Journal of Pharmaceutical Research International

30(1): 1-10, 2019; Article no.JPRI.51394
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Assessment of Toxicological Effects of Selected Popular Antidiabetic Drugs in Type II Diabetes Mellitus within Ota, Ogun State, Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. Authors OOO, OOG, OOE and EOO conceived and designed the research study. Authors OOO, OOG, OOE, ABT, AAO, TMD, OAR, SOR and EOO performed the experiment and data collection. Authors OOO and OOG carried out data analysis and interpretation with support from authors OOE, ABT, AAO, TMD, OAR, SOR and EOO. Authors OOO and OOG wrote the manuscript with support from authors OOE, ABT, AAO, TMD, OAR, SOR and EOO. Authors OOO, OOG, OOE, ABT, AAO, TMD, OAR, SOR and EOO revised the manuscript critically. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2019/v30i130259
Editor(s):
(1) Dr. Jongwha Chang, Department of Pharmaceutical, Social and Administrative Sciences, Samford University, McWhorter School of Pharmacy, USA.
Reviewers:
(1) Yun-Zhong Chen, Hubei University of Chinese Medicine, China.
(2) Ronald Bartzatt, University of Nebraska, USA.
Complete Peer review History: http://www.sdiarticle4.com/review-history/51394

Original Research Article

Received 08 July 2019
Accepted 10 September 2019
Published 20 September 2019

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ABSTRACT

Aim: The complications associated with diabetes and the new trend of using combination therapy in the management of the disease gave birth to this work, aimed at assessing the hepatotoxic and nephrotoxic effects of selected popularly used antidiabetic medications in type 2 diabetic patients within Ota, Ogun State, Nigeria.

Study Design: The participants, diabetic (n=195) and non-diabetic (n=30) were divided into the following groups based on their medications: 1 (Non Diabetic control), 2 (Metformin), 3 (Glimepiride), 4 (Glibenclamide), 5 (Metformin and Glimepiride), 6 (Meformin and Glibenclamide), 7 (Metformin, Glimepiride and Glibenclamide) and 8 (Diabetic Dietary control).

Methodology: Serum protein expression profiling, liver and kidney function parameters were assessed in participant's blood using Sodium dodecyl sulphate polyacrylamide gel electrophoresis **(**SDS-PAGE) and standard laboratory methods respectively.

Results: Glyceamic control within the diabetic groups was 29.23%. Urea concentration was significantly increased ($p < 0.05$) in groups 5 and 7 compared with groups 1 and 8 while the serum creatinine levels in the different groups showed no significant difference. Activities of alkaline phosphatase and aspartate aminotransferase increased significantly ($p < 0.05$) in group 5 compared with groups 1 and 8. A low molecular weight protein likely to be Leptin (molecular weight 18 kDa) was over-expressed in all the diabetic groups.

Conclusion: This study shows that use of multiple rather than single drugs caused significant functional changes in the liver and kidney. The control of diabetes may best be carried out with dietary control and lifestyle modification as well as good therapeutic drug monitoring for safe assessment of baseline organ function.

Keywords: Diabetes; liver function markers; kidney function markers; protein profile.

1. INTRODUCTION

Diabetes mellitus is an endemic metabolic disease characterised with hyperglycemia; which can be due to either the inability of the pancreas to produce enough insulin, or inability of cells to respond to the insulin produced. It is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control [1]. A chronic hyperglycemic condition in diabetes is associated with long term damage, dysfunction, and failure of various organs, such as eyes, kidneys, nerves, heart, and blood vessels [2]. Diabetes can be classified into Type I, Type II, and Gestational diabetes. Type II diabetes has been reported as the more prevalent form and has its underlying metabolic causes with combined effects of impairment in the insulin mediated glucose disposal and defective secretion of insulin by the β-cells of the pancreas [2]. Various genetic and environmental factors can result in the progressive loss of β-cell mass and/or function that manifests clinically as hyperglycemia in both type I and type II diabetes [3]. The leading cause of this metabolic disorder in Africa today include: aging population, increased urbanization; which can be due to changes in life style, dietary intake, lack of physical exercise, physiological stress, which is associated with obesity, a great risk factor of diabetes [4].

