

Comparative study between Metformin, Glibenclamide and their combination in newly diagnosed diabetic (type II) patients in Hawler City

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الخلاصة:

يتميز مرض السكري (من النمط الثاني) بحالات معقدة وغير مستقرة مع الحساسية الزائدة بصدد نسب الانسولين. عادة يكون افراز الانسولين منخفضا ويصاحبه فشل في نشاط خلايا البنكرياس (pancreatic β - cells). ان الطريقة القياسية الشائعة لتحديد نسبة خطورة مرض السكري (من النمط الثاني) هي فحص الدم قبل الفطور (تحديد نسبة الجلوكوز في البلازما FPG ونسبة جلوكوز بلازما PPG ونسبة الهيموكلوبين HbA1c ونسبة بلازما (lipid profile)). يعتمد وصف الادوية عادة على التغييرات التي تطرأ على نمط الحياة ونوعية النظام الغذائي والحمية والادوية التي تأخذ عن طريق الفم للحد من تأثير السكري ومن انواع الادوية Sulphonylurea (glibenclamide), Biguanide (metformin) او المزج بين اثنين او اكثر. ان الهدف الرئيس من ادارة معالجة المرض من خلال استخدام الادوية هو تحديد تأثير هذه الادوية وعدم خطورتها على صحة المريض كونها غير ضارة كدواء احادي او ممزوج و مختلط مع ادوية اخرى وكل هذا من خلال ابراز ادلة علمية تطبيقية. لقد تم دراسة 90 حالة لمعالجة مرض السكري (من النمط الثاني) من خلال عدم اخذ اية ادوية ضد المرض من قبل مراكز متعددة لمعالجة المرض. تم توزيع المرضى الى 3 مجاميع علاجية مختلفة (مجموعة 5mg glibenclamide مرة واحدة في اليوم ومجموعة glibenclamide/metformin (2.5mg/500mg b.i.d. و metformin 500mg t.i.d.)). كان المرضى (اربعون مريضا) ذو (FPG of 167.9±3.5; PPG of 276.3±5.4; HbA1c of 8.1±0.2) وقد اخذوا (metformin) و (15 مريضا) ذو (FPG of 165.1±4.3; PPG of 273.6±5.5; HbA1c of 7.9±0.2) اخذوا glibenclamide كدواء احادي و 35 مريضا ذو (FPG of 179±4.1; PPG of 304.4±5.6; HbA1c of 9.7±0.1) اخذوا glibenclamide/metformin كمزيج دوائي.

تم تسجيل كافة المعلومات بصدد نسبة الكوليسترول ونسبة (TG) ونسبة التركيز المنخفض للكوليسترول الدهنيات (LDL-C) ونسبة التركيز العالي للكوليسترول (HDL-C) ووزن المرضى وقياس دليل كتل الاجسام الخاصة بالمرضى وايضا لمجموعة السيطرة (control group). بعد مرور ثلاثة اشهر تبين بأن المرضى الذين كانوا يأخذون مزيج (glibenclamide/metformin combination 2.5/500mg) كدواء لمعالجة المرض كان لديهم نسبة منخفضة من (FPG, PPG, and HbA1c) (-70.6mg/dl, -125.3mg/dl, and -2.0%) على التوالي وكانت الكميات اقل بالمقارنة ب metformin (-48.8mg/dl, -88.5mg/dl, and -) او glibenclamide (1.6%) (-52.3mg/dl, -63.5mg/dl, and -0.8%), ولكن كان لمزيج metformin and glibenclamide/metformin كدواء لمعالجة المرض تأثيرا مشابه نوعا ما لتخفيض نسبة الكوليسترول والـ (TG) والنسبة المنخفضة للكوليسترول بالمقارنة مع glibenclamide كأحادي. ان اخذ الجرعات من الادوية Metformin monotherapy كدواء احادي او مزيج glibenclamide/metformin كأجراءات بدائية, كلاهما يتحليان بتأثير كبير لمعالجة المرضى الذين تم تشخيص مرضهم في وقت مبكر في مستشفيات اربيل/اقليم كردستان. ان تطبيق هذه الخطوات قد ادت فعليا الى انخفاض نسبة الجلوكوز و HbA1c, وكلاهما له تأثير فعلي على نسبة الدهنيات, ولكن metformin كان الوحيد الذي له تأثير على وزن المريض ونسبة الكتل BMI.

