

## Effect of metformin, glibenclamide and insulin on lipid profile in type 2 diabetic patients

Marwan M. Merkhan

Department of Pharmacology and Toxicology, College of Pharmacy, University of Mosul, Mosul, Iraq

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### Abstract

**Objective:** to investigate the differences between the effects of metformin, glibenclamide, a combination of metformin plus glibenclamide and insulin on glycemic control and lipid profile. **Subjects and methods:** this study was conducted in Mosul-Iraq. A total of 136 type 2 diabetic patients were enrolled in this study. Thirty two, apparently healthy volunteers, were also included in the study as a control group. Blood sample were taken from the patients and controls and the serum were analysed for measurement of fasting serum glucose (FSG), HbA1c and lipid parameters. **Results:** the FSG of the metformin group ( $8.78 \pm 3.55$  mmol/l) was significantly lower than that of glibenclamide and insulin groups ( $11.45 \pm 2.79$  mmol/l), ( $13.16 \pm 6.18$  mmol/l) respectively and there were non significant differences between the total cholesterol (TC) ( $4.49 \pm 0.93$  mmol/l), high density lipoprotein (HDL-c) ( $1.3 \pm 0.48$  mmol/l), low density lipoprotein (LDL-c) ( $2.43 \pm 0.95$  mmol/l) and atherogenic index (AI) ( $3.72 \pm 0.93$ ) of metformin group in comparison to that of the control group ( $4.69 \pm 0.39$  mmol/l), ( $1.34 \pm 0.38$  mmol/l), ( $2.80 \pm 0.62$  mmol/l) and ( $3.82 \pm 1.21$ ) respectively. The levels of TC ( $4.49 \pm 0.93$  mmol/l), LDL-c ( $2.43 \pm 0.95$  mmol/l) and the value of AI ( $3.72 \pm 0.93$ ) for the metformin group were significantly lower than that of other studied groups, while the HDL-c of the metformin group ( $1.3 \pm 0.48$  mmol/l) was significantly higher than that of other studied groups. The level of triglyceride (TG) of metformin and metformin plus glibenclamide groups ( $1.68 \pm 0.81$  mmol/l), ( $1.85 \pm 0.76$  mmol/l) respectively was significantly lower than that of the glibenclamide group ( $2.85 \pm 1.01$  mmol/l). **Conclusion:** this study concluded that antihyperglycemic therapy with metformin in type 2 diabetic patients may have uniquely beneficial metabolic effects in addition to their glucose lowering effect.

**Key words:** type 2 diabetes mellitus, lipid profile, metformin, glibenclamide, insulin.

### المخلص:

**الهدف:** لبيان الاختلاف بين تأثير عقاري المتفورمين والجلابيينكلامايد بشكل منفرد او مزدوج والانسولين على السيطرة السكرية ودهن الدم.

**الطرق المتبعة والاشخاص:** اجريت ه ذه الدراسة في مدينة الموصل حيث دخل الدراسة 136 مريضاً مصاباً بداء السكري من النوع الثاني و32 شخصاً سليماً كمجموعة ضبط. تم اخذ عينة دم من المرضى ومن مجموعة الضبط ثم تم تحليل الدم لقياس سكر المصل ونسبة الدهون.

**النتائج:** اظهرت النتائج ان سكر المصل في مجموعة عقار المتفورمين ( $3.55 \pm 8.78$  ملمول/لتر) منخفض معنوياً بالمقارنة مع مجموعتي الجلابيينكلامايد والانسولين ( $2.79 \pm 11.45$  ملمول/لتر)، ( $6.18 \pm 13.16$  ملمول/لتر) على التوالي، ولا يوجد اي فرق معنوي بين مستوى الكوليستيرول الكلي ( $0.93 \pm 4.49$  ملمول/لتر)

والبروتين الدهني عالي الكثافة ( $0.48 \pm 1.3$  مليمول/لتر) والبروتين الدهني منخفض الكثافة ( $0.95 \pm 2.43$  مليمول/لتر) ودليل تكون الخثرة ( $0.93 \pm 3.72$ ) لمجموعة عقار المتفورمين بالمقارنة مع مثيلاتها في مجموعة السيطرة ( $0.39 \pm 4.69$  مليمول/لتر)، ( $0.38 \pm 1.34$  مليمول/لتر)، ( $0.62 \pm 2.80$  مليمول/لتر)، ( $1.21 \pm 3.82$ ) على التوالي، وان مستوى الكوليستيرول الكلي ( $0.93 \pm 4.49$  مليمول/لتر) والبروتين الدهني منخفض الكثافة ( $0.95 \pm 2.43$  مليمول/لتر) ودليل تكون الخثرة ( $0.93 \pm 3.72$ ) لمجموعة عقار المتفورمين منخفض معنويا بالمقارنة مع بقية المجموع قيد الدراسة، بينما البروتين الدهني عالي الكثافة لمجموعة عقار المتفورمين ( $0.48 \pm 1.3$  مليمول/لتر) مرتفع معنويا بالمقارنة مع بقية المجموع قيد الدراسة، وان مستوى الشحوم الثلاثية لمجموعة عقار المتفورمين ( $0.81 \pm 1.68$  مليمول/لتر) ومجموعة المتفورمين مع الجلوبيبيدكلامايد ( $1.01 \pm 2.85$  مليمول/لتر) منخفض معنويا بالمقارنة مع مجموعة عقار الجلوبيبيدكلامايد ( $0.76 \pm 1.85$  مليمول/لتر).

