Original Article

Insulin Sensitivity and Mortality Risk Estimation in Patients with Type 2 Diabetes Mellitus

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Abstract

Background: There is at present the dearth of information on the possible contribution of insulin resistance to scores obtained from mortality risk estimation in patients with type 2 diabetes mellitus (T2DM). **Aim:** This study determined the mortality risk scores in patients with T2DM and its relationship with insulin resistance. **Methods:** Fasting plasma glucose, total cholesterol, high-density lipoprotein cholesterol (HDL), triglycerides, serum and urinary creatinine, glycated hemoglobin (HbA1c), serum insulin, and urinary albumin were determined in 111 T2DM patients. Thereafter, low-density lipoprotein cholesterol (LDL), quantitative insulin sensitivity check index (QUICKI), urinary albumin-to-creatinine ratio (UACR), and estimated glomerular filtration rate (eGFR) were calculated using the standard formula. Mortality risk was estimated using the validated Gargano mortality risk calculator with scores ≤0.67, 0.68–0.79, and ≥0.80 considered as low, intermediate, and high risks, respectively. **Results:** Of the total patients, 5 (4.5%), 28 (25.2%), and 78 (70.3%) patients had high, intermediate, and low mortality risk, respectively. There was no difference in the median QUICKI values when the three groups were compared. However, there was a significant elevation in the median eGFR in patients with high mortality risk compared with patients with low and intermediate mortality risks. Also, the median mortality risk score of patients with low insulin sensitivity (QUICKI ≤0.3) was similar to that obtained in patients with normal insulin sensitivity (QUICKI ≥0.31). No significant correlation was found between QUICKI and mortality risk scores. **Conclusion:** Insulin sensitivity status does not have a direct effect on scores obtained from the Gargano mortality risk prediction model.

Keywords: *Insulin resistance, mortality risk, type 2 diabetes mellitus, urinary albumin-to-creatinine ratio*

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Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disorder with a high mortality and morbidity rate due to a number of complications associated with it.[1] The increased global burden of diseases and their associated mortality risks led to the development of several risk prediction models with the view of predicting disease complications and short-term mortality.

In 2013, De Cosmo *et al*.[2] developed and validated a predicting model (Gargano mortality risk calculator) of all-cause mortality in patients with T2DM. On the basis of its calculation of categorical variables, the Gargano model, available online at http://www.operapadrepio.it/rcalc.php, stratifies patients into low, medium, or high risks of dying from any diabetes-related cause within 2 years. These categorical variables are as follows: age, body mass index (BMI), diastolic blood pressure, low-density lipoprotein cholesterol (LDL), triglycerides (TG), high-density lipoprotein cholesterol (HDL), urinary albumin-to-creatinine ratio (UACR), the use of anti-hypertensive, and insulin therapy.[2]

Insulin resistance has been established as an important pathogenic factor in T2DM, and reports have shown that insulin resistance is associated with increased adverse events in patients with T2DM.[3-5] Although the advent of

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mortality risk prediction models paved way for research on mortality risk estimation, there is at present no information on the possible contribution of insulin resistance on the scores generated from the various mortality prediction models. Understanding this relationship might be necessary as some components of the Gargano mortality risk calculator such as blood pressure and lipid profile are affected by insulin resistance.

This study was therefore carried out to determine the relationship between insulin resistance/sensitivity and scores obtained from the Gargano mortality risk calculator.

Materials and Methods

Subjects

A total of 111 adults with T2DM were recruited into this cross-sectional study from the Endocrinology Unit, Medical Out Patient Department (MOPD), and the Metabolic Research Ward (MRW), University College Hospital (UCH), Ibadan. They consisted of 29 males and 82 females between the age range of 40 and 85 years.

Ethical consideration

All the participants were enrolled after an approval from the University of Ibadan/University College Hospital (UI/UCH) Join Ethics Committee (UI/EC/14/0118). Written informed consent was also obtained from each participant.

Exclusion criteria

Patients with type 1 DM, gestational DM, and T2DM who were younger than 40 years were excluded from the study.