Abstract:

Type 2 diabetes mellitus is a complex progressive disorder characterized by impaired insulin sensitivity, reduced insulin secretion and progressive failure of pancreatic β – cells. Type 2 diabetes therapies are initiated with lifestyle changes (diet, exercise) and pharmacologic agents, including oral antidiabetic drug, among them: sulphonylurea (glibenclamide), Biguanide (metformin) and combination of them.

The objective of this study is to compare the efficacy of the drugs, both as monotherapy and in combination, and discussed evidence – based treatment. forty patients with (FPG of 167.9 ± 3.5 mg/dl; PPG of 276.3 ± 5.4 mg/dl; HbA1c of 8.1 ± 0.2 %) were received metformin (500mg tid), and 15 patients with (FPG of 165.1 ± 4.3 ; PPG of 273.6 ± 5.5 ; HbA1c of 7.9 ± 0.2) were received glibenclamide (5mg once daily) monotherapy, 35 patients with (FPG of 179 ± 4.1 ; PPG of 304.4 ± 5.6 ; HbA1c of 7.9 ± 0.1) were received glibenclamide/metformin (2.5mg/500mg bid) as combination therapy. Blood samples were withdrawn from the patients at pretreatment, then monthly for three months. After 3 months of treatment, patients who received glibenclamide/metformin combination (2.5/500mg) had greater reductions in FPG, PPG and HbA1c (-70.6mg/dl, -

125.3mg/dl, and -2.0% respectively), compared with metformin (-48.8mg/dl, and -88.5mg/dl, -1.6% respectively), or glibenclamide (-52.3mg/dl, -63.5mg/dl, 0.8% respectively). Metformin and glibenclamide/metformin combination had approximately similar effect in reduction of total cholesterol, triglyceride, and low – density lipoprotein cholesterol, compared with glibenclamide alone which showed elevation.

Metformin significantly increased high density lipoprotein cholesterol where as glibenclamide/metformin combination or glibenclamide alone did not show that, also metformin reduces body weight significantly in contrast to glibenclamide/metformin and glibenclamide alone (which is associated with weight gain).

Metformin monotherapy and glibenclamide/metformin combination both are effective as an initial treatment of newly diagnosed diabetic patients in Kurdistan region (Hawler city). These two strategies reduced plasma glucose and HbA1c significantly, and both have favorable effect on serum lipid profile, but only metformin had a significant reduction of body weight in diabetic patients.

Introduction:

Diabetes mellitus is a chronic disease that requires long-term medical care and patient self-management education to prevent acute complications and to reduce the risk of long-term complications ^[1]. Diabetes is a serious, costly and increasingly common disease ^[2], and there is great interest in identifying and implementing interventions to prevent or delay its onset ^[3]. Typically, at the time of diabetes diagnosis, nearly 50% of B-cell function has been lost and less than 60% of normal insulin sensitivity is present ^[4].

Type II diabetes is a complex heterogeneous group of metabolic conditions characterized by increased levels of plasma glucose due to impaired insulin sensitivity, reduced insulin secretion and progressive failure of β -cells^[5,6].

Several classes of oral antihyperglycemic agents are administered as monotherapy to ameliorate hyperglycemia, but due to the progressive nature of type 2 diabetes, some patients eventually require combination therapy ^[7]. These classes include among others sulfonylureas, biguanide and their combination.

Aims of the study are:

- 1 - To investigate the efficacy of metformin, glibenclamide and their combination in improving fasting plasma glucose (FPG), postprandial plasma glucose(PPG) and glycosylated hemoglobin (HbA1c) in newly diagnosed type2 diabetic patients.

- 2 - To investigate the effects of metformin, glibenclamide and their combination on serum lipid profile body weight and body mass index (BMI) in newly diagnosed type2 diabetic patients.

