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Research Article

A Strong, Rectangular Hyperbolic Relationship Links the I0*G60 with the Matsuda-Defronzo's Insulin Sensitivity Index

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Abstract

In a previous work of our group the "I0*G60" -a novel predictor of Insulin Resistance (IR)-, was found when we performed a ROC analysis of several biochemical predictors of IR, including the Matsuda-DeFronzo's Insulin Sensitivity Index test, ISI) against the Pancreatic Suppression Test (PST). ROC analysis defined the optimal diagnostic cut-offs of several biochemical predictors of IR, including the ISI. The I0*G60 is the product of the I0 (fasting serum insulin value) times the G60 (serum glucose value at 60 minutes of the OGTT). In 90 subjects having both a PST and an OGTT, the I0*G60 outperformed all the studied predictors of IR. The ISI value was calculated in Matsuda's webpage (ISI-OL). The I0*G60 and the ISI-OL were linearly correlated (r = -0.627). In this work, we plotted the I0*G60 against the ISI-OL in the initial cohort of 90 subjects. The graph was highly suggestive of a rectangular hyperbolic relationship between these two predictors. We, therefore, modelled the relationship as a non-linear regression and obtained an equation describing the I0*G60-based prediction of the ISI-OL: *ISI-OL = parameter1* "I0*G60" ^ parameter2*. The non-linear determination coefficient (r^2) was 0.899. We repeated the procedure with a total of 831 pair of values. The linear correlation coefficient between these variables was -0.573. The resulting graph was again highly suggestive of a rectangular hyperbolic relationship. The modelling produced the final predictive equation: *ISI-OL = 782.7 * "I0*G60" ^ - 0.744*. The determination coefficient (r^2) was 0.822. We conclude that the main reason for the excellent performance of the I0*G60 resides in its ability to accurately predict the ISI-OL value.

Keywords: *Predictors of Insulin Resistance; ISI-Composite; I0*G60; Hyperbolic Rectangular Relationship*

Introduction

Currently, the direct measurement of insulin sensitivity/resistance (IS/IR) is not carried out in clinical practice. The gold standard of the measurement of IS, the Hyperinsulinemic Euglycemic Clamp (HEC) [1], is beyond the resources and capabilities of most clinical facilities around the world. For this reason, physicians make use of the so-called "predictors" of IR. These predictors are either clinical surrogates (metabolic syndrome) or biochemical predictors of IR. The diagnostic performance of these predictors is less than satisfactory. The most typical problem with them is their insufficient sensitivity (high false-negative rate). So, it is easy to understand the current abundance of biochemical surrogates of IR, none of them able to solve satisfactorily the problem of diagnosing IR without actually measuring it.

On the other hand, the Pancreatic Suppression Test (PST) [2] measures IR directly (instead of measuring IS). The PST was published in its original form nine years before the HEC (1970 versus 1979). Its modified form (octreotide -instead of epinephrine or somatostatin-, is

used to suppress pancreatic hormone secretions) is a lot simpler and cheaper to perform than the HEC. A mild degree of hyperinsulinemia (around 50 mU/L) is achieved through the continuous iv infusion of crystalline insulin, while glucose is also being continuously infused. The induced hyperinsulinemia suppresses the hepatic glucose production and stimulates the muscle uptake of serum glucose.

Also, the continuously infused octreotide suppresses both pancreatic insulin and glucagon secretions. Under these conditions, the Steady State Plasma Glucose value (SSPG), achieved the last 30 minutes of the 3-hour test, becomes directly proportional to muscular IR. The test requires a measurement of 9 serum glucose values (0-30-60-90-120-150-160-170-180 minutes). An SSPG ≥ 150 mg/dL is diagnostic of IR [3-5]. Greenfield., *et al*. [6] reported that the HEC and the PST are strongly and positively correlated (r = 0.93), and Knowles., *et al*. have obtained accurate transformation equations between the HEC and the PST results [7].

During the last 15 - 16 years, we have performed around 800 PSTs to measure IR in patients suspected of being IR. We have concluded that the PST is readily applicable to clinical work, while everybody agrees that the HEC is not.

