terms of glucose tolerance and insulin sensitivity status. The I0*G60 is simple to perform, inexpensive, and easily calculable.

Keywords: *Insulin Resistance; Biochemical Predictors of Insulin Resistance; I0*G60; Matsuda-DeFronzo's ISI Composite; HOMA*

Abbreviations

BPIRs: Biochemical Predictors of Insulin Resistance; HEC: Hyperinsulinemic Euglycemic Clamp; HOMA: Homeostasis Model Assessment; I0*G60: I Zero Times G Sixty; ISI-OL: Matsuda-DeFronzo's Insulin Sensitivity Index Online; MS: Metabolic Syndrome; OGTT: Oral Glucose Tolerance Test; PST: Pancreatic Suppression Test; QUICKI: Quantitative Insulin Sensitivity Check Index; ROC curve analysis: Receiver Operating Characteristics Curve Analysis; SSPG: Steady State Plasma Glucose; WC: Waist Circumference or Perimeter

Introduction

Insulin resistance is a highly prevalent condition in clinical practice. Physicians around the globe must deal with it daily. The "block" we are alluding to is the almost chaotic field of the biochemical predictors of insulin resistance (BPIRs). The "I0*G60" (I zero times G sixty) is the new BPIR that our group just described in June 2019 [1]. We are fully aware of the fact that "block" where it belongs is crowded with a long list of competing predictors. So, why looking for another predictor of insulin resistance when we have so many others already in use?

There are several reasons to try to improve the diagnostic performance of the BPIRs. The most important one is the fact that the direct measurement of insulin sensitivity is out of reach of the regular physician: in fact, the Hyperinsulinemic Euglycemic Clamp (HEC, the gold standard of the direct measurement of insulin sensitivity) is complex and very expensive to perform. Moreover, the HEC is not only time-consuming, but it is performed according to multiple protocols, with no clear boundaries dividing normality from the abnormality.

Under these conditions, most clinicians just use a clinical surrogate of insulin resistance, the so-called "Metabolic Syndrome" (MS) to detect the condition. Although this strategy is highly popular, it has several serious drawbacks. The most important one is its low sensitivity: around half of the insulin-resistant subjects do not qualify as having MS [2]; secondly, the proponents of the concept of MS state that if a subject fulfils the required diagnostic criteria, the diagnosis of MS cannot be refuted even if the direct measurement of insulin sensitivity shows that the parameter is within normal limits. So, MS -a clinical surrogate of insulin resistance-, has a life of its own, independent of the presence or absence of the condition originally searched for. Moreover, the diagnostic criteria of MS of the International Diabetes Federation require the presence of abdominal obesity as an obligatory finding [3]. This requirement is problematic given the fact that it is not unusual to find non-obese insulin-resistant patients. Finally, there is a brutal discrepancy in the requirements to label a subject as "abdominally obese": the ATPIII definition of MS requires a waist perimeter (WC) > 102 cm in male patients [4], while the IDF definition requires ≥ 94 cm for europids [3]. For all these reasons we do not use the concept of MS to diagnose insulin resistance.

If the clinician is unable to measure insulin sensitivity and, besides, considers the MS concept unreliable to make a proper diagnosis of insulin resistance, the remaining alternative is to rely on the BPIRs.

The current status of the BPIRs

As stated in the Introduction, the whole field of the BPIRs seems to be in disarray. As in the case of a large number of diets to reduce weight, the fact that there is a large number of BPIRs, suggests that their performance is unsatisfactory. The BPIRs can be classified into two types: the so-called "homeostatic BPIRs", requiring fasting serum glucose and insulin values, and the "Oral Glucose Tolerance Test (OGTT)-derived BPIRs". The two more typical homeostatic BPIRs are the HOMA and the QUICKI. As they use the same data for their calculations, it is not surprising that they are strongly correlated. The Homeostasis Model Assessment (HOMA) is the oldest BPIR. It was published in 1985 [5]. The HOMA has two advantages: it is inexpensive and also, very easy to calculate. It is, by far, the most popular BPIR. As a whole, the BPIR group suffers from low sensitivity. In other words, they have a high rate of false-negative results. The Quantitative Insulin Sensitivity Check Index (QUICKI), on the other hand, is used much less frequently, probably because it is the reciprocal value of the sum of the base-10 logarithms of serum fasting glucose and insulin. At least in our country, physicians as a whole, are not quite familiar with logarithms.