Patients and methods:

This study was conducted during the period from the 15th November 2009 till the 25th May 2010, which was carried out in Layla Qassem Diabetic Center and many outpatient clinics in Erbil city. The study included 90 newly diagnosed type 2 diabetic patients to be treated with oral antidiabetic agents and 30 healthy individuals without drug treatment as a control group. Full informations were taken by a questionnaire paper. Our subjects were divided into four groups:

Group A patients:

Includes forty patients, 22 women and 18 men ranging 30–70 years (mean \pm SEM, 49.2 ± 0.8) taking metformin 500mg (glucophage, Merk serono) three times daily as antidiabetic drug.

Group B patients:

Includes thirty five patients, 19 women and 16 men ranging 42–60 years (48.5 ± 1.09) taking glibenclamide/metformin (2.5/500mg) (glucovance, Merk serono) two times daily as antidiabetic drug.

Group C patients:

Includes fifteen patients, 7 women and 8 men ranging 36–65 years (48 ± 1.9) taking glibenclamide 5mg once daily as antidiabetic drug.

Venous blood (8 ml) was collected from each patient. It was drawn after overnight fasting by venipuncture under basal condition using tourniquet with vacuon system. 2 ml of blood was transferred into EDTA tube for HbA1c testing, and the remaining blood was left for 15 minute at room temperature to be clotted then centrifuged at 3000 rpm for 5 minute. Two milliliters of the plasma was allowed for FPG and lipid profile tests. Two milliliters of venous blood was also collected after 2 hour of a meal for postprandial test.

Parameters used for analysis involved:

Estimation of plasma Glucose (fasting plasma glucose and postprandial blood glucose) ^[8] glycosylated hemoglobin (HbA1c) ^[9]; serum Total cholesterol ^[10, 11]; serum Triglycerides ^[12, 13]; serum HDL-c ^[14]; serum LDL-c ^[15] and estimation of Body mass index.

Statistical analysis:

Data were prepared as mean \pm standard error of mean (SEM) paired t–test were used for statistical analysis and p-value < 0.05 was considered significance.

Results:

Fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and glycosylated hemoglobin (HbA1c) in newly diagnosed diabetic patients treated with 1500 mg of metformin daily for 3 months shown in Table-1. Each value represented the mean \pm standard error. Number of patients were 40.

Month treatment	FPG mg/dl	PPG mg/dl	HbA1c %
Pretreatment	167.9 \pm 3.5	276.3 \pm 5.4	8.1 \pm 0.2
After 1 month	143.6* \pm 3.1	231.4* \pm 4.4	7.7 \pm 0.2
After 2 month	126.9* \pm 2.2	208.9* \pm 4.3	7.0* \pm 0.2
After 3 month	119.1* \pm 2.0	187.8* \pm 3.5	6.5* \pm 0.1

Table-1: FPG, PPG, HbA1c for patients received metformin (Group A)

Values are expressed by mean \pm SEM

*P< 0.05 considered significant difference between treated and pretreated values.

Body weight and body mass index (BMI) of diabetic patients treated with 1500 mg daily dose of metformin for 3 months (table-2).

Month Treatment	BW kg	BMI kg/m ²
Pretreatment	83.8 \pm 2.1	31.9 \pm 0.8
After 1 month	83.2 \pm 2.1	31.6 \pm 0.8
After 2 month	82.5* \pm 2.0	31.4 \pm 0.8
After 3 month	81.6* \pm 2.0	31.0 \pm 0.8

Table-2: Body weight and body mass index for patients received metformin (group-A).

Values are expressed by mean \pm SEM

*P<0.05 considered significant difference between treated and pretreated values.

Serum Total cholesterol ; serum Triglycerides ; serum HDL-c ; serum LDL-c in diabetic patients treated with 1500 mg daily dose of metformin for 3 months (table-3).

Month Treatment	TC mg/dl	TG mg/dl	HDL mg/dl	LDL mg/dl
Pretreatment	203.7 \pm 4.7	175.6 \pm 6.2	40 \pm 1.0	129.7 \pm 4.1
After 1 month	192* \pm 3.0	171.2 \pm 7.3	40.1 \pm 0.8	119.1* \pm 2.5
After 2 month	183.8* \pm 2.3	166.3* \pm 5.5	40.7 \pm 0.9	111.1* \pm 1.9
After 3 month	177.5* \pm 2.2	162.0* \pm 5.7	43.2* \pm 0.9	100.7* \pm 2.1

Table-3: TC, TG, HDL-c and LDL-c for patients received metformin (group-A)

Values are expressed by mean \pm SEM

*P<0.05 considered significant difference between treated and pretreated values.

Fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and glycosylated hemoglobin (HbA1c) in newly diagnosed diabetic patients treated with 2.5 mg glibenclamide and 500mg metformin twice daily for 3 months. Number of patients were 35 (table-4).

Month Treatment	FPG mg/dl	PPG mg/dl	HbA1C %
Pretreatment	179.0±4.1	304.5±5.6	7.9±0.1
After 1 month	156.0*±4.6	248.1*±5.3	6.9*±0.1
After 2 month	127.8*±4.5	206.0*±5.3	6.6*±0.1
After 3 month	108.4*±1.8	179.1*±2.2	5.9*±0.1

Table-4: FPG, PPG and HbA1c for patients received glibenclamide / metformin combination (group B).

Values are expressed by mean ± SEM

*P<0.05 considered significant difference between treated and pretreated values.

Body weight and body mass index of diabetic patients treated with 2.5 mg glibenclamide and 500mg metformin twice daily dose for 3 months (table-5).

Month Treatment	BW Kg	BMI kg/m²
Pretreatment	76.4±1.6	28.6±0.6
After 1 month	76.9±1.6	28.8±0.6
After 2 month	77.3*±1.6	29.0±0.6
After 3 month	77.4*±1.6	29.0±0.6

Table-5: Body weight and body mass index for patient received glibenclamide / metformin combination (group-B).

Values are expressed by mean ± SEM

*P<0.05 considered significant difference between treated and pretreated values.

Serum Total cholesterol ; serum Triglycerides ; serum HDL-c ; serum LDL-c in diabetic patients treated with 2.5 mg of glibenclamide and 500mg metformin twice daily dose for 3 months (table-6).

Month treatment	TC mg/dl	TG mg/dl	HDL mg/dl	LDL mg/dl
Pretreatment	204.5±3.5	170.1±6.7	41.4±0.9	130.7±3.1
After 1month	189.2*±3.3	162.2±5.7	41.5±0.9	117.2*±2.8
After 2month	186.2*±2.7	161.1*±3.2	42.0±0.6	113.0*±2.0
After 3 month	179.1*±1.7	157.2*±3.7	42.8*±0.6	103.5*±1.3

Table-6: TC, TG, HDL-c and LDL-c for patient received glibenclamide/metformin combination (group-B).

Values are expressed by mean ± SEM

*P<0.05 considered significant difference between treated and pretreated values.

Fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and glycosylated hemoglobin (HbA1c) in newly diagnosed diabetic patients treated with 5 mg of glibenclamide once daily for 3 months. Number of patients were 15 (table 7).

Month treatment	FPG mg/dl	PPG mg/dl	HbA1c %
Pretreatment	165.1±4.3	273.6±5.5	7.9±0.2
After 1 month	127.5*±1.6	218.8*±3.5	7.2*±0.1
After 3 month	112.8*±1.9	210.1*±4.4	7.1*±0.1

Table-7: FPG, PPG and HbA1c for patients received glibenclamide (group-C).

Values are expressed by mean ± SEM

*P<0.05 considered significant difference between treated and pretreated values.

Body weight and body mass index of diabetic patients treated with 5 mg daily dose of glibenclamide for 3 months (table-8).

Month Treatment	BW Kg	BMI kg/m²
Pretreatment	69.7±1.8	25.8±0.9
After 1 month	70.4*±1.8	26.1±0.9
After 3 month	71.4*±1.7	26.5±0.9

Table-8: Body weight and body mass index for patients received glibenclamide (group-C).

Values are expressed by mean ± SEM

*P<0.05 considered significant difference between treated and pretreated values.

Serum Total cholesterol; serum Triglycerides ; serum HDL-c ; serum LDL-c in diabetic patients treated with 5 mg daily dose of glibenclamide for 3 months (table-9).