Regrettably, the PST cannot be used in every patient in whom we need to disclose his/her IR status, given the costs and work involved in the procedure. For this very reason, it is crucially important to improve the performance of the biochemical predictors of IR. Currently, for each biochemical predictor of IR, there are variable cut-offs in use in different locations. The resulting situation is quasi chaotic because the same data from a given patient are considered diagnostic of IR by a group of clinicians. In contrast, the condition is disregarded by others using a different cut-off. In our country, for example, the usual cut-off to diagnose IR with the Homeostasis Model Assessment (HOMA) is > 2.6 [8]. However, in 2008 we reported unacceptably low sensitivity of this predictor with this particular cut-off locally when contrasted with the PST measurement of IR [9]. Therefore, we became convinced that the appropriate definition of a diagnostic cut-off for each predictor would require a Receiver Operating Characteristic (ROC) analysis to get the best combination of sensitivity and specificity.

Consequently, we collected a cohort of 90 non-diabetic people suspected of being insulin-resistant having both a PST, as well as an Oral Glucose Tolerance Test (OGTT) with serial measurement of both serum glucose and insulin values (0-30-60-90-120 min). We then extracted several homeostatic (obtained in fasting condition, HOMA1, HOMA2 and QUICKI), as well non-homeostatic predictors of IR (obtained in non-fasting conditions): Matsuda-DeFronzo's Insulin Sensitivity Index [10] and the new predictor, the I0*G60 [11], from the OGTT. All these predictors of IS/IR were subjected to a ROC-analysis against the SSPG value to find their most discriminant cut-off (the one associated with the highest sum of sensitivity and specificity).

Our cohort was composed of 37 insulin-resistant subjects (SSPG ≥ 150 mg/dL) and 53 non-insulin resistant subjects (SSPG < 150 mg/dL). The robust Matsuda-DeFronzos's Insulin Sensitivity Index (ISI) was computed with a new and slightly modified calculation method (ISI Online, ISI-OL, http://mmatsuda.diabetes-smc.jp/english.html). The ISI values have been reported to correlate strongly (r = 0.73) with the HEC values [10]. The I0*G60 was computed multiplying the basal insulin value times the serum glucose at 60 minutes.

We started our study by performing a ROC analysis of the ten values from the OGTT (five serum glucose and five insulin values). It turned out that every one of them significantly predicted the presence of IR beyond a given cut-off. The highest area under the ROC curve (AUROC) was exhibited by the fasting insulin value (I0 > 13.2, AUROC 0.822). Serum glucose value at 60 minutes (G60 > 133.5) exhibited an AUROC value of 0.722. We then multiplied the I0 value by the G60 value and obtained the I0*G60. When the diagnostic performance of the I0*G60 was compared with that of the ISI-OL, it had better sensitivity (0.865 versus 0.811), better specificity (0.793 versus 0.774) and better global accuracy (0.822 versus 0.789). Moreover, its Post Test Probability Ratio (the parameter most closely linked to the diagnostic power of a given predictor) exceeded that of the ISI-OL (7.0 versus 4.9). Moreover, the AUROC value of an I0*G60 value > 1,110 was higher than the respective value of an ISI-OL value <4.45 (0.867 versus 0.835).

The ROC-analysis determined cut-off predicting IR for the I0*G60 was > 1,100, equivalent to > 366.7 SI units (1,100*6/18). An I0 value > 13.2 predicted the presence of IR with very high specificity (0.981) but with insufficient sensitivity (0.568). On the other hand, a G60 >

133.5 had a mediocre sensitivity (0.653) and an equally mediocre specificity (0.698). In contrast, as mentioned before, an I0*G60 > 1,110 had both good sensitivity and specificity in the detection of insulin-resistant subjects.

The apparent superiority of the I0*G60 over the ISI-OL was quite surprising for us. So, the question arose: how come a very simple predictor, the I0*G60, was able to outperform the robust ISI-OL (at least in these 90 subjects)? To start with, both the I0*G60 and the ISI-OL values correlated strongly with the SSPG values, but the correlation coefficient of the former (r = 0.697) was more robust than the latter's (r = -0.547). This research, therefore, attempts to elucidate the reasons behind the apparent superiority of the I0*G60 over the ISI-OL.

Materials and Methods

Initially, we had just our original cohort of 90 subjects [11]. To start with, we graphed the I0*G60 (independent variable) versus the ISI-OL (dependent variable). Afterwards, we modelled the graph-suggested mathematical relationship with the help of the XLSTAT, a commercially available statistical add-on package to Excel.

Encouraged by the initial results, we collected a total of 831 OGTT curves and plotted the I0*G60 values versus the ISI-OL values: the 90 original subjects, plus 168 young women having anovulatory dysfunction. Besides, we added a cohort of 573 gynaecological patients of reproductive age, unaware of their glucose tolerance status.

