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*Original Research Article*

# Effects of Metformin, Sulfonyurea, and Insulin Therapy on Serum Insulin and Insulin Resistance in Type 2 Diabetic Subjects

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**Abstract**

**Type 2 diabetes mellitus is an endocrine metabolic disorder that is associated with insufficient insulin production from the pancreatic beta cells, and insulin resistance. The prevalence of this disorder is increasing both in developed and underdeveloped countries. Objective: Management of diabetes mellitus have been tailored to life style changes and synthetic anti-diabetic therapy. These synthetic drugs may affect the normal serum insulin level and insulin resistance which might increase the progression of the disease. This study was therefore conducted to evaluate the effect of metformin, sulfonylurea, and insulin therapy on serum insulin and insulin resistance in type 2 diabetic subjects. A total of 198 subjects (aged 35 to 70 years) (test) and 99 apparently healthy subjects (control) were recruited for the study. The test subjects were further grouped into 5: Group A were diabetics on metformin and sulfonylurea combination therapy, group B were diabetics on metformin monotherapy, group C were diabetics on metformin and insulin combination therapy, group D were diabetics on insulin monotherapy and group E were diabetics not on any anti-diabetic drug. FBS and lipid profile were estimated by enzymatic end point method, serum insulin was estimated by ELISA method while insulin resistance was calculated by homeostatic model assessment (HOMA) method. The result of this study showed that there was statistical significant difference in the mean level of FBS among the five groups (p = 0.005). The post hoc analysis of this result shows that FBS was significantly higher in group A when compared with group B (0.002). It was also higher in group E when compared with group B (p = 0.001), group C (p = 0.011) and group D (0.022). There was also statistical significant difference in the mean levels of insulin (p = 0.013) and insulin resistance (p = 0.028) among the five groups. Insulin resistance was significantly higher (p = 0.033) in group D when compared with group B. This study revealed that diabetic patients on metformin monotherapy have a better response to blood glucose monitoring when compared to other groups. Also, the highest level of insulin and insulin resistance were seen in diabetics on insulin monotherapy. There is need to monitor and control serum insulin and insulin resistance of diabetics on insulin therapy in order to enhance the efficacy of the therapy.**

**Keywords:** Metformin**,** insulin; insulin resistance, type 2 diabetes mellitus

## INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defect in insulin secretion, insulin action or both. The defect could be due to reduced production of insulin from the pancreatic beta cells or due to reduced cell response to the produced insulin (Shoback *et al.,* 2011). The prevalence of diabetes is increasing globally to epidemic level owing to population growth, aging, urbanization, and the increasing prevalence of obesity and a sedentary lifestyle (International Federation of Diabetes (IDF),

2014). World Health Organization (WHO) stated that diabetes affects more than 371 million adults worldwide (prevalence of 8.3%), with more than 90% of diabetes cases diagnosed as type 2 diabetes in 2014 ((IDF, 2014), WHO, 2011). This number is estimated to increase to approximately 552 million adults by 2030 (prevalence of 9.9%), mostly due to the growing burden of diabetes in developing countries (IDF, 2014). In Nigeria, the recent prevalence of type 2 diabetes mellitus is estimated to be 4.04% ((International Federation of Diabetes, IDF, 2012). The socio-economic consequences of type 2 diabetes mellitus and its complications could have a serious negative impact on the economics of developed and a developing country since diabetes mellitus is affecting many in the workforce (Alberti *et al.,* 2001). Several risk factors such as obesity, sedentary life style, poor diet, stress and urbanization are known to predispose individual to the development of type 2 diabetes (Ripsin *et al.,* 2009, Abdullah *et al.,* 2010). Despite advances in health care, diabetes is still a major cause of premature mortality, mainly due to associated cardiovascular disease (CVD), with an estimated 4.8 million deaths worldwide attributable to diabetes (Roglic *et al.,* 2010). According to World Health Organization (WHO) diabetes diagnostic criteria, presence of classic symptoms, two fasting blood glucose measurement $\geq$126mg/dl (7.0mmol/L) or with a glucose tolerance test, two hours after the oral dose, a plasma glucose $\geq$ 200mg/dl (11.1mmol/L) is considered diagnostic for diabetes mellitus (WHO, 2006). Immediately type 2 diabetes is diagnosed, it is very important that patients receive optimum standard of care to avoid complications. The management of type 2 diabetes mellitus focuses on keeping the blood glucose level as close to normal as possible without causing hypoglycemia. (Nathan *et al.,* 2005). Controlling blood glucose efficiently helps in preventing chronic complications of type 2 diabetes. This control can be achieved by administration of antidiabetic monotherapies and by lifestyle modification. Nevertheless, type 2 diabetes is a progressive disease and the majority of the patients experience decline in glycaemic control over time prompting the use of combination therapy and ultimately to exogenous insulin therapy (Fox *et al.,* 2006).This study was conducted to check how antidiabetic medications such as metformin, sulfonylurea, and insulin help in regulating the blood glucose, and their effect on serum insulin and insulin resistance levels of type 2 diabetic subjects with a view of evaluating their cardiovascular risk.