Data collection

Demographic characteristics and clinical history were obtained using a standard questionnaire. Blood pressure was determined using a mercury sphygmomanometer after the patients have rested for at least 10 minutes and in a sitting position. Body weight of each patient was measured to the nearest kilogram using a standard weighing scale and the height was measured to the nearest centimeter using a stadiometer. The body mass index (BMI) was calculated as the ratio of the body weight to the square of the height. Waist circumference was measured using a measuring tape placed at the umbilical level, whereas the hip circumference was measured at the widest circumference of the hip over light clothing, using a nonstretchable measuring tape. The waist-to-hip ratio was calculated as the ratio of waist circumference to hip circumference.

Sample collection and storage

After an overnight fast, 10 ml of venous blood was collected from each patient and dispensed into fluoride oxalate, lithium heparin, and plain bottles to obtain plasma and serum which were stored at –20 °C until analyses.

Laboratory analysis

Glucose, total cholesterol, HDL, TG, and creatinine levels were determined using enzymatic methods. HbA1c, urinary albumin, and insulin levels were determined using boronate affinity chromatography, immunoturbidimeric method, and ELISA (GenWay Biotech Inc., USA), respectively.

Calculation of the indices of insulin sensitivity

The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as:

HOMA-IR = [fasting insulin (U/mL) × fasting glucose (mmol/L)]/22.5

HOMA-IR values <3, 3–5, and >5 were considered as normal, moderate, and severe insulin resistance, respectively.[6]

Quantitative insulin check index (QUICKI) was calculated as:

QUICKI = 1/[log (fasting insulin, U/mL) + log (fasting glucose, mg/dL)

QUICKI values ≥0.31 and ≤0.30 were considered as normal and low insulin sensitivity, respectively.[7]

Estimated glomerular filtration rate (eGFR)

eGFR was determined using the Modification of Diet in Renal disease (MDRD) formula:

GFR = 175 × serum Cr –1.154 × age –0.203 × 1.212 (if patient is black) × 0.742 (if female).[8]

Calculation of urinary albumin-to-creatinine ratio (UACR)

UACR (mg/g) was calculated as: urine albumin (mg/dL)/urine creatinine (g/dL)

Since Gargano mortality risk calculator requires UACR in mg/mmol, the UACR values in mg/g were multiplied by 0.113 to give values in mg/mmol.

Determination of mortality risk

The online Gargano mortality risk calculator was used to derive the mortality risk score of each patient. Nine patient characteristics: age, BMI, diastolic pressure, LDL, HDL, TG, UACR, antihypertensive treatment, and insulin therapy were plugged into the calculator to generate the scores. Thereafter, patients were stratified into three groups: low (≤0.67), intermediate (0.68–0.79), and high (≥0.80) mortality risk groups.[2] The calculator is available online at http://www.operapadrepio.it/rcalc.php

Statistical analysis

After assessing the distribution of all the variables, ANOVA, Krukal Wallis, Student's *t,* and Mann-Whitney *U* were used to determine differences in means and medians of the variables as appropriate. Spearman's correlation was used to determine the strength of relationship between QUICKI and all other parameters. Data are presented as mean ± standard deviation or median (interquartile range) depending on the distribution of the data. $P<0.05$ was considered as statistically significant.

Results

A total of 111 patients were recruited into this cross-sectional study. Seventy-nine (71.2%) of the patients had had DM for 10 years or less, whereas the remaining 32 (28.8%) patients had had DM for more than 10 years. Also, majority of the patients (61.3%) had good glycaemic control (HbA1c ≤7.0%). Considering the drugs of the patients, 87 (78.4%) of the patients were on oral anti-hyperglycaemic drugs, whereas the remaining 24 (21.6%) patients were on insulin.

The Gargano mortality risk scores obtained showed that 78 (70.27%), 28 (25.23%), and 5(4.50%) of the patients had low, intermediate, and high mortality risk, respectively.

Classifying the patients into two groups based on QUICKI values, it was observed that 65.77% of the patients had normal insulin sensitivity, whereas 34.23% had low insulin sensitivity. Comparing these two groups, it was observed that the median levels of TG, urinary albumin, and not surprisingly, glucose, insulin, HbA1c, and HOMA-IR were significantly higher in patients with low insulin sensitivity (LIS) compared with patients with normal insulin sensitivity (NIS). However, the median mortality risk scores of the two groups were similar [Table 1].