Similarly, we modelled the resultant graph-suggested mathematical relationship between these two predictors with the help of the XLSTAT. We also graphed the SSPG values against the I0*G60 and again, modelled the corresponding mathematical relationships with the XLSTAT. The use of I0*G60 to predict the SSPG value during a PST was explored, and a prediction equation was obtained. To examine the usefulness of the predicted SSPG, we studied its relationship with a commonly used proxy of insulin sensitivity, the inverse value of fasting insulin (1/I0). We obtained a mathematical model of this relationship supporting the validity of the predicted SSPG value.

Results

There was a strong linear negative correlation between the I0*G60 and the ISI-OL (r = -0.627) in the initial cohort of 90 subjects. Figure 1A shows the plot of I0*G60 (independent variable) versus the ISI-OL (dependent variable) in the first 90 subjects. It was visually evident that a rectangular hyperbolic mathematical relationship linked these two variables. We then modelled this mathematical relationship with the help of the XLSTAT. We chose a non-linear regression. The determination coefficient (r^2) between the variables was 0.899. The mathematical equation linking these two variables was: *ISI-O-L = 1073.8 * "I0*G60" ^ -0.783*. An I0*G60 of 1,110 predicted an ISI-OL of 4.42, a figure very close to the ROC-analysis determined cut-off of this predictor (4.45). Figure 1B shows the plot of the I0*G60 values versus the ISI-OL values.

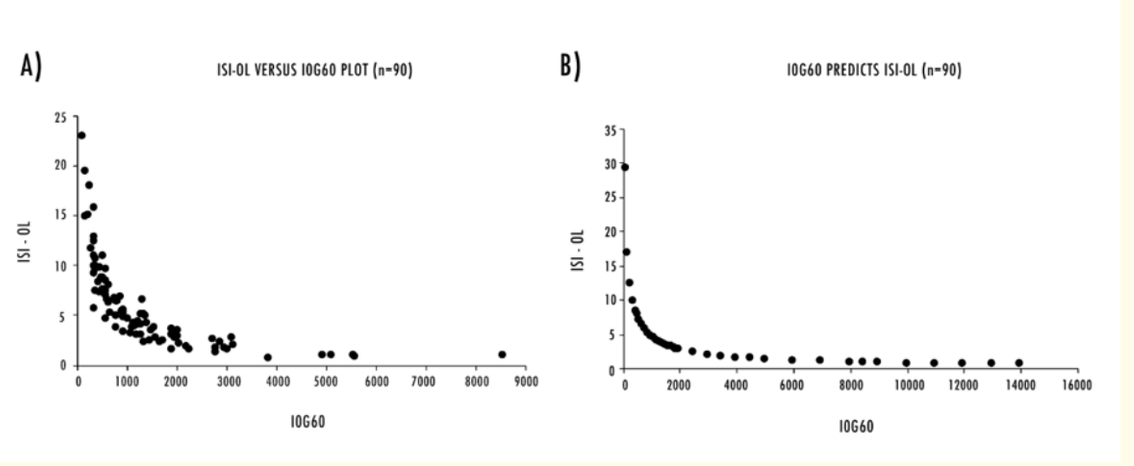

Figure 1: *Panel A shows that an apparent rectangular hyperbolic relationship exists between the I0*G60 and the ISI-OL values in the initial 90 subjects. Panel B shows the curve between these two parameters with the equation describing their mathematical relationship.*

Similarly, there was a robust linear inverse correlation between the I0*G60 and the ISI-OL (r = -0.573) in the 831 subjects. We then plotted the I0*G60 values of the 831 subjects against their ISI-OL values (Figure 2A). Again, the resulting graph indicated a rectangular hyperbolic relationship between these two variables in this large number of subjects. Similarly, we modelled this mathematical relationship with the help of the XLSTAT.

The determination coefficient (r^2) between the variables was 0.822. This time, the equation linking these two variables was: *ISI-OL = 782.66 * "I0*G60" ^ -0.744*.

An I0*G60 equal to 1,110 predicted an ISI-OL of 4.25. This figure is quite close to the ROC-analysis determined cut-off of this predictor (4.45). Figure 2B shows the graph of the I0*G60 values versus the ISI-OL values from 831 subjects.

