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ORIGINAL ARTICLE

The Reference Intervals and Roles of GIR, HOMA and QUICKI Indexes to Judge Insulin Resistance/Insufficiency for Newly Diagnosed Diabetes Mellitus

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SUMMARY

Background: **To establish the reference intervals of GIR, HOMA, and QUICKI index and to identify the clinical value of the three indexes for newly diagnosed diabetes mellitus.**
Methods: **The results of fasting glucose and insulin were acquired for 123 healthy individuals using Roche cobas-8000 to establish reference intervals of GIR, HOMA, and QUICKI based on Clinical and Laboratory Standards Institute (CLSI) EP28-A3. Meanwhile, 36 newly diagnosed type 1 and type 2 diabetes mellitus (DM) patients were enrolled to judge the effect of insulin resistance/insufficiency using the three indexes based on clinical initial treatment procedures. All the data were acquired from Wangjing Hospital, China Academy of Traditional Chinese Medicine.**
Results: **The reference intervals of GIR, HOMA, and QUICKI were 5.83 - 21.15, 0.87 - 4.22, and 0.309 - 0.392, respectively. Concerning to GIR, HOMA, and QUICKI, there were 57.7% (15/26), 80.8% (21/26), and 80.8% (21/26) outside of the reference limit among type 2 DM patients, respectively; The area under the curve (AUC) of the GIR > 10.937, HOMA < 5.436, and QUICKI > 0.299 were 0.937 (95% CI 0.681 - 1.000), 0.689 (95% CI 0.510 - 0.868), and 0.689 (95% CI 0.510 - 0.868) by ROC curves when insulin insufficiency was judged based on whether insulin was included in initial treatment procedures. There concordance rates were 77.8% (28/36), 50% (18/36), and 50% (18/36) using the three indexes, GIR, HOMA, and QUICKI, respectively.**
Conclusions: **We established reference intervals for GIR, HOMA, and QUICKI. HOMA and QUICKI were more reliable indexes to identify insulin resistance among type 2 DM patients, but GIR was a more reliable index to identify insulin relatively or absolutely insufficiency than HOMA and QUICKI among DM patients.**
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KEY WORDS

fasting blood glucose, insulin resistance, type 1 diabetes, type 2 diabetes

INTRODUCTION

Diabetes is a group of metabolic diseases characterized by hyperglycemia with insulin secretion and/or action deficiency. The lasting hyperglycemia can do harm to many organs, such as the eyes, kidney, nerves, heart, and blood vessels [1-3]. It was estimated that there are 451 million adults with diabetes worldwide in 2017. These figures were expected to increase to 693 million

by 2045 [4].

Diabetes can be classified into four general categories: type 1 diabetes, type 2 diabetes, gestational diabetes mellitus (GDM), and specific types of diabetes due to other causes. Type 1 diabetes is characterized of insulin absolute deficiency; however, type 2 diabetes accounts for 90 - 95% of all diabetes and encompasses individuals who have insulin resistance and usually relative insulin deficiency.

Fasting glucose to insulin ratio (GIR) is a useful measure of insulin resistance in women with polycystic ovary syndrome and girls with premature adrenarche [5,6]. However, this index was criticized that it does not appropriately reflect the physiology underlying the insulin sensitivity [7]. Meanwhile, HOMA and QUICKI were thought based on the product of fasting insulin and glucose and more reliable for assessing insulin resistance among young people [8].

There are fewer study concerning the three indexes in diabetes patients. The study established relevant reference intervals based on CLSI EP28-A3 and identified the clinical values for newly diagnosed diabetes.

MATERIALS AND METHODS

Reference individuals and patients

Apparently healthy subjects were recruited from the medical physical examination center of Wang Jing hospital of the China Academy of Chinese Medical Sciences from October 2018 to February 2019. The inclusion criteria of the reference individuals followed CLSI document EP28-A3 [9]. Exclusion criteria were the following: (i) the positive finding of Chest X-ray, electrocardiograph (ECG) or abdomen B-mode ultrasound; (ii) the abnormal result of fasting blood glucose; (iii) chronic kidney and liver disease; (iv) excessive alcohol consumption, taking medication, hereditary disease, allergic disease, or other diseases that might affect the results of serum glucose and insulin measurements; (v) body mass index below 19 or above 24, age not between 18 and 56 years old. All newly diagnosed DM were from the Department of Endocrinology of Wangjing Hospital of China Academy of Chinese Medical Sciences from March 2019 to September 2019. Initial treatment whether or not to include insulin was based on the guideline [10].

