Effects of Glibenclamide and Metformin on serum uric acid levels in patients with type 2 diabetes mellitus

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ABSTRACT

Objectives: To assess the effect of Glibenclamide and Metformin on serum uric acid level in patient with type 2 diabetes.

Study design: case control study.

Study period: from March 2009 to January 2010.

Subjects and Methods: Fasting blood sugar and serum uric acid level were measured in patient suffering from type 2 diabetes mellitus who were referred to Al-Wafa Diabetic Center in Mosul City: (group 1) 32 patients on glibenclamide therapy, (group 2) 42 patients on metformin therapy and (group 3) 42 patients on combination therapy, (group 4)32 patients on restricted diet, and 23 apparently healthy volunteers, were taken as a control group.

Results: Study showed a significant increase in the serum uric acid level of the diabetic patients as compared with the control. glibenclamide and/or metformin showed no significant difference in the serum uric acid level in patients with type 2 diabetes mellitus.

Conclusion: glibenclamide and / or metformin had no significant effect on serum uric acid level in patients with type 2 diabetes mellitus.

Key Words: Uric Acid, Hyperuricemia, type 2 diabetes mellitus, glibenclamide, metformin.

الخلاصة

أهداف البحث: لدراسة تأثير عقار الميتفورمين و عقار الكلايبينكلامايد على حامض اليوريك في مصل المرضى المصابين بداء السكري النمط الثاني.

تصميم الدراسة: دراســـة عينية مقارنة.

فترة الدراسة: من آذار ٢٠٠٩ الى كانون الثاني٢٠١٠.

الطرق المتبعة والأشخاص: تم قياس تركيز الكلوكوز في مصل الدم وقياس مستوى حامض اليوريك في مصل الدم لمجموعات المرضى المصابين بداء السكري النمط الثاني اللذين يراجعون مركز الوفاء للسكري : (المجموعة الأولى) ٣٢ مريض تحت علاج الكلايبينكلامايد ، (المجموعة الثانية) ٤٢ مريض تحت علاج الميتفورمين، (المجموعة الثالثة) ٤٢ مريض تحت علاج الكلايبينكلامايد والمتفورمين معا، (المجموعة الرابعة) مريض ٣٢ على الحمية و مجموعة الضبط ٢٣ مريض من الاصحاء غير السكريين .

النتائج: اظهر مرض السكري النمط الثاني ارتفاعا في حامض اليوريك كمقارنة مع مجموعة الضبط .لم يظهر عقار الميتفورمين او الكلايبينكلامايد أي تأثير معنوي على مستوى حامض اليوريك في مصل المرضى المصابين بداء السكري النمط الثاني .

الاستنتاج: لا يوجد تأثير للمتفورمين أو الكلابينكلامايد على مستوى حامض اليوريك في مصل الدم في مجموعات المرضى المصابين بداء السكري النمط الثاني .

Uric acid is the final catabolic, heterocyclic purine derivative resulting from the oxidation of purines in humans. Due to the loss of hepatic uricase activity during human evolution, uric acid is excreted as such and is not further metabolized into carbon dioxide and ammonia. A major

mechanism underlying hyperuricemia is impaired renal excretion of urate[1].There has been growing interest in the association of hyperuricemia with hyperglycemia[2]. uric acid may be a marker of oxidativestress[3] and may have a potential therapeutic role as an antioxidant[4,5]. Like other strong reducing substances such as ascorbate, uric acid can also act as a prooxidant particularly at elevated levels.

Patients with non-insulin-dependent diabetes mellitus (NIDDM) are at increased risk for cardiovascular diseases such as hypertension and stroke. Hyperuricemia is a common finding in NIDDM, but its significance as an independent risk factor for cardiovascular disease has remained uncertain[6,7], serum uric acid level is positively associated with the development of type 2 diabetes regardless of various study characteristics. Further research should attempt to determine whether it is effective to utilize serum uric acid level as a predictor of type 2 diabetes for its primary prevention[8].

The association of high serum uric acid with insulin resistance has been known since the early part of the 20th century, nevertheless, recognition of high serum uric acid as a risk factor for diabetes has been a matter of debate. In fact, Hyperuricemia has always been presumed to be a consequence of insulin resistance rather than its precursor[8]. Elevated levels of uric acid should alert physicians to the possibility of insulin resistance. The serum uric acid level was associated with insulin resistance and plasma glucose levels more strongly in females than in males in our study population[9]. serum uric acid is positively associated with serum glucose in healthy subjects[10].

Evidence has accumulated indicating that the generation of reactive oxygen species (oxidative stress) may play an important role in the etiology of diabetic complications. This hypothesis is supported by evidence that many biochemical pathways strictly associated with hyperglycemia (glucose autoxidation, polyol pathway, prostanoid synthesis, protein glycation) can increase the production of free radicals[11].

Drugs with other primary uses, that have known uricosuric properties which decrease serum uric acid levels, such as losartan[12], fenofibrate[13,14], where as diuretic[15] pyrazinamide[16], elevate serum uric acid levels.

The present study was conducted to investigate the effect of glibenclamide and metformin on serum uric acid level in a number of type 2 diabetic patients.