Although HOMA-IR has been reported not to be reliable in individuals with severely impaired or absent β-cell function, the insulin resistance status of the patients was assessed since the components of HOMA-IR were derived from the steady state (fasting). As shown in Table 2, it was observed that 20.7%, 49.6%, and 29.7% of the patients had normal (NIR), moderate (MIR), and severe (SIR) insulin resistance, respectively. Comparing the patients based on the insulin resistance, as expected, glucose and insulin levels increased progressively, whereas the median QUICKI values decreased progressively from the normal through the severe group. The median glucose and insulin levels were significantly higher, whereas QUICKI was significantly lower in

Table 1: Anthropometric, clinical, and laboratory parameters in patients with low insulin sensitivity (LIS) and normal insulin sensitivity (NIS) based on QUICKI

	LIS (n = 38)	NIS (73)	P-value
Body weight (kg)	67.4 ± 10.5	68.7 ± 13.1	0.574
Body mass index (kg/m2)	26.9 ± 3.5	26.8 ± 4.6	0.927
Waist circumference (cm)	87.0 ± 12.5	86.8 ± 12.3	0.921
Hip circumference (cm)	94.7 ± 11.3	95.6 ± 13.5	0.710
Waist-to-hip ratio	0.92 (0.90–0.93)	0.91 (0.88–0.94)	0.408
DBP (mm Hg)	84.0 ± 12.1	80.1 ± 10.6	0.666
SBP (mm Hg)	129.5 (120.0–138.5)	130.0 (119.0–139.0)	0.521
Cholesterol (mg/dL)	187.8 ± 37.5	179.8 ± 46.9	0.365
HDL-C (mg/dL)	40.2 ± 16.4	43.6 ± 16.6	0.311
LDL-C (mg/dL)	123.5 (00.5–141.3)	107.0 (86.7–130.4)	0.355
Triglycerides (mg/dL)	126.4 (102.1–156.5)	109.0 (86.9–130.4)	0.017*
Urinary albumin (g/dL)	2.7 (1.3–6.5)	1.8 (0.9–3.2)	0.016*
Urinary creatinine (mg/dL)	0.05 (0.03–0.15)	40.0 (24.0–70.5)	0.250
Serum creatinine (mg/dL)	0.7 (0.6–1.0)	0.7 (0.6–1.0)	0.979
ACR (g/mg)	61.3 (29–99.4)	45.8 (22.0–105.3)	0.285
eGFR (mL/min/1.73 m2)	91.0 (68.8–130.5)	88.0 (65.5–111.5)	0.497
FPG (mg/dL)	118.5 (112.0–160.3)	104.0 (94.5–111.0)	0.000*
FSI (μIu/mL)	19.9 (17.5–23.8)	13.6 (11.7–14.8)	0.000*
HbA1C (%)	7.1 (6.7–8.2)	6.5 (5.9–7.3)	0.009*
HOMA-IR	6.2 (5.3–7.9)	3.5 (2.9–4.1)	0.000*
Mortality risk score	0.58 (0.52–0.67)	0.61 (0.52–0.69)	0.728

*Significant at $P < 0.05$

Table 2: Anthropometric, clinical, and laboratory parameters in patients with normal, moderate, and severe insulin resistance based on HOMA-IR