Sample collection and measurement

Fasting blood samples were collected and allowed to clot at room temperature for at least 30 minutes using blood collection tubes containing separation gel (BD Vacutainer), followed by centrifugation according to the manufacturer's instructions. Separated serum was used to obtain the concentration of glucose and insulin using Roche cobas 8000 c701 analyzer and cobas e602 analyzer at the Department of Clinical Laboratory, Wangjing Hospital of China Academy of Chinese Medical Sciences. Daily internal quality control qualified and the laboratory was accredited according to ISO15189:2012. The means of coefficients of variation were 1.33% and 4.79%, respectively, which were less than optimal CV based on biological variability (1.40% and 5.28%) for serum glucose and insulin. The means of biases, which were from external quality assessment of National Center for Clinical Laboratories from October 2018 to September 2019 were -0.38% and 2.44%, respectively, which were less than optimal biases based on biological variability (1.17% and 7.75%) for serum glucose and insulin.

Statistical analyses and data processing

Statistical analyses of data were performed according to CLSI EP 28-A3. Outliers were identified and removed based on the method described by Dixon's rule [11]. Data distributions were evaluated by using the Kolmogorov-Smirnov test. Then, nonparametric analysis (2.5th - 97.5th percentiles) was used to establish reference intervals for GIR, HOMA, and QUICKI. The outcome variable was whether insulin was used in initial treatment procedures in newly diagnosed DM patients. The concordance rates were calculated based on established reference intervals of these three indexes, and the ROC curves were used to judge the clinical insulin treatment value of these three indexes. The GIR, HOMA, and QUICKI were calculated according to the formulas:

$$\frac{glucose}{0.0551\ x\ insulin}$$

$$\frac{glucose\ x\ insulin}{22.5}$$

$$\frac{1}{(\log\left(\frac{glucose}{0.0551}\right) + \log(insulin))}$$

respectively (the unit of glucose was mmol/L, the unit of insulin was μIU/mL). Statistical analysis was performed using the SPSS Statistics for Windows, version 24.0. (IBM Corp., Armonk, N.Y., U.S.A.), Microsoft Excel 2007 (Redmond, WA, USA) and R package version 3.5.1. in the R software platform [12].

RESULTS

Reference intervals for GIR, HOMA, and QUICKI

A total of 123 samples were included. No outliers were eliminated according to results of Dixon's rule for these three indexes. When Kolmogorov-Smirnov test was used to test data normal distribution, two of three indexes showed abnormal distributions (p = 0.001, 0.024, and 0.200). Therefore, log transformation was used to secure normality (p = 0.200, 0.200, and 0.200) (Figure 1). It was unnecessary to partition age and reference values based on the formulas in the document CLSI EP28-A3 (Table 1, 2). Finally, the reference intervals

Table 1. Distribution and partition of GIR, HOMA, and QUICKI after log transformation by age from reference individuals.

Index	Group	Age	No.	Mean	SD	Z	Z*	s2/s1	s2/(s2-s1)
GIR	1	18 - 20	8	-0.30	0.20				
	2	21 - 30	78	-0.23	0.15	-0.96	1.80	0.76	-3.10
	3	31 - 40	33	-0.21	0.16	-0.35	2.04	1.07	15.92
	4	41 - 56	4	-0.15	0.21	-0.62	1.18	1.28	4.56
HOMA	1	18 - 20	8	0.20	0.21				
	2	21 - 30	78	0.28	0.17	-1.09	1.80	0.82	-4.45
	3	31 - 40	33	0.29	0.19	-0.26	2.04	1.10	11.01
	4	41 - 56	4	0.38	0.26	-0.62	1.18	1.39	3.60
QUICKI	1	18 - 20	8	-0.297	0.202				
	2	21 - 30	78	-0.227	0.153	-0.96	1.80	0.76	-3.10
	3	31 - 40	33	-0.215	0.163	-0.35	2.04	1.07	15.92
	4	41 - 56	4	-0.148	0.208	-0.62	1.18	1.28	4.56

