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CORRELATION BETWEEN GLYCATED HEMOGLOBIN AND HOMA INDICES IN TYPE 2 DIABETES MELLITUS: PREDICTION OF BETA-CELL FUNCTION FROM GLYCATED HEMOGLOBIN

KORELACIJA IZMEĐU GLIKOLIZIRANOG HEMOGLOBINA I HOMA INDEKSA U DIJABETES MELITUSU TIPA 2: PREDVIĐANJE FUNKCIJE BETA ĆELIJA NA OSNOVU GLIKOLIZIRANOG HEMOGLOBINA

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Summary

Background: The present study aimed to determine the most efficient insulin resistance function related to glycemic control expressed as glycated hemoglobin (HbA1c) in type 2 diabetes mellitus patients (T2DM). The other aim is to derive equations for the prediction of beta cell functions containing HbA1c as a parameter in addition to fasting glucose and insulin.
Methods: T2DM Patients were grouped according to the following: (1) degree of control (good, fair, and poor control) and (2) insulin resistance as observed in obtained data and significant differences revealed by the homeostasis model assessment (HOMA) of related parameters (insulin resistance = HOMA2IR, beta-cell function = HOMA%B, and insulin sensitivity = HOMA%S) among groups. Correlations and forecasting regression analysis were calculated.
Results: HbA1c was found to be correlated with insulin resistance parameters in T2DM subgroups. This correlation was also significantly correlated with HOMA%B and the quantitative insulin sensitivity check index (QUICKI) in fair and poor control groups. Regression analysis was used to predict the forecasting equations for HOMA%B. The best applicable equations were derived for healthy control (HOMA2%B=-1.76*FBG+5.00*Insulin+4.69*HbA1c+

Kratak sadržaj

Uvod: Cilj ove studije bio je da se odredi najefikasnija funkcija insulinske rezistencije u odnosu na glikemijsku kontrolu izraženu kroz glikolizirani hemoglobin (HbA1c) kod obolelih od dijabetes melitusa tipa 2 (T2DM). Drugi cilj bio je da se izvedu jednačine za predviđanje funkcije beta ćelija koje, pored glukoze natašte i insulina, kao parametar sadrže HbA1c.
Metode: Pacijenti sa T2DM grupisani su prema sledećim obeležjima: (1) stepenu kontrole (dobra, zadovoljavajuća i slaba kontrola) i (2) insulinskoj rezistenciji utvrđenoj na osnovu dobijenih podataka i značajnih razlika između grupa otkrivenih pomoću procene modela homeostaze (HOMA) srodnih parametara (insulinske rezistencije – HOMA2IR, funkcije beta ćelija – HOMA%B i osetljivosti na insulin – HOMA%S). Korelacije i predikciona regresiona analiza su izračunate.
Rezultati: Utvrđeno je da je HbA1c bio u korelaciji sa parametrima insulinske rezistencije u podgrupama sa T2DM. Ova korelacija takođe je značajno korelisana sa HOMA%B i indeksom QUICKI (kvantitativni indeks insulinske osetljivosti) u grupama sa zadovoljavajućom i slabom kontrolom. Regresiona analiza je upotrebljena za predviđanje predikcionih jednačina za HOMA%B. Najprimenljivije jednačine izvedene su za grupu zdravih kontrolnih subjekata (HOMA2%B =-1,76*FBG+5,00*insulin+4,69*HbA1c+189,84) i grupu

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189.84) and poor control groups (HOMA2%B=0.001*FBG+0.5*Insulin-8.67*HbA1c+101.96). These equations could be used to predict β-cell function (HOMA%B) after FBG, insulin and HbA1c values were obtained for healthy and poor control groups. In the good and fair control groups, the applicability of the HOMA model fails to yield appropriate results.

Conclusions: Beta-cell function is correlated with QUICKI and HbA1c and could be predicted properly from HbA1c, insulin, and glucose in the healthy and poor control groups. New regression equations were established that involve HbA1c.

