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Homeostasis Model Assessment (Beta Cell Function) of a Type 2 Diabetes Nigerian Population

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ABSTRACT

Diabetes mellitus has been described to be a metabolic disorder characterized by the presence of hyperglycemia resulting from defective insulin secretion, action or both. This study was designed to determine serum insulin level, fasting plasma glucose and % β-cell function in treated and untreated complicated and uncomplicated diabetes subjects. Ninety subjects comprising of sixty test subjects (30 uncomplicated and 30 complicated diabetes subjects) and thirty control subjects were recruited for this study. Glucose was estimated using Glucose-Oxidase Peroxidase method, while Insulin was analyzed using ELISA. The results obtained showed thatBMI, Glucose, %βCF and insulin showed no significant difference in treated uncomplicated diabetes subjects compared to control ($p>0.05$). Glucose and %βCF were significantly higher ($p<0.05$) in untreated uncomplicated diabetes subjects compared to control, while BMI and insulin showed no significant difference ($p>0.05$).Glucose and %βCF were significantly higher ($p<0.05$) in untreated uncomplicated diabetes subjects compared to treated subjects, while insulin and BMI showed no significant difference ($p>0.05$).BMI, systolic blood pressure, diastolic blood pressure and insulin level were significantly higher ($p<0.05$) in treated complicated diabetes subjects compared to control, whereas Glucose and %βCF showed no significant difference ($p>0.05$). Glucose correlated positively with all parameters in untreated uncomplicated diabetes subjects. We conclude that insulin is increased, while % β-cell function is reduced in diabetes subjects especially in untreated complicated diabetes subjects. Insulin resistance and impaired β-cell function are important pathological basis for the deterioration of glucose metabolism in type 2 diabetes mellitus. Therefore, early screening and intervention for T2DM might help improve islet function and delay the progression of diabetes.

KEYWORDS: Homeostasis Model Assessment, Type 2 Diabetes, Insulin, β-cell function

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INTRODUCTION

Diabetes mellitus is referred to as a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin action, insulin secretion, or both. Pathogenic processes involved in the development of diabetes range from autoimmune destruction of the β-cells of the pancreas with consequent insulin deficiency, to abnormalities in insulin signaling that result in resistance to insulin action(1). The vast majority of cases of diabetes fall into two broad etiopathogenetic types (type 1 and type 2). In type 1 diabetes, the cause is an absolute deficiency of insulin secretion associated with autoimmune destruction of the pancreatic beta-cells. Individuals at increased risk of developing this type of diabetes can often be identified by serological evidence of an autoimmune process of the pancreatic islets and by genetic markers (2). Type 2 diabetes mellitus is a heterogeneous disorder characterized by insulin resistance with varying degrees of insulin secretory defects, followed by reduced insulin secretion from the pancreas (pancreatic beta-cell dysfunction) (3). Type 2 diabetes mellitus accounts for the majority of persons with diabetes cases (90–95%). The increased risk of morbidity and

mortality from vascular complications in diabetic patients is linked to genetic factors, elevated glucose levels, hypertension, obesity, oxidative stress, blood lipid disorders, and smoking (4).

Research have shown that individuals living with type 2 diabetes mellitus are more vulnerable to various forms of both short and long-term complications, which often lead to premature death (5). Two-third of patients with type 2 diabetes mellitus has arterial hypertension and hypertension increases the incidence of both macro and micro vascular complications (6). The coexistence of diabetes and hypertension is possible due to the fact that they show similar risk factors which include; being overweight, living an inactive life style, unhealthy diet among others. Diabetes increases blood pressure by decreasing the blood vessel's ability to stretch, increasing the amount of fluid in the body and changing the way the body manages insulin (7). The cause of hypertension is multifactorial. Aside genetic factors, metabolic risk factors like diabetes and raised blood lipids, obesity, several behavioural and socioeconomic factors can put an individual at risk and can also contribute to the development of hypertension and its complications (8).