## MATERIALS AND METHODS

This was a hospital based; case-control study carried out in Nnamdi Azikiwe University Teaching Hospital Anambra State. A total of 198 diabetic subjects aged between 35 to 70 years (test) and 99 apparently healthy non diabetic subjects (control) were recruited for the study. The test subjects were further grouped into 5: Group A were diabetics on metformin and sulfonylurea combination therapy, group B were diabetics on metformin monotherapy, group C were diabetics on metformin and insulin combination therapy, group D were diabetics on insulin monotherapy and group E were diabetics not on any anti-diabetic drug. Ten –twelve hours overnight fasting blood samples (5ml) were drawn each subject. Plasma glucose, total cholesterol (TC), High density lipoprotein (HDL), Low density lipoprotein (LDL-C), triglyceride (TG), Insulin, insulin resistance were analyzed using standard methods. Level of significant was taken at $p<0.05$

## RESULTS

Table 1 showed the Mean ± SD of biochemical parameters of the type 2 diabetic and non diabetic subjects. The mean FBS levels of both groups were 9.8 ± 3.88 & 4.9 ± 0.62 respectively. Showing that the mean levels of fasting blood sugar was significantly higher in diabetics when compared with non diabetics ($p = 0.000$). Lipid profile levels of the two groups were TC (5.00 ± 1.29 & 4.30 ± 1.08), TG (1.40 ± 1.05 & 1.20 ± 0.50), HDL-C (1.30 ± 0.66 & 1.20 ± 0.41), LDL-C (3.10 ± 1.21 & 2.60 ± 1.18), and their insulin levels (8.80 ± 7.73 & 4.80 ± 3.14) and insulin resistance (3.90 ± 3.56 & 1.10 ± 0.77 respectively). The results showed that TC and LDL-C were significantly increased in the diabetics when compared with non-diabetics ($P = 0.000$ and 0.003 respectively). There was no statistical significant difference in the mean levels of HDL- C and TG between the groups ($p>0.05$). Insulin and insulin resistance were also seen to be significantly increased in the diabetics when compared with the non-diabetics ($P = 0.000$ and 0.000 respectively).

Table 2 showed the mean concentration of fasting blood sugar (FBS), insulin and insulin resistance (HOMA-IR) of diabetic subjects on various anti-diabetic drugs. The FBS concentrations of the five groups were 10.20 ± 4.18; 7.30 ± 2.69; 9.20 ± 3.36; 7.60 ± 2.27; and 12.70 ± 3.56 for groups A-E respectively. FBS was significantly higher ($p = 0.002$) in group A when compared with group B. It was also higher ($p = 0.001$) in group E when compared with group B, group C ($p = 0.011$) and group D (0.022). Their mean insulin concentrations were 8.90 ± 4.94; 7.30 ± 3.89; 11.50 ± 6.00; 16.90 ± 7.86; and 7.50 ± 3.71 for groups A-E respectively. Insulin was significantly higher in group D when compared with group A ($p = 0.003$), group B ($p = 0.004$), C ($p = 0.047$), and group E ($p = 0.005$). Also, the mean insulin resistance were 4.00 ± 2.97, 2.60 ± 2.41, 4.60 ± 2.73, 9.0 ± 4.78, and 4.30 ± 2.23 for groups A-E respectively. Insulin resistance was