Keywords: Bennett index, HbA1c, insulin resistance, QUICKI, type 2 diabetes mellitus

sa slabom kontrolom (HOMA2%B=0,001*FBG+0,5*insulin-8,67*HbA1c+101,96). Ove jednačine mogle su se upotrebiti za predviđanje funkcije beta ćelija (HOMA%B) pošto su dobijene vrednosti FBG, insulina i HbA1c za zdravu grupu i grupu sa slabom kontrolom. U grupama sa dobrom i zadovoljavajućom kontrolom pokušaj primene modela HOMA nije dao odgovarajuće rezultate.

Zaključak: Funkcija beta ćelija koreliše sa QUICKI i HbA1c i može se pravilno odrediti na osnovu HbA1c, insulina i glukoze u zdravoj grupi i grupi sa slabom kontrolom. Ustanovljene su nove regresione jednačine koje uključuju HbA1c.

Ključne reči: Benetov indeks, HbA1c, insulinska rezistencija, QUICKI, dijabetes melitus tip 2

Introduction

Equations and software have been developed to estimate the parameters of insulin resistance (IR) in patients with type 2 diabetes mellitus (T2DM) because standard methods are difficult to perform in routine clinical investigation. These alternative methods [fasting insulin, the McAuley index, and the Bennett index] include (1) the quantitative insulin sensitivity check index (QUICKI) (2) and homeostasis model assessments (HOMA) (3), which have been recently computerized. This computer model can be used to determine insulin sensitivity (%S) and β-cell function (%B) from paired fasting plasma glucose and insulin. HOMA can be applied longitudinally to track changes in insulin sensitivity and β-cell function in individuals. This model can also be used in individuals to indicate whether or not reduced insulin sensitivity or β-cell failure predominates. The sensitivity and specificity of diagnosis are suitable and practical (4) compared with the results from standard methods, such as the euglycemic clamp method. FI is accurate in predicting IR in the normoglycemic population similar to HOMA, insulin to glucose ratio (I/G), and the Bennett index (1). However, the glycemic control expressed as HbA1c is not involved in the derived equations that deal with the beta-cell function or insulin resistance.

Glycated hemoglobin (HbA1c) concentration is an indicator of average blood glucose concentration for three months; this parameter has been applied as a diagnostic or screening tool for diabetes (5). Hence, the detected HbA1c in individuals at risk of diabetes enhances the ability to diagnose this disease at an early stage (6).

Lipid profile in diabetic patients should be estimated in the early diagnosis of atherosclerosis. An excessively high lipid concentration in the blood (hyperlipidemia) can seriously affect health because such excessive concentrations increase the risk of heart attack or stroke (7). The correlations between glycemic control and insulin sensitivity or resistance have been studied previously (8). However, the studied groups were taking insulin sensitizer drugs, namely metformin, which affects the results of insulin sensitivity and resistance. Furthermore, no forecasting equations were derived for the prediction of HOMA%B using HbA1c as a part of the formulas. Knowing that the change in insulin sensitivity by any means (8, 9) affects the glycemic control, the present study aimed to determine the most efficient IR function related to glycemic control, which is expressed as HbA1c. Correlated factors will be determined and the equation used to predict HbA1c from these factors will be established. The other aim is to derive equations for the prediction of beta-cell function containing HbA1c as a parameter in addition to fasting glucose and insulin.

Subjects and Methods

Subjects

Patients: Eighty-four male patients with T2DM were included in the study. Age range was 51.2 ± 12.4 years. The samples were collected from private clinics and laboratories in addition to the Center for Diabetes and Endocrinology at Al-Sadr Medical City in Najaf Governorate Iraq from March 2013 to August 2013. Patients fasted for 8 h to 12 h. All the patients were on one tablet (5 mg) of glibenclamide drug daily.

Exclusion criteria: The present study excluded patients who satisfied the following criteria: patients with serum TG ≥5.32 mmol/L based on Friedewald's equation; FBG >25 mmol/L and fasting insulin >57.6 mIU/L based on HOMA calculator software requirements. Patients with evident major diabetic complications, such as heart diseases, and those receiving lipid-lowering medications (e.g., simvastatin or atorvastatin) and metformin were also excluded. Patients using metformin cannot be used for insulin sensitivity studies because of the well-known effect of metformin on insulin resistance (10) and sensitivity (11).