Amongst the African Countries, Nigeria has the highest number of people living with diabetes (about 3 million people) [5]. This growth in diabetes prevalence, driven principally by increasing prevalence of type II diabetes, is occurring in both developing and developed countries which accounts for 5–10% of the total healthcare budget in many countries [4]. However, due to the prevalence of this disease in the world today and the serious threat posed to mankind's health especially the aging, a lot of glucose-lowering drugs, insulin therapy, diet control and exercises have been used for the management of diabetes but total recovery have not been recorded [6]. Antidiabetic therapeutic drugs are directed towards increasing insulin secretion, decreasing insulin resistance and increasing insulin penetration into the cells [7]. The types of glucose-lowering drugs, includes insulin secretagogues (sulfonylureas, meglitinides), insulin sensitizers (biguanides, thiazolidinediones), the alpha-glucosidase inhibitors (miglitol, acarbose) and the new peptide analogs being employed such as exenatide, liraglutide and dipeptidyl peptidase (DPP)-4 inhibitors [8].

The liver which is the largest visceral organ of the body is often targeted for chemically induced organ toxicity, due to its strategic metabolic activity [9]. More than 900 drugs have been implicated in causing liver injury (drug induced hepatotoxicity) [10]. Diabetic patients who take oral hypoglycemics have a higher risk of developing drug-induced liver disease than those not taking these medications [11]. The first generation of these medications have been reported hepatotoxic which is one of the reason of withdrawal from the market [7]. Therefore proper monitoring of liver function is a necessity in treatment of diabetes to avoid idiosyncratic hepatotoxicity.

The kidney is the major organ that carries out regulatory functions and excretion of toxic metabolites and drugs [12]. Nephrotoxic drugs exert toxic effects by altering intraglomerular hemodynamics, tubular cell toxicity, inflammation, crystal nephropathy, rhabdomyolysis, and thrombotic microangiopathy. Hypoglycaemia risk increases with increasing renal impairment (that is renal impairment is a major risk factor for hypoglycaemia), with hypoglycemia from antidiabetic drug therapy being among the four leading causes of hospitalisation for adverse drug reactions in the elderly [13].

The management of these complications can be a limiting factor to effective medication control due to possible drug-drug interactions and nonadherence to oral therapy by the diabetes patients [14]. Although previous researches have focused more on the oral treatment of diabetes, there is no well documented data on all these drugs with respect to their potential role in causing toxic effects. The management measures to achieve an effective blood glucose control or utilization, with a view to delaying or averting the onset of complications are however limited due to the associated toxic effects of antidiabetic medications. This work aims to assess the hepatotoxic and nephrotoxic effect of selected antidiabetic medications in type II diabetic patients within Ota, Nigeria.

2. MATERIALS AND METHODS

2.1 Participants

The study population for this study included 225 participants; 195 diabetic participants and 30 healthy non-diabetic participants. This study was carried out in two facilities in Ota, Ogun State, they are: General Hospital, Ota, Ogun state, and ACE Medicare, Ota, Ogun State. The inclusion criteria included clinically diagnosed diabetic participants, currently on one or more oral antidiabetic drug(s), aged 18 years and above and healthy non-diabetic participants who are currently on no medication, as control. Healthy non-diabetic participants, currently on medication and unwilling diabetic subjects, not interested in being included in the research were excluded.

2.2 Data Collection

Questionnaire was used to collect all relevant information about the participants' diabetes history, anthropometric and clinical data and life style habits. Intravenous blood sample (10 ml) was obtained from all participants by trained medical laboratory scientists for the assessment of the biochemical toxicological markers. Informed written consent was provided by all participants. Ethical approval was obtained from Covenant University Ethics Committee, Ogun state and Nigeria Institute of Medical Research (NIMR) Ethics Committee, Lagos state with project approval number IRB/13/227.

2.3 Sample Collection

Intravenous blood sample (10 ml) was collected by trained medical laboratory scientists from Covenant University and Ado-Odo Ota Local Government Medical Laboratory, Ota, Ogun State. Collected blood samples were centrifuged at 3000 rpm for 10 minutes (min) using table top centrifuge (Model 0508-1) to obtain the serum.

