

Comparison of Oral Glucose Insulin Sensitivity with Other Insulin Sensitivity Surrogates from Oral Glucose Tolerance Tests in Chinese

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Abstract

Introduction: There is no single method of measuring insulin resistance that is both accurate and can be easily performed by general researchers. We validate the accuracy of oral glucose insulin sensitivity (OGIS) in the Chinese by comparing the OGIS₁₂₀ and OGIS₁₈₀, homeostasis model assessment of insulin resistance (HOMA-IR), and quantitative insulin sensitivity check index (QUICKI) with steady-state plasma glucose (SSPG) in different glucose tolerance subjects. **Materials and Methods:** We enrolled 515 subjects, aged between 20 and 75 years old, during routine health evaluations. All subjects were divided into normal, obese, impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and type 2 diabetes (T2D) groups. Participants had a 3-hour oral glucose tolerance test (OGTT) and SSPG with an insulin suppression test. The relationships between SSPG and OGIS₁₂₀, OGIS₁₈₀, HOMA-IR, and QUICKI were evaluated. **Results:** The normal group had the highest OGIS₁₂₀, OGIS₁₈₀ and lowest SSPG as compared with the other 4 groups. OGIS₁₈₀, HOMA-IR and QUICKI in all 5 groups were significantly related to SSPG ($r = 0.397-0.621$, all $P < 0.05$). OGIS₁₂₀ in all 5 groups was not significantly related to SSPG ($r = 0.003-0.226$). Additionally, the r value of OGIS₁₈₀ against SSPG was not higher than the other 2 insulin sensitivity surrogates from OGTT. **Conclusions:** Although OGIS₁₈₀ was more accurate in estimating insulin sensitivity than OGIS₁₂₀ in the Chinese, it was not superior to the traditional surrogates such as HOMA-IR or QUICKI.

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Key words: Homeostasis model assessment, Insulin resistance, Quantitative insulin sensitivity check index

Introduction

Patients with type 2 diabetes mellitus are at an increased risk of developing atherosclerosis and cardiovascular diseases leading to higher morbidity and mortality. These complications cause serious economic burdens, not only to patients, but also to the family and society. It is well known that many patients with newly diagnosed type 2 diabetes have complications of macro- and microangiopathy at the time of diagnosis.¹ At present, both impaired insulin sensitivity (IS) [or insulin resistance (IR)] and insulin secretion are considered the most important pathophysiologies for type 2 diabetes. Further studies on family members of type 2 diabetes patients also show IR, even if family members do

not have diabetes.² IR is also considered to be the cornerstone of metabolic syndrome.³ Measuring IR effectively is a challenge for researchers.

A variety of methods for measuring IR were available in the past. The hyperinsulinaemic euglycaemic clamp⁴ is considered to be the “gold standard” to measure IR; however, the limitation of this method is due to its experimental complexity and the expertise required to obtain stable glucose concentrations. There are only a few centres and laboratories that can perform this measurement. An intravenous glucose tolerance test (IVGTT) with minimal model analysis⁵ is valuable for assessing β -cell response and IS, but the necessity of frequent blood sampling confines it

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to research studies. The steady-state plasma glucose (SSPG) concentration with an insulin suppression test (IST) is an accurate method for quantifying insulin-mediated glucose uptake and IR, but it requires infusion of somatostatin to suppress endogenous insulin secretion which requires a large expenditure on the test. The oral glucose tolerance test (OGTT) is simple and widely used in clinical practice and screening; however, it is less sensitive and does not measure IR directly and quantitatively. Various methods, based on the OGTT and empiric formulas, are derived from mathematical models, such as the Homeostasis model assessment of IR (HOMA-IR)⁶ and the quantitative insulin sensitivity check index (QUICKI);⁷ however, their correlations with the clamp still varies widely ($r = 0.58-0.88$).^{6,8-11} To date, there is no method which can be both accurately and easily performed by general researchers.

Recently, Mari et al¹² proposed a method based on a physiological glucose-insulin model for measuring IS from OGTT. They demonstrated that oral glucose insulin sensitivity (OGIS) was tightly correlated with glucose clamp and was more accurate than HOMA-IR; however, there were only 15 to 38 subjects in each group and the small sample size reduced the validity of the method. There is also evidence that suggests that different races may have different pathophysiologies or IS in type 2 diabetes.^{13,14}

We feel that it is important to evaluate the performance of OGIS in a large cohort of Chinese subjects with different degrees of glucose tolerance. The purpose of this study was to validate the accuracy of OGIS by comparing OGIS (both 120 minutes; OGIS₁₂₀ and 180 minutes; OGIS₁₈₀), HOMA-IR, and QUICKI with SSPG.

