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Insulin Resistance and Residual ß-Cell Function Among Persons with Impaired Fasting Glycaemia

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ABSTRACT

Impaired fasting glycaemia (IFG) is a condition, in which a person's fasting blood glucose levels are consistently higher than the normal range, but below the diagnostic cut-off for diabetes mellitus (DM). ß-cell dysfunction and insulin resistance (IR) have a principal role in the pathogenesis of IFG. Patients with IFG are at high risk of progression to diabetes, and developing atherosclerotic cardiovascular disease (ASCVD), The present study was designed, to determine the degree of IR (HOMA-IR) and ß-cell dysfunction (HOMA-B) among patients with IFG, and also to correlate HOMA-IR and HOMA-B with biochemical and anthropometric variables. The study included 143 patients with IFG, 61 males and 82 females, 14 – 70 years of age, and 150 apparently healthy subjects, 62 males and 88 females, 15-70 years age as a control group. Physiological measurements include weight, height, waist circumference (WC), and blood pressure (BP). Biochemical measurements include fasting blood glucose (FBG), glycated haemoglobin (HbA1c), insulin, total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C) and low-density lipoprotein-cholesterol (LDL-C). In addition, HOMA-IR and HOMA-B were also determined. Insulin level was significantly higher among patients with IFG in comparison to control subjects, ($P < 0.000$). There were no significant differences in FBG and HbA1c between IFG and control group, ($P > 0.05$). Concerning HOMA-IR and HOMA-B, patients with IFG showed a significantly higher HOMA-IR and a significantly lower HOMA-B values compared to control subjects, ($P = 0.000$). LDL-C was significantly higher among patients with IFG in comparison to control subjects, ($P < 0.05$). There were no significant differences in TC, TG and HDL-C between the two groups, ($P > 0.05$). Correlation analysis in patients with IFG revealed a positive correlation of HOMA-B with insulin, ($P < 0.01$) and a significant negative correlation with LDL-C, ($P < 0.01$). While, HOMA-IR showed a significant positive correlation with insulin, ($P < 0.01$), FBG ($P < 0.01$) and TG ($P < 0.05$). We concluded that patients with IFG have significantly higher insulin and HOMA-IR and significantly lower HOMA-B values compared with control subjects. This indicates that these patients are a high risk of progressing to T2D and its complications. In addition, the significantly higher LDL-C among patients with IFG in comparison to control persons may increases the risk of macro-vascular ASCVD.

1. Introduction

Impaired fasting glycaemia (IFG) is a category of impaired glucose regulation, where blood glucose levels during fasting are consistently above the normal range without exceeding the diagnostic cut-off value of diabetes mellitus (DM) [1- 3].

ß-cell dysfunction and insulin resistance (IR) have an important role in the pathogenesis of IFG [4]. Two conditions of impaired glucose homeostasis intermediate between normality and diabetes have been described. These are the state of IFG and impaired glucose tolerance (IGT). They couldn't considered as distinct clinical entities but in both, there is an increased risk of development of macro-cardiovascular disease (CVD), but not the micro-vascular complications of type 2 diabetes (T2D). Also, both increase the risk of developing diabetes in the future [5].

Initially, in IFG, a compensatory increase in insulin secretion occurs, keeping glucose levels within normal limits. However as the disease advances, insulin secretion is insufficient to maintain glucose homeostasis. People with IFG have a problem with their insulin secretory response to glucose in the early stages [6].

Hepatic IR and normal muscle insulin sensitivity are the hallmarks of the IFG. The development of T2D is linked to obesity and IR. ß-cell malfunction is thought to be necessary for hyperglycemia to arise. In addition, ß-cell malfunction, which develops early in the course of the disease, is an essential aberration in the presence of IR. A different hypothesis has been proposed, in which primary ß-cell overstimulation causes insulin hypersecretion, which leads to obesity and IR, and eventually to ß-cell exhaustion [7].

Patients with prediabetes typically has no distinct signs or symptoms except the sole sign of high blood sugar [8], [9]. Such individuals should be monitored for symptoms such as increased thirst, polyuria, weight loss and lethargy [10].

Persons with of IFG are at a high risk of developing T2D [4], [11]. The annual conversion rate of IFG to T2D ranges from 3-11% [12- 14]. Considerable proportion of people with prediabetes will progress to T2D with high risk in the co-existence of overweight or obesity [6]. Also, it has been found that sedentary lifestyle, obesity and hypertriglyceridemia independently increased the risk for T2D and persistence of prediabetes. HbA1c was the strongest single predictor progression of IFG into T2D [8]. People older than 45 years with visceral obesity and have risk factors such as, first-degree relative with diabetes, history of CVD, hypertension and dyslipidemia should be screened regularly [15], [16].