Note: s1 and s2 are the observed variances of the two subgroups. If the calculated z exceeds z*, partitioning was recommended. In addition, partitioning was recommended if s2/s1 exceeds 1.5, or equivalently, if |s2/(s2−s1)| is less than 3.

Table 2. Distribution and partition of GIR, HOMA and QUICKI after log transformation by gender from reference individuals.

Index	Group	Gender	No.	Mean	SD	Z	Z*	s2/s1	s2/(s2-s1)
GIR	1	male	62	-0.21	0.16				
	2	female	61	-0.24	0.16	0.88	2.15	1.02	63.12
HOMA	1	male	62	0.30	0.18				
	2	female	61	0.27	0.19	0.89	2.15	1.04	26.87
QUICKI	1	male	62	-0.213	0.59				
	2	female	61	-0.238	0.61	0.88	2.15	1.02	63.12

Note: s1 and s2 are the observed variances of the two subgroups. If the calculated z exceeds z*, partitioning was recommended. In addition, partitioning was recommended if s2/ s1 exceeds 1.5, or equivalently, if |s2/(s2−s1)| is less than 3.

Table 3. Reference intervals and confidence intervals for reference limits of GIR, HOMA, and QUICKI.

Index	Reference interval	90% confidence intervals *
GIR	5.83 - 21.15	lower limit 3.84 - 6.05
		upper limit 20.56 - 26.60
HOMA	0.87 - 4.22	lower limit 0.65 - 0.98
		upper limit 3.96 - 5.74
QUICKI	0.309 - 0.392	lower limit 0.297 - 0.312
		upper limit 0.384 - 0.413

*** lower and upper limit of 90% CI for 2.5th percentile in target population were equal to lowest sample value and 7th lowest sample value, respectively. To obtain limits corresponding to a 90% CI for the 97.5th percentile, these rank numbers are subtracted from 124, giving 117 and 123.**

