

Effects of metformin+sitagliptin versus metformin + glibenclamide combinations on lipid profile, body mass index and kidney function in Iraqi patients with type 2 diabetes mellitus.

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Abstract:

Until 1995, only two options for pharmacologic treatment were available for patients with diabetes; sulfonylurea (for type 2 DM only) and insulin (for type 1 or 2). Since 1995, a number of new oral agents, injectables, and insulins have been introduced in therapy. Currently, six classes of oral agents are approved for the treatment of type 2 diabetes: , sulfonylurea, α -glucosidase inhibitors, biguanides, meglitinides, thiazolidinediones or glitazones& dipeptidyl peptidase-4 inhibitors.

This study aimed to evaluate the lipid profile, kidney function and BMI by using two combinations of drugs metformin + glibenclamide and metformin + sitagliptin on patients with T2DM.

Sixty eight T2DM patients (and categorized in to two treatment groups) and 34 normal healthy individuals as control group were enrolled in this study group 1 (34 patients) received metformin 500 mg three times daily + glibenclamide 5 mg twice daily and group 2 (34 patients) received metformin 500 mg three times daily + sitagliptin 100 mg once daily. From each patients 10 ml of blood was obtained by veinpuncture and the serum was separated and used for estimating the lipid profile, kidney function (blood urea and serum creatinin).

The mean calculated serum total cholesterol(TC), serum triglyceride(TG), low density lipoprotein cholesterol (LDLc)and very low density lipoprotein cholesterol(VLDLc) were significantly($p<0.05$) lower for group 2 patients after 3 & 6 months of treatment (225.88 ± 6.62 mg/dl, 214.32 mg/dl ± 4.86 and 197.61 mg/ dl ± 3.4), (252.08 ± 9.07 mg/dl, 234.02 mg/dl ± 6.44 and 196.0 mg/dl ± 5.70), (96.2 ± 2.03 mg/dl, 94.26 mg/dl ± 2.58 , 88.17 mg/dl ± 1.79) and (78.38 ± 3.65 mg/dl, 68.50 mg/dl ± 2.9 , 60.52 mg/dl ± 2.26)respectively as compared to group 1 (245.7 ± 2.87 , 235.61 mg/dl ± 2.64 , 224.9 mg/dl ± 2.98), (257.38 ± 9.25 , 249.67 mg/dl ± 8.19 , 235.7 mg/dl ± 7.83), (103.14 ± 2.19 , 95.64 mg/dl ± 1.19 , 91.64 mg/dl ± 1.196) and (94.74 mg/dl ± 2.93 , 83.79 mg/dl ± 3.28) respectively. The picture was different for high density lipoprotein (HDLc) where, significantly ($p<0.05$) increased for group 2 patients after 3&6 months of treatment (48.37 ± 1.07 , 49.9 mg/dl ± 1.16 and 51.14 mg/dl ± 1.35) compared to group 1 patients (43.02 ± 1.24 , 44.67 mg/dl ± 1.28 , 46.52 mg /dl ± 1.22). The mean calculated body mass index (BMI) was significantly ($p<0.05$) lower for group 2 patients after 1&6 months of treatment (26.7 ± 0.35 and 25.3 ± 0.35) than in group 1 patients (28.5 ± 0.55 and 26.95 ± 0.43).

This study also showed significantly($p<0.05$) lower mean serum blood urea and serum creatinine level for group 2 patients after 3&6 months of treatment (42.9 ± 1.30 , 44.0 ± 1.48 and 44.0 ± 1.59 mg /dl),(0.89 ± 0.03 , 0.91 ± 0.03 and 0.98 ± 0.05 mg/dl) respectively compared to that of group 1(60.0 ± 4.25 , 63.0 ± 4.4 and 64.0 ± 4.34 mg/dl), (1.23 ± 0.54 , 1.26 ± 0.55 and 1.32 ± 0.54 mg/dl) respectively.

IN conclusion, the combination of metformin + sitagliptin improved lipid profile, kidney function and body mass index more than metformin +glibenclamide combination.