**الاستنتاج:** استنتجت الدراسة ان علاج النوع الثاني من السكري بعقار المتفورمين لديه تاثيرات ايجابية ايجابية بالإضافة الى تأثيره على مستوى سكر المصل

## Introduction

Diabetes is one of the leading causes of morbidity and mortality throughout the world. Approximately 2.2-3% of the world's population suffers from type 2 diabetes mellitus (1). In type 2 diabetes mellitus, disturbances of lipid profiles and especially increased susceptibility to lipid peroxidation is observed (2). An increased oxidative stress has been observed in diabetic patients as indicated by high free radical production (3). Although the pathophysiological mechanism of atherosclerosis in diabetic patients has not yet been fully understood, it is thought that hyperlipidemia, increased oxidation of low-density lipoproteins (LDL-c) and impaired vascular function promote atherogenesis in diabetic patients (4). Glucose deficiency in adipose tissue induces metabolic compensation, leading to the hydrolysis of triglycerides and release of fatty acids, which are oxidized by the liver and transformed to ketonic derivatives (5).

In patients with type 2 diabetes mellitus, besides controlling blood pressure and lipid levels, the major therapeutic goal is to optimize glycaemic control in order to reduce the development and/or severity of long-term diabetic complications (6).

Antidiabetic drugs control blood sugar levels in individuals with type 2 diabetes mellitus (7). Although oral antidiabetic agents may initially control hyperglycemia, most patients with type 2 diabetes mellitus will ultimately require insulin therapy, as  $\beta$ -cell function progressively declines (8, 9). Antidiabetic drugs may be subdivided into six groups: sulphonylureas, alpha-glucosidase inhibitors, biguanides, meglitinides, insulin and thiazolidinediones. Sulphonylurea derivatives are class of antidiabetic drugs used in the management of type 2 diabetes mellitus. Biguanides and sulphonylureas are widely used for the treatment of type 2 diabetes mellitus and have been used for the prevention of diabetes in non-diabetic patients (10).

Sulphonylureas act by increasing insulin release from the beta cells (11). Biguanides form a class of oral hypoglycemic drugs used for diabetes mellitus or prediabetes treatment. Metformin is the only available member of the Biguanide class. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and increases peripheral glucose uptake and use. Metformin may be used as monotherapy, or in combination

therapy with a sulphonylurea. Insulin and insulin analogs are responsible for glucose utilization. It is effective in both types of diabetes, since even in insulin resistance, some sensitivity remains and the condition can be treated with larger doses of insulin (7, 11).

**Aim of the study:**

The purpose of this study was to investigate the differences between the effects of metformin, glibenclamide, a combination of metformin plus glibenclamide and insulin on glycemic control and lipid profile.

**Subjects, materials and methods:**

This study was conducted in Mosul-Iraq during the period from 1st of November 2011 to the 1st of March 2012. A total of 136 patients were enrolled in this study, they were divided into four groups. The first group was 42 patients (18 male and 24 female) on metformin therapy; their mean age was  $53.12 \pm 9.18$  years. The second group included 33 patients (14 male and 19 female) on glibenclamide therapy; their mean age was  $56.61 \pm 8.04$  years. The third group involved 31 patients (11 male and 20 female) on a combination therapy of metformin plus glibenclamide; their mean age was  $50.77 \pm 6.89$  years and the fourth group included in this study involved 30 type 2 diabetic patients (9 male and 21 female) on insulin therapy; their mean age was  $52.13 \pm 7.93$  years. Thirty two apparently healthy volunteers (16 male and 16 female), were also included in the study as a control group; their mean age was  $54.28 \pm 6.64$  years.

The study design was case-control study and the patients were excluded if they had a history of hypertension, angina pectoris, myocardial infarction, heart failure, renal or hepatic failure or those taking antihypertensive drugs or

lipid lowering agents or hypoglycemic agents other than metformin, glibenclamide, a combination of metformin plus glibenclamide and insulin. Pregnant women and lactating mother were also excluded from the study.