The present study's aim was to determine the degree of IR (HOMA-IR) and ß-cell dysfunction (HOMA-B) among patients with IFG, and also to correlate them with biochemical and anthropometric variables.

2. Materials and Methods

2.1 Study Population

This is a case-control study conducted at Department of Biochemistry, University of Basrah, Basrah, Iraq, from January 2022 throughout May 2022. It included 293 participants, 143 patients with IFG, and 150

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apparently healthy individuals matched for both age and gender. All participants attended Al-Sadr Teaching Hospital, Basrah, Iraq, either for medical consultation or regular check-up. Patients with IFG, were 61 males and 82 females, 14-70 years of age. IFG is considered with fasting blood glucose (FBG) level of 100-125 mg/dL and glycated haemoglobin (HbA1c) value of 5.7-6.4% [17], [18]. With regard to control subjects, they were, 62 males and 88 females, 15-70 years of age, who were apparently health subjects with no history of diabetes and confirmed to be in good health state, by careful clinical examination and biochemical laboratory tests. Informed written agreement was obtained from all participants. Also, the study was accepted by the Ethical Committee at the College of Medicine, University of Basrah. Exclusion criteria include pregnant women, diabetes, patients with gastrostomy, history of thyroid dysfunction, renal disease, liver disease and critical cases. The participants were interviewed using a detailed questionnaire included enquiries regarding socio-demographic characteristics such as: age, gender, marital status, educational level, history of systemic diseases, family history of diabetes, smoking habit and alcohol consumption.

All participants in the study were underwent body weight, height and waist circumference (WC) measurements with light clothes and no shoes. Body mass index (BMI) was calculated using the formula (Kg/m2). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) was measured twice with mercury sphygmomanometer with at least 10 minutes between the two measurements.

2.2 Collection of blood samples

Blood sample were withdrawn from patients with IFG, and control subjects, after an overnight fast for at least for 8 hours. Five ml of venous blood were obtained by using disposable butterfly blood collection system in the sitting position.

The obtained blood was divided into two parts: 2 ml was dispensed in an anticoagulant tube containing a 1.5 mg/ml tri potassium ethylene diamine tetra acetic acid (K3EDTA tube) for the measurement of HbA1c. The remaining blood was transferred into tube containing gel, which aids clot formation permitting easier serum separation without anticoagulants and was set aside for a time at room temperature (20-25) ˚C for coagulation, and then centrifuged at 3000 rpm for 5 minutes to collect serum, which was used for the determination of FBG, lipid profile, and insulin.

2.3 Determination of Biochemical parameters

Quantitative determination of FBG [19], cholesterol (TC) [20], triglycerides (TG) [21], high density lipoprotein-cholesterol (HDL-C) [22], and low density lipoprotein-cholesterol (LDL-C) [23] were carried out by reference enzymatic methods. The level of HbA1c was measured by ion exchange high performance liquid chromatography (HPLC) method [24]. Interpreatation of HbA1c values was as follows [25]: Non-diabetic values of HbA1c are < 5.7% (National Glycohemoglobin Standardization Program “NGSP”) which is equivalent to < 39 mmol/mol (International federation of Clinical Chemistry and Laboratory Medicine “IFCC”). Prediabetic values are 5.7-6.4% (NGSP) or 39-47 mmol/mol (IFCC) and diabetic values were ≥ 6.5% (NGSP) or ≥ 48 mmol/mol (IFCC). Serum insulin level measured by electrochemiluminescence immunoassay “ECLIA” method [26].

2.4 Homeostatic model assessment (HOMA)

ß-cell function and IR were measured using the following equations [27- 29]:
HOMA-B = 360 × fasting insulin (µIU/ml) / FBG (mg/dL) - 63
Where, B: % of ß-cell function, FBG: Fasting blood glucose.
Normal value of HOMA-B: 100%.

HOMA-IR = FBG (mg/dL) × fasting insulin (µIU/ml) / 405
Where, IR: Insulin resistance, FBG: Fasting blood glucose.
Normal value of HOMA-IR: ≤ 2.5.

2.5 Statistical analysis

Statistical Package for Social Science (SPSS) program version 25 was used to analyze the data of this study and the results were expressed as Mean ± Standard Deviation (SD) and percentage. For continuous data, independent t-test was used to compare two different groups. Pearson correlation was used to find out the correlation coefficient (r- value) among HOMA-B and HOMA-IR with biochemical parameters and other variables in the study population. P-value of less than 0.05 was considered as the lowest limit for significance.