The most solid of the OGTT-derived BPIRs appears to be the Matsuda-DeFronzo's Insulin Sensitivity Index [6]. This predictor is highly correlated with the results of the HEC [6]. The current calculation (ISI online, ISI-OL, http://mmatsuda.diabetes-smc.jp/english.html) slightly differs from the published formula. It has two significant drawbacks: it is not only expensive (it requires 5 serum glucose values and 5 serum insulin values), but the cutoff suggested by Matsuda in his web site (≤ 2.5) appears to be erroneous, as it was demonstrated in our paper [1].

Generally speaking, the currently used BPIRs cutoffs suggesting the presence of insulin resistance were not determined by ROC (Receiver Operating Characteristics) Curve analysis against a direct measurement of insulin sensitivity. Moreover, to our knowledge, there is not a valid comparison in the literature on the diagnostic performance of the most used BPIRs. So, there is no way to know which BPIR is the most efficient one.

The ideal BPIR should be easy to perform, inexpensive and also, highly efficient. To summarize, two important tasks must be done with the BPIR. The most important one is to find scientifically their cutoffs (the ones associated with the highest sums of sensitivity and

specificity). This, in our opinion, should be done locally, using the insulin assays performed in each country. The second one is to perform appropriate comparisons of the various BPIRs to select the most suitable ones for each environment.

Our contribution in the field of the BPIRs

In 2003 we became disappointed with the performance of the BPIRs we had access to. We normally used the HOMA. Initially, we thought that the quality of the insulin assay was the main culprit for the poor performance of the various BPIRs. To solve the uncertainty surrounding the diagnosis of IR we decided to set up the Octreotide-Modified Pancreatic Suppression Test [7]. This test (PST) was initially developed by the group of Gerald Reaven [8], 9 years before the HEC was published [9]. Most of the gigantic scientific contribution of Reaven in the field of insulin resistance was carried out with the PST, not with the HEC.

The 3-h Octreotide-Modified PST [7] is simple to set up, highly reproducible, easily performed and, importantly, quite economical in comparison with the HEC. It just measures 9 serum glucose values (0-30-60-90-120-150-160-170 and 180 min), without requiring insulin measurements. The continuously infused Octreotide (0.27 mg/m^2/min) suppresses both insulin and glucagon pancreatic secretions. Regular insulin and glucose are continuously infused (32 mU/m^2/min and 267 mg/m^2/min, respectively). Serum insulin is raised to about 50 - 60 mU/L, which suppresses the hepatic secretion of glucose and induces muscle glucose uptake. Under these conditions, the Steady State Plasma Glucose (SSPG, the average of 4 glucose values 150 through 180 min) is directly proportional to muscular insulin resistance. In the population at large, the SSPG ranges between 2.775 and 22.2 mMol/L (50 - 400 mg/dL, 8 times of difference), between the most insulin-sensitive individuals (serum glucose 2.775 mMol/L, 50 mg/dL) and the most insulin-resistant ones (22.2 mMol/L, 400 mg/dL). An SSPG value of > 8.3 mMol/L (> 150 mg/dL) is characteristic of insulin resistance [10-12]. The correlation coefficient between the HEC result and the SSPG data is very high (0.93) [13]. Moreover, Knowles et al directly compared the HEC and the PST results in 15 non-diabetic subjects. The agreement was excellent and the authors were able to obtain precise transformation equations between the PST and the HEC results [14]. In the expert opinion of Ferrannini, the PST is the best test, next to the HEC, to quantify insulin resistance. It is easy, safe and it can be done at the patient's bedside with minimal training [15]. Simply stated, the PST is the easiest and the most affordable way to measure insulin resistance directly.

We have performed around 800 PSTs since 2003. Although the measurement of insulin resistance with the PST is highly satisfactory, it is not feasible to perform on every patient suspected of being insulin-resistant. For this reason, we decided to study the diagnostic performance of various BPIRs calculated with the OGTT data. We specifically wanted to study the diagnostic performances of the HOMA, the QUICKI, and the ISI-OL. Additionally, we looked into the OGTT data to extract any potential promising new BPIR.

To achieve our goals, we studied a group of 90 subjects highly suspected of being insulin-resistant [1]. All of them had both a PST and an OGTT. Of them, 53 subjects were non-insulin-resistant, and the remainder 37 were insulin-resistant. We determined the appropriate cutoffs of the HOMA, the QUICKI, and the ISI-OL with the ROC Curve Analysis against the SSPG value of the PST. The selected cutoffs exhibited the highest sums of sensitivity plus specificity. Using Bayesian analysis, we calculated sensitivity, specificity, false-negative rate, positive predictive value, and global accuracy for each BPIR.

