Original Article

Reference Interval, Optimal Threshold Value, and Correlates of Homeostasis Model Assessment of Insulin Resistance in Healthy Normal-weight Adults in a Nigerian Population

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Abstract

Background: Currently, there is paucity of locally–established reference intervals and optimal threshold values for homeostasis model assessment of insulin resistance (HOMA-IR) in Nigeria. **Aims:** The aim of this study was to determine the normative values and correlates of HOMA-IR among apparently healthy adults in a Nigerian population. **Materials and Methods:** A cross-sectional study was carried out among 210 healthy, normal-weight adults aged 18–64 years. Anthropometric, physical, and biochemical measurements were carried out including fasting plasma glucose and fasting plasma insulin levels. The HOMA-IR was calculated using a mathematical formula. The reference intervals and optimal threshold values for the HOMA-IR were derived using the nonparametric percentile method. **Results:** A total of 210 healthy normal-weight, nondiabetic adults, 110 males (52.4%) and 100 females (47.6%) participated in the study. The 2.5th, 75th, 90th and 97.5th percentile values of the HOMA-IR for total (n = 210), male (n = 110), and female (n = 100) study participants were 0.02, 1.2.28, 2.18 and 2.56; 0.02, 1.19, 2.0 and 2.54; 0.24, 1.66, 2.25, and 2.58 respectively. The 2.5th to 97.5th reference intervals for HOMA-IR for total (n = 100) were 0.02–2.56, 0.02–2.54, and 0.24–2.58 respectively. The 90th percentile optimal threshold value for total (n = 210), male (n = 110), and female (n = 100) participants were 2.18, 2.00 and 2.25 respectively. **Conclusion:** The HOMA-IR reference intervals and optimal threshold values in the Nigeria adult population are mostly similar to those reported by previous studies.

Keywords: Healthy adults, homeostasis model assessment of insulin resistance, insulin resistance, Nigeria, optimal threshold value, reference interval

Introduction

With respect to glucose homeostasis, insulin promotes transport of glucose into adipose tissue and skeletal muscle cells, but inhibits glucose production and release by the hepatocytes of the liver.[1] The inability of insulin to carry out its primary actions on glucose homeostasis despite normal or even elevated plasma insulin concentrations is called insulin resistance (IR).[2] IR and beta-cell dysfunction are the two major mechanisms involved in the pathogenesis of type 2 diabetes mellitus (T2DM).[3] Beside T2DM, IR is also associated with other disease conditions such as obesity, the metabolic syndrome, hypertension, dyslipidaemia, polycystic ovary disease, atherosclerosis and atherosclerotic cardiovascular disease.[4] Because IR is a well-known underlying pathogenetic mechanism and predictor of dysmetabolic and cardiovascular disease conditions, its evaluation/assessment in experimental, clinical and epidemiological studies has become significantly important.[5,6]

Several direct and indirect methods for assessment of insulin sensitivity/IR (IS/IR) have been described. The hyperinsulinaemic euglycaemic glucose clamp (HEGC) technique is regarded as the gold standard for assessment of

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IS/IR.[7] However, this HEGC technique is laborious, invasive, cumbersome, time-consuming and not amenable to routine laboratory and epidemiological applications.[8,9] Consequently, simpler surrogate measures of IS/IR have been developed and adopted for clinical, experimental and epidemiological studies that involve assessment of IS/IR. Chief among these surrogate markers of IS/IR is the homeostasis model assessment of IR (HOMA-IR). The HOMA-IR is a mathematical model developed by Matthews *et al*. in the year, 1985.[10] It evaluates the normal physiological dynamics of glucose and its major regulatory hormone, insulin. The HOMA-IR is frequently used in clinical, epidemiological and experimental studies to assess IR. It has been shown to correlate strongly with the HEGC technique.[11] It is simple, minimally invasive, consistent, precise and involves simple mathematical calculations that are amenable to routine laboratory application.[8,9] Nevertheless, the HOMA-IR, owing to its inherent characteristics, is a highly variable index of IR with notable limitations.[12] Hence, it has been recommended that each laboratory should establish its indigenous reference interval and optimal threshold value (cut-off point) for the population that it serves.[13]