**Table 1.** Mean ± SD of the biochemical parameters of the type 2 diabetic and non diabetic subjects

| Parameter | Diabetics (Test) n=198 | Non diabetics (Control) n=99 | p-value |
|---|---|---|---|
| FBS (mmol/L) | 9.80 ± 3.88 | 4.90 ± 0.62 | 0.000* |
| TC (mmol/L) | 5.00 ± 1.29 | 4.30 ± 1.08 | 0.000* |
| LDL-C (mmol/L) | 3.10 ± 1.21 | 2.60 ± 1.18 | 0.003* |
| HDL-C (mmol/L) | 1.30 ± 0.66 | 1.20 ± 0.41 | 0.214 |
| TG (mmol/L) | 1.40 ± 1.05 | 1.20 ± 0.50 | 0.116 |
| Insulin (µlu/ml) | 8.80 ± 7.73 | 4.80 ± 3.14 | 0.000* |
| HOMA-IR | 3.90 ± 3.56 | 1.10 ± 0.77 | 0.000* |

**Key**
*= significance (p<0.05); SD = standard deviation; BMI = body mass index; TC = Total cholesterol; TG = Triglyceride; HDL-C = High density lipoprotein-cholesterol; LDL-C = Low density lipoprotein-cholesterol; HOMA-IR = Homeostatic model assessment-insulin resistance. n= number of subjects in a group.

**Table 2.** Mean concentration of fasting blood sugar (FBS), insulin and insulin resistance (HOMA-IR) of diabetic subjects on various anti-diabetic drugs

| GROUPS | N | FBS (mmol/L) | INSULIN(µlu/ml) | HOMA-IR |
|---|---|---|---|---|
| Group A | 50 | $10.20\pm4.18_{a}$ | $8.90\pm4.94_{b}$ | 4.00±2.97 |
| Group B | 40 | $7.30\pm2.69_{a,d}$ | $7.30\pm3.89_{c}$ | $2.60\pm2.41_{c}$ |
| Group C | 43 | $9.20\pm3.36_{f}$ | $11.50\pm6.00_{e}$ | 4.60±2.73 |
| Group D | 35 | $7.60\pm2.27_{g}$ | $16.90\pm7.86_{b,c,e,g}$ | $9.0\pm4.78_{c}$ |
| Group E | 30 | $12\ 70\pm3.56_{d,f,g}$ | $7.50\pm3.71_{g}$ | 4.30±2.23 |
| P-value | | 0.005* | 0.013* | 0.028* |

**Key**
*=significance; Group A = diabetics on Metformin and sulfonyurea; Group B = diabetics on Metformin only; Group C = diabetics on metformin and insulin; Group D = diabetics on insulin only; Group E = diabetics not on therapy. a = significance difference observed in group A vs B, b= significance difference observed in group A vs D, c = significance difference observed in group B vs D, d = significance difference observed in group B vs E, e = significance difference observed in group C vs D, f = significance difference observed in group C vs E and g = significance difference observed in group D vs E.

**Table 3:** Correlation between FBS, Insulin, and HOMA-IR of different test groups.

| GROUPS | FBS/INSULIN r (p-value) | FBS/IR r (p-value) | INSULIN/IR r (p-value) |
|---|---|---|---|
| Group A (n=33) | 0.019(0.906) | 0.579 (0.000)* | 0.737 (0.000)* |
| Group B (n=13) | 0.641 (0.033)* | 0.885 (0.000)* | 0.878 (0.000)* |
| Group C (n=28) | -0.059 (0.764) | 0.619 (0.000)* | 0.711 (0.000)* |
| Group D (n=15) | 0.189 (0.602) | 0.344 (0.331) | 0.980 (0.000)* |
| Group E (n=10) | 0.234 (0.515) | 0.383 (0.274) | 0.765 (0.010)* |

**Key**
*=significance; Group A = diabetics on Metformin and sulfonyurea;
Group B = diabetics on Metformin only; Group C = diabetics on metformin and insulin; Group D = diabetics on insulin only; Group E = diabetics not on therapy

significantly higher in group D when compared with group B (p = 0.033).

