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Comparative Effects of Glibenclamide and Metformin on C-Reactive Protein and Oxidant/Antioxidant Status in Patients with Type II Diabetes Mellitus

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مقارنة تأثيرات الكليبنكلاميد مع الميتفورين على البروتين التفاعلي نوع (ج) وحالة الأكسدة/ مضادات الأكسدة عند مرضى السكري من النوع الثاني

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الملخص: **الهدف**: تهدف هذه الدراسة الى مقارنة تأثيرات الميتفورمين والكليبنكلاميد على البروتين التفاعلي عالي الحساسية نوع (ج) وضغط الأكسدة (ممثلا بالمالوندياليهايد وحالة مُضادات الأكسدة الكليّة) في مصل الدم عند مرضى السكري من النوع الثاني حديثي التشخيص في البداية، وبعد مرور شهرين من العلاج بالمقارنة مع المجموعة الضابطة. **الطريقة**: تطوّع في هذه الدراسة 103 مريضا مصابا بالسكري من النوع الثاني حديثي التشخيص من مركز الوفاء للبحوث وعلاج السكري، للفترة من تشرين الثاني/نوفمبر 2009 إلى كانون الثاني/يناير 2011، تم علاج 53 منهم بدواء الميتفورمين، بينما أعطي الباقون (50 مريضا) دواء الكليبنكلاميد. ضمّت المجموعة الضابطة 40متطوعا من الأصحاء. سُحبت عيّنات الدم من المشاركين بعد صيام الليل، وتم عزل عينات المصول وقياس مستويات البروتين التفاعلي عالي الحساسية نوع (ج) ، المالوندياليهايد وحالة مضادات الأكسدة الكليّة. بعد شهرين من العلاج الأحادي تم سحب عينة دم ثانية وإعادة الفحوصات أعلاه. **النتائج**: كانت هناك فروقا إحصائية مُعتدّة بين المرضى المعالجين بالميتفورمين والكليبنكلاميد والمجموعة الضابطة بالنسبة لكل من البروتين التفاعلي عالي الحساسية نوع (ج)، والمالوندياليهايد وحالة مضادات الاكسدة الكليّة، حيث كان هناك انخفاضا إحصائيا مُعتدًا في مستوى المالوندياليهايد مع ارتفاع مُعتد من الناحية الإحصائية في مستوى مضادات الأكسدة الكليّة مع عدم وجود تاثير معتدّ إحصائيا على مستوى البروتين التفاعلي عالي الحساسية نوع ج بعد الميتفورمين ولكن لم يكن هنالك تاثير مُعتدّ على تلك المفردات بعد الكليبنكلاميد. نسبة الاختلاف في هذه المفردات بعد العقارين أظهرت ارتفاعا معتدًا في مستوى مضادات الأكسدة الكليّة مع علاج الميتفورمين وتأثير غير معتد على مستوى المالوندياليهايد والبروتين التفاعلي عالي الحساسية نوع (ج). **الخلاصة**: أظهر الميتفورمين تاثيرا إيجابيا على الموازنة بين الاكسدة/مضادات الاكسدة في مرضى السكري من النوع الثاني حديثي التشخيص مع عدم وجود تأثير معتدّ على مستوى البروتين التفاعلي عالي الحساسية نوع (ج). من جهة أخرى لم يكن للكليبنكلاميد تأثير معتدّ على حالة الموازنة بين الأكسدة/مضادات الأكسدة ومستوى البروتين التفاعلي عالي الحساسية نوع (ج).

مفتاح الكلمات: مرض السكري، الميتفورمين، الكليبنكلاميد، المالوندياليهايد، حالة مضادات الأكسدة الكليّة، البروتين التفاعلي عالي الحساسية نوع (ج).

