The effect of metformin on some liver function tests in type 2 diabetic patients

Islam T.Q. Al-Mola*, Faris A. Ahmed**

Department of Pharmacology, *College of Pharmacy, ** Nineveh college of Medicine, University of Mosul

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ABSTRACT

Objectives: To study the effect of metformin on serum glucose and some liver function tests including serum alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin in type 2 diabetic patients.

Design: Case-control study.

Setting: The study was carried out in Al-Waffa centre for diabetes in Mosul, during the period from March 2004 to December 2004.

Participants: Fifty type 2 diabetic patients treated with metformin were included. In addition, two control groups were used, 50 nontreated diabetic patients and 50 apparently healthy subjects.

Results: Serum glucose in metformin treated diabetics was lower ($P<0.05$) than the nontreated diabetics; however, ALP and ALT were higher ($P<0.05$) in the treated diabetics. At the same time, AST and bilirubin did not change by metformin by using Duncan test.

Conclusion: Metformin causes increase in some liver function tests. Therefore, patients treated with metformin should be periodically examined for the liver function tests.

الخلاصـــة

أهداف البحث: لدراسة تأثير عقار المتفورمين على الكلوكوز في مصل الدم وبعض فحوصات كفاءة الكبد والتي تشمل الأنزيم الفوسفاتي القاعدي وامينوترانسفريز الالنين وامينوترانسفريز الاسبارتيت والبليروبين في مصل مرضى السكر نوع ٢.

التصميم: مقارنة الحالات العلاجية مع الحالات الضابطة.

مكان إجراء الدراسة والإطار الزمني لها: نفذت الدراسة في مركز الوفاء للسكر في الموصل خلال الفترة من آذار ٢٠٠٤ ولغاية كانون أول ٢٠٠٤.

المشاركون في البحث: شمل هذا البحث على خمسين مريض مصاب بداء السكر نوع ٢ وتحت علاج عقار الميتفورمين وعلى خمسين مريض مصاب بداء السكر نوع ٢ من دون علاج بالإضافة إلى خمسين مريض من الأفراد الأصحاء ظاهرياً كمجموعة سيطرة.

النتائج: كان مستوى الكلوكوز في مصل مرضى السكر وتحت علاج الميتفورمين أقل (ب< ٠,٠٥) منه في مرضى السكر دون علاج، بينما كانت فعالية الانزيم الفوسفاتي القاعدي وأنزيم امينوترانسفيريز الالنين في مصل مرضى السكر وتحت علاج الميتفورمين أعلى (ب<٠,٠٥) منه في مرضى السكر دون علاج. وفي نفس الوقت لم يتغير أنزيم امينوترانسفيريز الاسبارتيت والبليروبين في مصل مرضى السكر وتحت علاج المتفورمين باستعمال اختبار دنكن.

الاستنتاج: إن عقار المتفورمين يسبب زيادة في بعض فحوصات كفاءة الكبد ولذلك على مرضى السكر تحت علاج الميتفورمين ان يخضعوا بضرورة دورية لاختبارات وظيفة الكبد.

Metformin is the drug of choice in the treatment of type 2 diabetes mellitus.[1] Metformin is associated with a lower incidence of morbidity and diabetic related morbidity.[2,3]

Metformin produced an elevation in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in diabetic patients.[4] Swislocki and North[5] found that metformin increased alkaline phosphatase (ALP), ALT and AST without any change in bilirubin level. However, Desilets et al.[6] showed an elevation of bilirubin in diabetic patients treated by metformin. This elevation in bilirubin returned to normal level after metformin was withdrawn. Furthermore, acute hepatitis was induced by metformin in type2 diabetic patients.[7] The hepatotoxicity induced by metformin was due to idiosynacratic adverse reaction to metformin or its metabolites.[8]

This study was done to evaluate the effect of metformin on serum ALP, ALT, AST, bilirubin and glucose in diabetic patients.

Patients and methods

This study was carried out in Al-Waffa center for diabetes in Mosul from March 2004 to December 2004. Three groups were included in this study of 50 subjects each. The first group included 50 diabetic patients, their ages ranged between 38 and 55 years (mean±SD 48.7±7.8 years). The patients have received metformin (Glucosam®, SDI, Iraq) monotherapy for at least 6 months, the duration of treatment was between 6 and 24 months (13.6±6.5 months) with daily dose range of 500-1000 mg/day. The second group included 50 diabetic patients, newly diagnosed before treatment, their ages ranged between 37 and 60 years (49.2±9.1 years). The third control group included 50 apparently healthy subjects, their ages ranged between 30 to 60 years (46.5 ± 10.1 years). Patients and controls under other medications or any suggestive disease were excluded from this study.