	Normal (n = 23)	Moderate (n = 55)	Severe (n = 33)	F-value	P-value
Body weight (kg)	67.7 ± 11.2	69.4 ± 13.3	66.6 ± 10.7	0.591	0.500
BMI (kg/m2)	26.0 ± 3.9	27.3 ± 4.6	26.5 ± 3.7	1.469	0.235
Waist circumference (cm)	86.0 ± 11.5	87.7 ± 12.4	86.0 ± 13.0	0.902	0.409
Hip circumference (cm)	94.2 ± 13.9	96.4 ± 12.8	94.1 ± 11.9	0.418	0.660
WHR	0.91 ± 0.5	0.91 ± 0.5	0.91 ± 0.05	0.047	0.918
DBP (mm Hg)	80.1 ± 10.0	81.3 ± 11.5	82.6 ± 11.9	0.326	0.723
SBP (mm Hg)	130.0 (120.8-135.8)	130.0 (118.5-141.5)	127.0 (114-135.8)	0.640	0.529
Cholesterol (mg/dL)	192.3 ± 52.0	175.5 ± 42.3	188.4 ± 40.0	1.572	0.212
HDL (mg/dL)	45.2 ± 20.4	42.5 ± 14.5	40.4 ± 17.3	0.545	0.582
LDL (mg/dL)	113.0 (89.7-165.0)	106.7 (89.3-120.8)	125.7 (100.9-142.4)	1.867	0.160
Triglycerides (mg/dL)	125.1 (83.3-145.3)	106.7 (89.8-131.3)	123.0 (101.6-158.2)	1.649	0.197
Urinary albumin (g/dL)	1.2 (0.7-2.3)	2.3 (1.1-3.7)	2.7 (1.2-7.0)	0.546	0.581
Urinary creatinine (mg/dL)	83.0 (26.8-88.5)	86.0 (20.0-64.2)	0.04 (0.03-0.07)	0.966	0.389
Serum creatinine (mg/dL)	0.9 (0.6–1.0)	0.7 (0.6–1.0)	0.7 (0.6–1.1)	0.912	0.405
ACR (mg/g)	35.5 (13.6–81.5)	52.3 (27.0–105.3)	61.3 (27.0–103.8)	0.534	0.588
eGFR (mL/min/1.73 m2)	82.5 (62.0–127.5)	90.0 (68.0–131.0)	91.0 (68.0–131.0)	0.605	0.548
Glucose (mg/dL)	89.5 (77.5–100.3)	106.0 (100.0–116.0)a	126.5 (112.3–165.5)a,b	24.832	0.000*
Insulin (μIu/mL)	8.8 (7.0–12.6)	14.2 (13.3–16.5)a	20.0 (18.4–24.8)a,b	53.634	0.000*
HbA1C (%)	6.5 (5.8–7.2)	6.5 (5.9–7.1)	7.2 (6.7–8.5)a,b	5.543	0.005*
QUICKI	0.34 (0.33–0.36)	0.31 (0.31–0.32)a	0.29 (0.28–0.30)a,b	81.219	0.000*
Mortality risk score	0.63 (0.57–0.72)	0.58 (0.51–0.68)	0.58 (0.53–0.63)	0.145	0.865

*Significant at $P<0.05$, [a]Significantly different from normal insulin resistance (NIR), [b]Significantly different from moderate insulin resistance (MIR).

DBP = diastolic blood pressure, FSI = fasting serum insulin, SBP = systolic blood pressure, UACR = urinary albumin creatinine ratio, WHR = waist-to-hip ratio.

MIR and SIR compared with NIR. Furthermore, the median levels of glucose, insulin, and HbA1c were significantly higher, whereas the median QUICKI value was significantly lower in SIR compared with MIR. However, the median mortality risk scores were similar between the three groups.

In Table 3, the comparison was made between all the clinical and biochemical parameters based on mortality risk scores. It was observed that there was progressive increase in the mean age, waist-hip ratio (WHR), and the median UACR from the low-risk group (LR) through the high-risk group (HR). The median urinary albumin and UACR as well as the mean hip circumference (HC) and WHR were significantly higher in the intermediate risk group (IR) than LR. In HR, the mean WHR was significantly higher in HR compared with LR. However, QUICKI and HOMA-IR values were similar between the three groups.

As shown in Table 4, QUICKI had an inverse relationship with urinary albumin, UACR, glucose, insulin, HbA1c, and HOMA-IR.

Discussion

Type 2 diabetes mellitus (T2DM) is associated with various complications which increase the risk of mortality and morbidity.[9] In this study, the observed lower percentages of patients with high and intermediate mortality risk probably indicate that most of the patients are well managed. This observation is further supported by the observed lower number of participants with low insulin sensitivity. Majority (65.77%) of the patients had normal insulin sensitivity.