Materials and Methods

Subjects

We enrolled 515 subjects, aged between 20 and 75 years old, during routine health evaluations. There were 229 men and 286 women. Subjects with a history of hypertension, hyperlipidaemia, or other significant medical or surgical disease were excluded. Subjects who had taken medications affecting insulin sensitivity were also excluded from the study. The study was approved by the Hospital Ethics Committee, and the nature, purpose, and potential risks of the study were explained to the patients before obtaining their consent to participate. We divided the subjects into 5 groups according to diagnostic criteria of IFG, IGT and T2D based on the 1997 American Diabetes Association guideline,¹⁵ and obesity for the Asian region [body mass index (BMI) >25 kg/m²] from the World Health Organisation report of 2000.¹⁶

Laboratory Evaluation

The ability of insulin to dispose of a glucose load was

estimated by modification of IST, as described by Shen et al.¹⁷ After an overnight fast, intravenous catheters were inserted in both arms of each subject. One catheter was used for the administration of a 180 minute infusion of somatostatin (250 µg/h), insulin (25 mU/m²/min), and glucose (240 mg/m²/min). The catheter in the opposite arm was used for the collection of blood samples. Blood was collected every 30 minutes initially, and then at 10 minutes intervals from 150 to 180 minutes of the infusion, to determine the steady-state plasma insulin (SSPI) and SSPG concentrations for each individual. The SSPI concentrations were comparable in all individuals; thus, the SSPG concentrations provided the measure of efficacy of insulin in promoting disposal of the infused glucose load.

Plasma was separated from blood within an hour and stored at -30°C until analysed. The samples obtained at -5 and 0 minutes were analysed for fasting plasma glucose (FPG) and fasting plasma insulin (FPI). Plasma glucose levels were determined using the glucose oxidase method (YSI 203 Glucose Analyzer; Scientific Division, Yellow Spring Instrument Company, Inc., Yellow Spring, OH, USA). Insulin levels were measured by a commercial solid phase radioimmunoassay kit (11; Coat-A-Count Insulin Kit; Diagnostic Products Corporation, Los Angeles, CA, USA). The intra- and inter-assay co-efficients of variance for insulin were 3.3% and 2.5%, respectively.

The HOMA-IR⁶ was evaluated as a product of FPG and FPI, and applied for assessing insulin resistance from OGTT. The QUICKI⁷ reflects hepatic insulin sensitivity. The higher the QUICKI value the higher the predicted insulin sensitivity.

Statistical Analysis

Analysis was performed using SPSS version 10.0 statistical package for Windows (SPSS, Chicago, IL). Data were tested for normal distribution with the Kolmogorov-Smirnov test and for homogeneity of variances with Levene's test. Continuous variables are expressed as mean ± SD. The derived residuals of the particular variables were used for further analyses. One way analysis of variance (ANOVA) with the Bonferroni as post hoc test was used for comparison between the 5 groups and pairwise comparisons. Finally, in order to compare which surrogate (OGIS₁₂₀, OGIS₁₈₀, HOMA and QUICKI) was better correlated to the SSPG, Steiger *t*-test was used for comparing the difference of the reliability and validity between 2 correlations.¹⁸ All statistical tests were two-sided and *P* values <0.05 were considered statistically significant.

Results

Table 1 summarises the general characteristics in the 5 different groups. Not surprisingly, the normal group had

lower BMI and FPI concentrations. The BMI was highest in the obese group, and the FPG was highest in the T2D group. Figure 1 depicts the mean plasma glucose and insulin levels in the 5 groups during OGTT. It was expected that the normal group had the lowest plasma glucose and insulin levels during the OGTT. Compared to IGT, subjects in the IFG group had lower plasma glucose and insulin levels.

Table 2 shows the values of OGIS₁₂₀, OGIS₁₈₀ and SSPG. Among the 5 groups, the normal group had a significantly lower SSPG than the other 4 groups. The obese group and the IFG group had similar SSPG, and IR was the same in IGT and T2D groups. Interestingly, the changes in OGIS₁₂₀ and OGIS₁₈₀ were different from SSPG; it was noted that the highest values were in the normal group gradually declining from the IFG to T2D groups.