Eight milliliters of venous blood, for laboratory evaluation of biochemical parameters, were obtained from the patients and controls after an overnight fasting (12-hours) by antecubital vein puncture, 2.5ml of it were transferred into an anticoagulant EDTA-tube with gentle shaking to obtain whole blood sample that was used for HbA1c (glycosylated haemoglobin) measurement. The remaining blood was allowed to clot at room temperature and after centrifugation (centrifuge (Hitachi) Japan) the serum was collected in plain tube and analyzed.

Fasting serum glucose was estimated by glucose-oxidase-peroxidase colorimetric method (spectrophotometer (optima) Japan) (12), by using a kit supplied by Biocon company (Germany). HbA1c was measured in whole blood sample by ion exchange resin quantitative colorimetric determination using a kit supplied by Stanbio (USA).

TC was measured by enzymatic method (13) using a kit supplied by Biolabo (France) whereas TG was measured by enzymatic method (14), using a kit provided by Labkit (Spain), and HDL-c measured (15) by kit provided by Biolabo company (France). LDL value was calculated by Friedewald formula (16), the formula is  $LDL-c = TC - HDL-c - TG/2.2$ . The value of atherogenic index is calculated by equation  $AI = TC/HDL-c$ .

**Statistical analysis:**

Standard statistical methods were used to determine the mean and standard deviation. All values

expressed as Mean±SD and P value of  $\leq 0.05$  was considered to be statistically significant. Two sample t-test were used to compare the results of various parameters among the studied groups. Statistical analysis was done using Minitab for Windows statistical software, version 14.

### **Results:**

A total of 136 type 2 diabetic patients were enrolled in this case-control study and 32 apparently healthy volunteers were kept as a control group. The distribution of age, body mass index (BMI), duration of diabetes mellitus and sex for all studied groups and the control group are shown in table (1). There were non significant differences between the studied groups and control group regarding age and BMI as shown in table (1).

The statistical comparison of FSG, HbA1c, TC, HDL-c, TG, LDL-c and AI between the studied groups and between the studied groups and control group were shown in table (2). The FSG of metformin group was significantly lower than that of glibenclamide and insulin groups but still it was significantly higher than that of control group and their was non significant difference between the FSG of metformin group and metformin plus glibenclamide group also their was non significant difference between the FSG of glibenclamide and insulin groups. There were non significant differences between the HbA1c of each one of the studied group and others but each one of them was significantly higher than that of the control group. The TC, LDL-c and AI of metformin group was significantly lower than that of other studied groups with non significant differences between the TC, LDL-c and AI of metformin group and that of the control group also their was

non significant difference between TC and LDL-c of glibenclamide, metformin plus glibenclamide and insulin groups when compared with each others, the AI of metformin plus glibenclamide group was significantly lower than that of the glibenclamide group but there was non significant difference between the AI of metformin plus glibenclamide and insulin groups also their was non significant difference between AI of glibenclamide and insulin groups.

The HDL-c of the metformin group was significantly higher than that of other studied groups and their was non significant difference between the HDL-c of metformin group and that of the control group also there were non significant differences between the HDL-c of glibenclamide, metformin plus glibenclamide and insulin groups when compared with each others. The TG of the metformin or metformin plus glibenclamide groups were significantly lower than that of glibenclamide group but still they were significantly higher than that of the control group and their was non significant differences between the TG of metformin, metformin plus glibenclamide and insulin groups when compared with each others.

### **Discussion:**

A traditional stepwise approach to diabetes therapy involves the use of a single oral agent titrated to maximum dosage, each of which targets a single pathological defect of type 2 diabetes as its primary mechanism of action, with the requirement of poor glycaemic control as an indication for the addition of a second oral agent (17). Insulin is not usually a first line treatment for type 2 diabetes mellitus, but nearly 50% of patients of this group eventually need insulin to control their hyperglycemia. Insulin therapy can correct or improve many

of the metabolic abnormalities present with type 2 diabetes mellitus. Insulin regulates plasma glucose levels by decreasing hepatic glucose production (18) and increasing glucose uptake (19) by peripheral tissues. The major therapeutic goal in patients with type 2 diabetes mellitus is to optimize glycaemic control by controlling blood pressure and lipid levels, in order to reduce the development and/or the severity of long term diabetic complications (6).

