HOMA-IR Assessment for Impaired Glucose Tolerance, Impaired Fasting Glucose and Insulin Resistance Diagnosis

Erika Severeyn[1(✉)], Jesús Velásquez[1], Gilberto Perpiñán[2], Héctor Herrera[3], Sara Wong[4], José Díaz[5], and Miguel Altuve[6]

[1] Departamento de Termodinámica y Transferencia de Calor, Universidad Simón Bolívar, Caracas, Venezuela
severeynerika@usb.ve
[2] Faculty of Electronic and Biomedical Engineering, Antonio Nariño University, Cartagena, Colombia
[3] Departamento de Tecnología de Procesos Biológicos y Bioquímicos, Universidad Simón Bolívar, Caracas, Venezuela
[4] Departamento de Electrónica y Circuitos, Universidad Simón Bolívar, Caracas, Venezuela
[5] Departamento de Ingeniería Eléctrica y Computación, Universidad Autónoma de Ciudad Juarez, Ciudad Juarez, Mexico
[6] Faculty of Electrical and Electronic Engineering, Pontifical Bolivarian University, Bucaramanga, Colombia

Abstract. Impaired glucose tolerance (IGT), impaired fasting glucose (IFG) and insulin resistance (IR) are prediabetic conditions diagnosed by glucose and insulin values measured by oral glucose tolerance test (OGTT). In the OGTT, insulin and glucose levels are measured in five different blood samples: a sample in fasting (minute 0) and four others after oral intake of 75 gr of glucose, at intervals of 30 min (minute 30, 60, 90, and 120). The values of glucose at 0 and 120 min from OGTT are used for the diagnosis of IFG and IGT, respectively. The HOMA-IR is the most used method of determining IR in large population-based studies; it is mathematically derived from fasting glucose and insulin measurements from OGTT. One of the limitations of HOMA-IR is the difficulty of predicting IR in populations with IGT. The aim of this study is to evaluate the capability of a HOMA-IR and modified version of HOMA-IR (HOMA-IR calculated from glucose and insulin of 30, 60, 90 and 120 min of OGTT) to diagnose IGT, IR, and IFG. Receiver operating characteristic (ROC) curves and area under the ROC curve (AUC) were performed to assess the predictive capacity of HOMA-IR and modified versions. The present study demonstrated that modified versions of HOMA-IR calculated using glucose and insulin from 60 and 90 min of OGTT are alternative indexes (AUC $\geq$ 0.70) for IGT, IFG and IR detection.

Keywords: HOMA-IR · ROC curves · Impaired fasting glucose · Impaired glucose tolerance · Insulin resistance

C. A. González Díaz et al. (Eds.): CLAIB 2019, IFMBE Proceedings 75, pp. 1275–1283, 2020.
https://doi.org/10.1007/978-3-030-30648-9_164

1 Introduction

Impaired glucose tolerance (IGT) is an intermediate metabolic state between normal and diabetic glucose homeostasis [1]. This condition is the precursor of diabetes, but the progression to overt the disease is not straight-forward [2]. The IGT is diagnosed with postprandial glucose of 140–199 mg/dL [3]. Studies corroborate that patients who have been diagnosed with IGT have a high risk of developing diabetes in the next decade after the diagnosis, which is why early diagnosis of this condition is very important [4].

The IGT is a metabolic disorder that is highly related to other metabolic pathologies, such as impaired fasting glucose (IFG) and insulin resistance (IR). The IFG is defined as fasting glucose levels of 100–125 mg/dL [5]. Studies reveal that these diseases are in many cases in concomitance worsening the patient's prognosis making them more prone to the development of diabetes. The Hoorn Study [6] revealed that 33% of patients with IFG, but not impaired glucose tolerance (IGT), and 64.5% of patients with IFG and IGT developed diabetes over a follow-up of 5.8–6.5 years.