Currently, there is paucity of locally-established reference intervals and optimal threshold values for HOMA-IR in Nigeria. Most local studies that involved the assessment of IR adopted HOMA-IR values quoted by foreign studies. Based on this, this study was designed to establish the reference interval and optimal threshold value for HOMA-IR among apparently healthy glucose tolerant young and middle-age Nigerian adults with normal body mass index (BMI) based on the recommendations of the Clinical and Laboratory Standard Institute (CLSI) C28-A3 document.[13]

Materials and Methods

Study location

The study was conducted at the metabolic clinic of the Department of Chemical Pathology of a Nigerian University Teaching Hospital.

Study design

The study was a cross-sectional descriptive study. Purposive sampling technique was used to recruit eligible study participants.

Study participants

The study participants included healthy young and middle-age adults between the ages of 18–64 years that met the selection criteria. They comprised healthy volunteers that were recruited from both the metabolic clinic of the Department of Chemical Pathology of a Nigerian University Teaching Hospital and the university communities. Participants that met the selection criteria constituted the reference individuals. The inclusion criteria were as follows: (a) healthy adult between the ages of 18 and 64 years; (b) BMI of 18.5–24.9 kg/m^2 (c) waist circumference (WC) of <88 cm for females and <102 cm for males; (d) fasting plasma glucose (FPG) of <6.1 mmol/L; (e) glycated haemoglobin of <6.5%; (f) serum alanine aminotransferase of <31.0U/L; (g) serum creatinine concentration of <130 μmol/L; (h) fasting plasma triglyceride and high-density lipoprotein-cholesterol of <1.7 mmol/L and >1.0 mmol/L respectively. The exclusion criteria were based on the CLSI guidelines for selection of reference individuals for the establishment of a health-associated reference interval.[13] Study participants with the following conditions were excluded: Hypertension, liver disease, thyroid disorders, and inflammatory diseases. Chronic disorders requiring regular medications, chronic alcoholics, and heavy smokers were also excluded.

Ethical consideration

The ethical approval for the study was obtained from the Joint Ethical Committee of the university and Hospital. Selected study participants provided informed written consent before their final enrollment in the study.

Sample size determination

The sample size for the study was based on the minimum sample size (n) required for the establishment of reference intervals of biochemical analytes as recommended by the C28-A3 document of the CLSI.[13] The CLSI document recommends a minimum sample size of 120 reference individuals (n = 120) for the establishment of health-associated reference intervals. For this study, 210 healthy reference individuals consisting of 110 males (52.4%) and 100 females (47.6%) were recruited for the study with a sex ratio of 1.1:1.0.

General assessment of study participants

The clinical import of the study and the study protocol and procedures were adequately explained to the study participants. The socio-demographic data, present and past medical history were obtained from the study participants using a structured questionnaire. The participants were examined by trained physicians who also carried out review of systems to ascertain good health status of the participants. Prior to the day of examination and specimen collection, the study participants were instructed to fast overnight for a minimum period of 8 h before sample collection between 7:00 am and 10:00 am the next morning (for FPG and fasting plasma insulin [FPI] measurements).

Anthropometric and physical measurements

The body weight in kilogram (kg) and height in centimetres (cm) were measured using a stadiometer while the participant was standing erect, barefooted, with light clothing. The body weight and height were expressed to the nearest 0.1 kg and 0.1 cm respectively. The BMI was calculated using the formula, BMI = Weight in kg/(Height)^2 in m^2 and expressed to the nearest 0.1 kg/m^2. The WC was measure at the level of a point midway between the lower rib cage and the highest point of iliac crest using a graduated measuring tape. The hip circumference (HC) was measured at the level of a maximum extension of the buttocks using the measuring tape. Both WC and HC were expressed to the nearest 0.1 cm. The waist-to-hip ratio (WHR) was calculated using the formula, WHR = WC/HC and the final result was expressed as a whole

integer. The blood pressure (BP) was measured over the left arm using a standardised mercury sphygmomanometer after 10 min of rest by the participant. The systolic BP (SBP) was taken at the first appearance of the Korotkoff sound while the diastolic BP (DBP) corresponded to the 5th Korotkoff sound.