Pancreatic beta-cell dysfunction and insulin resistance (IR) form two major factors in the pathophysiology of type 2 diabetes (9). Beta-cell dysfunction occurs when the beta cells are unable to produce optimum insulin concentration needed to maintain glucose homeostasis, while IR occurs when a specific concentration of insulin results in biological responses lower than expected (10). Pathophysiologically, when the maximum insulin produced by the beta cells is no longer enough to surmount IR, persistent IR will eventually lead to beta-cell dysfunction (11). Recently, it has been shown that Homeostasis Model Assessment (HOMA) estimated insulin resistance is an independent predictor of cardiovascular disease in type-2 diabetic subjects (12). HOMA first described by Matthew *et al.* in 1985, is a method for estimating beta-cell function and insulin sensitivity which can be estimated from basal values of Glucose and Insulin (ratio of fasting plasma-to-fasting insulin). HOMA is calculated using steady state blood concentrations of fasting glucose and insulin to estimate the degree of beta cell deficiency and the target tissue sensitivity to insulin (13). The HOMA nevertheless is difficult to apply to patients with severe beta-cell dysfunction or those treated with insulin and those with poor glycaemic control. This study was therefore carried out to determine the HOMA of subjects with uncomplicated and complicated type 2 diabetes.

METHODS

Study Area

This study was carried out in Federal Teaching Hospital, Ido-Ekiti (FETHI), Ekiti State and its immediate environment. Ido-Ekiti is a town in Ekiti State in South-Western Nigeria. The state is mainly high land area about 50 meters above sea level. Its coordinates are 70 40'N 50 15'E.

Study Design

The study was a cross-sectional study using a stratified random sampling method. Stratification was by age, height weight, body mass index and therapy.

Sample size

The minimum sample size (N) was calculated by single proportion formula based on a 3.8% estimated prevalence of type 2 diabetes mellitus and a 95% control level, with a 0.05 margin of error.

Using; $N= Z^2 p (1-p) / d^2$

Where;

N = sample size

Z =control level at 95% =1.96

p = estimated percentage prevalence at 3.8%= 0.038

d= margin of error at 0.05

$N = 1.96^2 \times 0.038 (1-0.038)$

0.05^2

N= 56

A total of ninety (90) subjects comprising of sixty (60) test subjects (30 uncomplicated and 30 complicated diabetes subjects) and thirty (30) control subjects were recruited for this study.

Inclusion Criteria

Adult male and female subjects aged 18 – 65 years who were type 2 diabetic and hypertensive type 2 diabetic patients with or without treatment who gave their consent were included in this study.

Exclusion criteria

Subjects below the age of 18 years, pregnant women, nursing mothers, and those with chronic kidney disease and/or any other metabolic disorders were excluded from this study.

Ethical Clearance

Ethical approval was sought out from the Ethics and Health Research Committee, Federal Teaching Hospital, Ido-Ekiti, Ekiti State. Informed consent was obtained from each subject who participated in the study before sample collection.

Sample Collection

A total amount of 5ml venous whole blood sample was collected from the subjects, of which 2ml was dispensed into fluoride oxalate anticoagulant bottle and 3ml dispensed into plain bottle. The blood sample in the plain bottles was allowed to clot, retracted and centrifuged for 5minutes at 3,500rpm after which the serum was separated from the red cells and dispensed into another plain bottle and stored at -20˚C.

Anthropometric analysis

Blood Pressure: Blood pressure was determined with digital sphygmomanometer.

Height and weight were obtained using a meter gauge and a bathroom scale respectively.

Body Mass Index (BMI): BMI was derived from the height and weight using the formula:

BMI = Weight (kg)

Height (m^2). It was expressed in kg/m^2

Sample analysis

Estimation of Plasma Glucose: Plasma glucose was estimated spectrophotometrically using the Glucose-Oxidase Peroxidase method (Randox glucose kit).

Principle: Glucose is oxidized in the presence of gluconic acid and hydrogen peroxide. Peroxidase catalyzes the breakdown of hydrogen peroxide into atmospheric oxygen and water. The oxygen then reacts with phenol and 4-aminophenazone to give a pink colour which is read spectrophotometrically at 505nm.

Homeostasis Model Assessment (HOMA)

The % β-cell function was done using the C-Peptide Modified Formula:-

$$HOMA - \beta = \frac{Insulin \times 20\%}{Glucose\ (mmol/L) - 3.5}$$

Insulin

Insulin was done using an Enzyme-Linked Immunosorbent Assay (ELISA) (Biorex) according to manufacturer's instructions.