The IR diagnosis is made through the homeostatic model assessment (HOMA-IR). HOMA-IR is the most used method of determining IR in large population-based studies; and it is mathematically derived from fasting glucose and insulin measurements. The IR is diagnosed when the HOMA-IR $\geq$ 2.5. HOMA-IR has been used to assess longitudinal changes in insulin resistance in persons with type 2 diabetes of various ethnic groups in order to examine the natural history of diabetes and to assess the effects of treatment [7]. It can also be utilized in non-diabetic populations as it allows comparisons of insulin sensitivity among persons with IGT and in longitudinal assessment of people who later develop IGT [8].

Studies have suggested that HOMA-IR may not be a good predictor of insulin resistance in all individuals. Indeed, several investigators report that HOMA-IR and insulin action do not correlate highly or significantly, particularly in individuals with IGT and IFG [9, 10]. There are many methods that have been designed to diagnose IR. Some methods, such as Avignon and Matsuda [11], use glucose and insulin values during the oral glucose tolerance test (OGTT). These methods have been shown to be better predictors of IR than HOMA-IR in populations with IGT and normal values of fasting glucose and insulin [11]. Since HOMA-IR use the glucose and insulin fasting values to calculate insulin sensitivity, we found interesting to explore a modified version of HOMA-IR (constructed from the use of glucose and insulin during OGTT) in order to assess the capability in the diagnosis of IGT, IFG, and IR.

The receiver operating characteristic (ROC) curve had been used in bioengineering to assess the diagnostic capability of a binary classifier. The ROC curve analysis is a statistical method to determine the diagnostic accuracy of a classifier. In general, the roc curve is used for: (i) determining the cut-off point of a continuous scale in which the highest sensitivity and specificity is reached [12], and (ii) evaluating the discriminative capacity of a diagnostic test, that is, its ability to differentiate healthy versus sick subjects. ROC curves have been used to evaluate the HOMA-IR in the diagnosis of diabetes and obesity [12]. Also, with the ROC curves, it had been determined the optimal cut-off points of HOMA-IR in the insulin resistance determination on different types of populations according to ethnic origin [13] and age [14].

Table 1. Glucose and insulin values of the OGTT and the values of HOMA-IR_0 for the subjects with IGT, IFG, IR and control group.