Controls: Thirty-two healthy adult males were selected as the control group. Age range was comparable to that of the patients. None of these subjects manifested an evident systemic disease or took drugs.

Methods

Venous blood samples (5 mL) were drawn from each patient and control subject. Fresh blood (1 mL) was added to EDTA tubes to determine HbA1c in the blood. The remaining blood was left at room temperature for 10 min to induce clotting and then centrifuged at 3,000 rpm for 5 minutes; serum was separated and transferred into new disposable tubes.

Insulin concentration was measured using a DRG® Insulin ELISA kit, which is a solid-phase enzyme-linked immunosorbent assay based on the sandwich principle. Serum glucose, total cholesterol, and TG were determined spectrophotometrically by observing enzymatic reactions using commercially available kits (Biolabo®, France). Serum HDLc was determined after other lipoproteins were precipitated using a reagent containing sodium phosphotungstate and magnesium chloride. The cholesterol contents in the supernatant were determined using a cholesterol kit. VLDLc was calculated based on TG/2.19 and LDLc by using Friedewald's equation (LDLc = total cholesterol – HDLc – VLDLc). HbA1c percentage in the whole blood was determined by ion-exchange chromatography (Pre-Fil®, Stanbio, Germany).

IR parameters were calculated from fasting glucose and insulin concentrations by using the HOMA calculator software (http://www.dtu.ox.ac.uk/homacalculator/download.php). This software was used to generate the IR index (HOMA2IR), insulin sensitivity (HOMA%S), and β-cell function index (HOMA%B). An ideal normal-weight individual aged <35 years yields HOMA2IR of 1 mol × $\mu U/L^2$ and HOMA% β-cell function of 100% (12). A subject was considered insulin resistant if HOMA2IR >3 (13). IR results were obtained from patients with fasting insulin concentration ≥12 mU/L (1, 14). Other formulas were used to estimate IR state:

Bennett index=1/[log(FBG in mmol/L)* × (log (Insulin in uU/mL)] (15)

McAuley=exp [2.63 – 0.28 ln (insulin in mU/L) – 0.31 ln (TG in mmol/L)]

QUICKI=1/(log insulin + log FBG in mg/dL).

Patients were considered as insulin resistant when McAuley ≤5.8 and QUICKI ≤0.33 (1).

Patients were grouped according to the IR state into insulin resistant (HOMA2IR ≥ 3) and non-insulin resistant (HOMA2IR < 3). Furthermore, the patients were subdivided according to the control state into a good control group (HbA1c=5.5 to 6.8), fair control group (HbA1c=6.9 to 7.6) and poor control group (HbA1c > 7.6). Regression analysis results revealed an equation that could be used to predict HbA1c from these parameters.

Biostatistical analysis

Statistical analysis was performed using SPSS 19.0.1 software (2010; IBM, USA) and the Regression Forecasting Model software (Business Spreadsheets, USA). One-sample Kolmogorov–Smirnov test was used to examine the normality of variable results. The results were expressed as mean ± standard deviation and median values for normally distributed data and non-parametric variables, respectively. A pooled *t* test was used to compare the measured parameters with normal distribution between the patients and the control subjects. The pairs of non-parametric variables were compared using Mann–Whitney U test. Spearman's coefficient (Spearman's ρ or r) was used to identify any correlation between parameters. The significance of correlation results was set at $\rho<0.05$ and $p<0.05$. Multivariate regression analysis was performed to characterize the effect of the most effective predictor of IR related to HbA1c. Forecasting equations were obtained from the Regression Forecasting Model software purchased from Business Spreadsheets, USA. F-test was used to compare the groups and auto-correlation among the independent variables was assessed using the Durbin-Watson statistic.