Correlations between SSPG and OGIS₁₂₀, OGIS₁₈₀, HOMA-IR and QUICKI are summarised in Table 3. Except for OGIS₁₂₀, the OGIS₁₈₀, HOMA-IR and QUICKI were all significantly related to SSPG. After comparing with relations of different methods with Steiger *t*-test, the *r* value of OGIS₁₂₀ was significantly poorer than those of OGIS₁₈₀, HOMA-IR and QUICKI not only in a total of 515 cases but also in each group. In general, the *r* values between SSPG and OGIS₁₈₀ were similar to those between HOMA-IR or QUICKI in each group.

Discussion

Mari et al¹² enrolled 104 Caucasian subjects, and performed a comparable study in America. It is interesting

to compare our results between different groups with Mari's study. The value of OGIS₁₈₀ in normal glucose tolerance was from 440 ± 16 mL/min/m² in Mari's study. In our study, the value of OGIS₁₈₀ with normal glucose tolerance was 445.1 ± 59 mL/min/m². In subjects with IGT, OGIS₁₈₀ was 302 ± 17 mL/min/m² in Mari's study and 352.9 ± 72.9 mL/min/m² in ours. Finally, in the T2D group, it was 239 ± 7 mL/min/m² in Mari's study and 305 ± 52 mL/min/m² in ours. In general, by using absolute values, we have relatively consistent results with other publications.

After OGIS was proposed in 2001, some studies used OGIS₁₂₀ and others used OGIS₁₈₀ to assess IS. Kautzky-Willer et al¹⁹ used OGIS₁₂₀ in women with previous gestational diabetes, and showed that they had lower values of OGIS₁₂₀. Another study, done by Rask et al,²⁰ performed OGIS₁₈₀ and demonstrated lower OGIS₁₈₀ in non-obese subjects with IGT, which was also associated with hepatic insulin extraction. However, there is no study that critically examined the 2 different formulas. It should be mentioned that the SSPG and OGIS₁₈₀ are reciprocal to each other. In other words, subjects with IR should have higher SSPG and lower OGIS₁₈₀. Disappointingly, the correlations between OGIS₁₂₀ and SSPG were not significant in this study. The *r* values ranged from 0.4 to 0.6 between SSPG and OGIS₁₈₀ in different groups, which were similar to the *r* values of either HOMA-IR or QUICKI. When compared to Mari's report, the differences became even more distinct (*r* = 0.77). Apparently, the *r* values are not superior to all other surrogates. Based on our findings, the OGIS is not

Table 1. General Characteristics in 5 Different Groups

Normal	Obese	IFG	IGT	T2D	
n	207	44	108	134	22
Age (y)	40.6 ± 11.3 ^{O,IFG,IGT}	48.9 ± 12.6 ^N	47.6 ± 11.2 ^N	50.1 ± 11.0 ^{N, T2D}	42.5 ± 9.2 ^{IGT}
BMI (kg/m ²)	21.8 ± 1.9 ^{O,IFG,IGT,T2D}	27.4 ± 2.1 ^{N,IFG,IGT,T2D}	24.5 ± 3.1 ^{N,O}	25.3 ± 3.3 ^{N,O}	24.5 ± 3.5 ^{N,O}
FPG (mmol/L)	5.06 ± 0.31 ^{IFG,IGT,T2D}	5.17 ± 0.32 ^{IFG,IGT,T2D}	5.86 ± 0.31 ^{N,O,T2D}	5.67 ± 0.56 ^{N,O,T2D}	7.28 ± 1.41 ^{N,O,IFG,IGT}
FPI (pmol/L)	66.1 ± 36.5 ^{IFG,IGT,T2D}	82.8 ± 39.0	95.1 ± 62.2 ^N	100.3 ± 57.5 ^N	94.5 ± 45.8 ^N

BMI: body mass index; FPG: fasting plasma glucose; FPI: fasting plasma insulin; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; T2D: type 2 diabetes

Data are shown as mean ± SD, ^N*P* < 0.05: against normal groups, ^O*P* < 0.05: against obese group, ^{IFG}*P* < 0.05: against IFG groups, ^{IGT}*P* < 0.05: against IGT groups, ^{T2D}*P* < 0.05: against T2D groups