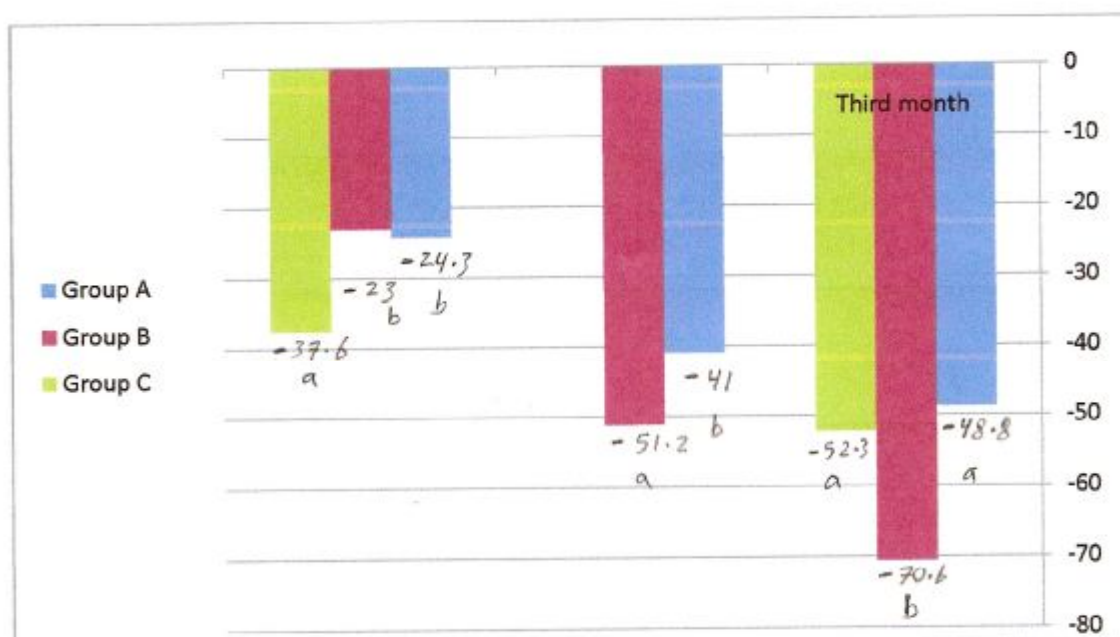
Month Treatment	TC mg/dl	TG mg/dl	HDL mg/dl	LDL mg/dl
Pretreatment	196.3±7.3	163.6±11.5	40.0±1.1	127.3±5.7
After 1 month	200.6*±7.4	172.0*±11.0	40.0±1.0	125.6±6.5
After 3 month	216.0*±13.2	181.6*±7.1	41.0±1.0	138.6*±12.8

Table-9: TC, TG, HDL-c and LDL-c for patients received glibenclamide (group-C).

Values are expressed by mean ± SEM

*P<0.05 significant difference between treated and pretreated values.

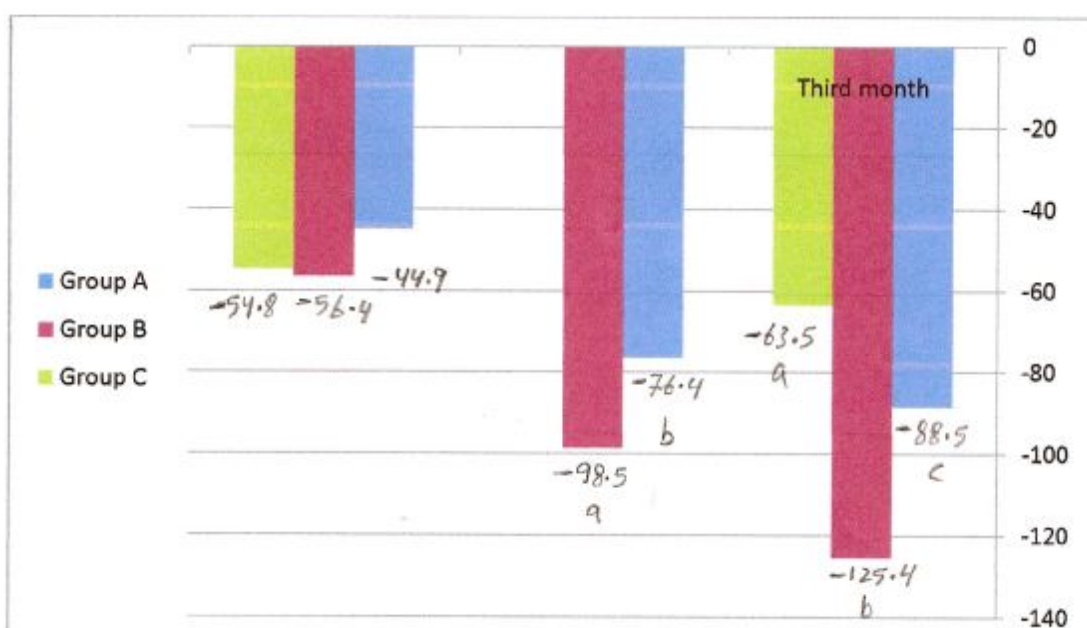
FPG			
Time	Groups		
	A	B	C
1 month	- 24.3	-23	- 37.6
2 months	- 41	- 51.2	-
3 months	- 48.8	- 70.6	- 52.3