Variables	Control[e] Male = 9, n = 53	IGT Male = 15, n = 29	IFG Male = 30, n = 55	IR Male = 19, n = 39
Age[a, c, d] [years]	37.15 ± 14.62[f] 14.00–75.00[g] 33.22–41.09[h]	48.10 ± 13.42 20.00–72.00 43.22–52.99	49.69 ± 14.24 15.00–78.00 45.93–53.45	41.03 ± 12.78 15.00–66.00 37.02–45.04
G_0[a, b] [mg/dL]	90.66 ± 5.74 80.00–99.00 89.11–92.21	100.17 ± 9.32 77.00–115.00 96.78–103.57	106.31 ± 5.13 100.00–118.00 104.95–107.66	100.26 ± 10.16 77.00–117.00 97.07–103.44
G_{30}[a] [mg/dL]	134.11 ± 21.75 87.00–186.00 128.26–139.97	170.17 ± 29.28 100.00–230.00 159.52–180.83-	165.69 ± 27.56 113.00–230.00 158.41–172.97	160,77 ± 32,51 89.00–230.00 150.57–170.97
G_{60}[a] [mg/dL]	125.21 ± 26.85 73.00–184.00 117.98–132.44	183.03 ± 33.79 80.00–231.00 170.74–195.33	164.42 ± 39.51 95.00–256.00 153.98–174.86	158.64 ± 41.87 77.00–227.00 145.50–171.78
G_{90}[a, b, c, d] [mg/dL]	110,83 ± 23,91 53,00–181,00 104,39–117,27	175.07 ± 34.14 85.00–245.00 162.64–187.49	144.53 ± 38.85 71.00–245.00 134.26–154.80	140.23 ± 41.21 67.00–245.00 127.30–153.16
G_{120}[a, b, c, d] [mg/dL]	104.08 ± 17.74 64.00–139.00 99.30–108.85	161.66 ± 15.13 140.00–192.00 156.15–167.16	125.42 ± 26.71 72.00–181.00 118.36–132.48	119.64 ± 29.02 67.00–181.00 110.53–128.75
I_0[a, c, d] [μUI/mL]	3.86 ± 2.10 2.00–10.30 3.30–4.43	8.91 ± 5.66 2.00–22.00 6.84–10.97	9.62 ± 6.42 2.00–28.00 7.93–11.32	17.97 ± 8.17 9.55–55.00 15.41–20.54
I_{30}[a, b, c, d] [μUI/mL]	54.50 ± 37.00 12.70–189.00 44.54–64.46	76.09 ± 66.41 21.40–276.00 51.92–100.26	87.70 ± 57.77 16.80–276.00 72.43–102.96	120.53 ± 68.41 25.60–293.00 99.06–142.00
I_{60}[a, b, c, d] [μUI/mL]	62.75 ± 40.91 10.80–193.00 51.74–73.77	97.81 ± 80.38 26.30–300.00 68.55–127.07	110.64 ± 69.70 10.00–300.00 92.21–129.06	151.81 ± 85.53 5.00–300.00 124.96-178.65
I_{90}[a] [μUI/mL]	51.67 ± 28.24 8.26–137.00 44.07–59.28	110.57 ± 79.52 12.70–300.00 81.63–139.51	104.43 ± 68.16 12.70–300.00 86.42–122.45	136.81 ± 82.69 34.00–300.00 110.86–162.77
I_{120}[a] [μUI/mL]	46.21 ± 21.78 5.63–101.00 40.35–52.08	110.55 ± 72.31 27.50–300.00 84.23–136.87	86.80 ± 62.06 19.70–300.00 70.40–103.20	104.98 ± 73.72 21.90–300.00 81.84–128.11
HOMA-IR_0[a, c, d]	0.87 ± 0.48 0.40–2.44 0.74–1.00	2.27 ± 1.52 0.42–5.60 1.72–2.82	2.55 ± 1.73 0.50–7.60 2.09–3.00	4.39 ± 1.73 2.52–10.59 3.85–4.93

[a]Statistically significant differences between the control group and each pathology group (IGT, IFG, and IR).
[b]Statistically significant differences between IFG and IGT group.
[c]Statistically significant differences between IGT and IR group.
[d]Statistically significant differences between IFG and IR group.
[e]Control subjects are those who do not belong to any of the groups with pathology.
[f]Average and standard deviation.
[g]Maximum and minimum value.
[h]95% confidence interval.

The aim of this study is to evaluate the capability of a HOMA-IR and the modified version of HOMA-IR to diagnose IGT, IR, and IFG. A database of 137 subjects with values of glucose and insulin during OGTT was used. To assess the predictive capacity of HOMA-IR, ROC curves were performed. In the next section the methodological procedure will be explained. In section three and four, results and discussion will be presented. And finally, in section five, the conclusions and future work proposals will be presented.

2 Methodology

2.1 Database

Between 2010 and 2013, 137 adults (male = 48 subjects) between 14 and 78 years old without diabetes were enrolled at the Clinical Research Laboratory of the Venezuela Central University. Each participant underwent the 5-sample-OGTT. In the 5-sample OGTT, insulin and glucose levels are measured in five different blood samples: a sample in fasting of 8 h (G_0, I_0) and four others after oral intake of 75 gr. of glucose at 30 min (G_{30}, I_{30}), 60 min (G_{60}, I_{60}), 90 min (G_{90}, I_{90}),and 120 min (G_{120}, I_{120}) [15–17].