Keywords: Dipeptidyl peptidase – 4 (DPP-4) \ Diabetes mellitus

الخلاصة:

المجموعة العلاجية (المتفورمين + السيتاكلبتين) او (المتفورمين+ الكلبنكلمايد) تؤدي إلى تأثيرات بتقليل نسبة السكر بالدم لمرضى عراقيين مصابين بداء السكري من النوع الثاني. هذه الدراسة أجريت في مستشفى بغداد التعليمي/مدينة الطب وتحت إشراف طبيب اختصاص وبموافقة المرضى إضافة إلى موافقة الجهات المختصة فترة الدراسة كانت من تموز 2011 و حتى آذار 2012 تقييم إمكانية السيطرة على نسبة الدهون بالدم , وظائف كلى وكذلك الزيادة كتلة الجسم. تم اختيار (68 مريض) يعانون المرض وتم مقارنتهم ب (34) شخص من الأصحاء لغرض المقارنة. تم توزيع المرضى إلى مجموعتين: المجموعة الأولى: 34 مريض تراوحت أعمارهم بين 40-59 سنة (المتوسط = 52 ± 0.86). استخدمت هذه المجموعة (المتفورمين 500 ملغم ثلاث مرات يوميا+الكلبنكلمايد 5 ملغم مرتين يوميا). المجموعة الثانية: 34 مريض تراوحت أعمارهم بين 44-59 سنة (المتوسط = 52 ± 0.9). إن هذه المجموعة تستخدم (المتفورمين 500 ملغم ثلاث مرات يوميا +السيتاكلبتين 100 ملغم يوميا). بينت الدراسة إن المتوسط الحسابي للدهون كالكولسترول، الترايكلسيراييد، البروتينات الدهنية قليلة الكثافة والبروتينات الدهنية قليلة الكثافة جدا هي أقل في المجموعة الثانية مقارنة بالمجموعة الأولى حيث كانت النتائج (4.86 ± 214.32 , 3.4 ± 197.61 ملغم/مل)، (6.44 ± 234.04 , 5.7 ± 196)، (1.19 ± 94.26 , 1.79 ± 88.17 ملغم/مل) و (2.9 ± 68.5 , 2.26 ± 60.52) بالتتابع، بينما كانت النتائج للمجموعة الأولى (2.61 ± 235.64 , 2.98 ± 224.61)، (8.19 ± 249.67 , 7.83 ± 235)، (1.19 ± 95.64 , 1.19 ± 91.64) و (2.9 ± 94.74 , 3.82 ± 83.79) بالتتابع. بينما تختلف الصورة بالنسبة إلى البروتينات الدهنية عالية الكثافة حيث بينت الدراسة زيادتها في المجموعة الثانية بشكل ملحوظ مقارنة بالمجموعة الأولى، حيث كانت النتائج بالنسبة إلى المجموعة الثانية (1.16 ± 49.9 , 1.35 ± 51.14) بينما للمجموعة الأولى (1.28 ± 44.67 , 1.22 ± 46.52). كما بينت الدراسة ان مستوى اليوريا بالمصل وكذلك الكرياتينين هي أقل بالنسبة إلى المجموعة الثانية مقارنة بالمجموعة الأولى حيث ان المتوسط الحسابي لليوريا للشهر 3,1 و6 من الدراسة للمجموعة الثانية هو (1.3 ± 42.9 , 1.48 ± 44 و 1.59 ± 44 ملغم/مل) والكرياتينين (0.03 ± 0.89 , 0.03 ± 0.91 و 0.03 ± 0.98) (0.05 ملغم/مل) اما المتوسط الحسابي لليوريا للشهر 3,1 و6 من الدراسة للمجموعة الأولى هو (5.23 ± 60.9 , 4.4 ± 63 و 4.34 ± 64 ملغم/مل) والكرياتينين (0.54 ± 2.23 , 0.55 ± 1.26 و 0.54 ± 1.32 ملغم/مل). كما بينت الدراسة إن دليل كتلة الجسم قد تأثر بصورة ملحوظة للمجموعة الثانية حيث كان التغييرين الشهر الاول والسادس (من 26.7 ± 35 إلى 25.3 ± 35) مقارنة بالمجموعة الأولى حيث كان التغييرين الشهر الاول والسادس (من 28.5 ± 55 إلى 26.7 ± 43). يمكن الاستنتاج ان المجموعة العلاجية (المتفورمين+السيتاكلبتين) قد شهدت تحسنا ملحوظا من حيث السيطرة على نسبة الدهون وكذلك نسبة اليوريا والكرياتينين و دليل كتلة الجسم (BMI) مقارنة بالمجموعة العلاجية (المتفورمين + الكلبنكلمايد).