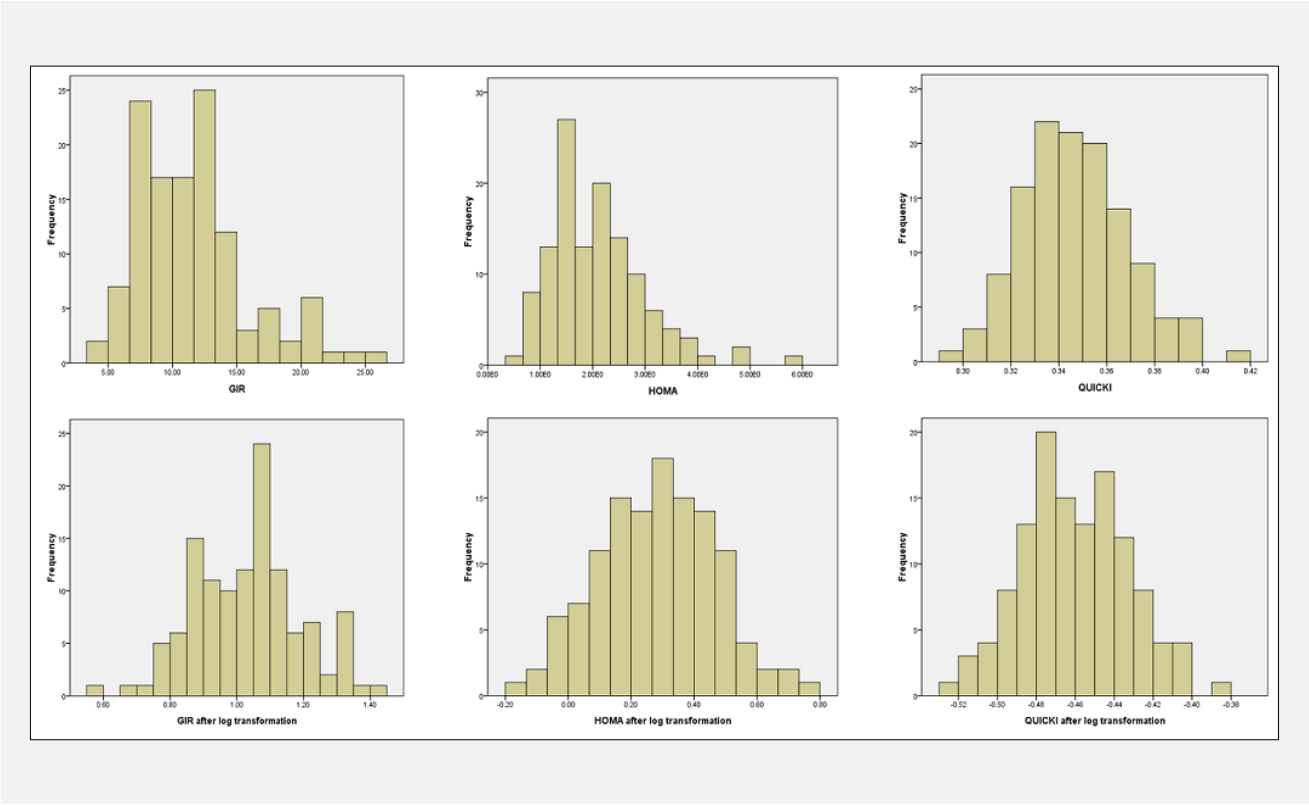

Figure 1. The distribution of GIR, HOMA, and QUICKI before and after log transformation in 123 healthy individuals.