2.4 Biochemical Analysis

The blood serum was analyzed for parameters such as: Urea, Creatinine, Alanine Aminotransferase (ALT), Albumin and Aspartate aminotransferase (AST) using Randox test kit (Randox Laboratories Limited, UK); Alkaline phosphatase (ALP) using ALP assay kit (TECO diagnostics).

2.5 Determination of Protein Profile

The Total protein in the blood serum was quantified using Biuret method according to the method described by Janairo et al. [15]. The protein profile in the blood serum was determined using Sodium dodecyl sulphate polyacrylamide gel electrophoresis **(**SDS-PAGE)

according to standard experimental procedures of BIO- RAD laboratories, Inc.

2.6 Clinical Limits for Blood Glucose Levels

(American Diabetics Association (ADA), 2016) [1].

Normal fasting blood glucose - ≥ 90 ≤ 126 mg/dl,

Normal random blood glucose - < 200 mg/dl

2.7 Statistical Analysis

The results obtained from this study was grouped and expressed as mean ± standard error of mean (SEM). Statistical analysis was carried out by one way analysis of variance with the Statistical Package for the Social Sciences (SPSS) version 15.0 (SPSS Inc., Chicago, IL, USA). The test for statistical significance was carried out at 95% confidence limit.

3. RESULTS

3.1 Effect of Antidiabetic Medications on Fasting and Random Blood Glucose Level of Diabetic Patients

The effect of antidiabetic medications on fasting blood glucose and random blood glucose of diabetic patients was illustrated in Table 1. According to the criteria of (ADA, 2016), the mean range of controlled fasting blood glucose, random blood glucose are 90-126 mg/dl; <200 mg/d respectively in diagnosed diabetic patients.

Based on these criteria, in this study, diabetic groups on dietary control and metformin had their fasting and random blood glucose controlled, while diabetic groups on glimepiride; glibenclamide; metformin and glimepiride; metformin and glibenclamide and metformin, glibenclamide and glimepiride had uncontrolled fasting and random blood glucose (Table 1).

3.2 Effect of Antidiabetic Medications on Kidney Function Markers in Blood Sample of Diabetic Patients

The effect of antidiabetic medications on kidney function markers in diabetic patients was determined by assessment of the concentration of urea and creatinine (Table 2). There was no significant difference ($p > 0.05$) in the concentration of creatinine in all the diabetic medication groups when compared with diabetic dietary and non diabetic control groups, though there was insignificant increase ($p > 0.05$) in the concentration of creatinine in all the groups except in the diabetic group using combination therapy of metformin, glimepiride and glibenclamide (Table 2). However, there was significant increase ($p < 0.05$) in the concentration of urea in diabetic group using meformin; metformin and glimepiride; metformin and glibenclamide when compared with diabetic dietary and non diabetic control groups (Table 2).

3.3 Effect of Antidiabetic Medications on Liver Function Marker in Diabetic Patients

The effect of antidiabetic medications on liver function markers in blood sample of diabetic patients was determined by evaluating the activity of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, the concentration of albumin and total protein. There was significant increase ($p < 0.05$) in albumin concentration in diabetic groups using metformin; glimepiride; glibenclamide; metformin and glimepiride; metformin and glibenclamide, while there was no significant difference ($p > 0.05$) in the diabetic groups using combination therapy metformin, glimepiride and glibenclamide when compared to non-diabetic control group. Also, there was significant difference ($p < 0.05$) in the concentration of albumin in diabetic groups using glibenclamide and in the group using metfomin and glimepiride, while there was no significant difference ($p > 0.05$) in the diabetic groups using metformin; glimepiride; metformin and glibenclamide and in the group using metformin, glimepiride and glibenclamide when compared with diabetic dietary control group (Table 3).