Introduction:

Type 2 diabetes is a complex and multifactorial disease frequently characterized by increased levels of plasma triglycerides (TG), reduced levels of high-density lipoprotein-cholesterol (HDL-c) and increased concentrations of small, density lipoprotein particles^[1].

Several lines of evidence indicate that insulin-resistance are associated with an increased hepatic secretion of apoB-100 containing very low density lipoprotein and an increased intestinal secretion of apo B-48- containing chylomicrons^[2], leading to accumulation of atherogenic TG-rich lipoproteins^[3].

The incretin hormones play a major role in glucose homeostasis by stimulating insulin secretion, suppressing glucagon secretion, inhibiting gastric emptying and

reducing appetite and food intake^[4]. Both incretin hormones (GLP-1, GIP) are degraded and removed from circulation by the enzyme dipeptidyl peptidase-4 (DPP-4)^[5].

Therefore, there is considerable interest in enhancing incretin action for the treatment of type 2 diabetes. Sitagliptin, a selective DPP-4 inhibitor, reduces both fasting and postprandial plasma glucose presumably by inhibiting the inactivation of GLP-1 and GIP, thereby prolonging their duration of action on the pancreatic islets^[6]. Although clinical studies to date indicate that fasting lipid levels are minimally affected by DPP-4 inhibitor treatment^[7], animal studies suggested that incretin hormones reduce intestinal TG absorption and apo B-48 production^[8] and increased chylomicron catabolism^[9].

Diabetic nephropathy, the main impact of diabetes on the kidneys, can lead to scarring changes in the kidney tissue, loss of small progressively larger amount of protein in urine, and eventually chronic kidney disease requiring dialysis^[10] Also other studies showed that sitagliptin provide effective glycemic control in patients with T2DM and moderate to severe renal insufficiency, including patients with end stage renal disease (ESRD) on dialysis^[11].

Weight gain is common with sulfonylurea. It is likely that the addition of sitagliptin to metformin and at least a small dose of sulfonylurea may be effective in reducing HbA1c without weight gain^[11].

The aim of this study is to evaluate the effects of metformin+sitagliptin versus metformin+glibenclamide combinations on lipid profile, body mass index and kidney function in Iraqi patients with type 2 diabetes mellitus.

Materials and Methods:

This study was carried out at Baghdad teaching hospital/Medical city directorate & the National Diabetic Center for Treatment and Research/Al-mustansiriyah University and at the private clinic of a consultant physician during the period of July 2011 to March 2012. The study was conducted on 100 Iraqi type 2 diabetes mellitus patients only 68 patients completed the course of study successfully.

Those patients were recruited into the following groups:

Group (1): Includes 34 patients tested at zero time and after 3 months and 6 months. The patients were already treated by metformin & glibenclamide.

Group (2): Includes 34 patients tested at zero time and after 3 months and 6 months

The patients were previously treated by sitagliptin 3-6 months before start the study and they continue on this regimen of treatment. The age of patients for group (1) ranged from 40–59 years (52.5 ± 0.86), 20 patients of them (58.8 %) were male and 14 patients (41.2 %) were

female. The age of patients for group (2) ranged from 44–59 (52.44 ± 0.9), 20 patients of them (58.8 %) were male and 14 patients (41.2 %) were female. Diagnosis was made by consultant endocrinologist; for patients as having T2DM depending on patient history, clinical examination laboratory investigations and vital signs. For the purpose of comparison, 34 control subjects were enrolled (group 3). The age of control group ranged from 44–59 (52.44 ± 0.9), of them 20 patients (58.8 %) were male and 14 patients (41.2 %) were female.