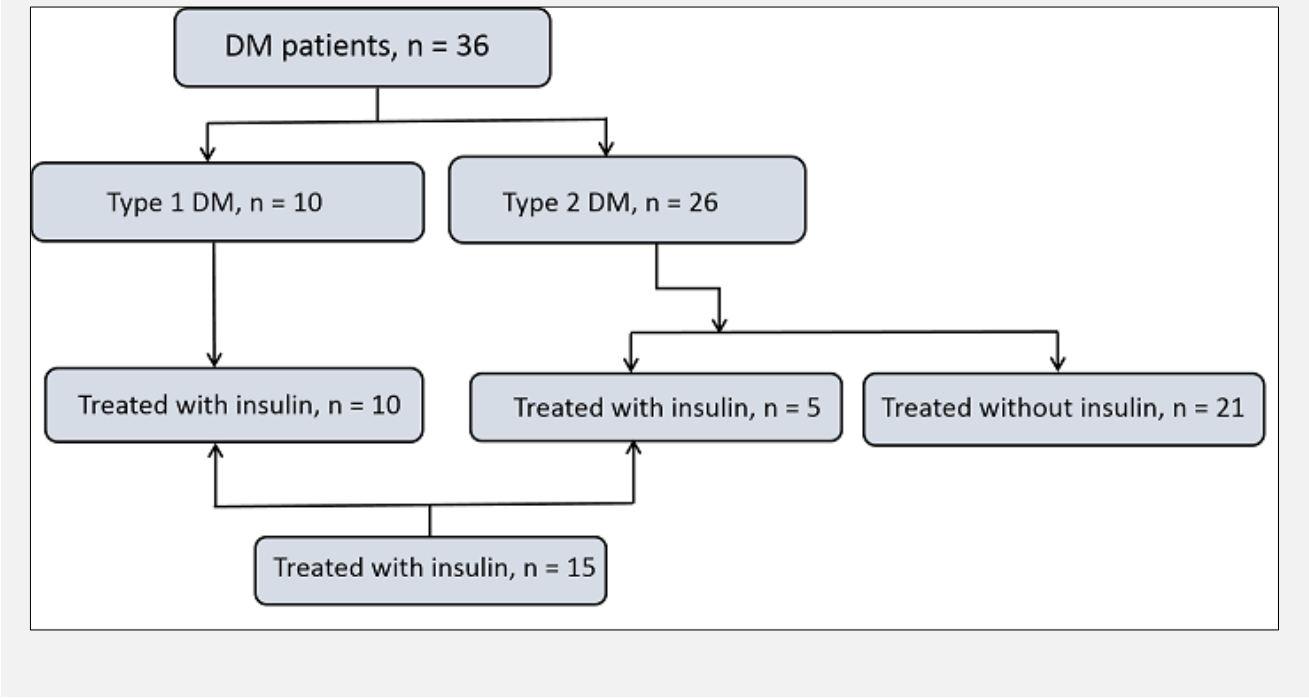

Figure 2. Diagram of DM patient types and insulin treatments.

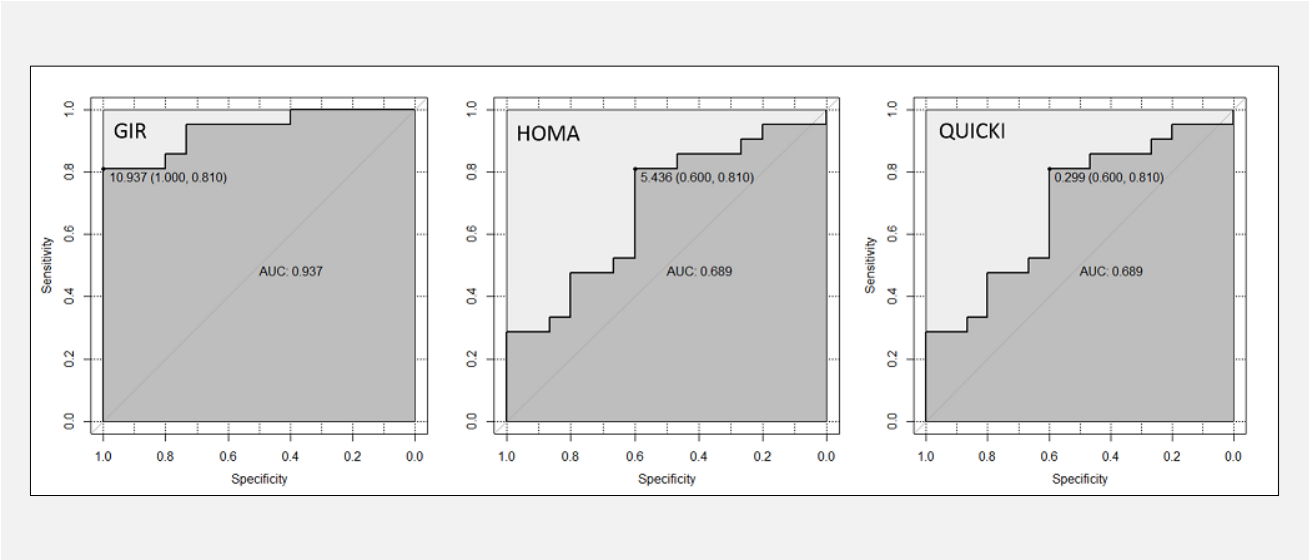

Figure 3. The ROC curve analysis of GIR, HOMA, and QUICKI in type 1 and type 2 DM patients.

for GIR, HOMA, and QUICKI were listed in Table 3.

The role of the three indexes in type 2 newly diagnosed DM

In this study, 36 DM patients were enrolled, 26 of 36 were newly diagnosed as type 2 DM. Patients type was presented in Figure 2. To GIR, among type 2 DM patients 57.7% (15/26) were below the lower reference limit; To HOMA, among type 2 DM patients 80.8% (21/26) were above upper reference limit; To QUICKI, among type 2 DM patients 80.8% (21/26) was below lower reference limit. Abnormal results of patients were filled with yellow, blue, and red (Supplemental Table2), respectively.