There was no significant difference ($p > 0.05$) in total protein in all the diabetic groups when compared with non-diabetic control group. However, there was significant increase ($p < 0.05$) in total protein in diabetic groups using metformin; glibenclamide; metformin and glimepiride and the group using metformin and glibenclamide, while glimepiride; metformin, glimepiride and glibenclamide showed no significant difference ($p > 0.05$) when compared with diabetic dietary control (Table 3).

Table 1. Effects of antidiabetic medications on blood glucose of diabetic patients

Markers/ Groups	FBG (mg/dl)	RBG (mg/dl)
C	63.76 ± 9.04^{N}	50.9 ± 9.10^{N}
DC	103.71 ± 4.35^{C}	120 ± 5.00^{C}
MET	123.3 ± 4.56^{C}	189.18 ± 13.11^{C}
GLIM	145.25 ± 7.90^{NC}	201.20 ± 14.57^{NC}
GLIB	136.5 ± 7.83^{NC}	215.00 ± 19.23^{NC}
MET&GLIM	162.57 ± 13.48^{NC}	274.17 ± 33.78^{NC}
MET&GLIB	145.17 ± 6.4^{NC}	215.03 ± 10.11^{NC}
MET, GLIM &GLIB	147.00 ± 17.76^{NC}	225.00 ± 7.16^{NC}

C = Control; DC = Dietary control; MET = Metformin; GLIM = Glimepiride; GLIB = Glibenclamide; FBG = Fasting blood glucose; RBG = Random blood glucose; BP = Blood pressure; ^{N}, ^{C}, and ^{NC} represents normal; controlled; and uncontrolled values respectively. Result expressed as mean ± SEM in 2 replicates

Table 2. Effect of antidiabetic medications on kidney function markers in blood sample of diabetic patients

Markers/ Groups	Creatinine (Umol/L)	Urea (mmol/l)
C	57.46 ± 7.28	1.76 ± 0.26
DC	59.9 ± 14.03	1.95 ± 0.49
MET	68.12 ± 6.60	3.00 ± 0.42*#
GLIM	62.56 ± 8.08	2.42 ± 0.36
GLIB	88.32 ± 6.58	3.24 ± 0.26
MET & GLIM	68.16 ± 11.35	3.47 ± 0.59*#
MET & GLIB	74.21 ± 4.81	3.13 ± 0.33*#
MET, GLIM & GLIB	31.89 ± 15.95	0.95 ± 0.47

*C = Control; DC = Dietary control; MET = Metformin; GLIM = Glimepiride; GLIB = Glibenclamide. Values marked with * and # are significantly different at $p < 0.05$ when compared with healthy non diabetic control group and diabetic dietary control group respectively. Result expressed as mean ± SEM in 2 replicates*

Table 3. Effect of antidiabetic medication on liver function marker

Markers/ Groups	Albumin (g/l)	T. Protein (mg/ml)	ALP (U/l)	AST (U/l)	ALT (U/l)
C	22.01±3.21	0.45±0.031	14.60±1.72	6.39±0.25	4.11±0.31
DC	23.22 ±5.93	0.36 ± 0.08	8.18 ± 3.07*	3.63 ± 1.20*	2.32 ±0.85*
MET	33.36±2.89*	0.54±0.03#	17.18±1.54#	8.24±0.26#	2.92±0.32*
GLIM	33.23±3.84*	0.44±0.04	17.10±2.12#	9.53±0.93#	3.07±0.41
GLIB	50.40±1.37*#	0.55 ± 0.07	22.66 ± 0.12#	7.5 ± 0.22#	4.00 ± 0.10*
MET & GLIM	35.08±4.15*#	0.50±0.05#	22.21±1.67*#	12.26±0.88*#	3.67±0.52
MET & GLIB	35.11±1.99*	0.53±0.02#	18.28±1.19#	8.5±0.31#	2.71±0.21*
MET,GLIM&GLIB	15.95±4.99	0.45±0.02	13.41±3.39	10±1.34#	0.50±0.25*

*C = Control; DC = Dietary control; MET = Metformin; GLIM = Glimepiride; GLIB = Glibenclamide; ALP = Alkaline Phosphatase; AST = Aspartate Aminotransferase; ALT = Alanine Aminotransferase; T. PROT = Total Protein. Values marked with * and # are significantly different at $p < 0.05$ when compared with healthy non diabetic control group and diabetic dietary control group respectively. Result expressed as mean ± SEM in 5 replicates*