Results

Comparison between T2DM patients and control group

The characteristics of the patients and the control subjects are presented in *Table I*. The results showed that patients with T2DM were more insulin resistant, dyslipidemic, and had poorer control, as obtained from the values of HbA1c, than the control group. The results further indicated that IR, sensitivity, and β-cell functions differed between T2DM patients and control subjects. The highest significant difference in IR was obtained by comparing the FIRI between the two groups in which the lowest *p*-value was obtained.

Comparison between T2DM patient subgroups

Patients with T2DM were grouped according to the degree of control and revealed several results (*Table II*). The results showed that the HOMA parameters of IR in the good control group were the most affected among the IR functions measured with other equations. Therefore, HbA1c was possibly correlated with IR parameters in different control groups.

Comparison between IR and Non-IR patients

The results in the IR subgroups (HOMA2-IR >3) revealed a significant increase in the Bennett index which represents the insulin sensitivity indicator, FIRI, HOMA2%B, and McAuley index (data not cited). HOMA2%S in the IR subgroup decreased compared

Table I Characteristics of patients and control subjects.

Parameters	All patients (n=84)	Control (n=32)	p-value
Age (years)	52.78±13.42	47.65±18.71	N.S.
BMI (kg/m^2)	28.37±3.71	26.42±3.44	N.S.
FBG (mmol/L)	12.62±5.69	5.09±1.57	<0.0001
HbA1c %	8.46±2.01	5.28±1.12	<0.0001
Insulin (mIU/L)	18.43	6.89	0.006
HOMA2%B	67.51	102.49	0.013
HOMA2%S	56.78	93.44	0.028
HOMA2IR	4.11	1.37	0.002
1/HOMA2IR	0.24	0.73	0.019
McAuley	3.49±0.95	3.33±0.40	0.048
QUICKI	0.36±0.04	0.30±0.03	0.042
1/QUICKI	2.87±0.88	3.41±0.92	0.042
InsuIU/mL/FBG mmol/L	1.71±1.56	1.61±0.97	0.033
FIRI	9.8	1.9	<0.0001
Bennett Index	1.07±0.43	1.39±0.72	0.024
TG (mmol/L)	2.12±0.71	1.79±0.63	0.038
Cholesterol (mmol/L)	5.57±1.23	4.13±1.21	0.031
VLDL-C (mmol/L)	1.45±0.76	0.82±0.29	0.028
HDL-C (mmol/L)	0.98±0.45	1.09±0.57	0.066
LDL-C (mmol/L)	3.16±1.28	2.31±1.11	0.008
LDL-C/HDL-C	3.44±1.91	2.16±1.96	0.488
TG/HDL-C	5.40±2.11	3.08±1.81	0.030
Chol/HDL-C	5.87±2.37	4.29±1.98	0.027

Table II Comparison between parameters in different control groups.

Parameters	Good control HbA1c=5.5–6.8 (n=22)	Fair control HbA1c=6.9–7.6 (n=19)	Poor control HbA1c=>7.6 (n=43)	p-value
Age	55.92±11.730	51.00±6.23	54.63±10.40	N.S.
FBG	8.71±2.47	9.35±2.96	12.12±4.12	a, b
HbA1c %	6.61.±.56	7.34±.22	8.71±1.49	a, b, c
INSULIN, mIU/L	18.47	20.51	17.85	N.S.
HOMA2%B	79.69±68.28	70.12±44.25	28.44±19.74	a, c
HOMA2%S	62.78	47.88	44.98	a, b
HOMA2IR	4.11	4.27	5.4	b, c
1/HOMA-IR	0.59±.80	0.16±.08	0.50±.55	a, c
McAuley	3.42±1.19	3.25±.91	3.57±.82	N.S.
QUICKI	0.31±.05	0.29±.04	0.30±.04	N.S.
1/QUICKI	3.32±.50	3.51±.46	3.49±.58	N.S.
Insulin/FBG	1.95	1.62	1.48	N.S.
FIRI	9.11	10.45	9.73	N.S.
Bennett Index	1.01	1.15	1.03	N.S.