3. Results

The distribution of patients with IFG and control subjects by socio-demographic and anthropometric variables is shown in (Table 1). There were no significant differences between patients with IFG and control subjects with regard to age, gender, BMI, SBP and DBP, P > 0.05. On the other hand, WC in either gender was significantly higher among patients with IFG compared to control persons, (P < 0.05).

Table (1). Socio-demographic and anthropometric characteristics of patients

Characteristic		**IFG (n=143)**	**Controls (n=150)**	**P- value#**
Age (years)		04.04±74.01	04.07±72.21	> 0.05
Gender	Male	57)02.56%(	56)01.11%(	> 0.05
	Female	52)61.10%(	56)65.55%(	
SBP (mm. Hg)		123.57+13.21	120.75±12.43	< 0.05
DBP (mm. Hg)		75.19+ 10. 78	70.19± 6.74	< 0.05
BMI (Kg/m2)		35.836±5.101	32.785±6.28	> 0.05
WC (cm) Male	≤ 102	104.04±22.11•	96.95±8.82	< 0.05
	>102			

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WC (cm) Female	≤ 88	101.32± 12.71•	93.10± 13.51	< 0.05
	>88			

with IFG and control subjects.

Data are presented as Mean + SD, #: Student t-test

Table (2) presents FBG, HbA1c and insulin levels among patients with IFG and control persons. Insulin level was significantly higher among patients with IFG in comparison to control subjects, (P < 0.000). On the other hand, FBG and HbA1c were non-significantly higher in the IFG group compared to the control one, (P > 0.05).

Table (2). FBG, HbA1c and insulin levels in patients with IFG and controls

Variables	**IFG (n=143)**	**Controls (n=150)**	**P - value#**
FBG (mg/dL)	777.715±1.445	04.52±5.556	4.241
HbA1c%	6.570±4.116	6.1046±4.105	4.210
Insulin (µIU/ml)	22.7520±76.466	77.067±1.20	0.000*

Data are presented as Mean + SD,
#: Student t-test, *: Statistically significant

Table (3) presents HOMA-IR and HOMA-B values among patients with IFG and control persons. Patients with IFG showed a significantly higher HOMA-IR and a significantly lower HOMA-B values compared to control subjects, (P = 0.000).

Table (3). HOMA-IR and HOMA-B in patients with IFG and control subjects

Variables	**IFG (n=143)**	**Control (n=150)**	**P - value#**
HOMA-IR	6.170±1.127	2.600±7.511	0.000*
HOMA-B	710.10±10.21	751.24±716.455	0.000*

Data are presented as Mean+ SD, #: Student t-test
*: Statistically significant

Lipid profile among patients with IFG and control group is presented in (Table 4). LDL-C was significantly

higher among patients with IFG in comparison to control subjects, (P = 0.017). There were no significant differences in TC, TG and HDL-C among patients with IFG and the control group, (P > 0.05).

Table (4). Lipid profile in patients with IFG and control group

Variables	**IFG (n=143)**	**Control (n=150)**	**P - value#**
TC (mg/dL)	716.20±06.50	717.50±10.06	4.00
TG (mg/dL)	700.10±17.54	704.55±760.10	4.011
LDL-C (mg/dL)	745.20±15.15	00.25±12.10	4.471*
HDL-C (mg/dL)	07.55±77.51	01.11±20.41	4.011

Data are presented as Mean+ SD, #: Student t-test
*: Statistically significant

The results of correlation analysis in patients with IFG are presented in (Table 5). The study revealed that HOMA-B showed a significant positive correlation with insulin, (P < 0.01), and a significant negative correlation with LDL-C, (P < 0.01). On the other hand, HOMA-IR showed a significant positive correlation with insulin, (P < 0.01), FBG (P < 0.01) and TG (P < 0.05).

Table (5). Correlation analysis in patients with IFG

Variables		HOMA-B	HOMA-IR
Age(years)	Pearson correlation	0.001	0.088
	P value	0.994	0.297
BMI (Kg/m^2)	Pearson correlation	0.058	0.14
	P value	0.494	0.872
Insulin (MU/ML)	Pearson correlation	0.849**	0.828**
	P value	0.000	0.000
FBG (mg/dL)	Pearson correlation	0.009	0.324**
	P value	0.915	0.000
HbA1C%	Pearson correlation	-0.037	-0.011
	P value	0.658	0.896
TC (mg/dL)	Pearson correlation	-0.149	-0.152
	P value	0.75	0.070
TG (mg/dL)	Pearson correlation	0.163	0.186*
	P value	0.51	0.026

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LDL-C (mg/dL)	Pearson correlation	-0.228**	-0.164
	P value	0.006	0.050
HDL-C (mg/dL)	Pearson correlation	-0.57	-0.103
	P value	0.498	0.220

**: Correlation is significant at the 0.01 level (2-tailed)

*: Correlation is significant at the 0.05 level (2-tailed).