Statistical Analysis

Results obtained were subjected to statistical analysis using SPSS (version 23.0 software, SPSS Inc. Chicago, Illinois, USA). Values of all parameters were expressed as mean ± SD. Student's t-test and ANOVA were the tool of choice in comparing the means. Correlation was done using Pearson Moment Correlation Coefficient. Significant difference was accepted at $p<0.05$.

RESULTS

Table 1 showed the mean values of BMI, Glucose, Insulin and %βCF of treated and untreated uncomplicated diabetes subjects and control. The results obtained showed that BMI, Glucose, %βCF and insulin showed no significant difference in treated uncomplicated diabetes subjects compared to control ($p>0.05$). Glucose and %βCF were significantly higher ($p<0.05$) in untreated uncomplicated diabetes subjects compared to control, whereas BMI and insulin showed no significant difference ($p>0.05$). Furthermore, Glucose and %βCF were significantly higher ($p<0.05$) in untreated uncomplicated diabetes subjects compared to treated subjects, whereas insulin and BMI showed no significant difference ($p>0.05$).

Table 2 showed the mean values of BMI, Blood pressure, Glucose, Insulin and %βCF of treated and untreated complicated diabetes subjects and control. The results obtained showed that BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP) and insulin level were significantly higher ($p<0.05$) in treated complicated diabetes subjects compared to control, whereas Glucose and %βCF showed no significant difference ($p>0.05$). Similarly, BMI, Glucose, SBP, DBP and %βCF were significantly higher ($p<0.05$) in untreated complicated diabetes subjects compared to control, whereas insulin showed no significant difference ($p>0.05$). Furthermore, glucose, SBP, DBP and %βCF were significantly higher ($p<0.05$) in untreated complicated diabetes subjects compared to treated subjects, whereas BMI and insulin showed no significant difference ($p>0.05$).

Table 3 showed the correlation of Glucose with other parameters in treated and untreated uncomplicated diabetes subjects. The results obtained showed negative correlation between glucose and DBP and %βCF, but there was no correlation between glucose and other parameters in treated uncomplicated diabetes subjects. Furthermore, there was negative correlation between glucose and BMI, SBP, DBP and %βCF and positive correlation between glucose and insulin in untreated uncomplicated diabetes subjects.

Figure 1 to 4 showed the Glucose, Insulin and %βCF of specific group of drugs in uncomplicated and complicated treated and untreated diabetic subjects and control. The results obtained showed that %βCF, insulin and glucose were significantly affected by treatment and the effect of treatment varied with the type of drug used.

Table 1: Mean values of BMI, Glucose, Insulin and %βCF of treated and untreated uncomplicated diabetes subjects and control

Parameters	Treated Un-complicated DM mean ± SD (n = 15)	Untreated Un-complicated DM mean ± SD (n = 15)	Control mean ± SD (n=30)	p-value
BMI (kg/m^2)	26.29 ± 6.84^a	28.07 ± 3.64^a	26.45 ± 0.49^a	0.079
Glucose (mmol/L)	4.75 ± 0.81^a	8.65 ± 1.40^b	4.74 ± 0.73^a	0.000
Insulin (mIU/L)	4.71 ± 1.68^a	4.73 ± 0.80^a	4.18 ± 1.41^a	0.251
%βCF	170.70 ± 220.70^a	19.59 ± 4.54^b	159.41 ± 205.40^a	0.033

*Values in a row with different superscript is significant at $p<0.05$

Keys: **BMI** – Body Mass Index, **%βCF –** Percentage Beta Cell Function

Table 2: Mean values of BMI, Glucose, Insulin and %βCF of treated and untreated complicated diabetes subjects and control

Parameters	Treated complicated DM mean ± SD (n = 15)	Untreated complicated DM mean ± SD (n = 15)	Control mean ± SD (n=30)	p-value