(a): p<0.05 between Good & Fair Control groups; (b): p<0.05 between Good & Poor Control groups; (c): p<0.05 between Fair & Poor Control groups.

with that in the non-IR patients. However, insulin concentration was not significantly different ($p>0.05$) between the two subgroups.

Correlation between HbA1c and IR parameters

Table III shows the correlation between HbA1c and IR parameters. HbA1c was correlated with HOMA2%B in all of the subgroups but not in the whole group. HbA1c is correlated with QUICKI in the fair and poor control groups.

Predicting Regression Analysis

From the above results, forecasting regression analysis produced equations that can predict, with

Table III Correlation between HbA1c and the insulin resistance parameters in T2DM subgroups.

Parameters		Whole Group	Good Control	Fair Control	Poor Control
FBG	r	0.19	0.20	0.21	–0.05
	p	0.20	0.33	0.10	0.72
Insulin	r	–0.01	–0.02	–0.06	0.03
	p	0.93	0.94	0.88	0.86
HOMA2%B	r	0.17	0.26	0.69	0.44
	p	0.36	0.06	<0.01*	.018*
HOMA2%S	r	–0.12	–0.29	0.56	0.44
	p	0.28	0.15	0.12	0.32
HOMA2IR	r	0.10	0.29	0.13	–0.09
	p	0.37	0.15	0.74	0.54
McAuley	r	0.02	–0.15	0.02	–0.11
	p	0.87	0.47	0.96	0.44
QUICKI	r	–0.07	0.12	0.29	0.45
	p	0.50	0.92	0.04*	0.01*
1/QUICKI	r	0.07	–0.12	–0.29	–0.45
	p	0.48	0.92	0.04*	0.01*
Insulin/FBG	r	–0.09	–0.09	–0.23	0.01
	p	0.40	0.66	0.54	0.98
FIRI	r	0.06	0.07	0.16	–0.04
	p	0.60	0.75	0.69	0.79
Bennett Index	r	–0.11	–0.17	–0.27	–0.07
	p	0.32	0.39	0.48	0.61

(*): Significant difference ($p<0.05$).

Table IV Forecasting regression analysis parameters for the prediction of HOMA%B from fasting glucose, insulin, and HbA1c. (Adj.R2: Adjusted for Sample Size bias, SE: standard error, F: F-test value, D-W (Dl-Du): Durbin-Watson Statistic (lower value–upper value).

Group	Forecasting equation	R2(Adj.R2)	SE	D-W (Dl-Du)	F
Healthy	HOMA2%B=–1.76*FBG+5.00*Insulin+4.69*HbA1c+189.84	0.77(0.75)	13.46	2.96(1.24–1.65)	31.89*
Good	HOMA2%B=–0.34*FBG-0.55*Insulin-1.24*HbA1c+132.46	0.13(0.01)	30.32	1.63(1.05–1.66)	0.91
Fair	HOMA2%B=–0.18*FBG + 0.36*Insulin+15.28*HbA1c-49.68	0.35(0.23)	11.68	1.53 (1.00–1.68)	2.85
Poor	HOMA2%B=0.001*FBG+0.5*Insulin-8.67*HbA1c+101.96	0.64(0.61)	7.99	2.38 (1.34–1.66)	22.36*

(*): Analysis is significant ($p<0.05$).

applicability that depends on the control state, the beta-cell function from fasting glucose, insulin, and HbA1c, as seen in *Table IV*.

The best forecast was obtained in the healthy and poor control groups followed by the fair control group while there was no significant correlation in the good control state. Equations of the regression analyses, which predicted HOMA%B from the known FBG, insulin and HbA1c values in the good, fair, poor control groups and healthy subjects, revealed that 1%, 23%, 61%, 77% of the change in HOMA%B (standard error ±30.32, 11.68, 7.99, 13.46) respectively could be attributed to the change in the three independent variables.