Patients were excluded from this study if they having the following criteria: CNS disease, renal failure, liver dysfunction, pregnant with diabetes, concomitant endocrine disease & inflammatory Disease.

From each patients, 10 ml of blood was obtained by veinpuncture, using 10 ml syringe. This blood was dispensed in a plane tube and left for an hour to clot at room temperature then, it was centrifuged at 3000 rpm for 10 minutes to collect serum. The serum was separated and used for estimating lipid profile (TC, TG, LDL-c, VLDL-c and HDL-c), serum urea and serum creatinine using laboratory kits.

BMI were calculated using the following equation: $BMI = \text{weight (kg)} / \text{Ht}^2(\text{m})$ (National Institute of Health, 1998)

The statistical analysis of our results include:

- 1- Mean \pm Standard error of mean.
- 2- ANOVA two ways (was used to examine the difference of the mean of parameters test between studies group).

The results of analysis with P values < 0.05 was considered significant.

Results:

Lipid profiles Table 1 and 2 compared between the effects of two groups on lipid profile. There was significant improvement (because HDL-c increase and not decrease) in lipid profile for both groups after 3 and 6 months of treatment as compared to 1st reading. However, group 2 (treated by metformin +

sitagliptin) showed more significant improvement in lipid profile compared to

group 1 (treated by metformin+ glibenclamide) after 3 and 6 months of treatment.

Table-1: Effect of (metformin 500 mg 3 times daily + glibenclamide 5 mg twice daily) on Lipid Profile

Serum lipid profile mg/dl	metformin + glibenclamide group (n=34)			Control group (n=34)
	1 month	3 month	6 month	
TC	245.7± 2.87 ^a	235.61 ± 2.64 ^{a b}	224.9 ± 2.98 ^{ab}	152.91 ± 3.24
TG	257.38 ± 9.25 ^a	249.67 ± 8.19 ^{ab}	235.7 ± 7.83 ^a	169.79 ± 79
LDLc	100.73 ± 1.71 ^a	95.64 ± 1.19 ^a	91.64 ± 1.196 ^{ab}	79.94 ± 2.87
HDLc	43.02 ± 1.24 ^a	44.67 ± 1.28 ^a	46.52 ± 1.22 ^a	53.57 ± 0.89
VLDLc	103.14 ± 2.19 ^a	94.74 ± 2.93 ^{ab}	83.79 ± 3.28 ^{ab}	28.70 ± 1.41

. Values expressed as mean ± standard error of mean

a significantly difference ($p < 0.05$) as compared with control values.

b significant difference ($p < 0.05$) as compared 1st, 2nd and 3rd reading

Table-2: Effect (metformin 500mg 3 times daily+sitagliptin 100mg daily) on Lipid Profile.

Serum lipid profile mg /dl	Metformin + sitagliptin group (n=34)			Control
	1 month	3 month	6 month	
TC mg/dl	225.88 ± 6.62 ^{ac}	214.32 ± 4.86 ^{abc}	197.61 ± 3.4abc	152.91 ± 3.24
TG mg/dl	252.08 ± 9.07 ^{ac}	234.02 ± 6.44 ^{abc}	196 ± 5.70abc	169.79 ± 79
LDLc mg/dl	96.20 ± 2.03 ^a	94.26 ± 2.58 ^{abc}	88.17 ± 1.79abc	79.94 ± 0.97
HDLc mg/dl	48.73 ± 1.07 ^a	49.9 ± 1.16 ^{abc}	51.14 ± 1.29bc	53.38 ± 0.47
VLDLc mg/dl	78.38 ± 3.65 ^{ac}	68.50 ± 2.9 ^{abc}	60.52 ± 2.26abc	28.70 ± 1.41

Values expressed as mean ± standard error of mean

a significantly differe ($p < 0.05$) as compared with control values.

b significant differece ($p < 0.05$) as compared 1st, 2nd and 3rd reading

c significant differece ($p < 0.05$) as compared group 2 to 1.