Every database's subject was diagnosed of IGT according to the WHO criteria ($140 \leq G_{120} \leq 199$ mg/dL) [5], IFG to ADA criteria ($100 \leq G_0 \leq 125$ mg/dL) [3], and IR with a HOMA-IR ≥ 2.5 [18]. The characteristics of the database are shown in Table 1. The clinical protocol adhered to the principles of the Declaration of Helsinki and was approved by the Bioethical Committee of the Medical Science Faculty of Venezuela Central University; all the subjects gave a written informed consent.

2.2 HOMA-IR Assessment

In this investigation, five indexes (HOMA-IR and four indexes constructed from calculating the HOMA-IR with the glucose and insulin values at the 30, 60, 90, and 120 min points of the OGTT) were used to assess the IGT, IFG and IR diagnosis. For IGT diagnosis the HOMA-IR$_0$, HOMA-IR$_{30}$, HOMA-IR$_{60}$, and HOMA-IR$_{90}$ ROC curves were constructed. The HOMA-IR$_{120}$ ROC curve was not created for IGT because the IGT diagnosis has a dependent functionality with postprandial glucose. In IFG and IR the HOMA-IR$_{30}$, HOMA-IR$_{60}$, HOMA-IR$_{90}$, and HOMA-IR$_{120}$ ROC curves were constructed. In this case, the HOMA-IR$_0$ ROC curves were not built because the IFG and IR diagnosis have dependent functionality with fasting glucose. The expressions of the five indexes are presented in the Eqs. (1), (2), (3), (4), and (5).

$$HOMA{-}IR_0 = \frac{I_0 G_0}{405} \tag{1}$$

$$HOMA{-}IR_{30} = \frac{I_{30} G_{30}}{405} \tag{2}$$

$$HOMA{-}IR_{60} = \frac{I_{60} G_{60}}{405} \tag{3}$$

$$HOMA{-}IR_{90} = \frac{I_{90}G_{90}}{405} \tag{4}$$

$$HOMA{-}IR_{120} = \frac{I_{120}G_{120}}{405} \tag{5}$$

Where I_0, I_{30}, I_{60}, I_{90} and I_{120} are the values of insulin at 0, 30 60, 90 and 120 min of the 5-samples-OGTT, and G_0, G_{30}, G_{60}, G_{90} and G_{120} are the values of glucose at 0, 30, 60, 90 and 120 min of the 5-samples-OGTT.

2.3 Performance Measurements

To assess the HOMA-IR (HOMA-IR_0), and the modified versions (HOMA-IR_{30}, HOMA-IR_{60}, HOMA-IR_{90}, and HOMA-IR_{120}), ability for IGT, IR, and IFG detection, the ROC curves and the area under the ROC curve (AUC) were estimated. To construct and analyze the ROC curves, the sensitivity (SEN), specificity (ESP), positive predictive value (PPV), and negative predictive value (NPV) were calculated for each subject. An AUC $\geq$ 0.70 was considered as an acceptable predictive value [19]. The optimal cut-off point was defined as the shortest distance between the ROC curve and the point [0,1] of the ROC curve plot.

2.4 Statistical Analysis

Non-paired samples were handled with a different distribution than normal. To determine the differences between groups of two, the non-parametric Mann-Whitney U test was used, and between groups of three or more, the non-parametric statistical test of Kruskal Wallis were used; a p-value less than 0.01 was considered statistically significant [20]. The data in the text and in the tables are presented as values of mean and standard deviation, minimum and maximum values and 95% confidence interval.

3 Results

Table 1 reports the glucose and insulin values of the OGTT and the values of HOMA-IR_0 for the subjects with IGT, IFG, IR, and control group. The database consists of 137 subjects, 21.1% of subjects have two or more of the pathologies in concomitance (6.6% subjects of the total database with IFG, IGT and IR, 9.5% with IFG and IR, 5.1% with IGT and IFG, and none with IGT and IR).