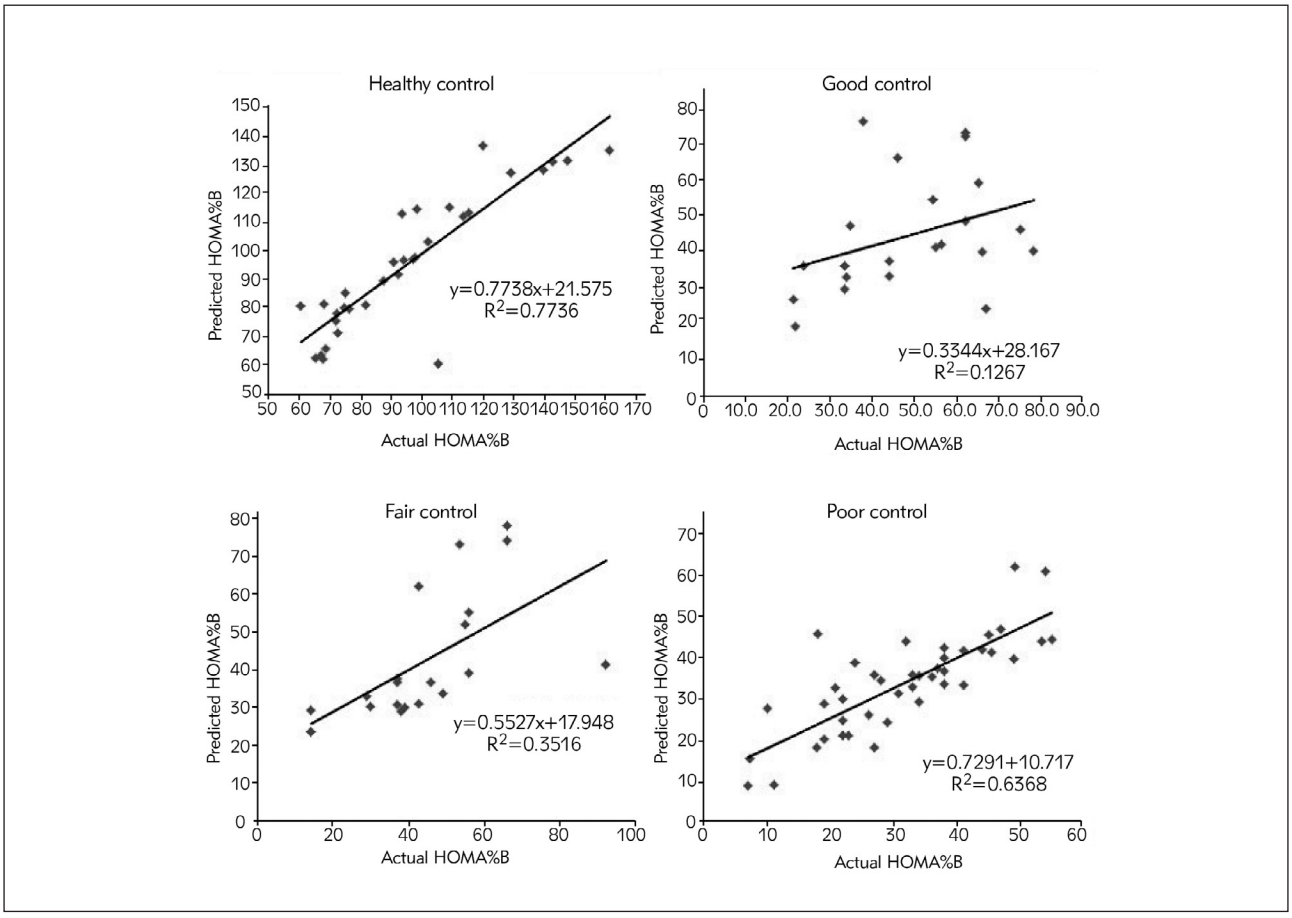

Figure 1 Correlation between actual and predicted HOMA%B levels from the regression equation in healthy subjects and good, fair, and poor control patients.

The multivariate analysis revealed significant results ($F=31.89$, $p<0.05$ and $F=22.36$, $p<0.05$) in the healthy and poor control groups, respectively, but not in the good and fair control groups that showed insignificant differences. Durbin–Watson statistic of the good and fair control groups showed positive auto-correlation while negative auto-correlation in the healthy and poor control groups was noticed among the independent parameters (FBG, insulin, and HbA1c) at the 95% confidence level.