ABSTRACT: ***Objectives:*** This study aimed to compare the effects of metformin and glibenclamide on high sensitivity serum C-reactive protein (hs-CRP) and oxidative stress, represented by serum malondialdehyde (MDA) and total antioxidant status (TAS) in newly-diagnosed patients with Type 2 diabetes mellitus (DM) at baseline and after 2 months of therapy in comparison to controls. ***Methods:*** The subjects, recruited from Al-Wafaa Centre for Diabetes Management and Research, Iraq, November 2009 to January 2011, were 103 newly-diagnosed Type 2 DM patients; 53 were prescribed metformin and 50 glibenclamide. The control group was 40 apparently healthy volunteers. Blood samples were taken from all subjects after overnight fasting. Sera were separated and assays of hs-CRP, MDA and TAS were done. After 2 months monotherapy, the blood samples and assays were repeated. ***Results:*** There were significant differences between patients prescribed metformin and glibenclamide and the controls with regard to serum hs-CRP, MDA and TAS. There was a significant reduction in the serum MDA and a significant raise in the serum TAS levels, with no significant effects on serum hs-CRP levels after metformin therapy, but no significant effects on these parameters after glibenclamide therapy. The percentage of variation in these parameters after both drugs, showed a significant raise in serum TAS levels with the metformin therapy with no significant effects in serum MDA and hs-CRP. ***Conclusion:*** Metformin positively affected the oxidant/antioxidant balance in newly-diagnosed Type 2 DM patients with no significant effects on acute phase reaction protein. Glibenclamide had no

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significant effects on oxidant/antioxidant balance and acute phase reaction protein.

Keywords: Diabetes mellitus; Metformin; Glibenclamide; Malondialdehyde (MDA); Total antioxidant status (TAS); High sensitivity serum C-reactive protein (hs-CRP).

Advances in Knowledge

1. *Type II diabetes mellitus is shown by this study to be associated with oxidative stress and metformin (an oral hypoglycaemic agent) to have a positive effect on oxidant/antioxidant balance.*

Applications to Patient Care

1. *Metformin possesses an advantage over glibenclamide with regard to the effects on oxidant/antioxidant status.*

Type II diabetes mellitus (DM) is extremely common and increasing rapidly worldwide. The diabetes epidemic is driven, in part, by a parallel epidemic of obesity.[1] Inflammation has been strongly implicated in Type II DM.[2] Long-term cytokine-mediated acute-phase response has been postulated to play an important role in the pathogenesis of Type II DM.[3] Oxidative stress (OS) has been suggested to play an important role in the development and progression of diabetes mellitus.[4,5] It has been suggested that in diabetic patients a major factor responsible for enhanced free radical generation is hyperglycaemia[6] through auto-oxidation of glucose[7] and production of advanced glycation end products (AGEs),[8] which is known to progress at an extremely accelerated rate in Type II DM.[9]

Metformin is recommended as an oral hypoglycemic core therapy in diabetes management worldwide and the guidelines of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend its use in patients irrespective of age, body weight and degree of baseline hyperglycaemia, due to its favourable effect on metabolic indices of glucose, lipid, and weight control.[10] On the other hand, glibenclamide is a well-known second generation sulfonylurea (SU) that has been the mainstay for treatment of patients with Type II DM for years.[11] The aim of this study was to assess and compare the effects of metformin and glibenclamide on acute phase protein (represented by high sensitivity serum C-reactive protein [hs-CRP]) and on oxidative/antioxidant status (represented by serum malondialdehyde [MDA] and total antioxidant status [TAS]) in newly-diagnosed patients with Type II DM at baseline and after 2 months of therapy.

Methods

The study was conducted at Al-Waffaa Center of Diabetes Management and Research in Mosul City, Iraq, from November 2009 to January 2011. It was approved by the Regional Research Committee of Mosul Health Administration, A follow-up design was adopted for the study.