There was significant increase ($p < 0.05$) in the concentration of alkaline phosphatase (ALP) only in diabetic group using metformin and glimepiride, while the other diabetic groups using metformin; glimepiride; glibenclamide; metformin and glibenclamide and metformin, glibenclamide and glimepiride showed no significant difference ($p > 0.05$) when compared with non-diabetic control group. Furthermore, there was significant increase ($p < 0.05$) in the concentration of ALP in diabetic groups using metformin; glimepiride; glibenclamide; metformin and glimepiride; and metformin and glibenclamide, while there was no significant difference ($p > 0.05$) in the concentration of ALP only in diabetic group using combination therapy metformin, glimepiride

and glibenclamide when compared with diabetic dietary control group (Table 3). Also there was significant decrease ($p < 0.05$) in the concentration of ALP in the diabetic dietary control group compared with non-diabetic control group.

However, there was significant increase ($p < 0.05$) in concentration of aspartate amino-transferase (AST) in diabetic group using combination therapy metformin and glimepiride and in the diabetic dietary control group, while there was no significant difference ($p > 0.05$) in the diabetic groups using metformin; glimepiride; glibenclamide; metformin and glibenclamide and metformin, glibenclamide and glimepiride, when compared with non-diabetic control group. Also, there was significant increase ($p < 0.05$) in the concentration of AST in all the diabetic medication groups when compared with diabetic dietary control group.

There was no significant difference ($p > 0.05$) in concentration of alanine aminotransferase (ALT) in all the diabetic medication groups when compared with diabetic dietary control group (Table 3). However, there was significant decrease ($p < 0.05$) in the concentration of ALT in diabetic groups using metformin; glibenclamide; metformin and glibenclamide; metformin, glimepiride and glibenclamide and in the diabetic dietary control when compared with non-diabetic control group. While there was no significant difference ($p > 0.05$) in diabetic group using glimepiride and in the group using metformin and glimepiride (Table 3).

3.4 Protein Profile Using Sodium Dodecyl Sulphate Polyacrylamide Gel Electrophoresis (Sds-Page)

There was over-expression of a low molecular weight protein in the protein profile of diabetic participants using different medications in comparison with protein profile of non-diabetic participants. The molecular weight of the protein was determined in Plate 1. The molecular weight of the protein was determined to be 18 Kda.

4. DISCUSSION

Fasting blood glucose and random blood glucose (after meal) are part of the diagnosing criteria of diabetes and its control [1]. This study showed that diabetic groups using metformin and dietary control had well controlled blood glucose level this was reported in approximately 29.23% of the total diabetic participants in this study. Metformin and dietary control have been reported to be effective in reducing blood glucose level in diabetes patients mostly with newly diagnosed diabetes [16]. However, diabetic groups using glimepiride; glibenclamide; metformin and glimepiride; metformin and glibenclamide; metformin, glimepiride and glibenclamide had uncontrolled blood glucose level. The reasons for this are unknown but might be drug related which include drug-drug interactions, non-compliance by the patients, or other factors such as inappropriate dietary control where funds are limited, level of literacy, diabetic ketoacidosis or occult infections [17].

Diabetes is one of the leading causes of chronic renal disease and end stage renal disease. Drug-induced nephrotoxicity may cause up to 20% of community and hospital acquired episodes of acute kidney injury (AKI) with incidence of approximately 30–40% among older adults. Kidney function was assessed in this study by measuring the concentration of urea, and creatinine in the serum of diabetic participants. The result of this study showed that there was no significant difference ($p > 0.05$) in the concentration of creatinine in the serum of diabetic groups compared to non-diabetic and dietary diabetic control groups (Table 2). This is in agreement with the findings of Stefan et al. (2004) and Thomsen et al. (2014), that creatinine is not a reliable biomarker in determining early damage to the kidney as it does not give an optimum expression of renal function [18,19]. However, the levels of urea increased significantly ($p < 0.05$) in the diabetic groups using metformin; metformin and glimepiride; metformin and glibenclamide. This can be as a result of associated lactic acidosis with metformin and prolonged hypoglycemia of the sulfonureas [20]. A report published by Strugaru et al. (2013) stated that the main situations that favor metformin-associated lactic acidosis are renal impairment and tissue hypoxia, which is dependent on associated pathologies and medication [21]. Therefore a baseline diagnosis and continuous renal diagnosis is required, when prescribing metformin. There was no significant increase ($p > 0.05$) in the concentration of creatinine and urea in diabetic patients using glibenclamide, when compared with non-diabetic and diabetic dietary control groups. This report is supported by the observation of Diwan et al. (2014) who stated that glibenclamide improves kidney and heart functions [22].