Table 3 showed the correlation between FBS, Insulin, and HOMA-IR of different test groups. When FBS was correlated with Insulin, there was positive correlation and a significant difference observed only in group B (r = 0.641, p = 0.033) while no statistical significance difference was observed in groups A, C, D, and E (p>0.05). When FBS was correlated with Insulin resistance, there was positive correlation and statistical significant difference in groups A, B and group C (r = 0.579, p = 0.000, r = 0.885, p = 0.000, & r = 0.619, p = 0.000 respectively) while no statistical significance difference was observed in group D, and E (p>0.05).

When Insulin was correlated with Insulin resistance there was positive correlation and statistical significant difference in all the groups A ($r = 0.737$, $p = 0.000$), B ($r = 0.878$, $p = 0.000$), group C ($r = 0.711$, $p = 0.000$), D ($r = 0.980$, $p = 0.00$) and group E ($r = 0.765$, $p = 0.010$).

## DISCUSSION

This present study showed that diabetics on metformin monotherapy had reduced plasma levels of fasting blood sugar, insulin, and insulin resistance when compared with other groups. Guidelines from the American Diabetes Association/ European Association for the Study of Diabetes (ADA/EASD) and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) recommend early initiation of metformin as a first-line drug for monotherapy and combination therapy for patients with T2DM. One of the reasons for this recommendation is based mainly on the fact that metformin has glucose-lowering effects with low level of side effects, including the absence of weight gain (ADA; 2011, Rodbard *et al.,* 2009). However, the reduced fasting blood sugar, reduced plasma level of insulin and insulin resistance observed in diabetics on metformin only in this study could indicate that metformin improves sensitivity to the action of insulin due to its inhibitory action on hepatic gluconeogenesis, secondarily, by augmenting glucose uptake in the peripheral tissues, mostly muscle (Hundal *et al.,* 2000, Kirpichnikov *et al.,* 2002). The decreased gluconeogenesis from alanine, pyruvate, and lactate results in accumulation of lactic acid which may give rise to metformin-induced lactic acidosis (Wiholm *et al.,* 1993).

More so, this present study showed that diabetics on combination of metformin and insulin therapy, had a higher level of fasting blood sugar, insulin, and insulin resistance compared with those on metformin monotherapy. The most important function of insulin is in reducing blood glucose. It does this by inducing glucose uptake in insulin-sensitive tissue such as skeletal muscle, fat and heart. It also inhibits glucose production in liver, kidney and small intestine in the control of blood glucose. Also, insulin stimulates synthesis of fatty acids and glycogen, promotes mitochondrial function, improves microcirculation and induces cell proliferation (Ye, 2007, He *et al.,* 2011). Although metformin and insulin augment glucose uptake in the peripheral tissues, mostly muscle (Kirpichnikov *et al.,* 2002, Hundal *et al.,* 2000), the increased fasting blood sugar observed in the diabetics on combination of metformin and insulin therapy in this study could be as a result of insulin insensitivity which gave rise to hyperinsulinaemia as also observed in these individuals. It could also be that the stimulated pancreatic β-cells of these diabetics produce a large amount of insulin in an effort to control the blood glucose. Furthermore, high Insulin resistance also observed in these individuals could be due to insulin-induced glucose uptake impairment in the insulin-sensitive tissue.