BMI (kg/m²)	30.46± 5.55[a]	30.96±5.477[a]	26.45±0.49[b]	0.001
SBP (mmHg)	143.90± 10.25[a]	152.50±9.54[b]	111.5 ± 4.91[c]	0.000
DBP (mmHg)	91.00±5.77[a]	96.79±6.52[b]	72.76 ± 7.57[c]	0.000
Glucose (mmol/L)	4.98±1.01[a]	9.86±3.16[b]	4.74±0.73[a]	0.000
Insulin (mIU/L)	5.36±1.58[a]	4.931±0.29[a]	4.18±1.41[b]	0.028
%βCF	71.34±53.10[a]	18.24±6.13[b]	159.41±205.40[a]	0.000

*Values in a row with different superscript is significant at p<0.05

Keys: **BMI** – Body Mass Index, **%βCF –** Percentage Beta Cell Function, **SBP –** Systolic blood pressure, **DBP** – Diastolic blood pressure

Table 3: Pearson correlation between Glucose and other parameters in treated and untreated uncomplicated diabetes subjects

Parameters	**Treated Uncomplicated DM r(p)**	**Untreated Uncomplicated DM r(p)**
BMI	0.143 (0.611)	-0.327 (0.048)*
SBP	-0.039 (0.889)	-0.627 (0.038)*
DBP	-0.205 (0.465)	-0.643 (0.032)*
Insulin	0.021 (0.942)	0.636 (0.035)*
%βCF	-0.893 (0.000)**	-0.672 (0.023)*

* Significant at p<0.05, while ** significant at p<0.001

Keys: **BMI** – Body Mass Index, **%βCF –** Percentage Beta Cell Function, **SBP –** Systolic blood pressure, **DBP** – Diastolic blood pressure

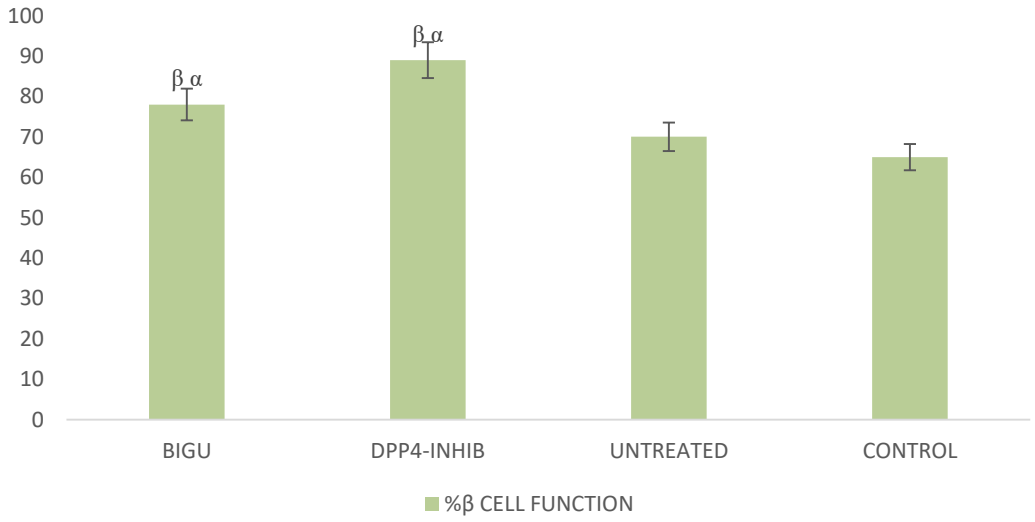

Fig1. %βCF in specific group of drugs in uncomplicated diabetes subjects relative to control and untreated subjects