2. Body mass index(BMI):

Table-3 Compared between the effects of two treatment groups (metformin+glibenclamide and metformin+ sitagliptin) on BMI in patients with T2DM

There was significant reduction in BMI for both groups after 3 and 6 months of treatment as compared to 1st reading.

However, there is significantly higher decline in BMI for group 2 treated by (metformin+sitagliptin) compared to group 1 (treated by metformin+glibenclamide) after 3 and 6 months of treatment .

Table-3: Effect of (metformin 500mg 3 times daily + glibenclamide 5mg twice daily) versus group 2 (metformin 500 mg3 times daily + sitagliptin 100mg once daily on BMI.

Groups	Body mass index (BMI) (kg/m ²)	
	1 month	6 month
Group 1	28.5 ±0.55 ^a	26.95 ± 0.43a
Group 2	26.7 ± 0.35 ^{ab}	25.3 ± 0.35ab
Group 3	24.23 ± 0.97	24.23 ± 0.97

Values expressed as mean ± standard error of mean.

a significantly different ($p < 0.05$) as compared with control values.

b significant different ($p < 0.05$) as compared group 2 to 1.

Serum urea:

The data in table.4 showed that serum urea level in group 1 patients (treated with metformin 500mg + glibenclamide 5mg) and group 2 patients (treated by metformin 500 mg + sitagliptin 100 mg). Its obvious from this table that all patient groups had significant ($p < 0.05$) different value of serum urea between group 2 and other groups i.e. group 1 and 3. For group 1; the values were [60.0±4.25, 63.0±4.4 and 64.0±4.34 mg/dl] for 1,3 and 6 months respectively compared to control

group [32.0±0.87, 32.0±0.87 and 32.0±0.91 mg/dl] respectively which indicated significant ($p < 0.05$) increase serum urea in patients treated by metformin and glibenclamide compared to control normal healthy individuals. While for group 2 , the serum urea values were [42.9±1.30, 44.0±1.48 and 44.0±1.59 mg/dl] for 1,3 and 6 months respectively compared to control group [32.0±0.87, 32.32±0.87 & 32.41±0.91] respectively which indicated significant ($p < 0.05$) increase as compared to control normal healthy individuals.

Table-4: Effect of treatment with group 1 (metformin 500mg 3 times daily + glibenclamide 5 mg twice daily) versus group 2 (metformin 500 mg3 time daily + sitagliptin 100 mg once daily on serum urea.

Duration/months	Group 1(n=34) mg /dl)B.urea(Group 2(n=34) mg /dl) B.urea(Group 3(n=34) (mg / dl) B.urea
1	60.7 ± 4.25 ^a	42.91 ± 1.30 ^{ab}	32.2 ± 0.87
3	63.52 ± 4.4 ^a	44.38 ± 1.48 ^{ab}	32.32 ± 0.87
6	64.82 ± 4.34 ^a	44.47 ± 1.59 ^{ab}	32.41 ± 0.91

Values expressed as mean ± standard error of mean.

a significantly difference ($p < 0.05$) as compared with control values.

b significant difference ($p < 0.05$) as compared group 2 to 1.

Serum creatinine:

Data in table 5 showed that serum creatinine levels in group 1 patients (treated with metformin 500 mg + glibenclamide 5mg) and group 2 patients

(treated by metformin 500 mg + sitagliptin 100 mg).

Its obvious from this table that all patients had significant ($p < 0.05$) different value of serum creatinine between group 2 and other group i.e. Groups 1 and 3. For

group 1 ; the serum creatinine values were [1.23 ± 0.54 , 1.26 ± 0.55 and 1.32 ± 0.54 mg/dl] for 1,3 and 6 months respectively compared to control group [0.72 ± 0.01mg/dl, 0.7± 0.01 & 0.71± 0.01] respectively.

While for group 2 , the serum creatinine values were 0.89 ± 0.03 , 0.91 ± 0.03 and 0.98 ± 0.05 mg/dl for 1,3 and 6

months respectively compared to control groups [0.72 ± 0.01, 0.72 ± 0.01 and 0.72 ± 0.01mg/dl] respectively.