Table 2. OGIS₁₂₀, OGIS₁₈₀ and SSPG in Different Groups

	Normal	Obese	IFG	IGT	T2D
OGIS ₁₂₀	404.3 ± 62.0 ^{O,IFG,IGT,T2D}	368.9 ± 53.4 ^{N,IGT,T2D}	346.2 ± 53.8 ^{N,IGT,T2D}	318.9 ± 62.6 ^{N,O,IFG}	288.7 ± 55.2 ^{N,O,IFG}
OGIS ₁₈₀	445.1 ± 59.2 ^{O,IFG,IGT,T2D}	414.3 ± 58.0 ^{N,IGT,T2D}	397.7 ± 53.4 ^{N,IGT,T2D}	352.9 ± 72.9 ^{N,O,IFG,T2D}	305.1 ± 52.0 ^{N,O,IFG,IGT}
SSPG	7.40 ± 3.25 ^{O,IFG,IGT,T2D}	9.52 ± 3.73 ^{N,IGT}	9.29 ± 3.87 ^{N,IGT}	11.33 ± 4.02 ^{N,O,IFG}	11.12 ± 4.52 ^N

IFG: impaired fasting glucose; IGT: impaired glucose tolerance; T2D: type 2 diabetes; OGIS₁₂₀: 120-min oral glucose insulin sensitivity; OGIS₁₈₀: 180-min oral glucose insulin sensitivity; SSPG: steady state plasma glucose; mean ± SD; ^N*P* < 0.05; against normal groups, ^O*P* < 0.05; against obese group, ^{IFG}*P* < 0.05; against IFG groups, ^{IGT}*P* < 0.05; against IGT groups, ^{T2D}*P* < 0.05; against T2D groups

Table 3. Correlations between SSPG and OGIS₁₂₀, OGIS₁₈₀, HOMA-IR, QUICKI

r	All	Normal	Obese	IFG	IGT	T2D
OGIS ₁₂₀	-0.273	-0.003	-0.226	-0.145	-0.107	-0.015
OGIS ₁₈₀	-0.595*	-0.397*	-0.388*	-0.522*	-0.621*	-0.544*
HOMA-IR	0.559*	0.442*	0.389*	0.516*	0.558*	0.591*
QUICKI	-0.576*	-0.406*	-0.404*	-0.589*	-0.598*	-0.559*

IFG: impaired fasting glucose; IGT: impaired glucose tolerance; HOMA-IR: homeostasis model assessment of insulin resistance; QUICKI: quantitative insulin sensitivity check index; OGIS₁₂₀: 120-min oral glucose insulin sensitivity; OGIS₁₈₀: 180-min oral glucose insulin sensitivity; SSPG: steady state plasma glucose; T2D: type 2 diabetes;

* $P < 0.05$

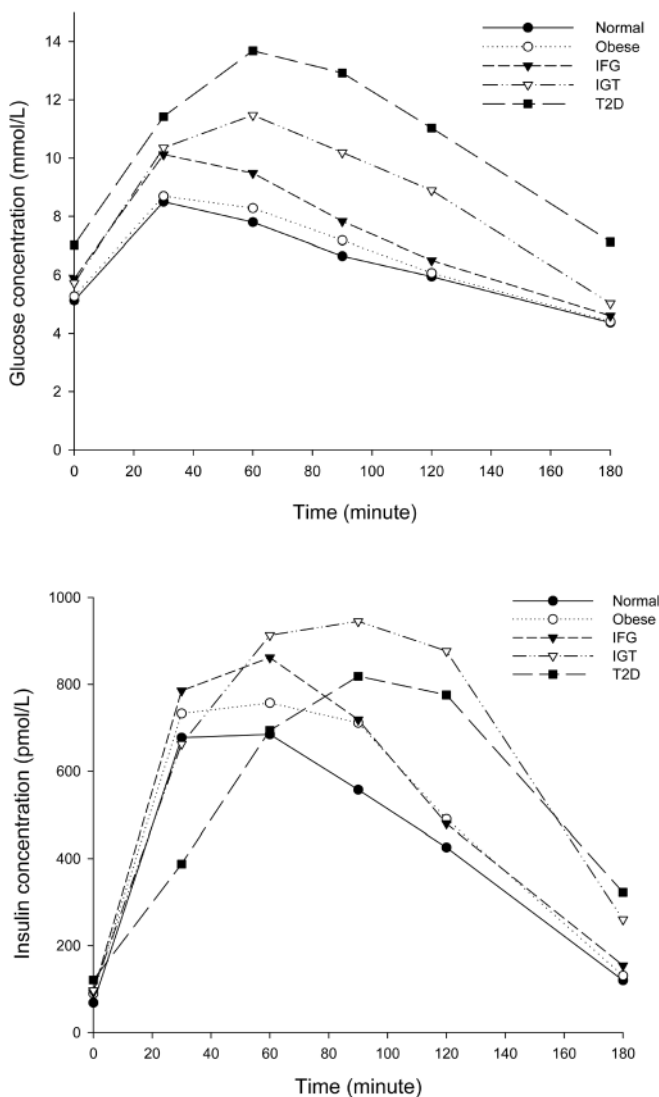


Fig. 1. Changes of plasma glucose and insulin concentrations in normal, obese, IFG, IGT, and T2D groups.

recommended as an alternative method for IST in clinical use or epidemiological study in Chinese.

