Macrovascular and microvascular complications in type 2 diabetic Iraqi patients treated by metformin and glibenclamide versus metformin and sitagliptin

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المستخلص

الهـدف: المجموعة العلاجية (المتفورمين + السيتاكلبتين) او(المتفورمين + الكلبنكلمايد) قد تؤدي إلى تأثيرات إضافية بتقليل المضاعفات على الجهاز العصبي والوعائي لمرضى عراقيين مصابين بداء السكري من النوع الثاني.

المنهجية: هذه الدراسة أجريت في مستشفى بغداد التعليمي \ مدينة الطب وتحت أشراف طبيب اختصاص وبموافقة المرضى إضافة إلى موافقة الجهات المختصة وان فترة الدراسة من تموز ٢٠١١ و حتى آذار ٢٠١٢ لتقيم إمكانية السيطرة على حدوث المضاعفات المصاحبة لمرض السكري. تم اختيار(٦٨ مريض)يعانون المرض وتم مقارنتهم ب (٣٤) شخص من الأصحاء لغرض المقارنة. تم توزيع المرضى إلى مجموعتين:المجموعة الأولى :٣٤ مريض تراوحت أعمارهم بين ٤٠-٥٩ سنة (المتوسط =٥٠. ٥٢ ± ٠،٨٦) . إن هذه المجموعة تستخدم (المتفورمين ٥٠٠ ملغم ثلاث مرات يوميا + الكلبنكلمايد ٥ ملغم مرتين يوميا).المجموعة الثانية :٣٤ مريض تراوحت أعمارهم بين ٤٤-٥٩ سنة (المتوسط =٤٤. ٥٢ ± ٠،٩) . إن هذه المجموعة تستخدم (المتفورمين ٥٠٠ ملغم ثلاث مرات يوميا +السيتاكلبتين ١٠٠ ملغم يوميا).

النتائج: بينت الدراسة إن النسبة المئوية لوجود الالبومين في الادرار هي اقل في المجموعة الثانية مقارنة بالمجموعة الأولى حيث كانت النتائج (٩,٣%، ٨,٥%)بالتتابع بينما كانت النتائج للمجموعة الأولى (٢٢,١٣،١٨,١٢%) لمدة ثلاثة وستة اشهر من العلاج.وبينت الدراسة ان النسبة المئوية لخدر الاطراف ، تنمل الاطراف وحدوث حرقة في القدمين هي اقل بالنسبة الى المجموعة الاولى (١٦,٧١ ، ٨،٧١%)، (٢٠,٥٩،٨,٥٣%) و (١٣,٣،٧,٥٤%) مقارنة الى المجموعة الاولى (٣٩,٧،٣٤,٣٦%) ،(٣٥,١٨،٢٩,٢٩%)و(٣٧,٨٨، ٣١,١٨%). كانت النسبة المئوية لحدوث هبوط في ضغط الدم و لحدوث احتشاء العضلة القلبية في المجموعة الثانية (٨,٨٢،٧,١٢%) و (١١,٧٦،٨,٨٢%) مقارنة بالمجموعة الاولى (١٤,٥٦،١٨,٧٦%)و(١٧,٦٥، ١٤,٧%) بالتتابع.كما بينت الدراسة ان النسبة المئوية لتاثر شبكية العين البسيطة والمعقدة في المجموعة الاولى (٧,٨٣و ٦,٢٢%)و(٢,٨٢و٢,٧%) هي اقل بشكل ملحوظ مقارنة بالمجموعة الاولى (١٥,٧٦، ١٤,٦٥%) و (٦,٦٥،٧,٧١%) بالتتابع.

التوصيات :ان المجموعة العلاجية مع (المتفورمين + السيتاكلبتين) قد شهدت تحسنا ملحوظا من حيث السيطرة على المضاعفات المصاحبة لمرض السكري مقارنة بالمجموعة العلاجية (المتفورمين + الكلبنكلمايد). كما نلاحظ تأثير المتابعة والتعليمات من قبل فريق العمل حيث كان لها التأثير بتحسن النتائج لكلا المجموعتين.