Increased incidences of hepatotoxicity have been observed in patients with diabetes receiving drug therapies [23]. Hepatotoxicity in diabetic patients were assessed by evaluating the levels of albumin, total protein, alkaline phosphatase (ALP), aspartate aminotransaminase (AST), alanine aminotransferase (ALT) in serum of diabetic patients. The result obtained showed that there was significant increase ($p < 0.05$) in the level of AST and ALP in the medication diabetic groups. This increase in ALP level might be due to possible billary dysfunction, while increase in AST might be due to pathological changes such as necrosis of hepatocytes, which causes increase in the level of amino-transferases in the blood stream [24]. This result is consistent with the findings of Cone et al. (2010) who reported that metformin induce hepatic damage in type II diabetes mellitus with nonalcoholic fatty acid disease [25]. Also, combination of metformin with glimepiride has been reported to cause cholestatic hepatic injury associated with glimepiride [26]. There was significant decrease ($p < 0.05$) in the concentration of ALT in the diabetic groups using metformin; glibenclamide; metformin and glibenclamide; metformin, glimepiride and glibenclamide. This decrease signifies the hepatic protective property of these antidiabetic drugs.

Increase in ALT has been reported to be specific for acute hepatocellular injury [27]. There was significant increase ($p < 0.05$) in the albumin concentration in diabetic groups using metformin; glimepiride; glibenclamide; metformin and glimepiride; metformin and glibenclamide; metformin, glimepiride and glibenclamide when compared with non-diabetic control group. This explains liver absence of hepatocellular dysfunction or damage to the liver [28]. Also, there was significant increase ($p < 0.05$) in serum total protein in diabetic groups using metformin; metformin and glimepiride; metformin and glibenclamide when compared with diabetic dietary control group. Total protein and albumin concentration has been reported to be qualitatively and quantitatively affected during liver damage [28].