Meanwhile, patients treated with metformin and glibenclamide showed significant ($p < 0.05$) increased in serum creatinin as compared to that of patients treated by metfomin + sitagliptin and control normal healthy subjects.

Table-5: Effect of treatment with group 1 (metformin 500 mg 3 times daily + glibenclamide 5 mg twice daily) versus group 2 (metformin 500 mg 3 times daily + sitagliptin 100 mg once daily) on serum creatinin.

Durations/ months	Group 1(n=34) (mg/dl)s.cr	Group 2(n=34) (mg/dl) s.cr.	Group 3(n=34) (mg/dl) s.cr.
1	1.23 ± 0.54 ^a	0.89 ± 0.03 ^b	0.72 ± 0.01
3	1.26 ± 0.55 ^a	0.91 ± 0.03 ^b	0.70 ± 0.01
6	1.32 ± 0.54 ^a	0.98 ± 0.05 ^{ab}	0.71 ± 0.01

Values expressed as mean ± standard error of mean.

a significantly differ ($p < 0.05$) as compared with control values.

b significant difference ($p < 0.05$) as compared group 2 to 1

Discussion:

Our study showed that combination of metformin + sitagliptin improved lipid profile better than combination of metformin + glibenclamide. There is an interest in identifying novel therapeutic approaches that would beneficially affect postprandial concentrations of both glucose and lipids.

Although clinical studies to date indicate that fasting lipid levels are minimally affected by DPP-4 inhibitor treatment^[13], animal studies suggested that incretin hormones reduces intestinal TG absorption and apo production^[14] and increased chylomicron catabolism^[8].

Moreover, a recent study in patients with T2DM revealed that therapy with the DPP-4 vildagliptin reduced postprandial lipaemia with no significant effect on fasting lipid levels^[15].

Therefore, the objective of the present study was to extend these findings and gain further insight on the impact of DPP-4 inhibition on lipoprotein metabolism by examining the effect of sitagliptin on fasting lipid levels. Therefore, the impact of sitagliptin on

pancreatic hormone release could result in decreased VLDL production, as FFA flux to the liver has been previously shown to directly stimulate hepatic VLDL production^[16,17].

Other studies showed that postprandial concentrations of TG, apo B and VLDL-C were significantly reduced following sitagliptin administration, providing a mechanism for potential cardiovascular benefit of therapy with sitagliptin^[18].

According to this study, sitagliptin significantly reduced the postprandial area under the curves (AUCs) for plasma apolipoprotein (apo0B (-5.1%), apo B-48 (-7.8%), TG (-9.4%), VLDL-c (-9.3%). Further studies indicated that, in patients initiating sitagliptin, change in weight mass was significantly associated with improvements in triglyceride and total cholesterol, with exception of HDL-c, which remained essentially unchanged^[19].

Metformin also has positive effects on several components of the insulin resistance syndrome. Metformin decreases plasma triglycerides and LDL-C by approximately 8% to 15%, as well

increasing HDL-C very modestly (2%). Metformin reduces levels of plasminogen activator inhibitor-1 and causes a modest reduction in weight (2 to 3 kg) ^[20].

Our results regarding lipid profile indicate that there was a successful improvement in lipid profile after treatment courses of 3 and 6 months with metformin 500 mg three times daily + glibenclamide 5 mg twice daily and combination of metformin 500 mg three times daily + sitagliptin 100 mg once daily as was shown in tables 1 and 2; values were improved significantly after treatment with above mentioned drugs. However, this improvement was not enough to reach that of normal healthy individuals. In other words, there were partial improvements or reversibility achieved by these drugs. Accordingly, and based on the comparison of the treatment groups with that of control group that continue for the same period, we do detect that combination of metformin + sitagliptin significantly reduced the values of TC, TG, LDL-c, VLDL-c and significantly increased levels of HDL-c after 3 and 6 months significantly compared to combination of metformin + glibenclamide.

This might be due to additive effect of these two drugs i .e metformin + sitagliptin, since there are studies showed that; Metformin decreases plasma triglycerides and LDL-C by approximately 8% to 15%, as well increasing HDL-C very modestly (2%) ^[20].