Fifty-three patients newly-diagnosed with Type II DM were selected and prescribed metformin monotherapy (Dialon, Julphar, United Arab Emirates). They were 23 females and 30 males with a mean age of 51.27±9.07 years, and a body mass index (BMI) of 29.18±2.86. Another 50 newly-diagnosed patients with Type II DM were also recruited in this study and were prescribed glibenclamide monotherapy (Glibesyn, Medochemie, Cyprus). They were 25 females and 25 males with a mean age of 49.40±7.81 years, with a mean BMI of 26±2.70.

Inclusion criteria included: newly-diagnosed cases of Type II DM with fasting glucose ≥7.00 mmol/L (126 mg/dL, or 2-hour post-load glucose ≥11.1 mmol/L [200 mg/dL]) in accordance with the ADA and the World Health Organization (WHO) diagnostic criteria for Type II DM.[12,13] Patients excluded from this study were pregnant or lactating women, those requiring insulin, or a combination of oral hypoglycemic therapy, or those known to have hypertension, or cardiac, renal or hepatic disorders.

Forty apparently healthy volunteers were also recruited as a control group. They were 21 females and 19 males, with a mean age of 46.90±11.91 years and a mean BMI of 26.90±2.77.

The sampling was performed as follows. At 8.30 am, 5 ml venous blood samples were taken from both the diabetic patients and control subjects after overnight fasting. Sera were separated and measurements of hs-CRP, MDA and TAS were

done. After 2 months of monotherapy, repeated blood samples were taken and the same parameters measured using the same kits and the same analytical methods: 1) hs-CRP was measured by enzyme–linked immunosorbent assay (ELISA), using BioCheck hs-CRP ELISA kit (BioCheck Inc., California, USA); 2) Serum MDA was measured using the thiobarbituric acid (TBA) assay method;[14] 3) Serum TAS was measured according to the method of Miller *et al.*[15] using a kit supplied by Randox Laboratories (Co. Antrim, Ireland), and 4) BMI was calculated according to the following equation: BMI = weight (kg)/height (m2).[16]

Standard statistical methods were used to determine the mean and standard deviation (SD). The unpaired t-test was used to compare the results of various parameters between diabetic patients and controls and to between diabetic patients on metformin and those on glibenclamide monotherapy. The paired t-test was used to compare the results of various parameters between diabetic patients before and after therapy. A *P* value of ≤0.05 was considered to be statistically significant.[17]

Results

There were significant differences between patients prescribed metformin [Table 1], glibenclamide therapy [Table 2] and the control subjects with regard to serum hs-CRP, MDA and TAS.

There was a significant reduction in serum MDA with a significant rise in the serum TAS levels and an insignificant effect on serum hs-CRP after metformin therapy [Table 3]. Patients on glibenclamide therapy showed non-significant differences with regard to serum levels of MDA,TAS and hs-CRP [Table 4].

There was a significant rise in the serum TAS levels after metformin therapy compared to glibenclamide therapy, while no significant effects on serum MDA and hs-CRP levels were found [Table 5].

Table 1: Comparison between patients prescribed metformin therapy and controls with regards to serum levels of high sensitivity serum C-reactive protein (hs-CRP), malondialdehyde (MDA) and total antioxidant status (TAS)

Parameters	Mean ± Standard Deviation		*P* value
	Controls	Patients prescribed metformin	
hs-CRP (µg/ml)	1.66±0.81	6.95±3.19	<0.05
MDA (µmol/ L)	1.09±0.13	1.70±0.36	<0.05
TAS (mmol/ L)	2.41±0.30	2.17±0.41	<0.05

Note: Comparison done using unpaired t-test.

Table 2: Comparison between patients prescribed glibenclamide therapy and controls with regards to serum levels of high sensitivity serum C-reactive protein (hs-CRP), malondialdehyde (MDA) and total antioxidant status (TAS)

Parameters	Mean ± Standard Deviation		*P* value
	Controls	Patients prescribed glibenclamide	
hs-CRP (µg/ml)	1.66±0.81	4.95±2.71	<0.05
MDA (µmol/ L)	1.09±0.13	1.76±0.26	<0.05
TAS (mmol/ L)	2.41±0.30	1.33±0.31	<0.05

Note: Comparison done using unpaired t-test.