Specimen collection and storage

Specimen collection procedure was explained to each of the study participants. Thereafter, the participants were instructed to rest in the sitting position for about 30 min before venipuncture. Five millilitres (5 mL) of venous blood were collected from each of the participant with 2.5 mL each transferred to a fluoride oxalate bottle (for FPG determination) and a lithium heparin bottle (for FPI determination). The anticoagulated venous blood samples were allowed to stand for 20 min before centrifugation at 3000 rpm for 10 min. The supernatant oxalated plasma was used for measurement of FPG while the heparinised plasma was stored at −20°C for a maximum period of two weeks before batch analysis for FPI.

Laboratory analysis

FPG concentration was measured using the standard colorimetric glucose oxidase method produced by Biolabo® (Biolabo SA, 02160, Maizy, France). FPI concentration was measured using a commercially available enzyme-linked immunosorbent assay kit produced by Bio-Inteco® (Inteco Diagnostics UK, Ltd).

Calculation of homeostasis model assessment of insulin resistance index

The HOMA-IR was calculated using the formula:[8,9]
HOMA-IR = (FPI [mIU/L) × FPG [mmol/L])/22.5

Statistical analysis

The Shapiro-Wilk test was used to assess for the normality or nonnormality of the data distributions. Data for quantitative variables that were nonnormally distributed were presented as median (interquantile range) and percentiles. Data that were normally distributed were expressed as mean ± standard deviation (SD). The 2.5th percentile value represented the lower reference limit (LRL) while the 97.5th percentile represented the upper reference limit (URL).[13] The 75th and 90th percentile values represented the optimal threshold values. Comparisons between quantitative variables were done using nonparametric Mann–Whitney *U*-test while comparison of quantitative variables among groups was performed using nonparametric analysis of variance (Kruskal–Wallis test). Correlations among nonparametric quantitative variables were evaluated using the Spearman's correlation coefficients. A $P < 0.05$ was considered as statistically significant. The statistical package "Statistica" (Statsoft Corp, Tulsa, OK, USA) was used for all the statistical analyses.

Results

A total of 210 healthy, normal-weight nondiabetic adults, 110 males (52.4%) and 100 females (47.6%) participated in the study. The background characteristics of the study participants are shown in Table 1. The median (interquartile range, IQR) of age for the male and female participants were 31.50 (26.00–41.75) years and 27.00 (24.0–35.0) years respectively and the difference was statistically significant ($P = 0.026$). There were statistically significant differences between the male and female median (IQR) values of WHR, DBP, FPG, FPI, FGIR, HOMA-IR among the study participants.

A histogram (not shown) representing the distribution of the HOMA-IR reference values of all the study participants showed a non-Gaussian (non-parametric) distribution in the HOMA-IR values. Thus, the nonparametric percentile method was applied for the statistical determination of the lower and URLs. Using the basic bootstrap method, the 2.5th and 97.5th reference interval and their corresponding 95% confidence limits were 0.02 (0.02–0.02) and 2.56 (2.52–3.40) respectively for the total study participants ($n = 210$).