Figure 1(a), (b), and (c) show the ROC curves of HOMA-IR_0, HOMA-IR_{30}, HOMA-IR_{60} and HOMA-IR_{90} for IGT diagnosis, and ROC curves of HOMA-IR_{30}, HOMA-IR_{60} HOMA-$IR_{90,}$ and HOMA-IR_{120} for IR and IFG diagnosis. Table 2 shows the AUC as well as the sensitivity, specificity, positive predictive value, and negative predictive value for the optimal detection cut-off point for each HOMA-IR version.

Table 2. HOMA-IR ROC curves for the predictability of IGT, IR and IFG.

HOMA-IR		SEN	SPE	PPV	NPV	Optimal cut-off point	AUC
IGT	0 min	0.68	0.59	0.30	0.88	1.50	0.58
	30 min	0.61	0.45	0.22	0.82	17.85	0.50
	60 min	0.68	0.54	0.27	0.87	22.56	0.59
	90 min	0.75	0.66	0.36	0.91	24.88	0.72
IR	30 min	0.75	0.76	0.56	0.88	26.85	0.80
	60 min	0.75	0.78	0.58	0.88	34.06	0.80
	90 min	0.70	0.72	0.51	0.86	25.98	0.77
	120 min	0.75	0.63	0.45	0.86	17.09	0.69
IFG	30 min	0.61	0.74	0.62	0.73	25.98	0.69
	60 min	0.68	0.70	0.60	0.76	25.16	0.70
	90 min	0.73	0.57	0.54	0.76	19.25	0.67
	120 min	0.59	0.72	0.59	0.72	20.19	0.66

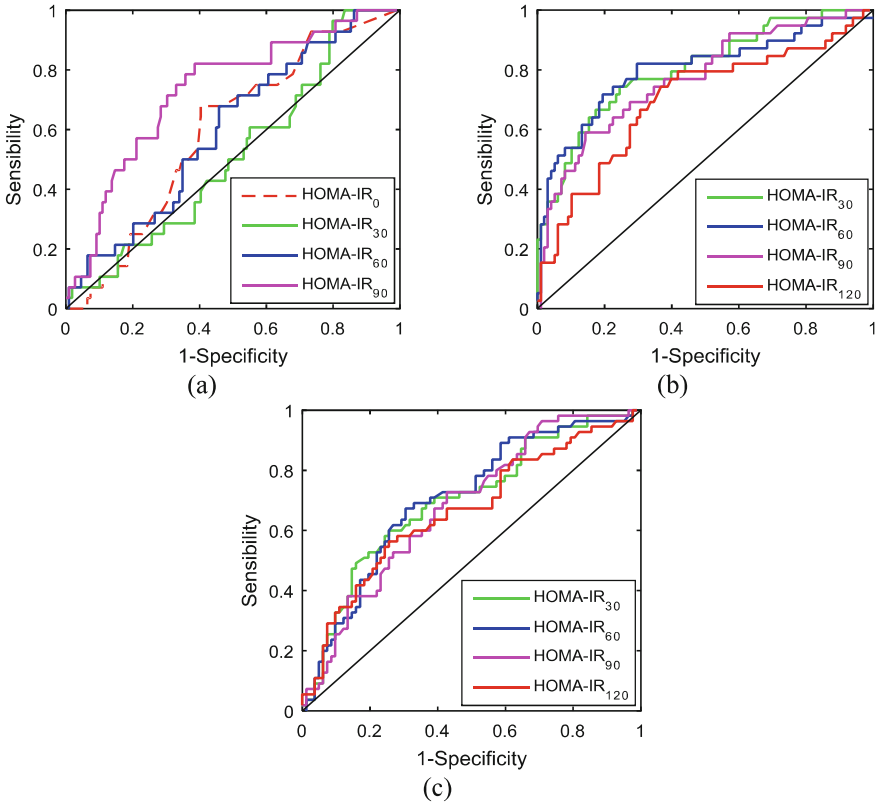

Fig. 1. HOMA-$IR_{0,30,60,\text{ and }90}$ ROC curves for the predictability of (a) IGT, HOMA-$IR_{30,60,90,\text{ and }120}$ ROC curves for the predictability of (b) IR and (c) IFG.