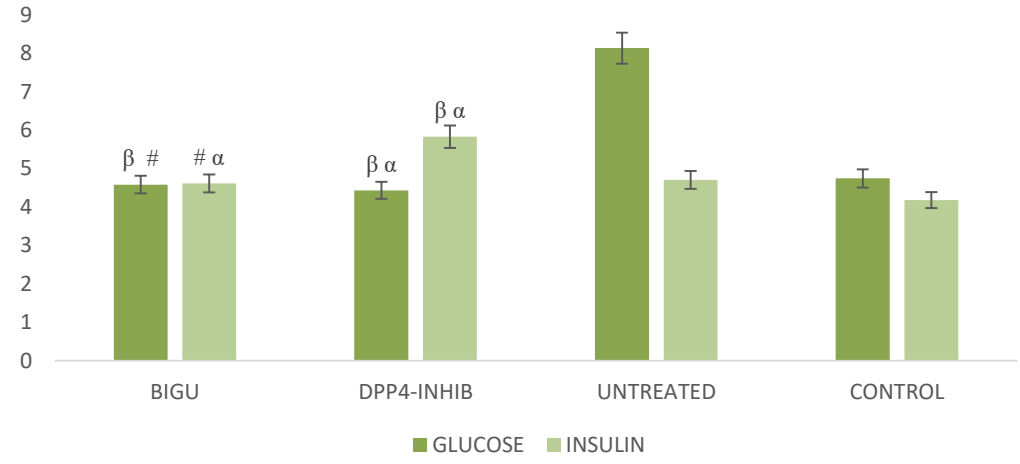

Fig 2. Glucose and Insulin level of specific group of drugs in uncomplicated diabetes subjects relative to control and untreated subjects

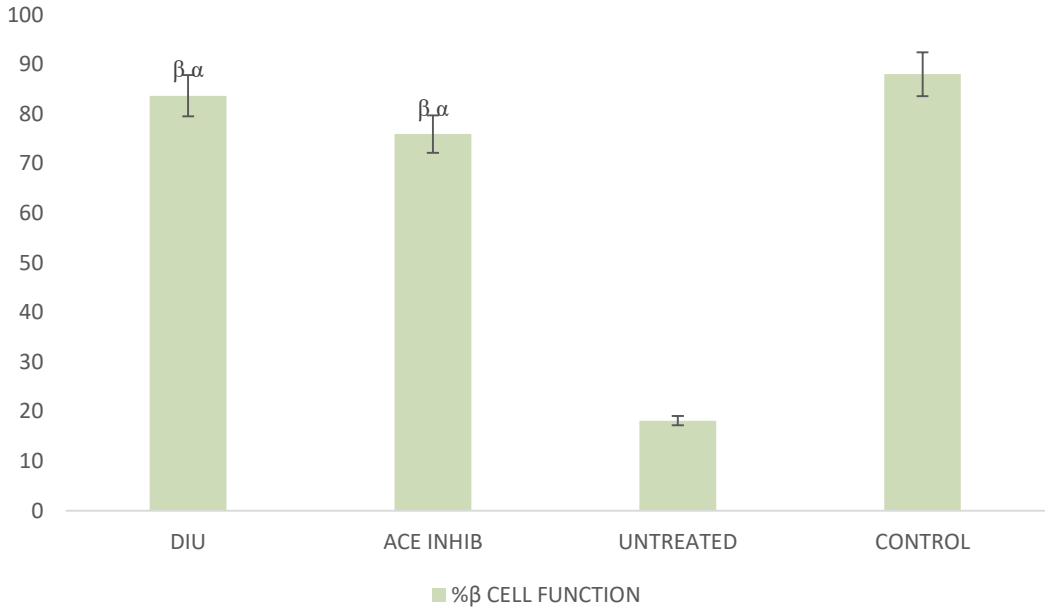

Fig 3. %βCF of specific group of drugs in complicated diabetes subjects relative to control and untreated subjects