Abstract:

Background: In type 2 diabetes mellitus there is a progressive loss of beta cell function. One new approach yielding promising results is the use of the orally active dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus.

Objective: This study aims at comparing the possible occurrence of macrovascular & microvascular complications in Iraqis patients with type 2 diabetes mellitus using two combinations of drugs metformin + glibenclamide and metformin + sitagliptin.

Methodology: Sixty eight T2DM patients and 34 normal healthy individuals as control group were enrolled in this study and categorized in to two treatment groups. The group 1 (34 patients) received metformin 500 mg three times daily + glibenclamide 5 mg twice daily and the group 2 (34 patients) received metformin 500 mg three times daily + sitagliptin 100 mg once daily. The urine sample was collected for estimation of microalbumin urea and patients' examination was made by specialist consultant endocrinologist.

Results: The percentages of microalbuminurea were significantly (p<0.05) lower for group 2 patients for 3 & 6 months of treatment (9.3%, 8.5%) respectively compared to group 1 (22.13%,18.12%) respectively. The percentages of parasthesia, numbness and burning sensation of feet was significantly(p<0.05) lower for group 2 patients for 3 & 6 months of treatment(16.71%,8.71%), (20.59%,8.53) and (13.3,7.54) respectively as compared to group 1 (39.7%,34.36), (35.18,29.29)and (37.88%,31.18%).The picture was same for postural hypotension & ischemic heart disease the percentages were significantly (p<0.05) lower for group 2 patients for 3 & 6 months of treatment (8.82%,7.12%)and (11.76%,8.82%) respectively as compared to group 1 (18.76%,14.65%) and (17.65%,14.7%) respectively. The same was true for simple and proliferative retinopathy the percentages were significantly (p<0.05) lower for group 2 patients for 3 & 6 months of treatment (7.83%, 6.22%) and (2.82%,2.7%) respectively as compared to group 1 (15.76%,14.65%) and (6.65%,7.71%) respectively.

Recommendations: Combination of metformin + sitagliptin significantly lower microvascular and macrovascular complications than combination of metformin + glibenclamide.

Keywords: Macro vascular, Micro vascular, Diabetes, Metformin, Glibenclamide, Sitagliptin

Introduction:

In patients with type 2 diabetes previous studies have shown an association between the degree of hyperglycemia and increased the risk of microvascular complications [1] .sensory neuropathy [2] .myocardial infarction [3] .stroke [4] .macrovascular mortality [5] .and all cause mortality [6, 7] .Actually, inflammation and oxidative stress play a major role in type 2 diabetes mellitus (T2DM) pathophysiology, contributing for obesity, insulin resistance and cardiovascular complications, which further aggravate the disease. However, so far, there are no therapeutic options able to efficiently act not only on the glucose control but, and specially, on the prevention of type 2 diabetes mellitus evolution and its complications, namely, by beta- cell function preservation. In type 2 diabetes mellitus patients, the effect of the glucose-dependent insulinotropic polypeptide (GIP), as well as the secretion of glucagon like- peptide-1(GLP-1), is diminished or absent, contributing to insulin secretion deficiency [8] .These two incretin are secreted by the intestine [9] .and stimulate insulin secretion by beta-cells, in glucose dependent manner [10] .Sitagliptin is an orally available dipeptidyl peptidase – 4 (DPP-4) inhibitor developed to be used as a once daily treatment of T2DM, has shown beneficial effects on glycemic control, reducing HbA1c, and preventing hypoglycemia, as well as on islets mass and function, with no relevant adverse effects.[11] Considering the vast physiological actions promoted by the incretins, not only related with the control of glucose by insulin and glucagon secretion, but also with insulin sensitization, cardiac and neunoral protection and beta cell preservation, the use of an incretin enhancer (such as sitagliptine) might present beneficial effects on diabetes pathophysiology and on prevention of its serious complications, which deserves better elucidation. The Aim of the study was, to compare the effects of metformin + sitagliptin versus the effects of metformin + glibenclamide on the macrovascular and microvascular complications.