4 Discussion

Subjects with IGT have a HOMA-IR_0 of 2.27 ± 1.52 (Table 1), and in this group, there were no subjects with IR. On the other hand, the subjects who showed IFG and IR reported a HOMA-IR_0 of 3.98 ± 1.13, which is higher ($p < 0.001$) than the one reported in the group with IFG (2.55 ± 1.52, see Table 1). Furthermore, from the total database, there were subjects who had the three pathologies in concomitance. This group obtained a HOMA-IR_0 of 4.47 ± 1.56. All these facts could suggest that IGT could be the starting point for IR followed by metabolic disorders associated with altered fasting glucose and insulin values. Studies corroborate that to have two or more prediabetic conditions (IFG, IGT, and IR) is a sign that the metabolic dysfunction is getting worse [5, 6].

Age plays an important role in the development of pre-diabetic condition. Control subjects (Table 1) have a lower average age ($p < 0.001$) than subjects who have already developed any of the three pathologies. No significant differences were found between the IGT and IFG. All these facts imply that prediabetic conditions tend to increase their prevalence with increasing age [21].

Studies have suggested that using OGTT glucose and insulin values could improve the predictability of methods that measure insulin sensitivity [11]. In this case, the ROC curves with the best predictability for the pathologies studied (AUC $\geq$ 0.70) were the HOMA-IR_{90} for the case of IGT and the HOMA-IR_{60} for the case of IR and IFG. This implies that the HOMA-IR improves its predictability to prediabetic disorders if it is calculated from glucose and insulin values of OGTT that are not the fasting ones. Additionally, the glucose values at 60 min of the OGTT have been explored in the predictability of diabetes obtaining an AUC $\geq$ 0.80 [22]. In this work, the glucose and insulin values were able to determine subjects with IR and IFG with an AUC of 0.8, and 0.7, respectively. All these findings imply that glucose and insulin values at 60 min of OGTT could predict diabetes and prediabetes [23].

On the other hand, it can be observed that the curves with the best AUC (HOMA-IR_{90} for IGT diagnosis, HOMA-IR_{60} for IR, and IFG diagnosis) have a higher negative predictive value (NPV = 0.91 for IGT diagnosis, NPV = 0.88 for IR diagnosis and NPV = 0.76 for IFG diagnosis) than their corresponding positive predictive value (PPV = 0.36 for IGT diagnosis, PPV = 0.45 for IR diagnosis, and PPV = 0.59 for IFG diagnosis). These results suggest that all methods detect normal subjects more efficiently than subjects who are suffering from the pathologies (Table 2).

While analyzing the optimal cut-off points obtained from the best detectors for IR (HOMA-IR_{60}), and IFG (HOMA-IR_{60}), it may be seen that the cut-off point for IFG ($HOMAIR_{60} > 25.16$) is lower than the cut-off point for IR ($HOMAIR_{60} > 34.06$). These facts indicate that when a subject is diagnosed with IR, is automatically diagnosed with IFG. These results corroborate some studies that suggest there is a high prevalence of IFG in subjects with IR [24].

5 Conclusion

The OGTT is an important tool that allows the study of glucose metabolism, and the design of new indexes that allow extracting information from the OGTT is one of the most explored objectives by physicians nowadays. The present study demonstrated that modified versions of HOMA-IR which are calculated using glucose and insulin from 60 and 90 min of 5-samples-OGTT could be used as a diagnostic method for IFG, IGT, and IR.

In future works, the modified versions of the HOMA-IR could be compared with other methods that use glucose and insulin during the OGTT, such as Avignon method, whose correlation with the hyperinsulinemic-euglycemic clamp is 0.89 [11].

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