Discussion

The results of the present study showed no significant decrease in serum hs-CRP levels in newly-diagnosed patients with Type II DM after two months metformin therapy, and only insignificant differences in serum hs-CRP levels in diabetic patients on glibenclamide therapy.

In regard to metformin therapy, our findings were in accordance with the results of previous studies,1[8-20] while the results of the glibenclamide therapy were in agreement with the study conducted by Yudkin, *et al.* who found that markers of acute phase activation measured by concentrations of CRP in patients with Type II DM were not significantly influenced by SU.[21] Moreover, these findings were in concordance with those reported by Derosa *et al.* who reported that no variations in hs-CRP levels were observed in patients with Type II DM treated with glibenclamide.[22]

On the other hand, Akbar found that serum CRP level in well-controlled Type II DM patients with metabolic syndrome was significantly lower in patients using metformin compared with those using glibenclamide; he concluded that metformin

Table 3: Comparison of serum levels of high sensitivity serum C-reactive protein (hs-CRP), malondialdehyde (MDA) and total antioxidant status (TAS) for patients before and after metformin therapy

Parameters	Mean ± Standard Deviation		*P* value
	Patients before metformin therapy	Patients after metformin therapy	
hs-CRP (µg/ml)	6.95±3.19	6.12±2.71	NS
MDA (µmol/ L)	1.70±0.36	1.57±0.31	<0.05
TAS (mmol/ L)	2.17±0.41	2.35±0.43	<0.05

NS = Not significant using paired t-test

Table 4: Comparison of serum levels of high sensitivity serum C-reactive protein (hs-CRP), malondialdehyde (MDA) and total antioxidant status (TAS) for patients before and after glibenclamide therapy.

Parameters	Mean ± Standard Deviation		*P* value
	Patients before glibenclamide therapy	Patients after glibenclamide therapy	
hs-CRP (µg/ml)	4.95± 2.71	5.46± 2.76	NS
MDA (µmol/ L)	1.76± 0.26	1.73± 0.26	NS
TAS (mmol/ L)	1.33± 0.31	1.35± 0.26	NS

NS = Not significant using paired t-test

produces a greater decrease in the level of circulating CRP than glibenclamide.[23] Kahn, *et al.* reported that the reduction in serum hs-CRP in patients recently diagnosed with Type II DM was greater with metformin monotherapy (26%) versus glyburide (10%) after 12 months of therapy.[24]

This study showed a significant elevation in serum MDA levels (P <0.001) in patients with Type II DM prescribed metformin therapy compared to their matched healthy controls. OS is proposed to be an early event in the pathology of DM and may influence the onset and progression of late complications.[25] Furthermore, elevated levels of serum MDA, as a marker of OS, have been reported in Type II DM.[26]

Conflicting data were obtained regarding the effects of metformin on OS in diabetic patients.[27] The present work revealed a significant decrease in serum MDA levels in newly-diagnosed Type II DM patients after a 2-month therapy with metformin. These results were in agreement with the study conducted by Pavlovic, *et al.* who reported a significant reduction in MDA levels in both erythrocytes and plasma in newly-diagnosed patients with Type II DM who had been on metformin therapy for a period of 4 weeks.[28] These results were also in line with those reported by Tessier *et al.* who observed that metformin therapy significantly decreased serum MDA levels in adult patients with Type II DM after a period of treatment for 24 weeks.[29]

Conversely, Skrha *et al.* observed that 3-month therapy with metformin was accompanied by significantly increased plasma MDA levels in Type II DM patients.[30] They concluded that initiation of metformin treatment in such patients was associated with activation of OS. Gupta *et al.*, observed no change in MDA levels at the end of the 12 weeks treatment with metformin, in newly-diagnosed Type II DM patients.[31]