Subjects and Methods:

This study was carried out at Baghdad teaching hospital / Medical city and the National Diabetes Center for Treatment and Research at Al-mustansuriyah University and the private clinic of consultant physician during the period of July 2011-March 2012 .The study was conducted on (100) Iraqi type 2 diabetes mellitus only (68) patients completed the course of study successfully . These 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 regime of treatment. The age of patients for

group (1) ranged from 40 – 59 years (52.5 ± 0.86), of them 20 patients (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) ,of them 20 patients (58.8 %) were male and 14 patients (41.2 %)were female . Diagnosis was made by consultant endocrinologist & ophthalmologist; for patients as having T2DM depending on patients historyclinical examination laboratory investigations and vital signs. For the purpose of comparison, 34 control subjects were enrolled. The age of control for group (3) 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 as having the following criteria: CNS disease, renal dysfunctions, liver dysfunction, and pregnancy with diabetes, concomitant endocrine disease & inflammatory Disease. The urine was collected for estimation of microalbuminurea.

Results:

1.Microalbuminurea

Table 1. Effect of treatment with group 1 (metformin 500 mg 3 times dailly + glibenclamide 5 mg twice daily) and group 2 (metformin 500 mg 3 times daily + sitagliptin 100 mg once daily on the occurrence of microalbuminurea in patients with T2DM and group 3 control normal healthy individuals after 1,3 and 6 months of treatment .(n = 34 individuals for each group).

Groups	Microalbuminurea		
	1st visit	2nd visit	3rd visit
Group 1	25.42%ac	22.13%ac	18.12%a
Group 2	11%abc	9.3%abc	8.5%abc
Group 3	0.00%	0.00%	0.00%

%= Percent

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.

c significant different ($P < 0.05$) as compared 1st, 2nd , and 3rd reading

Table 1 showed comparison between the effects of two groups on microalbuminurea. There were significant ($p<0.05$) decreased in microalbuminurea for group 2 after 3 and 6 months of treatment as compared to 1st reading and to group 1.

Table 2. Parasthesia, numbness and burning sensation of feet.

parameters	Gp 1			Gp 2			Gp 3		
	1st visit	2nd visit	3rd visit	1st visit	2nd visit	3rd visit	1st visit	2nd visit	3rd visit
parasthesia	41.18%ac	39.7%ac	34.36%a	20.94%abc	16.71%abc	8.71%ab	0.00%	0.00%	0.00%
numbness	41.53%ac	35.18%ac	29.29%a	23.34%abc	20.59%abc	8.53%ab	0.00%	0.00%	0.00%
Burning sensation of feet	44.59%ac	37.88%ac	31.18%a	16.5%abc	13.3%abc	7.45%ab	0.00%	0.00%	0.00%

%= Percent

Table.2 shows comparison between the effects of two groups (metformin + glibenclamide and metformin + sitagliptin) treatment on parasthesia, numbness and burning sensation of feet in patients with T2DM .There were significant reduction in parasthesia, numbness and burning sensation of feet for both groups after 3 and 6 months of treatment as compared to 1st reading . However, there is significant decline for group 2 treated by metformin + sitagliptin compared to group 1 treated by metformin + glibenclamide after 3 and 6 months of treatment.