In the present study the patient and the control groups were matched regarding age ( $P > 0.656$ ) and BMI ( $P > 0.550$ ). This matching has a beneficial effects in that it exclude any effects of differences in age and BMI on the outcome of the study (table 1). The present study found out that the FSG, HbA1c and lipid parameters in the control group appear to be within the accepted normal ranges (table 2). The FSG and HbA1c for all studied groups were significantly higher than that of the control group, these findings were in agreement with other studies (20, 21) which evaluated glycaemic state of the diabetic patients by measuring FSG and HbA1c. The FSG of the metformin group was significantly lower than that of glibenclamide and insulin groups, but there were non significant differences between FSG of metformin group and those treated by a combination therapy of metformin plus glibenclamide, this finding was in agreement with other study (22).

With the differences in the plasma glucose, one would anticipate a difference in HbA1c between the studied groups but there were non significant differences between the HbA1c of all studied groups, this finding was in agreement with many other studies (23, 24) which compare pioglitazone, glibenclamide and

metformin as a monotherapy and combination.

The literatures showed discrepant results about the influence of metformin on lipid parameters (25). Some studies, in agreement with ours, reported reduction of TC and TG with an increase of HDL-c (26, 27) while others reported reduction only in TC level (28, 29). Still other studies showed no changes in lipid parameters (30, 31). Another investigation showed an association of metformin with an improvement in the lipid parameters even in non-diabetic patients (32). New studies are needed to clarify this issue, since TG and HDL-c are very important parameters for the evaluation of metabolic syndrome.

The results of this study showed that there were significant differences between all lipid parameters of metformin group in comparison to that of glibenclamide or insulin group and these results were in agreement with many other studies (22, 33).

#### **Conclusion:**

The present study concluded that therapy with metformin achieved better metabolic effects beside their hypoglycemic effect, in comparison to glibenclamide or insulin, which may help prevent coronary events in type 2 diabetes mellitus.

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**Table (1): demographic characteristics of the control and studied groups.**

Parameter	Control group (No.=32)	Metformin group (No.=42)	Glibenclamide group (No.=33)	Metformin plus Glibenclamide group (No.=31)	Insulin group (No.=30)
Age (years)	54.28±6.64	53.12±9.18 <sup>NS</sup>	56.61±8.04 <sup>NS</sup>	50.77±6.89 <sup>NS</sup>	52.13±7.93 <sup>NS</sup>
BMI (kg/m <sup>2</sup> )	29.48±6.17	31.37±4.28 <sup>NS</sup>	30.88±4.68 <sup>NS</sup>	31.41±5.01 <sup>NS</sup>	31.86±5.09 <sup>NS</sup>
Duration of DM (years)	-----	7.45±5.62	9.27±7.16	7.74±4.51	10.10±6.64
Sex (male/Female)	16/16	18/24	14/19	11/20	9/21

<sup>NS</sup>

Non significant differences as compared to same parameter in the control group (P > 0.5).

**Table (2): the FSG, HbA1c, TC, HDL-c, TG, LDL-c and AI for the control and studied groups.**

Parameter	Control group (No.=32)	Metformin group (No.=42)	Glibenclamide group (No.=33)	Metformin plus glibenclamide group (No.=31)	Insulin group (No.=30)
FSG (mmol/l)	4.87±0.63	8.78±3.55 <sup>a</sup>	11.45±2.79 <sup>ab</sup>	10.24±4.36 <sup>a</sup>	13.16±6.18 <sup>ab</sup>
HbA1c (%)	5.50±0.26	8.68±1.63 <sup>a</sup>	8.68±2.03 <sup>a</sup>	8.37±1.51 <sup>a</sup>	9.08±1.81 <sup>a</sup>
TC (mmol/l)	4.69±0.39	4.49±0.93	5.51±0.82 <sup>ab</sup>	5.22±0.94 <sup>ab</sup>	5.22±1.35 <sup>ab</sup>
HDL-c (mmol/l)	1.34±0.38	1.3±0.48	0.97±0.2 <sup>ab</sup>	1.04±0.18 <sup>ab</sup>	1.07±0.3 <sup>ab</sup>
TG (mmol/l)	1.21±0.39	1.68±0.81 <sup>a</sup>	2.85±1.01 <sup>ab</sup>	1.85±0.76 <sup>ac</sup>	2.20±1.44 <sup>a</sup>
LDL-c (mmol/l)	2.80±0.62	2.43±0.95	3.23±1.01 <sup>ab</sup>	3.32±0.91 <sup>ab</sup>	3.15±1.01 <sup>ab</sup>
AI	3.82±1.21	3.72±0.93	5.86±1.38 <sup>ab</sup>	5.04±0.67 <sup>abc</sup>	5.20±1.90 <sup>ab</sup>

<sup>a</sup> as compared to same parameter in the control group (P ≤ 0.05).

<sup>b</sup> as compared to the same parameter in the metformin group (P ≤ 0.05).

<sup>c</sup> as compared to the same parameter in the glibenclamide group (P ≤ 0.05).