The actual HOMA%B values were plotted against the predicted values obtained from the regression equations of *Table IV* and the regression lines of healthy, good, fair, and poor control groups are presented in *Figure 1*. From the straight line equations, the best correlation between the predicted and actual values was obtained from the line of the control group ($Y=0.7738X+21.575$, $R^2=0.77$) followed by poor control group ($Y=0.7291X+10.717$, $R^2=0.64$).

Discussion

The most appropriate parameter affected by (correlated with) HbA1c should be determined because this parameter can be used to control blood glucose concentrations for several weeks. Therefore, the consequences of poorly controlled T2DM may be affected. In the present study, the correlation between IR parameters and lipid profile parameters with HbA1c was analyzed. The results in *Table I* showed that patients with T2DM were more insulin resistant. In contrast to the control subjects, patients with T2DM exhibited poor glycemic control and were dyslipidemic. An increase in HbA1c indicated a poor control of diabetic patients, and treatment was inadequate or diet control was very poor for two months to four months (16). Excessive glycosylation of various proteins has been considered as a major pathogenic factor in microvascular and neuropathic complications of diabetes (17, 18). Dyslipidemia observed in the patients included in this study is common in diabetic patients and can be attributed to different factors (19, 20). The results further indicated that IR, sensitivity, and β-cell functions differed between T2DM patients and control subjects. The highest significant difference in IR was obtained by comparing the FIRI between the two groups in which the lowest p value was obtained. Most T2DM patients are associated with insulin resistance as noticed previously (21).

The results in *Table II* showed that the HOMA parameters of IR in the good control group were the most affected among the IR functions measured with other equations. Therefore, HbA1c was possibly correlated with IR parameters in different control groups. The largest declines in beta-cell function were noticed in the poor control group indicating an exhaustion of cells and they exhibit only about a fifth of their normal function. The results indicated that the HOMA%B was decreased in diabetics as compared with the control group (22).

The significant increase in the Bennett index, FIRI, HOMA2%B, and McAuley index and the decline in HOMA2%S in the IR subgroups (HOMA2-IR>3) compared with non-IR patients were attributed to the effect of IR factors related to the equations used to determine IR. However, insulin concentration was not significantly different ($p>0.05$) between the two subgroups. The HOMA model is used to estimate insulin sensitivity and β-cell function from the fasting plasma insulin and glucose concentrations (3). Therefore, the most important determinant of IR in the equations used is FBG; in this study, FBG showed a significant difference. Reaven (1995) (23) postulated that diabetes would not be developed as a consequence of the severity of IR found in most T2DM patients; this condition is possible because of the positive feedback between glucose concentration (the major stimulus for insulin release) and β-cell insulin secretion, unless the ability to secrete additional amounts of insulin to compensate for IR is impaired. IR individuals suffer from several abnormalities, including glucose intolerance, dyslipidemia, endothelial dysfunction, increased concentrations of pro-coagulant factors, hemodynamic changes, and increased concentrations of inflammatory markers (24). As such, IR patients exhibit increased vulnerability to cardiovascular diseases, hypertension, polycystic ovary syndrome, non-alcoholic fatty liver disease, and cancer (25). Therefore, diabetic patients with IR are at a higher risk for these complications than the control subjects and non-IR patients. In IR patients, the decrease in insulin sensitivity (HOMA%S) develops initially to compensate for hyperinsulinemia (increased HOMA%B); however, the first phase of insulin secretion is lost in the early stage of the disease. As glucose levels increase, β-cell function decreases (decreased HOMA%B) further. Glucose sensitivity is also decreased and hyperglycemia is exacerbated. Diabetic patients also manifest a reduced pancreatic islet cell mass; in this condition, humoral and endocrine factors may be important to maintain normal islet cell mass (26). Other parameters embedded in the HOMA software consider the constant status between blood glucose concentration, insulin secretion, and β-cell activity in response to changes in glucose levels. HOMA%B corresponds to β-cell activity and does not indicate the health or pathology of β-cells (27). These data illustrated that the HOMA model of β-cell function indicates insulin secretion rather than the health status of β-cells (26). The HOMA2 model (Version 2.2.2) used to calculate IR parameters was calibrated to yield 100% HOMA%B and HOMA%S in normal young subjects when a suitable insulin assay was used. Many patients with values higher than one unit exhibited irregular insulin secretion in response to any change in blood sugar concentration. A good correlation was observed between β-cell function based on HOMA estimated using other practical methods, such as hyperglycemic clamps ($R_s=0.61$, $p<0.01$) (3) and continuous infusion glucose model assessment (28, 29).