Table 2 Effect of treatment with group 1 (metformin 500 mg 3 times dailly + glibenclamide 5 mg twice daily) and group 2 (metformin 500 mg 3 times daily + sitagliptin 100 mg once daily on the occurrence of numbness,patasthesia and burning sensation of feet in patients with T2DM and group 3 control normal healthy individuals after 1,3 and 6 months of treatment .(n = 34 individuals for each group).

a significantly different ($p< 0.05$) as compared with control values.
b significant different ($P<0.05$) as compared group 2 to 1 .
c significant different ($P<0.05$) as compared 1st, 2nd, and 3rd reading

Table 3. Simple and ptoliferative retinopathy

parameters	Group (1) percentage of effected patients			Group (2) percentage of effected patients			Group (3)		
	1st visit	2nd visit	3rd visit	1st visit	2nd visit	3rd visit	1st visit	2nd visit	3rd visit
Simple retinopathy	16.59a	15.76a	14.65a	9.76ab	7.82 ab	6.22 ab	0.00	0.00	0.00
Proliferative retinopathy	6.65a	6.65a	7.71a	3.76ab	2.82 ab	2.7a b	0.00	0.00	0.00

Table.3 shows comparison between the effects of two groups (metformin + glibenclamide and metformin + sitagliptin) treatment on simple and proliferative retinopathy in patients with T2DM .There were significant reduction in simple and proliferative retinopathy for both groups after 3 and 6 months of treatment as compared to 1st reading. However, there is significant decline 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 treatment with group 1(metformin 500 mg 3 times dailly + glibenclamide 5 mg twice daily) versus group 2 (metformin 500 mg 3 times daily + sitagliptin 100 mg once daily on development of simple and proliferative retinopathy in patients with T2DM and group 3 control normal healthy subjects after 1,3 and 6 months of treatment .(n = 34 subjects for each group)
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.
C significant different (P<0.05) as compared 1st, 2nd, and 3rd reading.

parameters	Group (1) percentage of effected patients			Group (2) percentage of effected patients			Group (3)		
	1st visit	2nd visit	3rd visit	1st visit	2nd visit	3rd visit	1st visit	2nd visit	3rd visit
Postural hypotension	20.59a	18.76a	14.65ac	11.76ab	8.82ab	7.12ab	0.00	0.00	0.00
Ischemic heart disease	17.65a	17.65a	14.71ac	11.76ab	8.82abc	5.88abc	0.00	0.00	0.00

4.Postural hypotension and ischemic heart disease

Table 4. shows comparison between the effects of two groups (metformin + glibenclamide and metformin + sitagliptin) treatment on postural hypotension and ischemic heart disease in patients with T2DM .There were significant reduction in postural hypotension and ischemic heart disease for both groups after 3 and 6 months of treatment as compared to 1st reading . However, there is significant decline for group 2 treated by metformin + sitagliptin compared to group 1 treated by metformin + glibenclamide after 3 and 6 months of treatment.

Table 4 Effect of treatment with group 1(metformin 500 mg 3 times dailly + glibenclamide 5 mg twice daily) versus group 2 (metformin 500 mg 3 times daily + sitagliptin 100 mg once daily on development of postural hypotension, ischemic heart disease1n patients with T2DM and group 3 control normal healthy subjects after 1,3 and 6 months of treatment .(n = 34 subjects for each group)
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

Discussion:

The present study showed that there is significant differences among microvascular and macrovascular complications associated with group of patients receiving metformin + sitagliptin as compared to group of patients receiving metformin + glibenclamide . However , after 3 & 6 months patients treated by metformin + glibenclamide showed significant (p<0.05) increased in postural hypotension, ischemic heart disease (IHD) , retinopathy , nephropathy & neuropathy Our finding consistent with other studies that indicate " good glycemic control can decrease the risk of microvascular , and possibly macrovascular complication , many people with type 2 diabetes are not achieved glycemic goals , partly because of low efficacy and adverse side – effects of available drugs " [12].Further studies indicate that each 1 % reduction in hemoglobin A1c was associated with a 37% decreased in microvascular complication and 21% decreased in the risk of any end point or death related to diabetes .The association with glycemia was less steep for stroke and heart failure , for which blood pressure is a major contributing factor [13-15]. In the patients with the lowest category of