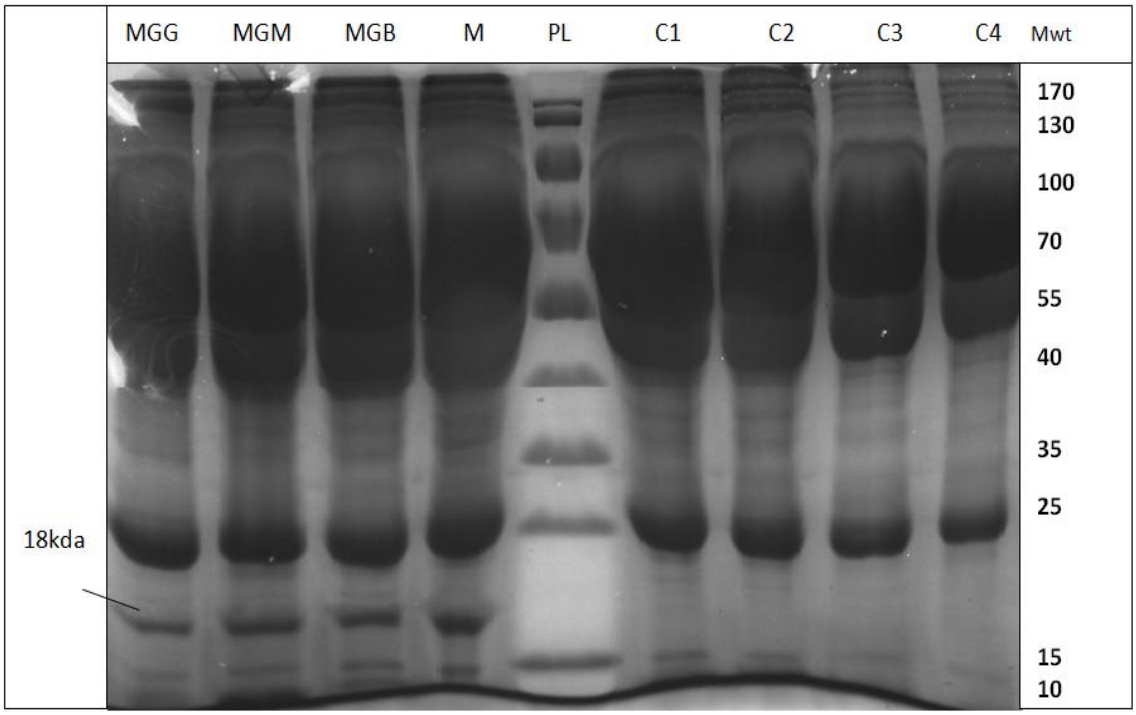

Plate 1. Protein profiling of diabetic patients and non-diabetic patients' using SDS PAGE electrophoresis

MGG = Metformin, glimepiride, and glibenclamide; MGM = Metformin and glimepiride; MGB = Metformin and glibenclamide; M = Metformin; PL = Page Ruler Prestained Protein ladder (model 26616, Thermo Scientific, USA); C1, C2, C3, C4 = Control groups; Mwt (Kda) = Molecular weights of protein ladder expressed in kilo dalton

Result obtained from this study showed an over-expression of a low molecular weight protein in the protein profile of diabetic groups using different medications, which was absent in the protein profile of the non-diabetic control groups. The molecular weight of the protein might be leptin. The significance of the over-expression of the proteins might be a signal for an increased risk in diabetes.

Leptin has been reported as 18 kDa adipocytes secreted proteins, which not only affect the glucose homeostasis in the blood but also serve as important marker to study the progression of diabetes mellitus in obese individuals [29]. Leptin controls body weight by regulating metabolic behavior including; control of appetite and regulating energy expenditures [30]. It exerts pleiotropic effects by binding and activating specific leptin receptors (obR) in the hypothalamus and other organs [30]. However, in obese diabetic subjects, leptin binds with insulin receptors thereby causing insulin resistance. It also directly affects insulin sensitivity by regulating the efficiency of insulin-mediated glucose metabolism by the skeletal muscle [31]. Also, leptin was reported as a marker of inflammation, which is closely associated with cardiovascular risk factors and cardiovascular and non-cardiovascular causes of death. This may explain the increased risk of diabetes, heart disease, increased blood pressure, insulin resistance and other chronic diseases in obese [31].

6. CONCLUSION

In conclusion, increased organ toxicity and lack of proper glycemic control were reportedly associated with glimepiride and glibenclamide and their combination with metformin in diabetic groups in this study. Metformin was also reported in this study to induce renal and hepatic toxicity which might be due to the side effect of lactic acidosis, but the reported good glycemic control had made it effective. Emphatically, in this study, diabetic group using combination therapy of metformin and glimepiride had increased hepatotoxicity, increased nephrotoxicity and uncontrolled blood glucose level, indicating the damaging effect of this combination on this diabetic group in this study. Therefore it is suggested that control of diabetes is best carried out with dietary control and lifestyle modification as well as good therapeutic drug monitoring for safe assessment of baseline organ function and avoidance of nephrotoxic drug combination. There was over-expression of a molecular weight protein which was suggested to be Leptin. This low molecular weight protein might serve as useful biomarkers in the monitoring of the progression of diabetes and its associated risk factors. Further studies with broader research are required as this may serve as useful tool in the assesssment of medication toxicity.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

Ethical approval was obtained from Covenant University Ethics Committee, Ogun state and Nigeria Institute of Medical Research (NIMR) Ethics Committee, Lagos state with project approval number IRB/13/227.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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