Furthermore, the highest levels of insulin and insulin resistance in this study were obtained in diabetics on insulin monotherapy when compared with other groups. A decrease in the number of functional insulin-producing β-cells contributes to the pathological decline in glycaemic control typically seen in type 2 diabetes (Kahn, 2001). It is commonly accepted that hyperinsulinemia results from insulin resistance but research has also shown that hyperinsulinemia may lead to insulin resistance, especially in the presence of fatty acid (Ye, 2007). Since these groups of diabetics are on insulin, the hyperinsulinemia observed could be as a result of over production from both the endogenous (pancreatic β-cell) and exogenous (drugs) sources or decreased clearance of insulin. This finding agrees with Koro *et al.,* (2005) who stated that despite the traditional therapies, it is often difficult to both adhere and maintain adequate glycaemic control in the majority of patient with type 2 diabetes. Insulin resistance is a core feature of type 2 diabetes and may contribute to the decline in β-cell function by inducing endoplasmic reticulum stress as a consequence of an increased demand for insulin (Hayden *et al.,* 2005).

This study also revealed that diabetics on metformin and sulfonylurea combination therapy had higher levels of fasting blood sugar, insulin and insulin resistance when compared with diabetics on metformin monotherapy. This variation could be attributed to the fact that individual who are managed with metformin monotherapy still have most of their pancreatic β-cells intact and functionally producing insulin that help in controlling the high blood glucose unlike in diabetes on metformin and sulfonylurea therapy whose β-cell or insulin secretion capacity may have declined, necessitating the combination therapy earlier in the course of type 2 diabetes with the aim of preserving glycaemic control and β-cell function and thereby improving long-term outcomes as a better approach to meet the dual defect in pathophysiology of type 2 diabetes (Lebovitz, 2001 and Luna *et al.,* 2001). Sulfonylureas are insulin secretagogues that act to increase insulin secretion while metformin are biguanides that reduces hepatic glucose output and increase the uptake of glucose by peripheral tissues. In the present study blood glucose was poorly controlled giving rise to hyperinsulinaemia and finally insulin resistance, all serving as cardiovascular risk factors. The result of this study agrees with Wright et al., (2002) who stated that despite the initial efficacy of Sulfonylurea in the early stages of type 2 diabetes when β-cell function is at its greatest, glycaemic control is inevitably lost over time with the sulfonylureas, necessitating the introduction of combination therapy to regain control and prolong the time before progression to exogenous insulin therapy.

This study also revealed the positive correlation

between FBS and insulin, and FBS and insulin resistance in diabetes on metformin monotherapy, metformin and sulfonylurea combination therapy, and metformin and insulin implying that as the plasma level of FBS is increasing (hyperglycemia), the level of insulin also increases aiming at controlling the blood glucose and this hyperinsulinaemia may finally induce insulin resistance. The positive correlation observed between insulin and insulin resistance among the five groups could be due to Leptin resistance in β cells which may be contributing to over production of insulin by β cells, giving rise to hyperinsulinemia and finally insulin resistance (Gray *et al.,* 2010). There is also possibility of over production or supply of insulin leading to hyperinsulinemia, causing insulin resistance in the diabetics as observed in this study. Insulin stays about 2-4min in the blood before being cleared and during clearance; it binds to its cell membrane receptor and get degraded by insulin degrading enzyme in the cytosol after internalization. In this way, liver and kidney each remove 50% of insulin in the blood stream (Valera *et al.,* 2003). Insulin clearance is dependent on the insulin receptor and insulin degrading enzyme. When these two molecules are deficient, insulin clearance will be blocked leading to hyperinsulinemia and finally insulin resistance (Michael *et al.,* 2000, Farris *et al.,* 2003). Therefore, delay in insulin clearance in the liver and kidney could have contributed to this positive correlation as both organs produce glucose as well in the control of blood glucose. And impairment of insulin clearance may have caused insulin resistance as a consequence of hyperinsulinemia as observed in this recent study.

## CONCLUSION

This study revealed that diabetic patients on metformin monotherapy have a better response to blood glucose monitoring when compared to other groups. Also treatment of diabetes with insulin alone, causes insulin resistance that may lead to eventual poor glucose controls.

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