Different letters represent significance in values

Table-10: Values of FPG mg/dl represented as difference between values of different time intervals and the pretreatment values in different patients groups.

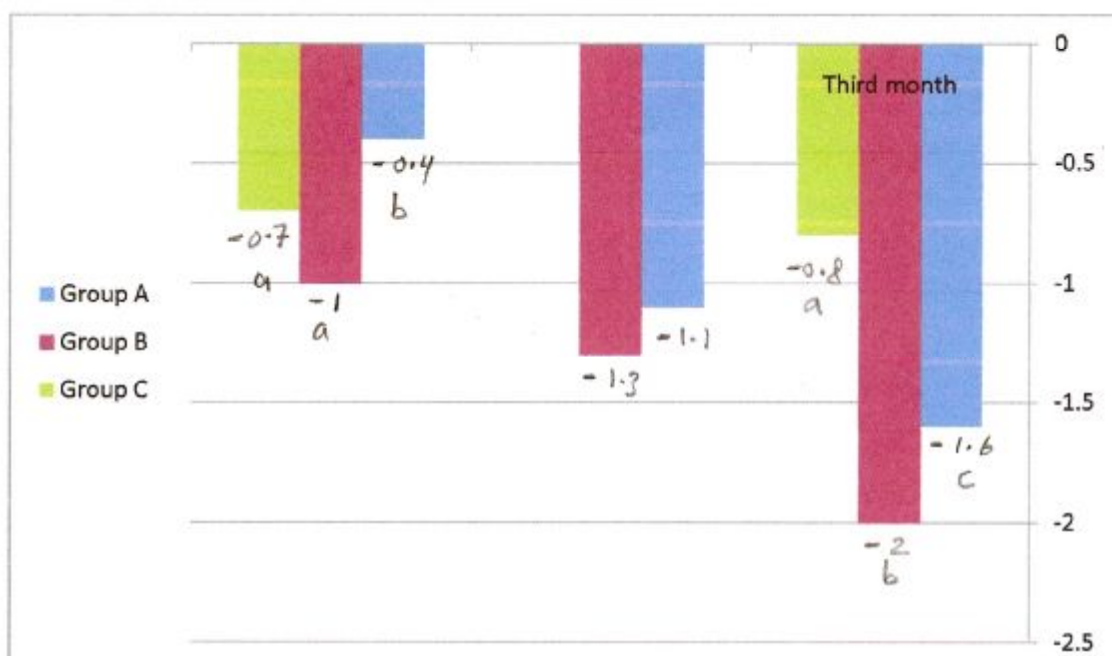
PPG			
Time	Groups		
	A	B	C
1 month	- 44.9	-56.4	- 54.8
2 months	- 76.4	- 98.5	-
3 months	- 88.5	- 125.4	- 63.5



Different letters represent significance in values

Table-11: Values of PPG mg/dl represented as difference between values of different time intervals and the pretreatment values in different patients groups.

HBA1c			
Time	Groups		
	A	B	C
1 month	-0.4	-1	-0.7
2 months	-1.1	-1.3	-
3 months	-1.6	-2	-0.8



Different letters represent significance in values

Table-12: Values of HBA1c (%) mg/dl represented as difference between values of different time intervals and the pretreatment values in different patients groups.