updated mean hemoglobin A1c the incidence of myocardial infarction was higher than that of microvascular disease[16] .These results suggest that , in these people , the effect of hyperglycemia itself may account for at least part of the excess cardiovascular risk observed in diabetic compared with non – diabetic people beyond that explained by the conventional risk factors of dyslipidemia , hypertension , and smoking [17] . The rate of increase of relative risk for microvascular disease with hyperglycemia was greater than that for myocardial infarction , which emphasizes the crucial role of hyperglycemia in the etiology of small vessels disease and may explain the greater rate of microvascular complications seen in populations with less satisfactory control of glycemia [18] .In reality , it is difficult to obtain and maintain near normal concentrations of hemoglobin A1c in patients with type 2 diabetes , particularly in those with a high concentration of hemoglobin A1c at diagnosis of diabetes [19]. The newest classes of antidiabetic drugs are the dipeptidyl peptidase- 4 (DPP-4) inhibitors. Some diabetes experts are already suggesting these as agents of choice when cardiovascular health or the possible effects of hypoglycemia are a worry [20]. In the UK, the National Center for Health and Clinical Excellence (NICE) has issued draft guidelines proposing their use as second – line therapy for this reason. However , there are as yet been no prospective trials evaluating the impact of DPP-4 in patients with established heart disease or cardiovascular risk factors . Another study, using a model of obese T2DM (the ZDF rat) , demonstrated that chronic inhibition of DPP-4 by sitagliptin can correct the glycemic dysmetabolism , hypertriglyceridemia , inflammation and hypertension , reduce severity of histopathological lesions of endocrine and exocrine pancreas , jointly with favorable influence on the pancreas and heart lipid peroxidation , which have been identified as the key pathophysiological mechanism underlying insulin resistance , beta – cell degradation and associated micro- and macrovascular complications . These influences here reported may become further advantages in the therapeutics of type 2 diabetes in the prevention / management of its proatherogenic macrovascular complications [21] . Sitagliptin – metformin combination therapy may have impact on beta – cell function . However , long term studies will be needed to determine if the improvement in markers of beta cell function will translate in to preservation of beta cell mass or greater durability of glycemic control than that seen with more traditionally prescribed therapies. As is required of all new antihyperglycemic therapies , the long term cardiovascular safety of sitagliptin is currently under evaluation in TECOS (Trial of Evaluate Cardiovascular Outcomes After Treatment with Sitagliptin) .Inclusion of a large number of patients on the combination of sitagliptin and metformin is expected [22] . Although the data available from clinical trials of sitagliptin to date have not raised concern about the drugs cardiovascular safety , sitagliptin trials prior to TECOS were of relatively short duration , did not consistently enroll a high cardiovascular risk population , and were not designed to assess reliably the cardiovascular impact of sitagliptin [23] . No major trials of DPP-4 inhibitors looking at cardiovascular outcomes have been announced although there may be several small studies in academic center, e.g. , a small study at the karolinska Institute plan to investigate treatment in a small number of patients with MI or angina pectoris and another at Stanford University is looking at effects in patients with heart failure [24-25].Sulfonylurea showed a reduction of microvascular complications in type 2 DM patients in theUKPDS[26]. In the largest study to date, the UKPDS, no significant benefit or harm was seen in newly diagnosed type 2 DM patients given sulfonylureas over 10 years. The University Group Diabetes Program study documented higher rates of coronary artery disease in type 2 patients given tolbutamide, when compared to patients given insulin or placebo, although this study has been widely criticized[27,28] . Some sulfonylureas bind to the SUR- 2A receptor that is found in cardiac tissue. Binding to the SUR-2A receptor has been implicated in blocking ischemic

preconditioning via K+ channel closure in the heart. Ischemic preconditioning is the premise that prior ischemia in cardiac tissue can provide greater tolerance of subsequent ischemia .Thus patients with heart disease potentially have one compensatory mechanism to protect the heart from ischemia blocked. Conclusions are controversial, and readers are referred to the pertinent articles for further discussion [29.–31].

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