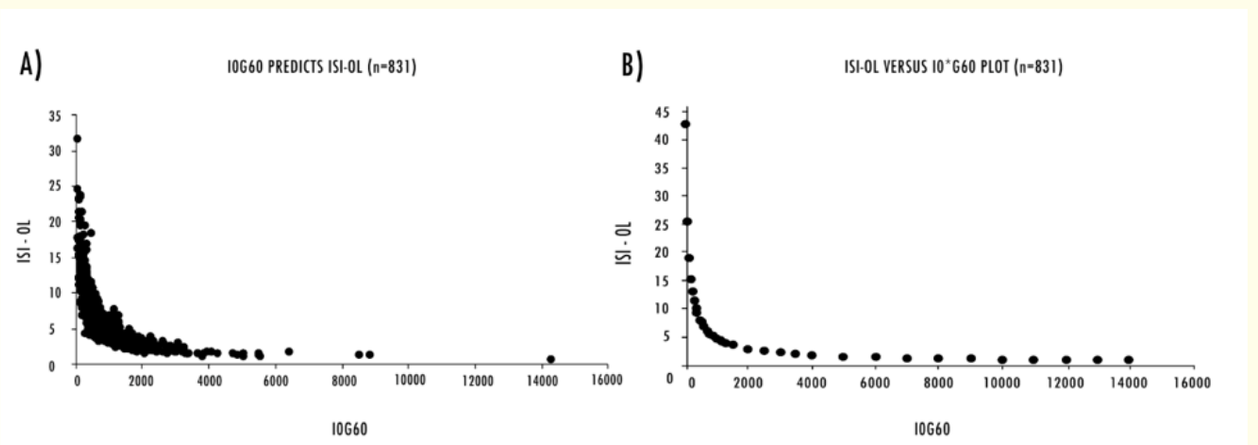

Figure 2: *Panel A shows that an apparent rectangular hyperbolic relationship exists between the I0*G60 and the ISI-OL values in the 831 subjects. Panel B shows the curve between these two parameters with the equation describing their mathematical relationship.*

Since the plot of the SSPG values against the I0*G60 values suggested a positive non-linear relationship, we modelled the mathematical relationship between these variables. We obtained the following prediction equation: *Predicted SSPG = 6.35+("I0*G60" ^ 0.445)*. The correlation coefficient between these variables was 0.736. To test the validity of the predicted SSPG, we contrasted its value against the inverse value of I0 (as a proxy of insulin sensitivity) in 568 non-diabetic individuals (468 glucose-tolerant subjects and 100 prediabetic patients). The graph of the data (Figure 3A) strongly suggested a rectangular hyperbolic relationship between these two variables, so we mathematically modelled the data (Figure 3B) and obtained the prediction equation: *Predicted SSPG = 52.9128*("1/I0" ^ 0.454093)*. The coefficient of determination (r^2) of the relationship was 0.868.

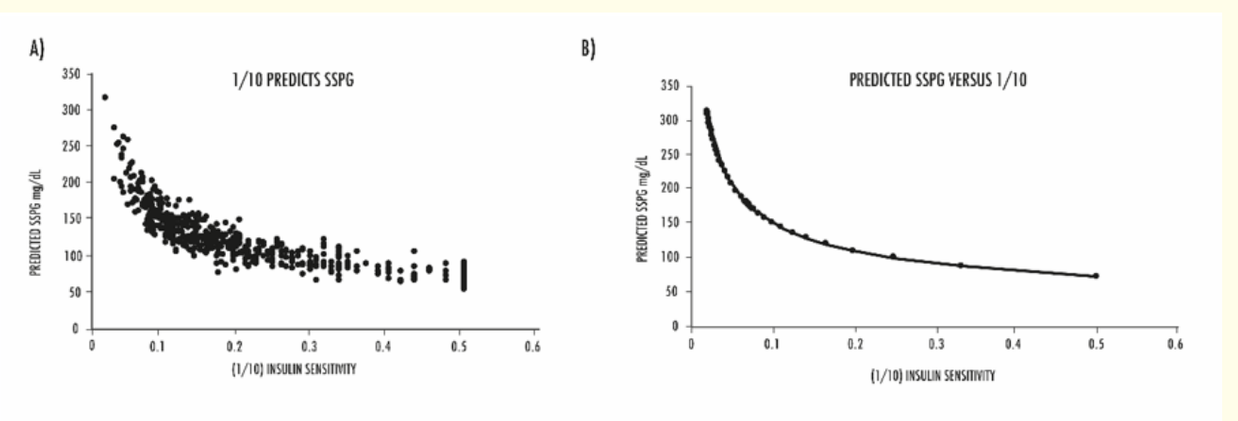

Figure 3: *Panel A shows that an apparent rectangular hyperbolic relationship exists between the Insulin Sensitivity (1/I0) variable and the Predicted SSPG variable in 568 non-diabetic individuals. Panel B shows the curve between these two parameters with the equation describing their mathematical relationship.*