The present study also revealed a significant increase (P <0.05) in TAS of newly-diagnosed Type II DM patients after a 2-month metformin therapy, which is consistent with those reported by Tessier *et al.*[29] They observed that a 24-week therapy with metformin significantly increased serum levels of antioxidant vitamin E in adult patients with Type II DM. This is in agreement with the results of Pavlovic *et al.* who reported that metformin significantly increased the erythrocyte activities of copper, zinc, superoxide dismutase, catalase and glutathione (GSH) levels, and decreased erythrocyte susceptibility to OS in patients with Type II DM.[28] In line with these studies, *Skrha et al.* observed that 3 months of metformin treatment

Table 5: Percentage of variations in measured parameters after metformin and glibenclamide therapy

Parameters	(% variations after therapy) Mean ± Standard Deviation		*P* value
	Glibenclamide group	Metformin group	
hs-CRP (µg/ml)	0.51±2.94	-0.83±1.9	NS
MDA (µmol/ L)	-0.03±0.09	-0.13±0.20	NS
TAS (mmol/ L)	0.01±0.07	0.19±0.33	<0.05

NS = Not significant using unpaired t-test

was accompanied by significantly increased ascorbic acid concentrations and concluded that initiation of metformin treatment in Type II DM patients was associated with activation of the antioxidant system.[30]

With regards to glibenclamide therapy, this study showed an insignificant decrease in serum MDA levels in newly-diagnosed Type II DM patients after a 2-month therapy. These findings were in agreement with those reported by Stefanovic *et al*.[32] They reported no significant decrease in the plasma MDA levels of patients treated with glibenclamide at the end of 3 months treatment. On the other hand, Chugh *et al.* reported a significant fall in serum MDA levels in patients with Type II DM at the end of 12 weeks using glibenclamide, although the MDA levels were not normalised and stayed higher than those in controls.[33] This study also showed an insignificant increase in TAS levels of newly-diagnosed Type II DM patients after therapy with glibenclamide. These results were in line with those mentioned by Jennings *et al.* who found no significant difference in red blood cell superoxide dismutase activity, or in plasma thiols (PSH) levels, in Type II DM patients with retinopathy after 3 months of treatment with glibenclamide.[34] Similarly, Chugh *et al*. reported increased levels of GSH in patients with Type II DM at the end of a 12-week glibenclamide treatment period and concluded that this revealed beneficial effects on OS, although normalisation was not achieved.[33]

The present study showed an insignificant decrease in serum MDA levels, with a significant increase in TAS in patients treated with metformin compared with those treated with glibenclamide. This is in line with the findings of the study conducted by Faure *et al*.[35] They found that the MDA levels were significantly lower in metformin-treated Type II DM patients compared to those treated with SU. It is possible that the short-term treatment durations in our study may have influenced the endpoints of the present study.[36]

With regard to antioxidant status, our findings were in agreement with Faure *et al.*[35] where there was a significant increase in antioxidant protection, as shown by TAS, total blood GSM and plasma thiols in patients with Type II DM receiving metformin compared with those receiving SU, and those authors concluded that a significant protection of serum albumin was found in patients with Type II DM treated with metformin, and that this leads to an increased antioxidant protection.

Conclusion

This study has shown that metformin therapy for 2 months in newly-diagnosed Type II DM patients positively affected the oxidant/antioxidant balance while having insignificant effects on acute phase reaction protein. On the other hand, glibenclamide had insignificant effects on the oxidant/antioxidant balance and on acute phase reaction protein.

CONFLICT OF INTEREST

The authors reported no conflict of interest.

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This study was conducted at the Al-Wafaa Centre for Diabetes Management and Research, Mosul, Iraq, during the period November 2009 to January 2011. The laboratory work was done in the Department of Pharmacology, College of Medicine, University of Mosul, Iraq.

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