Table 2 shows the 2.5th, 25th, 50th (median), 75th, 90th, and 97.5th percentile values of the anthropometric and biochemical parameters. The 2.5th 25th, 50th (median), 75th, 90th, and 97.5th values of the HOMA-IR were 0.02, 0.32, 0.68, 1.28, 2.18, and 2.56 respectively. By convention, in the determination of reference intervals using the nonparametric percentile method,

Table 1: Background characteristics of the total, male and female study participants

Name	Total ($n=210$)	Male ($n=110$)	Female ($n=100$)	*P*
Age (years)	30.0 (24.25–38.0)	31.5 (26.0–41.75)	27.0 (24.0–35.0)	0.026**
BMI (kg/m^2)	23.0±1.69	22.71±1.84	23.33±1.44	0.007**
WC (cm)	78.26±6.36	78.63±7.21	77.85±5.28	0.378
WHR	0.8 (0.8–0.9)	0.8 (0.8–0.9)	0.8 (0.7–0.9)	0.0**
SBP (mmHg)	115.49±10.53	115.56±9.56	115.41±11.56	0.916
DBP (mmHg)	70.0 (60.0–80.0)	70.0 (70.0–80.0)	70.0 (60.0–80.0)	0.042**
FPG (mmol/L)	4.5 (4.0–4.8)	4.5 (4.0–5.07)	4.3 (4.0–4.8)	0.022**
FPG (mg/dL)	80.1 (72.0–86.4)	81.0 (72.0–90.0)	77.4 (72.0–83.7)	0.018**
FPI (mIU/L)	3.45 (1.8–7.0)	3.15 (1.4–5.8)	4.0 (2.2–8.45)	0.003**
HOMA-IR	0.68 (0.32–1.28)	0.66 (0.27–1.19)	0.84 (0.46–1.66)	0.019**
LogHOMA-IR	−0.17 (−0.49–0.11)	−0.18 (−0.57–0.08)	−0.08 (−0.34–0.22)	0.019**

**Statistically significant values with 0.0 meaning 0.0001. Data are reported as mean±SD or median (IQR). *P* refers to the statistically significance difference between male and female parameters. IQR: Interquartile range, SD: Standard deviation, DBP: Diastolic blood pressure, SBP: Systolic blood pressure, FPG: Fasting plasma glucose, FPI: Fasting plasma insulin, HOMA-IR: Homeostasis model assessment of insulin resistance, WC: Waist circumference, WHR: Waist-to-hip ratio, BMI: Body mass index

the 2.5th percentile value for the HOMA-IR (0.02) corresponds to the LRL while the 97.5th percentile value (2.56) represents the URL for the total number of participants (n = 210). That is, HOMA-IR reference interval for both male and female participants is 0.02-2.56. Respectively, the 2.5th and 97.5th reference intervals for male participants (n = 110) was 0.02–2.54 while that of female participants (n = 110) was 0.24–2.58. By convention, the optimal threshold value for HOMA-IR may be determined by the 90th percentile value or 75th percentile value of the distribution. Based on the above, the 90th percentile value of HOMA-IR for total, male, and female study participants were 2.18, 2.00 and 2.25 respectively. Similarly, the 75th percentile values of the HOMA-IR for total, male, and female participants were 1.28, 1.19, and 1.66 respectively.

Table 3 shows the correlations between HOMA-IR and the anthropometric, physical and metabolic parameters. There were statistically significant positive correlations between HOMA-IR and age (r = 0.316, P = 0.0001), BMI (r = 0.211, P = 0.002), WC (r = 0.323, P = 0.0001) SBP (r = 0.157, P = 0.023), FPG (r = 0.304, P = 0.0001), and FPI (r = 0.985, P = 0.0001). Figures 1 and 2 showed scatter diagrams illustrating linear correlations between HOMA-IR and the obesity-defining anthropometric variables, BMI and WC.