The results in *Table III* are useful for determining the correlation between different forms of IR parameters and HbA1c in the good, fair, and poor control groups in addition to the T2DM patients as a whole group. The correlations between HbA1c and HOMA2%B in all of the subgroups were noticed previously (30). HbA1c was also correlated with QUICKI in the fair and poor control groups. These results indicated that the most important determinant of HbA1c was β-cell function, that is, as the functions of β-cells increase, the control status of blood glucose is enhanced. A good correlation is also observed between IR-derived estimates from HOMA and the euglycemic clamp (31). However, the use of multiple blood samples is recommended to decrease the variation in results when HOMA is used to determine β-cell function and insulin sensitivity in individuals (27). In the present study, only one sample was used and similar results were obtained. Other equations did not yield any significant correlation with HbA1c in all of the groups.

The multivariate analysis in *Table IV* revealed significant results ($F=31.89$, $p<0.05$ and $F=22.36$, $p<0.05$) in the healthy and poor control groups, respectively, but not in the good and fair control groups that showed insignificant differences. In healthy persons, the independent parameters (FBG, insulin, and HbA1c) correlated well because beta cells work properly. Increased blood glucose induces the increase in insulin level as secreted from the healthy beta cells to maintain normal blood glucose levels over long periods (32). Therefore, HbA1c was still within the normal values and correlated well with the ability of beta cells to secrete suitable amounts of insulin. The equation in *Table IV* is applicable and comparable with the beta-cell function percentage derived from the HOMA model. The mild deviation from the values of HOMA%B is due to the involvement of HbA1c in the equation of the forecasting of beta-cell function which is not involved in the original derivation of HOMA. The good applicability of the beta-cell function derived from the equation of poor control T2DM patients in *Table IV* is an important phenomenon since the good and fair control groups showed less applicability with the actual value of HOMA%B. In poor control patients, blood glucose cannot be compensated by adequate insulin because

beta cells cannot secrete enough insulin working only in a small percentage of their ideal activity (33). Therefore, when beta cells function increased, the blood glucose level and HbA1c were reduced. Hence, the results of beta-cell function obtained from the equation correlated well with the levels of the independent parameters FBG, insulin and HbA1c and the produced HOMA%B corresponds to the actual percentage obtained from the HOMA model by 64%.

Durbin-Watson statistic of the good and fair control groups showed positive auto-correlation, while negative auto-correlations in the healthy and poor control groups were noticed among the independent parameters (FBG, insulin, and HbA1c) at the 95% confidence level. The actual HOMA%B values plotted against the predicted values for healthy and poor control groups produce the best straight lines ($Y=0.7738X+21.575$, $R^2=0.77$) for the control group followed by poor control group ($Y=0.7291X+10.717$, $R^2=0.64$). These figures and squared R values confirm the current findings of the forecasting equations and the ability of these equations to predict with good applicability the beta cells function percentage. The main limitations must be considered in the interpretation of the results including the small number of patients per group, the fact that patients with T2DM were male only, and the exclusion of patients using metformin.

Conclusions

A beta-cell function is correlated with QUICKI and HbA1c and can be predicted properly from HbA1c, insulin, and glucose in the healthy and poor control groups. New forecasting regression equations were derived that involve HbA1c as a parameter for the determination of beta-cell function.

Conflict of interest statement

The authors stated that have no conflicts of interest regarding the publication of this article.

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