The role of the three indexes in newly diagnosed DM with insulin treatment

Fifteen of thirty-six DM patients were treated with insulin in their initial treatment procedures, 5 of whom were type 2 DM. To GIR, there were 71.4% (15/21) below the lower reference limit among DM patients whose clinical initial treatment procedures did not include insulin, 86.7% (13/15) were above the upper reference limit among DM patients whose clinical initial treatment procedures included insulin. In our DM population, a GIR > 10.937 was sensitive in 100.0% and specific in 81.0% with the area under the curve (AUC) 0.937 (95% CI 0.681 - 1.000) by receiver-operator characteristic (ROC) curve (Figure 3); To HOMA, There were 85.7% (18/21) above the upper reference limit among DM patients whose clinical initial treatment procedures did not include insulin, 0% (0/15) were below the lower reference limit among DM patients whose clinical initial treatment procedures included insulin. A HOMA < 5.436 was sensitive in 60.0% and specific in 81.0% with AUC 0.689 (95% CI 0.510 - 0.868) by ROC (Figure 3); To QUICKI, there were 85.7% (18/21) below the lower reference limit among DM patients whose clinical initial treatment procedures did not include insulin, 0% (0/15) were above the upper reference limit among DM patients whose clinical initial treatment procedures included insulin. A QUICKI > 0.299 was sensitive in 60.0% and specific in 81.0% with AUC 0.689 (95% CI 0.510 - 0.868) by ROC (Figure 3); when insulin insufficiency was judged based on whether insulin was included in the initial treatment procedures. Concordance rates with clinical treatment using the three indexes were 77.8% (28/36), 50% (18/36), and 50% (18/36), respectively. Concordance results of patients were filled with yellow, blue and red (Supplemental Table 3), respectively.

DISCUSSION

The results of serum glucose and insulin are important considerations in the diagnosis, response, and treatment to monitor patients with diabetes. Serum glucose is mediated by insulin, which is secreted by β-cells of the pancreatic Islets of Langerhans [13]. GRI, HOMA, and QUICKI were all relevant to serum glucose and insulin. In this study, we established the three reference intervals according to EP28-A3, respectively (Table 3). No gender and age difference in GRI, HOMA and QUICKI was observed in reference healthy individuals (Table 1 and Table 2).

Patients with insulin resistance has been of considerable interest in hyperlipidemia, ovarian hyperandrogenism, and early markers of adult diseases such as type 2 diabetes mellitus, hypertension, and cardiovascular disease

[8]. The biological mechanism of insulin resistance complicates type 2 diabetes mellitus, but the evaluation index usually used was the relationship between insulin and glucose [14,15]. Previous studies only analyzed a few samples to identity the meaning of GRI, HOMA, and QUICKI [8,16], even using an arbitrary cutoff point [15,17]. Therefore, we used reference intervals to obtain the situation of insulin resistance in type 2 DM. The prevalence (80.8%) was higher according to HOMA and QUICKI than GIR, which was similar to a previous report [18].

Insulin is the most potent antihyperglycemic agent, which is essential to type 1 DM patient [2], but many factors should be considered when deciding to start insulin therapy [10]. In this study, we found GIR was a reliable index to use insulin in type 1 and type 2 DM in initial treatment procedures, with higher AUC (0.937) and concordance rates (77.8%). However, HOMA and QUICKI were not good indexes to guide clinical initial insulin treatment due to lower AUC (0.689) and concordance rates (50.0%).

This study has strengths and limitations. The reference intervals were established according to EP28-A3. The reference individuals were selected based on strict inclusion and exclusion criteria, abnormal BMI individuals whose three indexes might be abnormal [19] were excluded. The limitation was that the number of DM patients was small. More studies are needed to verify our conclusions.

In conclusion, our findings underscore the importance of reference intervals and to identify the roles in untreated diabetes. These finding expand our understanding of the three indexes and highlight their potential clinical implications.

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Author Contributions:
Conceived and designed the experiments: Fei Cheng, Yanwei Li and Yongde Chen. Performed the experiments: Fei Cheng, Dianhong Wang and Lei Sun. Analyzed the data: Fei Cheng and Haopeng Chao. Wrote the paper: Fei Cheng.

Declaration of Interest:
The authors declare that they have no conflict of interests.

Ethical Approval and Consent Statement:
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration. Written informed consents were obtained from all subjects.

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