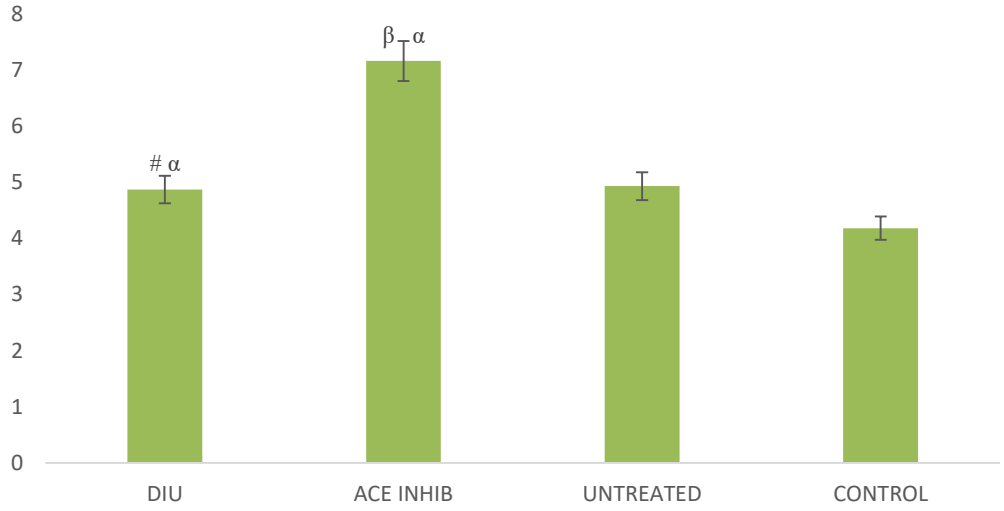

Fig 4. Insulin level in specific group of drugs in complicated diabetes subjects relative to control and untreated subjects

DISCUSSION

Diabetes mellitus is a chronic disease occurring as a result of decreased production of insulin in the pancreas, or inability of the body to effectively utilize the insulin being produced (3). Diabetes have been shown to increase blood pressure by decreasing blood vessels ability to stretch, increasing the amount of fluid in the body which tend to raise blood pressure, thereby changing the way the body handles and produces insulin (14). Since hypertension and diabetes has been associated with disturbances in insulin action and glucose utilization, a research design that assess the serum insulin level, fasting plasma glucose and %β-cell function of treated and untreated complicated and uncomplicated diabetes subjects becomes imperative.

In this study, BMI showed no significant difference in treated and untreated uncomplicated diabetes subjects when compared to control, and in treated uncomplicated diabetes subjects compared to untreated subjects. This finding is in line with the works of (15), who reported that no significant difference in the BMI of uncomplicated diabetic subjects with or without treatment. On the other hand, BMI was significantly higher in treated and untreated complicated diabetes subjects compared to control, but showed no significant difference in treated complicated diabetes subjects compared to untreated subjects. Obesity, as measured by BMI, which could cause chronic low-grade systemic and local inflammation that leads to the emergence of insulin resistance linked diabetes mellitus, has been reported as an independent risk factor for type 2 diabetes (16). In addition, insulin resistance and hyperinsulinemia can contribute to the development of obesity seen in diabetic subjects. This finding is in agreement with previous studies which reported significantly higher BMI in untreated and treated complicated diabetes subjects (17-19).

In this study, we reported significantly higher systolic and diastolic blood pressures in treated and untreated complicated

diabetes subjects compared to control and in treated complicated diabetes subjects compared to untreated subjects. The pathophysiology of hypertension in diabetes have been linked to abnormal changes in blood pressures and attributed to multiple interactions between the vascular endothelial system, enhanced activation of the rennin-angiotensin-aldosterone system, autonomic nervous system, alterations in immune function and several environmental and genetic factors (20). The increased values of systolic and diastolic blood pressures in diabetic subjects contribute significantly in raising the blood glucose levels in diabetic subjects. This finding is in agreement with previous studies (19-21) who reported significant higher blood pressures in complicated and uncomplicated diabetic subjects.

In this study, glucose showed no significant difference in treated complicated and uncomplicated diabetes subjects compared to control, but was significantly higher in untreated complicated and uncomplicated diabetes subjects compared to control, and in treated complicated and uncomplicated diabetes subjects compared to untreated subjects. Diabetes has been associated with remodeling of the blood vessels thereby causing hypertension which in turn limits how the body handles glucose (22). Hyperglycemia in a patient with type 1 diabetes is a result of genetic, environmental, and immunologic factors. These lead to the destruction of pancreatic beta cells and insulin deficiency. In patients with type 2 diabetes, insulin resistance and abnormal insulin secretion lead to hyperglycemia (23). Furthermore, several factors can play a role in hyperglycemia in people with diabetes which include food, physical activity, illness and medications. This finding is in line with previous findings (19,21,24-25). The significant reduction in glucose level in treated uncomplicated and complicated diabetic subjects compared to untreated diabetic subjects have been attributed to life style modification, DASH diet, therapeutic interventions and medications used in the management of diabetes mellitus (19-20).