Patients and methods

This is a case-control study which was conducted in the Department of Pharmacology, College of Medicine,Univrsity of mosul and Al-Wafa Diabetic Center in Mosul from March, 2009 to January, 2010. Five groups were enrolled for this study: the first group included 32 type 2 diabetic patients , their ages ranged between (32-70 years) treaded with glibenclamide, the second group included 42 type 2 diabetic patients, their ages ranged between (27-75 years) treated with metformin, the third group included 42 type 2 diabetic patients, their ages ranged between (42-66 years) treated with combination of these two drugs (glibenclamide and metformin), the fourth group included

32 type 2 diabetic patients on restricted diet therapy only, their ages ranged between (28-85 years) and the fifth group included 23 apparently healthy volunteers participated as a control group, their ages ranged between (28-56 years) .

Five ml of venous blood samples were collected from each individual (patient and control) after at least 12 hours fasting. Fasting blood sugar was measured using a glucose oxidase method[17] which is available as a kit manufactured by Biomaghreb. Serum uric acid was assessed by uricase enzymatic method[18] by using a special kit (Biolabo).

Statistical analysis

The values were quoted as mean ± SE. P-values <0.05 was considered to be statistically significant. Unpaired- test was used to compare the data obtained in this study.

Results

Table 1 shows the characteristics of the study participants. The table shows the ages of the individual and the number of males and females in the five groups.

Comparison between fasting blood sugar and serum uric acid level of Glibenclamide, Metformin, combination and diet groups with those of the control showed a significant elevation of all parameters. Comparison of fasting blood sugar and serum uric acid level of glibenclamide, metformin and combination groups with those of diet showed a significant elevation for fasting blood sugar and a non significant differences for serum uric acid level. Comparison between fasting blood sugar and serum uric acid level of glibenclamide and metformin, no significant differences were found between them. (Table 2)

Table 1.The characteristic of study participants

CHARACTERISTIC	Control group N=23	Glibenclamide group N=32	Metformin group N=42	Combination group N=42	Diet group N=32
Sex M	8	21	20	23	19
F	15	11	22	19	13
Age (year)	28-56	32-70.	27-75	42-66	28-85
	45 ±2.4	50±2.0	47 ±1.6	44±1.3	50±2.1

Table 2. The comparison between different groups

Parameters	Control group	Glibenclamide group	Metformin group	Combination group	Diet group
Fasting blood sugar (mmol/l) All groups and Control	5.32±0.24	12.87±1.28 **	11.02±0.75 **	10.97±0.62 **	9.74±0.74 **
Serum uric acid (µmol/l) All groups and Control	265.95±17.52	404.18±27.39 **	470±61.01 *	452±38.35 **	461±28.39 **
Fasting blood sugar (mmol/l) All groups and Diet	---	12.87±1.28 *	11.02±0.75 **	10.97±0.62 *	9.74±0.74
Serum uric acid (mmol/l) All groups and Diet	---	404.18±27.39 P=0.15 (NS)	470.04±61.01 P=0.9 (NS)	452±38.35 P=0.85 (NS)	461±28.39
Fasting blood sugar (mmol/l) Glibenclamide and Metformin	---	12.87±1.28 P=0.219 (NS)	11.02±0.75 P=0.219 (NS)	---	---
Serum uric acid (mmol/l) Glibenclamide and Metformin	---	404.18±27.39 P=0.32 (NS)	470.04±61.01 P=0. 32 (NS)	---	---

(NS) Non significant, * P <0.05, ** P <0.01

Discussion

Hyperuricemia has previously been described as strong predictor of well defined cerebrovascular complications in patients with type 2 diabetes[7].

The present study showed a significant elevation of serum uric acid level of the diabetic patients as compared with the control individuals. The patients are hyperglycemic, as evident by the high concentration of fasting blood sugar.

Variations in uric acid levels have been increasingly associated with insulin resistance, hyperinsulinemia, and diabetes[19, 20]. In 2009, a study was conducted by kodama and saito[8], they reported that uric acid levels are higher in subjects with prediabetes and early type 2 diabetes than in healthy. In type 2 diabetes, Hyperuricemia seems to be associated with the insulin-resistant syndrome and with early onset or increased progression to overt nephropathy, while hypouricemia is associated with worse metabolic control, hyperfiltration and a late onset or decreased progression to overt nephropathy[21], Interestingly, serum

uric acid levels were increased in type 2 diabetic patients and this phenomenon seemed to be more profound in male diabetic patients[22].

This study is in contrast to the study conducted by Gotoh et al, they reported that serum uric acid levels in diabetics are significantly lower than those in non-diabetic subjects[23].

The finding of this study showed no significant difference between serum uric acid levels of diet group with glibenclamide, metformin group, this findings are similar to those of Luque etal, where they reported that there was no change in serum uric level observed with metformin for treatment of polycystic ovary syndrome[24], so as the study done by Fruehwald and Oltmanns[25].

In contrast to these results, Gregorio and Manfrini in 1996, reported that metformin lowered uric acid in elderly type 2 diabetic patients[26]. Gokcel and Gumurdulu in research concerning the evaluation of the safety and efficacy of metformin in the treatment of obesity, they reported that metformin administration resulted in a significant reduction in serum uric acid levels in obese patients[27]. Barskova etal reported that metformin reduce production of uric acid in patient with gout and insulin resistant[28].

The present study revealed that glibenclamide had no significant effect on serum uric acid levels in patients with type 2 diabetes. These finding are similar to the studies conducted by Cheach[29], and Carvalho[30]. Their findings might indicate that, hypoglycemic agents have no effect on the serum uric acid level of the diabetic patients and does not affect the balance between urate production and renal excretion.

Conclusion glibenclamide, metformin or their combination had no significant effect on serum uric acid level in patient with type 2 diabetes mellitus as evident by non significant differences between patients taking these drugs and patients on diet only.

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