Discussion and Conclusion

In our I0*G60 description [11], as well as in a recent Mini-Review published in this journal [12], we erroneously stated that an I0*G60 > 1,1100 was equivalent to 428.2 SI units. To make this calculation, we multiplied 1,100 by a commonly used erroneous factor (6.945, insulin conversion) and divided the resultant figure by 18 (glucose conversion). By using the correct insulin conversion factor (6, instead of 6.945) [13] an I0*G60 > 1,1100 is equivalent to 366.7 SI units (1,100*6/18). When using 6.945 instead of 6 to convert insulin values from mU/L to pmol/l, the resultant figure is reduced by 13.6% (6/6.945).

As previously mentioned, the SSPG and HEC values have a strong and negative correlation (r = -0.93). Moreover, the ISI values correlate strongly (r = 0.73) with the HEC values [10], whereas the I0*G60 values correlate strongly (r = 0.697) with the SSPG values [11]. Therefore, it should not be a surprise that the ISI-OL was strongly correlated with our new predictor, the I0*G60. We were surprised by the fact that the correlation coefficient of the I0*G60 with the SSPG (0.697) was higher than the correlation coefficient of the ISI-OL with the SSPG, (r = -0.547). This finding is puzzling since it suggests that the I0*G60 outperforms the ISI-OL in predicting IR.

However, it is conceivable that crucial information of the OGTT (in terms of predicting the presence of IR) resides basically in both I0 and G60 values. We speculate that the remaining eight OGTT values (G0, G30, G90, G120, I30, I60, I90 and I120), may produce more noise than signal in the prediction of IR. This possibility could explain the improved diagnostic performance of the I0*G60 compared with that of the ISI-OL [11]. The very high coefficient of determination of the prediction equation of SSPG (0.868), supports the use of the I0*G60 to predict the presence IR (defined by a predicted SSPG ≥150 mg/dL, 8.33 mmol/L).

The ISI-OL value is a robust tool to diagnose IR. However, it has some disadvantages. In the first place, it requires computer software to calculate. In the second place, the cut-off value suggested in Matsuda's website is ≤ 2.5, well below its ROC-analysis determined cut-off of < 4.45. Consequentially, using Matsuda's suggested ISI-OL's cut-off will undoubtedly underdiagnose IR. In the third place, it requires internet access. Lastly, it requires the measurement of five insulin values plus five glucose values, thereby increasing the cost of the test.

On the other hand, the I0*G60 needs just a single insulin value (I0) and a single glucose value (G60). The calculation can be made very quickly by hand with very little consumption of time. An OGTT with just three glucose values (0-60-120 minutes), along with a fasting insulin value, will inform the glucose tolerance categorization of the subject and will give us the possibility of calculating not only the I0*G60 but also the HOMA1 (manual calculation) and the QUICKI (needing a calculator). Additionally, the I0*G60 value allows us to predict an SSPG value.

Ideally, the lab tests report of the OGTT should provide the clinician with all these results (glucose tolerance categorization, I0*G60, HOMA1, and QUICKI, as well as predicted SSPG). We should bear in mind that it is not uncommon finding insulin-resistant subjects with normal levels of basal serum glucose and insulin values. 43.8% of our IR subjects from our original cohort of 90 subjects, had normal serum insulin levels [11]. Therefore, it may be advantageous to have a non-homeostatic predictor of IR, such as the I0*G60 or the ISI-OL.

In summary, the excellent performance of the new predictor of IR, the I0*G60, may be explained by its ability to predict the result of the Matsuda-DeFronzo's ISI Composite, a robust biochemical predictor of IR accurately. However, the apparent superiority of the I0*G60 over the ISI-OL, if proven independently, might eventually be explained by its use of two critical values in the OGTT (I0 and G60), both endowed with high potential to predict IR, while excluding the remainder glucose and insulin values of the OGTT. Consequentially, the cost of the I0*G60 (requiring 2 -instead of 10- OGTT values) is comparatively cheaper compared to the ISI Composite, and its calculation can be made by hand.

Conflict of Interest

The authors declare none.

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