Blood samples were taken from patients and controls after overnight fasting and analysed for serum glucose, ALP, ALT, AST and bilirubin by colourimetric method.[9-12] Commercial kits were obtained from syrbio/Syria.

Data was represented by mean ±SD. ANOVA was used to find the difference between groups then Duncan test was used to find the factor effect.

Results

Table 1 shows that metformin decreased blood glucose ($P<0.05$); however, ALT, ALP and bilirubin were increased significantly ($P<0.05$). At the same time, AST was not changed by metformin. These results were compared with the measurements obtained from diabetic nontreated group.

In diabetic patients only blood glucose was higher ($P<0.05$) than that in non-diabetic control group. Other parameters of the liver function test were not changed as shown in table 1.

A poor correlation was found between the age and serum glucose, ALT, AST, ALP and bilirubin in the controls, diabetic non-treated and treated patients (data not shown).

Poor correlation was noticed between the duration of treatment of metformin and serum glucose, ALT, AST and bilirubin (data not shown).

Discussion

Serum ALP activity was significantly higher in metformin treated patients than the non-treated diabetic patients. These results was in agreement with Nammour et al.[4] who found that 4 weeks of metformin treatment produced an elevation in liver function tests and when meformin was discontinued, liver function tests were normalized. Belcher and schernthaner[13] demonstrated that metformin treatment showed increased liver function tests including ALP, the mechanism of this effect is not clear. However, a greater reduction in ALP occurred after one year of treatment with a combination therapy of metformin and sulfonylurea.[14]

In this study, ALT activity was significantly higher in the metformin treated patients than that in the nontreated diabetics. These results were consistent with Tiikainen et al.,[15] and Blecher and Schernthen.[13] In other study, ALT remained unchanged after metformin treatment. However, only 0.4% of patients received metformin or sulfonylurea or insulin having ALT level 3 times greater than normal range.[16]

AST and bilirubin were not changed in the present patients treated with metformin. Swislocki and North[5] found that metformin had no effect on bilirubin but AST was increased after 2 months of treatment. In addition, metformin developed jaundice, gradually disappeared when metformin was discontinued.

Blood glucose was decreased significantly by metformin in the treated patients but it did not reach normal level. Metformin alone may not be enough for the treatment of diabetic patients. Therefore, metformin requires another hypoglycaemic drugs in combination therapy to improve glycaemic control and reduce mortality associated with diabetic patients.[17]

Table 1. *The effect of metformin on blood glucose level and liver function tests. Data was represented as mean ±SD, different letters represent significant differences at P<0.05.*

Parameters	Mean ± SD		
	Controls N=50	Diabetic non-treated patients N=50	Metformin treated patients N=50
Glucose mmol/L	5.65±0.97 a	11.34±3.56 b	9.84±2.40 c
ALT U/L	4.47±2.26 a	3.56±1.29 b	5.33±1.80 c
AST U/L	9.26±3.13 a	10.15±3.48 a	9.39±3.22 a
ALP U/L	65.35±17.33 a	63.26±14.90 a	91.83±33.50 b
Bilirubin mmol/L	9.56±3.63 a	10.31±4.29 ab	11.43±5.46 b

Diabetes itself can cause change in the liver function tests[18] Vozarova et al.[19] demonstrated an elevation in ALT and AST which indicated risk for type 2 diabetes and suggested a potential role of the liver in the pathogensis of type 2 diabetes. However, in this study, no change in the liver function tests was noticed between the control healthy subjects and the diabetic non-treated patients, the present study only directed to metformin for the change in liver function tests.

No correlation was detected between the age and blood glucose or liver function tests for the present control, nontreated and treated diabetics; therefore, age discrimination was not used. However, Nadean et al.[20] found an elevation in serum ALT among children with type 2 diabetes. In addition, koapman et al.[21] found that diabetes mellitus occurred at a greater frequency in young adults.

The duration of treatment of this study was between 6-24 months. The change in the liver function tests during this period was not significant. However, Swisloki and North[5] found an elevation in ALT, AST and ALP after 2 months of treatment with metformin. Follow up study could give a good results for the effect of the duration of treatment on liver function tests.

In ***conclusion***, metformin causes increase in ALP and ALT without any change in AST and bilirubin. Patients with type 2 diabetes treated with metformin should be periodically examined for liver function tests. Metformin might not be efficient as a sole drug for diabetes.

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