Discussion:

Many specialists recommended the use of metformin as first drug of choice in newly diagnosed diabetic patients in Hawler city, strategy which was in parallel to the strategy used in the treatment of diabetes mellitus in other countries [16]. In order to investigate the advantage of this strategy and to

compare the efficacy of metformin or glibenclamide and their combination, the present work was conducted. The present work was designated to compare the effect of metformin, glibenclamide and their combination on fasting plasma glucose, postprandial plasma glucose, glycemic control, body weight and body mass index, lipid profiles in newly diagnosed diabetic patients.

Metformin reduced FPG, PPG levels by 48.8 mg/dl and 88.5 mg/dl after 3 months of treatment respectively from the base line, with a percent reduction of 29%, 32%, respectively. Glibenclamide reduce FPG, PPG, levels by 52.3 mg/dl and 63.5 mg/dl after 3 months of treatment respectively from the base line, with a percent of reduction 31.6% and 23.2%,. HbA1c was significantly achieved the recommended target after 3 months of treatment, so the change from the base line level was -1.6% for metformin and -0.8% for glibenclamide respectively with a percent reduction of 29% and 10.1% respectively. It was obvious from these results that metformin or glibenclamide reduced the FPG, PPG and HbA1c to about normal boarder values after 3 months of treatment. Similar results were observed by other workers used metformin or glibenclamide for the treatment of newly diagnosed diabetic patients ^[17, 18].

Diabetic patients who received metformin showed a significant reduction in the TC, TG and LDL-c values as compared to the pretreatment values. The HDL-c was significantly increased by 3.2 mg/dl after 3 months of treatment with a percent increase of 8%. These results were comparable to the results of other workers who demonstrated a reduction in bad lipids and an increase in good lipids after metformin therapy ^[19,20]. In contrast, diabetic patients receiving glibenclamide showed a significant increase in the TC, TG, and LDL-C values, However, HDL-C level was also increased by 1 mg/dl from base line after 3 months of treatment with a percent of elevation 2.5%. Several workers showed comparable results of glibenclamide on serum lipid profile of diabetic patients ^[21,22].

Patients administered metformin therapy had a significant decrease in body weight of 2.6kg from base line after 3 months of treatment, and percent reduction of 2.6 of body mass index, while patients administered glibenclamide had a significant increase in body weight of 1.7kg with a percent increase of 2.4% of body mass index. These results were comparable to that observed by others ^[23,24]. So the results of the present study suggested that metformin is an oral hypoglycemic drug which had a comparable efficacy to glibenclamide and it had a favorable effect on serum lipid profile and body weight.

Treatment with glibenclamide /metformin combination (2.5/500 mg) had resulted a greater reduction of FPG and PPG from base line as compared to the previous values of metformin or glibenclamide alone. However, HbA1c was reduced by 2.0 from base line with a percent reduction of 25.3%. This could

indicate that achieving the recommended target of HbA1c by a combination therapy produces greater improvements in glycaemic control.

Treatment with glibenclamide –metformin combination also showed a significant reduction of serum lipid profile in newly diagnosed diabetic patients. Significant reduction was observed in TC, TG and LDL-c. The HDL-c was significantly increased by 1.0 mg/dl only after 3 months with a percent increase of 1.3 %. These results were comparable to the values observed in metformin treated group, which could be indicated that in combination therapy, metformin still had the advantage of lowering bad cholesterol and increasing good lipid, even in the presence of glibenclamide ^[25,26].

Type II diabetes patients have a dual pathophysiologic defects, insulin resistance and progressive beta-cell dysfunction ^[27]. In combination therapy, metformin reduced the basal rate of hepatic glucose production ^[28], and increased glucose uptake by peripheral tissues ^[29], where as glibenclamide stimulate insulin secretion by the pancreatic β -cells ^[30], so these two agents were used to correct the dual defect of glucose in diabetic patients ^[7]. On the other hand the use of a single antihyperglycemic agent corrected only one of these defects, so the management of type 2 diabetes may be less than optimal with initial monotherapy ^[31].

Conclusion:

Metformin monotherapy and glibenclamide/metformin combination therapy both provide superior efficacy as an initial management of type 2 diabetes in kurdistan region. The two strategies improve fasting blood glucose, postparandial blood glucose and glycolated hemoglobin significantly, and both have favorable effect on serum lipid profile. Combination treatment is more effective than either drug alone in improving glycemic control in type 2 diabetes.

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