4. Discussion

The prevalence of IFG and IGT continuously rising worldwide, and could reach a figure of 8.4% by 2045 [30]. The risk of progression of people with prediabetes to T2D is appreciable particularly in the absence of intervention [4], [31]. It has been found that, and 23.0% of individuals with prediabetes progressed to T2D, an 4.6% annual rate of progression of 4,6% [8]. People with undiagnosed and untreated prediabetes are at risk of sustained hyperglycaemia which may results in serious complications [32], [33]. In patients with IFG, the demand for an increase in insulin exceeds the limited capacity of pancreatic β-cells to produce insulin. This results in a decrease in insulin secretion which in turn aggravated by the toxic effect of free fatty acids, and hence hyperglycemia ultimately occurs [34]. Diabetes is a chronic metabolic disorder representing a global public health problem with dramatically increasing prevalence [35], [36]. T2D is the most common type of diabetes, its prevalence is dramatically increasing, and quickly became an epidemic around the world [30], [37], [38]. In Basrah, Southern Iraq, diabetes received considerable interest, and several studies have been conducted in this regard. In addition, the frequency of diabetes in Basrah is high, where a high proportion of patients have undiagnosed diabetes [39- 41].

Concerning FBG, HbA1c and insulin levels, insulin level was significantly higher among patients with IFG in comparison to control subjects, (Table 2). This indicates a state of hyperinsulinaemia in association with IFG, which represents a compensatory phenomenon to overcome IR to maintain blood glucose concentration within normal limits [6]. This finding also indicates a state of IR which happened mainly due to a receptor defect and positive feedback between glucose concentration, which is the principal stimulus for insulin release, and β –cell producing insulin [42]. The development of diabetes due to severe IR may be retarded unless the capacity to secret additional amounts of insulin to compensate for IR is impaired. In addition, Individuals with IR suffer from several abnormalities including impaired glucose tolerance, dyslipidemia, endothelial dysfunction, and elevated inflammatory markers [42]. HOMA-IR index was used to determine the level of IR, whereas the HOMA-B index was used to determine the level of ß-cell function and insulin secretion. Also, HOMA-IR is linked to some risk factors for the occurrence complications due to diabetes, including CVD and decreasing renal function [43]. With regard to HOMA-IR and HOMA-B, patients with IFG showed a significantly higher HOMA-IR and significantly lower HOMA-B values compared to control subjects, (Tables 3). β-cells fail to compensate for the predominant IR, therefore prediabetes ensues, and diabetes may ultimately develop. As glucose levels are elevated, β-cell function deteriorates (low HOMA-β), with decreasing sensitivity to glucose, thus exacerbating hyperglycemia. The pancreatic islet cell mass has been reported to be reduced in size in patients with diabetes [44]. In addition, the observed hyperinsulinaemia may be attributed to the associated visceral obesity with the consequent resistance to the effect of insulin. Regarding lipid profile, LDL-C was significantly higher among patients with IFG in comparison to control subjects (Tables 4). This higher LDL-C may increases the risk of macro-vascular atherosclerotic CVD in patients with IFG. Lipid abnormalities are common in patients with T2D, and also in patients with prediabetes [45]. Furthermore, patients with diabetes developed diverse forms of dyslipidaemia, where treatment is essential to prevent long-term complications [46]. Correlation analysis in patients with IFG revealed a positive correlation of HOMA-B with insulin and a significant negative

correlation with LDL-C. While, HOMA-IR showed a significant positive correlation with insulin, FBG and TG (Table 5). These results may suggest that HOMA-IR could be helpful tool in predicting diverse macro-vascular and macro-vascular complications. This is of paramount importance in patients with other risk factors such as visceral obesity, hypertension and dyslipidaemia.

5. Conclusion

Patients with IFG have significantly higher insulin and HOMA-IR, and significantly lower HOMA-B values in comparison to with control persons. This implies that patients with IFG a considerable risk of progressing to T2D and, hence, to its diverse complications. LDL-C was significantly higher among patients with IFG compared to control subjects. The elevated LDL-C among patients with IFG may aggravate the risk of macro-vascular atherosclerotic CVD.

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