Hypertriglyceridemia has been reported as the commonest abnormality in individuals with insulin resistance.[10,11] The observed higher TG level in LIS compared with NIS supports earlier report.[12] This observation indicates that

Table 3: Age, anthropometric, clinical, and laboratory parameters in patients with low, intermediate, and high mortality risk

	Low risk (n = 78)	Intermediate risk (n = 28)	High risk (n = 5)	F-value	P-value
Age	59.5±8.7	63.3±8.8	67.2±11.6	3.314	0.040*
Body weight (kg)	69.4±13.4	65.4±8.2	66.4±8.7	1.211	0.302
BMI (kg/M2)	27.4±4.6	25.4±2.8	25.2±2.4	2.785	0.066
Waist circumference (cm)	87.6±12.9	84.1±11.5	91.0±8.3	1.145	0.322
Hip circumference (cm)	97.2±12.8	89.1±11.5a	96.8±5.0	3.853	0.024*
WHR	0.90±0.1	0.92±0.1a	0.94±0.1a	5.643	0.005*
DBP (mm Hg)	82.1±11.4	79.4±11.3	82.2±10.4	0.631	0.534
SBP (mm Hg)	130.0(120–140.0)	130.0(116.5–137.0)	135.0(124.0–137.5)	0.610	0.545
Cholesterol (mg/dL)	181.6±41.1	189±50.6	157.1±46.1	1.264	0.287
HDL-C (mg/dL)	43.7±16.8	39.8±16.2	37.0±13.9	0.875	0.420
LDL-C (mg/dL)	110.4(93.0–131.3)	109.3(94.3–146.8)	77.0(62.2–153.4)	0.946	0.392
Triglycerides (mg/dL)	107.2(89.9134.3)	130.2(104.5–158.6)	109.0(78.0–155.7)	1.740	0.180
Urinary albumin (mg/dL)	2.03(0.93–2.81)	3.59(1.26–7.4)a	2.47(1.55–8.52)	6.624	0.002*
Urinary creatinine (g/dL)	0.04(0.03–0.06)	0.05(0.02–0.09)	0.04±0.02	0.665	0.517
Serum creatinine (g/dL)	0.70(0.60–1.0)	0.80(0.60–1.1)	0.90(0.19–1.5)	0.007	0.993
UACR (mg/g)	45.4(24.0–74.7)	82.0(20.4–171.8)a	83.0(27.0–322.6)a	4.361	0.015*
Glucose (mg/dL)	108.5(98.8–119.3)	108.5(98.3–113.0)	106.0(104.5–125.0)	0.265	0.767
Insulin (μIu/mL)	14.5(12.9–18.5)	14.6(12.1–19.3)	14.5(13.6–15.2)	0.326	0.722
HbA1C (%)	6.8(6.0–7.7)	6.7(5.7–7.8)	6.5(6.5–8.9)	0.213	0.809
HOMA-IR	4.2(3.3–5.3)	4.0(2.6–6.0)	3.8(3.0–4.1)	0.213	0.801
QUICKI	0.31(0.30–0.32)	0.31(0.29–0.33)	0.31(0.31–0.32)	0.008	0.992

*Significant at $P<0.05$, [a]Significantly different from low risk, [b]Significantly different from intermediate risk.

DBP = diastolic blood pressure, FSI = fasting serum insulin, SBP = systolic blood pressure, UACR = urinary albumin creatinine ratio, WHR = waist-to-hip ratio.