The disappearance of significant correlation between OGIS₁₂₀ and SSPG suggested the importance of 180 minute

plasma insulin levels. In Figure 1, it is noted that the orders of the plasma glucose levels did not change at 120 minutes and 180 minutes. However, the plasma insulin levels of the obese group were higher than the IFG group at 120 minutes, but lower at 180 minutes. Similar changes in the plasma insulin orders are also noted between the normal and IGT groups. Evidently, these reverse insulin levels at 120 to 180 minutes suggest that the interactions between glucose and insulin do not reach the “steady-state” until at the 180 minutes mark. Including the plasma glucose and insulin levels at 180 minutes in the equation is crucial for estimating IS with OGIS.

It is peculiar with the similar range of values of OGIS₁₈₀ that the r values of the correlations were only around 0.5. R values are even lower in the normal and obese groups. When further examining the scatter graph in the normal group, it is interesting to note that most study subjects had SSPG values of less than 10 mmol/L. This is predictable since only 25% of the normal subjects have IR.²¹ The IS subjects had a narrow range of OGIS₁₈₀ between 400 and 500 mL/min/m². This may be the main reason for the r value becoming lower in the normal group. In the obese group, the SSPG values were evenly distributed throughout a larger range with a corresponding dispersal of OGIS; however, there were 2 IR subjects with high OGIS₁₈₀. Again, we believe that the correlation became weaker due to these 2 cases. Finally, although the number of subjects was less in the T2D group, both SSPG and OGIS were even in the other 3 groups (IGT, IFG and DM). Therefore, the correlation was higher than 0.5. From the changes between the different severity of IR and r values, we can draw the conclusion that OGIS₁₈₀ is less accurate in subjects with normal glucose tolerance.

There are several possible explanations for the difference in performance of the OGIS₁₈₀ in Chinese subjects. First, ethnic difference may play an important role. It is known that Asian T2D patients are thinner than Caucasian patients with T2D.^{22,23} The thrifty gene was proposed to be one of the causes for this difference.²⁴ From data in the United Kingdom Prospective Diabetes Research study, the IR seems to be more severe in Asians.²⁵ Alternately, the β

cell function is better reserved in obese type 2 diabetes patients than in thin patients.^{26,27} Based on these studies, there is a high possibility that different pathophysiologies for T2D exist in different ethnic groups. At the least, these discrepancies may be the cause of poorer r values related to OGIS in the Chinese subjects.

Second, there are 6 needed parameter assumptions in Mari's OGIS model. These assumptions are necessary for the completion of the equations, but they also increase the uncertainties which might further decrease the accuracy of the model. The volume of distribution of glucose (Vd) is also an important parameter used in the model. Whether different ethnic groups have different volumes of distribution of the glucose is also questionable. In Mari's study, the Vd used was calculated in 6 young lean Caucasians by Ferrannini et al in 1985.²⁸ They concluded that the Vd was correlated with insulin-stimulated rate of total glucose turnover. In other words, subjects with different glucose tolerances might have different Vd values. This raises the question that could the same Vd be used in different ethnic groups, ages, or even glucose intolerance? Further studies defining the Vd in the Chinese should be performed to elucidate this issue.

Finally, other than the normal group, the body weights were quite different between Mari's study and ours (33 ± 1 vs. 27 ± 2 in OB, 34 ± 1 vs. 25 ± 3 in IGT and 34 ± 2 vs. 25 ± 4 kg/m² in T2D, respectively). The ages and study numbers were all slightly different in these 2 studies. All differences might contribute to the poorer correlation in our study.

In conclusion, although OGIS₁₈₀ was more accurate to estimate IS than OGIS₁₂₀ in the Chinese, it was not superior to the traditional surrogates such as HOMA-IR or QUICKI. Its use in the Chinese is not recommended.

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