Table 2: 2.5th, 25th, 50th, 75th, 90th and 97.5th percentile homeostasis model assessment of insulin resistance values of total, male and female study participants

Number of subjects	Percentile	2.5th	25th	50th	75th	90th	97.5th
Total	HOMA-IR	0.02	0.32	0.68	1.28	2.18	2.56
Male	HOMA-IR	0.02	0.27	0.66	1.19	2.0	2.54
Female	HOMA-IR	0.24	0.46	0.84	1.66	2.25	2.58

HOMA-IR: Homeostasis model assessment of insulin resistance

Table 3: Correlation between homeostasis model assessment of insulin resistance and anthropometric and biochemical parameters

Variables	HOMA-IR	
	r	*P*
Age (years)	0.316	0.0001**
BMI (kg/m^2)	0.211	0.002**
WC (cm)	0.323	0.0001**
WHR	0.24	0.0001**
SBP (mmHg)	0.157	0.023
DBP (mmHg)	−0.006	0.934**
FPG (mmol/L)	0.304	0.0001**
FPG (mg/dL)	0.299	0.0001**
FPI (mIU/L)	0.985	0.0001**

**Statistically significant correlations. DBP: Diastolic blood pressure, SBP: Systolic blood pressure, FPG: Fasting plasma glucose, FPI: Fasting plasma insulin, HOMA-IR: Homeostasis model assessment of insulin resistance, BMI: Body mass index, WC: Waist circumference, WHR: Waist-to-hip ratio

Discussion

To the best of our knowledge, this study was the first of its kind to establish a health-associated reference interval and optimal threshold value (clinical decision limit or diagnostic cut-off point) for HOMA-IR in a Nigerian adult population. The HOMA-IR is a surrogate measure of IS/resistance that is in common use for experimental, clinical and epidemiological studies involving the assessment of IS/resistance.[8,9] It is simple, inexpensive, convenient, and amenable to routine laboratory application. It involves on the spot measurement of FPG and FPI which are used to calculate the HOMA-IR from a simple mathematical formula.[8-10] In addition, previous studies have reported good correlations between the HOMA-IR and the HEGC technique that is regarded as the gold standard for the assessment of IS/resistance in man and experimental animals.[11]

Reference interval and optimal threshold value are two of the commonly used decision-making parameters in the clinical laboratory practice.[14,15] Both parameters may be obtained by estimation of nonparametric percentiles of the reference values obtained from selected reference individuals. Whereas the reference interval is defined as the interval between the 2.5th percentile value (LRL) and 97.5th percentile value (URL), the optimal threshold value can be determined as the 75th or 90th percentile value.[13,15,16] In accordance to the guidelines recommended by CLSI and IFCC on the generation of reference intervals for biochemical parameters, the reference intervals of HOMA-IR for the total, male, and female reference individuals in this study were 0.02–2.56, 0.02–2.54, and 0.02–2.58 respectively. Owing to the non-Gaussian distribution of the HOMA-IR values in this study, the nonparametric percentile method was conveniently employed in the statistical determination of the lower and URLs stated above. This is in line with the CLSI and IFCC recommendations.[13,15]

Our findings were similar to values reported by previous related studies in other populations. For instance, Yamada

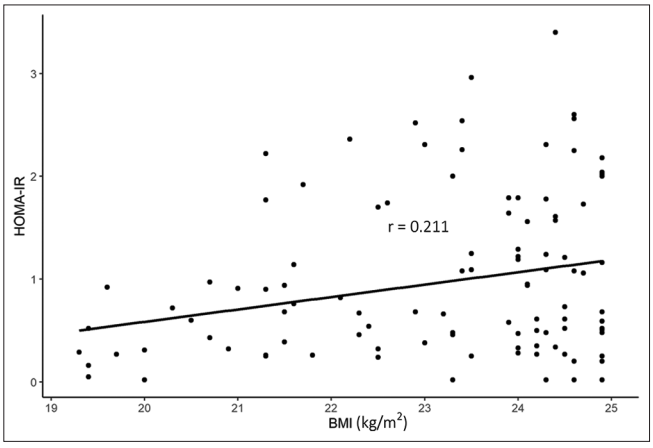

Figure 1: Scatter plots showing correlations between HOMA-IR and BMI. HOMA-IR: Homeostasis model assessment of insulin resistance, BMI: Body mass index