Table 4: Correlation between QUICKI and other parameters

	QUICKI	
	r-value	P-values
Age	0.123	0.198
Body weight	0.025	0.797
BMI	–0.055	0.566
Waist circumference	–0.084	0.350
Hip circumference	–0.043	0.651
WHR	–0.107	0.265
DBP	–0.134	0.160
SBP	–0.011	0.909
Cholesterol	–0.105	0.274
HDL-C	0.052	0.687
LDL-C	–0.094	0.324
Triglycerides	–0.167	0.080
Urinary albumin	–0.336	0.000*
Urinary creatinine	0.012	0.899
Serum creatinine	0.037	0.702
UACR	–0.216	0.023*
Glucose	–0.682	0.000*
Insulin	–0.829	0.000*
HbA1C	–0.310	0.001*
HOMA-IR	–0.975	0.000*
Mortality risk score	–0.045	0.638

the LIS group is prone to various cardiovascular diseases associated with insulin resistance. In the insulin resistant state, insulin is unable to inhibit lipolysis; thus, there is over production of free fatty acids (FFA) in the plasma and increased FFA uptake by the liver.[13]

Higher levels of albuminuria are associated with increased risk of mortality and cardiovascular events in patients with diabetes mellitus.[14] Urinary albumin is an early indicator of renal failure and typically progresses from micro-albuminuria to overt nephropathy if not properly managed. The observed elevated urinary albumin in LIS compared with NIS is in line with the report of Mykkanen *et al*.[15] Accumulating evidence suggests that there is an association between insulin sensitivity and albuminuria.[16]

The observed higher levels of glucose, insulin, and HbA1c in patients with low insulin sensitivity (LIS) compared with patients with normal insulin sensitivity (NIS) are not surprising. Hyperglycemia, hyperinsulinemia, and increased glycation of hemoglobin are important features of T2DM. Usually, insulin resistance manifests as impaired insulin-mediated glucose disposal, inhibition of lipolysis, or inhibition of gluconeogenesis, which often results in hyperinsulinemia.[17] The observed higher HOMA-IR in LIS compared with NIS is also not unexpected. It has been shown that there is an inverse relationship between QUICKI and HOMA-IR.[18]

Reports have shown that HOMA-IR may not give appropriate results in subjects with severely impaired or absent β-cell function. However, since the components of HOMA-IR were derived from the steady (fasting) state, the insulin resistance status of the patients was assessed. The observed progressive rise in glucose and insulin levels and the progressive decrease in the QUICKI values in NIR through SIR are in line with our observations in LIS compared with NIS. Similarly, HbA1c demonstrated a similar trend as it was significantly higher in SIR compared with MIR and NIR. These observations further confirm that insulin resistance initiates a cascade of physiological and biochemical changes in patients with T2DM.

The waist-to-hip ratio (WHR), a marker of visceral obesity, correlates positively with fasting plasma glucose and has been reported to be a risk factor for T2DM development.[19] This probably explains the observed elevated WHR in IR and HR groups compared with LR.

It is at present unknown whether insulin resistance and albuminuria emerge in parallel as a consequence of a common pathogenic pathway or whether insulin resistance is a causal factor for the pathogenesis of albuminuria.[16] It is, however, known that albuminuria is an important biomarker to predict micro and macrovascular complications and mortality in patients with T2DM.[20] The observed higher UACR in IR and HR compared with LR corroborates the report of Basi *et al*.[14] Albuminuria is an important predictor of end-stage renal disease (ESRD) and of mortality in T2DM.[21] This might explain why UACR was included as a component of the mortality risk predictor model.

Insulin resistance has been shown to be a predictor of increased mortality in patients with diabetes and end-stage renal disease.[22-24] Surprisingly, however, QUICKI and HOMA-IR values were similar between LR, IR, and HR. This observation might indicate that insulin sensitivity status might not contribute directly to increased mortality in T2DM but indirectly, through T2DM-associated complications. This observation is further supported by the observed nonsignificant correlation between the mortality risk score and QUICKI.

The small sample size was a limitation of this study. Therefore, there is need for a prospective larger population study to confirm the findings in this study. Although the observed lower percentage of participants (4.5%) with high risk of mortality (HR) was a positive finding, the observation in this study cannot be generalized as it might not be the same in rural areas of Nigeria where access to good health and specialized physicians might not be available to T2DM patients.

Conclusion

It could be concluded from this study that insulin sensitivity status does not have a direct effect on scores obtained from mortality risk estimation. Also, majority of our patients have low mortality risk and are, therefore, not likely to die from diabetes-related complications within the next 2 years, as the Gargano mortality risk prediction model portends.

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Conflicts of interest

There are no conflicts of interest.

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