The beneficial impact of sitagliptin on postprandial lipid levels could also be secondary to the reduction in glucose levels and improved metabolic state.

In fact many different oral hypoglycemic agents have been shown to improve postprandial lipaemia, although this is not universal finding.

Both metformin ^[21] and glipizide ^[22] can improved postprandial lipid levels in poorly controlled type 2 diabetic patients, presumably by improving glycaemic control and reducing insulin resistance. However, the secretagogues

nateglinide and glibenclamide had no significant impact on postprandial lipaemia, despite their associated insulinotropic effect and improvement in glycemic control^[23]. The recent demonstration that GLP-1 influence intestinal TG absorption ^[24], potentially through gastric lipase inhibition,^[8] provides another potential mechanism underlying the beneficial impact of DPP-4 inhibitors on postprandial lipaemia. Animal studies in mice and hamster have shown that DPP-4 inhibitor or GLP-1 receptor agonist significantly reduced intestinal secretion of TG, cholesterol and apo B-48, a finding supporting the hypothesis that GLP-1 could directly regulate lipoprotein assembly and/or secretory machinery in the enterocytes, ^[8] also its obvious that good patients educations and instructions given by the workers to the patients are of great value in controlling the lipid profile after the 1st reading. combination of metformin and sitagliptin showed a significant ($p<0.05$) decrease in BMI as compared to that of metformin and glibenclamid treated group of patient Previous studies showed that patients treated with sitagliptin experienced significant weight loss (mean– 1.5kg) from base line at 52 weeks ^[25].

Other studies showed that DPP-4 inhibitors have shown clinical significant HbA1c reduction up to 1 year of treatment and offer many potential advantages over existing diabetes therapies including low risk of hypoglycemia, no effect on body weight ^[26]; also other studies showed that , DPP-4 inhibitors were weight neutral (do not cause weight gain or loss) and appear to decrease beta – cell apoptosis and increased beta cell survival ^[27].

Orally administered DPP-4 inhibitors, such as sitagliptin and valdagliptin, reduce HbA1c by 0.5 - 1.0 % ,with few adverse events and no weight gain ^[28]; other studies showed ,that , DPP-4 inhibitors prolongs and enhances the activity of endogenous GLP-1 and GIP, which serves as important prandial

stimulators of insulin secretion and regulators of blood glucose control. In clinical trials DPP-4 inhibitors (or gliptins) have shown efficacy and tolerability in management of hyperglycemia in the type 2 diabetes, without causing weight gain or hypoglycemia^[29].

In the randomized cohort study, all metformin – based groups and the placebo group experienced small but significant reduction in body weight, while there was no change in sitagliptin group^[30], these results are consistent with previous finding for both treatments^[31].

Since weight gain has been observed with intensive glycemic control^[23], the substantially greater glycemic improvements with coadministration therapy might have been expected to lead to an attenuation of the weight loss typically seen with metformin. Of interest, the weight loss in the co administration groups relative to the monotherapy metformin groups was similar^[30]. Weight gain is common with sulfonylurea^[32].

It is likely that the addition of sitagliptin to metformin and at least a small dose of sulfonylurea may be effective in reducing HbA1c without weight gain^[12].

The present study also showed that combination of metformin and sitagliptin improved kidney function parameter as (serum urea and serum creatinine) better than combination of metformin + glibenclamide (table 4 and 5).

Other studies showed that sitagliptin may be used as monotherapy in patients who cannot tolerate metformin or sulfonylurea, and sitagliptin may be used as alternative to metformin in renal insufficiency^[15].

Also other studies showed that sitagliptin provide effective glycemic control in patients with T2DM and moderate to severe renal insufficiency, including patients with end stage renal disease (ESRD) on dialysis^[11]. However further long term studies is needed to established the safety and tolerability of

sitagliptin on kidney function in type 2 diabetic Iraqi patients due to its lacking.

Conclusion:

The combination of metformin + sitagliptin improved lipid profile, kidney function & body mass index more than metformin +glibenclamide combination.

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