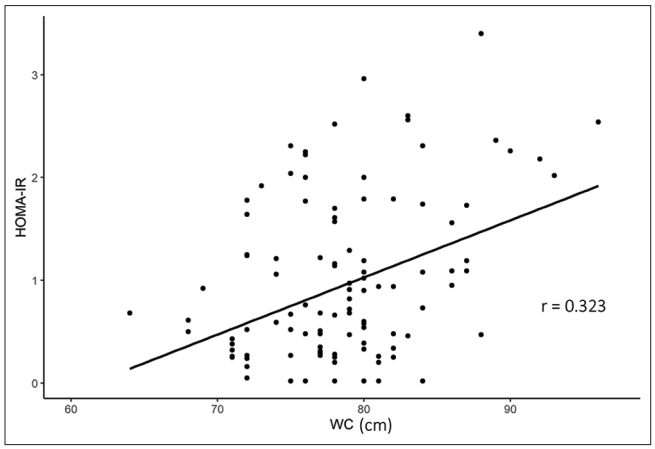

Figure 2: Scatter plots showing correlations between HOMA-IR and WC. HOMA-IR: Homeostasis model assessment of insulin resistance, WC: Waist circumference

et al. reported a HOMA-IR reference interval of 0.40–2.40 in a Japanese adult population.[17] Also, a pilot study by Ramadan to establish a reference interval for HOMA-IR in healthy adult male Egyptians, reported a reference interval of 0.4–3.5.[18] While Yamada *et al*. in their study, applied the parametric method of calculating the mean ± 2 SD of the HOMA-IR reference values after inverse transformation of logHOMA-IR values, Ramadan in his study, used the nonparametric 2.5th and 97.5th percentile values for determining the lower and URLs.[17,18] The slight variations in the HOMA-IR reference intervals obtained by this study and those of related previous studies mentioned above, may be due to different ethnicity, gender, age, insulin assay method, as well as the statistical method used to calculate the reference intervals. Age, gender, and ethnicity have been recognized to significantly influence the development of IR in man.[19-21] Presently, insulin immunoassays are yet to be universally standardised. Thus, the use of different insulin immunoassay platforms may influence the value of FPI measured and by extension, the calculated HOMA-IR values.[22]

Besides reference interval estimation, a more common way of diagnosing IR is by the use of optimal threshold value of HOMA-IR. By convention, either the 75th or the 90th percentile values of the HOMA-IR reference values in a healthy population have been suggested for determination of the optimal threshold value.[16] Usually, IR is diagnosed when the calculated HOMA-IR value is equal to or greater than the optimal threshold value. In this study, the 75th and 90th percentile values for HOMA-IR were 1.28 and 2.18 for all the participants; 1.19 and 2.00 for the male participants; and 1.66 and 2.25 for the female participants. Our values are similar to those generated by previous related studies. Lee *et al*. in their cross-sectional study involving Chinese adults, obtained baseline 75th and 90th percentile HOMA-IR values of 1.44 and 2.33 respectively.[16] Radikova *et al*. and Hedblad *et al*. reported 75th percentile optimal threshold values of 2.29 and 2.00 in healthy nondiabetic populations.[23,24]

Although the use of the 75th percentile values as the optimal threshold value was recommended by the World Health Organization (WHO),[25] most clinical and epidemiological studies involving HOMA-IR calculation used the 90th percentile value as the optimal threshold value. Studies by Demir *et al*., Rogero Blanco *et al*., Timóteo *et al*., and Geloneze *et al*. all used the 90th percentile to generate their respective optimal threshold values of 2.46, 3.15, 2.33 and 2.70 respectively.[26-29] Comparatively, the 75th and 90th percentile threshold HOMA-IR values obtained in this study were similar to those reported by the above-mentioned previous studies.