The Area Under the ROC curve was highest for the ISI-OL (0.835), and lower, but identical, for the HOMA and the QUICKI (0.829). The cutoff for the ISI-OL was < 4.45, quite different from the cutoff proposed by Matsuda in his website (≤ 2.5). The cutoff for the HOMA was > 2.09, also quite different from the cutoff used in our country (> 2.6). The cutoff of the QUICKI was < 0.341, similarly quite different from the cutoff used by most people (< 0.330). The new cutoffs represented a big gain in sensitivity for each BPIR so studied. So, by determining correctly the cutoff for each BPIR we gained a lot in terms of sensitivity and, consequently, reduced the false-negative rate. For instance, when we used the wrong HOMA's cutoff (> 2.6), the sensitivity of the predictor was a mere 56.8%; in contrast, when the appropriate cutoff was used (> 2.09), the sensitivity of the predictor rose to 75.7%.

The sensitivity was highest for the ISI-OL (0.811) and lower, but identical, for the HOMA and the QUICKI (0.757). The false-negative rate was lower for the ISI-OL (0.189), and higher for the HOMA and the QUICKI (0.243). The global accuracy was identical for the three BPIRs (0.789). We concluded the ISI-OL exhibited the best diagnostic performance of these 3 already "classical" BPIR. The HOMA's and QUICKI's performances were identical, but inferior to that of the ISI-OL.

The discovery of the I0*G60

We found out that all the glucose and insulin values of the OGTT significantly predicted the SSPG. Of course, their AUROCs were different [1]. The single best predictor of insulin resistance among the OGTT data was the I0 value. The best AUROC of the five serum glucose values was that of the G60 (0.722) and the best AUROC of the five serum insulin values was that of the I0 (0.822). When we multiplied the I0 value by the G60 value to obtain the I0*G60 parameter, we found out that it predicted the SSPG with a very high AUROC (0.867). Besides, it exhibited a very high correlation with the SSPG (0.697), higher than that of the ISI-OL (-0.547). The cutoff of the I0*G60 predicting insulin resistance [1] was > 428.2 mMol/L*pMol/L (> 1,110 mg/dL*mU/L).

We then compared the diagnostic performance of the I0*G60 with that of the best performing traditional BPIR, the ISI-OL. To our surprise, this simple and inexpensive BPIR outperformed the ISI-OL. Sensitivity was 0.811 for the ISI-OL and 0.865 for the I0*G60. In other words, the false-negative rate dropped from 0.189 to 0.135 when using the I0*G60. The AUROC rose from 0.835 to 0.867. Similarly, specificity rose from 0.774 to 0.793. Finally, the global accuracy rose from 0.789 to 0.822.

We concluded that the I0*G60 outperformed the best performing of the traditional BPIRs, the ISI-OL. Aside from being enthusiastic with the discovery, we were intrigued by it. How come a very simple BPIR was able to do that? The first thing we did was graphing the I0*G60 against the ISI-OL. We found out a very strong non-linear relationship between these two BPIRs. We were able to model a mathematical equation to predict the ISI-OL result by inputting the I0*G60 value (submitted for publication). The correlation coefficient between these two BPIRs exceeds -0.9. The I0 and the G60 values play key roles in the diagnosis of insulin resistance (I0) and the prediction of diabetes mellitus (G60). Although the I0 has a low sensitivity to predict IR (0.568), it has a very high specificity (0.981), meaning that non-insulin-resistant subjects will have a very high probability of having an I0 ≤ 91.67 pM/L (≤ 13.2 mU/mL, below the diagnostic cutoff of I0). On the other hand, a G60 value > 8.6 mMol/L (> 155 mg/dL,) predicts the future development of diabetes [16,17] better than a G120 >7.8 mMol/L (>140 mg/dL). Likely, the I0 and the G60 values enclose more signal than noise in comparison with the whole set of 10 serum values of the OGTT.

Conclusion

Should the diagnostic value of the I0*G60 get several independent confirmations, maybe the best and the most economically sound solution to characterize both the glucose tolerance status and the insulin resistance of a given patient would be to perform an OGGT with 3 glucose values (0-60-120 min) and a fasting insulin. This alternative is attractive, given the enormous amounts of subjects being at risk of becoming type 2 diabetes patients in populations that are increasingly fatter, sedentary and older, compared with the same populations just 50 years ago. We, as physicians, are in dire need of simple, economical and efficient procedures to study such huge amounts of subjects.

We believe that the cutoffs of the BPIRs should be continuously monitored in a given country by ROC Curve analysis against a direct measurement of insulin sensitivity. The Octreotide-Modified PST represents the most economical and feasible procedure to measure directly the insulin resistance in such BPIR-continuous monitoring. A university-associated medical facility widely respected by the medical community might be the ideal place to do such a job.

Conflict of Interest

The authors declare none.

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