In this study, serum insulin level showed no significant difference in untreated complicated and uncomplicated diabetes subjects compared to control and in treated uncomplicated diabetes subjects compared to untreated subjects. Serum insulin level was significantly higher in treated complicated diabetes subjects compared to control, but showed no significant difference in untreated complicated diabetes subjects when compared to control and in treated complicated diabetes subjects when compared to untreated subjects. Hyperglycaemia, the hall mark of established type 2 diabetes is known to induce and sustain insulin resistance making it impossible to distinguish defects of insulin secretion or action that are pathogenically involved in the development of type 2 diabetes and those that result from the effects of hyperglycaemia (7). However, if insulin resistance precedes the onset of type 2 diabetes mellitus, this anomaly is expected to be found in a fraction of the non-diabetic population which is supported by this study. This finding is in agreement with previous studies (7,9,26).

Beta (β) cells are cells located in the islets of Langerhans. %β-cell function is assessed by homeostasis model assessment using values of glucose and insulin. In this study, %β-cell function showed no significant difference in treated uncomplicated diabetes subjects when compared to control, but was significantly higher in untreated uncomplicated diabetes subjects compared to control, and significantly higher in treated uncomplicated diabetes subjects compared to untreated subjects. A decline in pancreatic beta-cell function has been defined as key factor contributing to progression of type 2 diabetes mellitus (T2DM) (27). In fact, a significant proportion of beta-cell secretory capacity is thought to be lost well before the diagnosis of T2DM is made. Several models have been proposed to explain the reduction in beta-cell function, including reduced beta-cell number, beta-cell exhaustion and dedifferentiation or trans-differentiation into other cell types (28). However, there have been reports that suggest remission of T2D is possible, and it is believed that beta-cell dysfunction may be, in part, reversible (29). This finding is in agreement with previous studies (28-30).

Report showed that hyperglycemia and lipotoxicity played major roles in the possible mechanisms underlying impaired β-cell function (31). Exposure of β-cells to hyperglycemia might promote efflux of insulin secretory granules from the β-cell, leaving less insulin available for release in response to further hyperglycemia (32). In addition, it was suggested that increased glucose levels could activate the hexosamine pathway, resulting in excess generation of reactive oxygen species and the inhibition of insulin gene transcription and insulin secretion. Accumulated fatty acids and their metabolic products might have a negative effect on the conversion of proinsulin to insulin and decrease nitric oxide production, inhibiting glucose oxidation and inducing β-cell apoptosis (33).

In this study, treatment included two classes of antihypertensive drugs: Diuretics and ACE inhibitors, and two classes of diabetes drugs: Biguanides and DPP-4 inhibitors respectively. Treatment was seen to be more effective in those treated with ACE inhibitors by improving %β-cell function in both uncomplicated and complicated diabetes subjects. Furthermore, treatment with Biguanides was effective in the regulation of insulin and glucose levels. The finding of this study agrees with previous studies (3,32,34). Lower beta cell function have been associated with higher rate of treatment failure, poorer glycemic control and greater glycemic fluctuation in patients with T2DM, which are probably related to higher risk of diabetic complications in these patients (35). Furthermore, T2DM is characterized by a progressive failure of pancreatic β-cell function with insulin resistance. Once insulin over-secretion can no longer compensate for the degree of insulin resistance, hyperglycemia becomes clinically significant and

deterioration of residual β-cell reserve accelerates (32). This pathophysiology has important therapeutic implications. Ideally, therapy should address the underlying pathology and should be started early along the spectrum of decreasing glucose tolerance in order to prevent or slow β-cell failure and reverse insulin resistance (3). The development of an optimal treatment strategy for each patient requires accurate diagnostic tools for evaluating the underlying state of glucose tolerance.

CONCLUSION

This study reported that insulin is increased, while % β-cell function is reduced in diabetes subjects especially in untreated complicated diabetes subjects. Insulin resistance and impaired β-cell function are the important pathological basis for the deterioration of glucose metabolism in type 2 diabetes mellitus. Therefore, early screening and intervention for T2DM might help improve islet function and delay the progression of diabetes. First line drugs for treatment for % β-cell function followed by life style changes such as dietary changes and physical exercise are important considerations in the control and management of diabetes mellitus.

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