In Nigeria, there is paucity of data regarding indigenously generated optimal threshold value for HOMA-IR that may be used for the diagnosis of IR. Few reviewed local studies only used optimal threshold values that were previously generated or adopted by other studies. For instance, studies by Oli *et al*. and Young *et al*. in Enugu, Adaja and Ayinbuomwan in Benin, both used the HOMA-IR value of >2.0 (optimal threshold value of 2.00) to diagnose IR among their study participants.[30-32] In contrast, Lawal *et al*. in Abuja, FCT and Akande *et al*. in Ibadan, used optimal threshold values of 2.2 and 3.8 respectively for the diagnosis of IR.[33,34] Going by our findings of the 90th percentile HOMA-IR values of 2.18, 2.00 and 2.25 for the total, male, and female study participants, the use of threshold value of >2.0 to identify insulin resistant adult Nigerians may not be totally out of place. However, owing to the variability in insulin immunoassay methods, there may be need for each clinical laboratory to carry out establishment, verification or validation of the optimal threshold value for local application, in line with the recommendations of CLSI and IFCC.[13,15]

This study showed a statistically significant positive correlations between HOMA-IR and the obesity-defining anthropometric variables, BMI and WC. This finding is similar to those reported by previous studies. Horáková *et al*. in their study, reported a linear association between HOMA-IR and BMI in a group of 1947 individuals with normal glucose tolerance in a Czech Republic population.[35] In contrast, Chen *et al*. in a recent study, reported a nonlinear association between BMI and HOMA-IR.[36] In line with our study, Zadeh-Vakili *et al*. reported a linear relationship between WC and HOMA-IR in a cross-sectional study involving reproductive aged Iranian women.[37]

Our study also showed positive linear relationship between the HOMA-IR and age, SBP, and FPI. This is also similar to the observations reported by related studies in different human populations. Timóteo *et al*., Horáková *et al*. and Soriguer *et al*., reported an increase in the HOMA-IR values with age in their study populations.[28,35,38] Regarding the relationship between HOMA-IR and SBP, Bakari and Onyemelukwe, Sinha *et al*. and Agbecha *et al*. reported linear correlations between BP and IR.[39-41] A linear correlation between HOMA-IR and FPI levels has been demonstrated by several studies in the past. Notably, IR is often associated with concomitant hyperinsulinaemia that

is compensatory in nature.[33,42] On the influence of gender on HOMA-IR, our study showed similar reference intervals and optimal threshold HOMA-IR values in both males and females. This observation is line with other studies that reported lack of gender-associated difference in HOMA-IR values.[28] In contrast, Gayoso-Diz *et al*., in their study, reported significant gender specific difference of HOMA-IR values in nondiabetic individuals.[20]

Conclusion

Reference interval and optimal threshold value (clinical decision limit) are two of the commonly used decision-making parameters in the clinical laboratory practice. The HOMA-IR is a common surrogate marker of IS/resistance that is used in clinical and epidemiological studies. In line with the recommendations of the CLSI and IFCC, this study has been able to establish reference intervals and optimal threshold values for the HOMA-IR score that will be of much clinical and epidemiological utility in the diagnosis of IR among apparently healthy individuals of the Nigerian adult population.

Limitations

This study is not without limitations. First, the sample size was relatively small and may not be representative of the entire local or national Nigerian adult population. Secondly, the HOMA-IR scores were calculated from single measurements of FPG and FPI levels taken at single time points. Under physiological circumstances, the FPG and FPI values may vary over a short period of time. Thirdly, the HOMA-IR score somewhat varies with age and due to the relatively small sample size, we were not able to stratify the HOMA-IR normative values according to age of the study participants. Further studies with large sample sizes and age-specific stratification are suggested in the future. Above all, this present study, to the best of our knowledge, remains the pioneer study and will serve as a good reference to further studies involving the diagnosis of IR in the Nigerian adult population.

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Authors' contribution

OHC conceived and designed the study.

OHC, NCA, IECO, IOU, and EAB collected the data.

NCA and OHC participated in data analysis and interpretation.

NCA performed the statistical data analysis.

OHC drafted the manuscript.

OHC, NCA, IECO, IOU, and EAB reviewed, revised and edited the manuscript and approved the final manuscript for publication.

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Conflicts of interest

There are no conflicts of interest.

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