ORIGINAL RESEARCH

THE INFLUENCE OF METFORMIN TREATMENT ON LIVER FUNCTION OF DIABETIC PATIENTS ATTENDING JORDANIAN ROYAL MEDICAL CITY

Jehan Fayez Sweis,[1] Sawsan Sami Al-Maani[1],AlaaMadallah Al braikat[1], Hazar Musa Hijazeen[1],GhadeerHayelMoh'd Al_zu'bi[1],Jaafar AbuAbeeleh[1], Ahed J Alkhatib[2, 3*]

[1]Royal Medical Services, Jordan
[2]Department of legal medicine, Toxicology of Forensic Science and Toxicology, School of Medicine, Jordan University of Science and Technology, Jordan
[3]Council for Nutritional and Environmental Medicine, Mo i Rana, Norway

Submitted on: 29.05.17; Revised on: 06.06.17; Accepted on: 10.06.17

ABSTRACT:

Introduction: Liver is a vital organ and mediates many cellular processes. Liver may be injured in diabetes. Metformin treatment shows a high potential to lower the risk of liver injury or to ameliorate its damage.

Study objective: To explore the potential of metformin treatment in reducing the level of liver injury.

Methods and subjects: The present study employed the retrospective study design to review the files of diabetic patients. Study variables includedgender, age, duration of diabetes, metformin treatment, and liver function tests. Datawere analyzed using SPSS version 21. The relationship between variables was examined using Chi-square test, and T test. Significance was considered if $p \leq 0.05$.

Study results: The study included 62 diabetic patients. The mean age of study participants was 62.95± 11.98 years, a total of 33 (53.22%) of study participants were males, duration of diabetes was 7.51±5.86 years, metformin was used as a diabetic therapeutic option by 41 (66.13%), the mean dose of metformin was 1617.32±694.49 mg, the mean level of AST was 16.01±7.79 (U/L), the mean level of ALT was 18.500±8.89 (U/L), and the mean level of bilirubin was 0.38±0.18 (mg/dl). A significant relationship was found between metformin dose and each of liver enzymes (p=0.000). When the mean levels of liver enzymes were compared between metformin group and without metformin group, no significant differences were observed.

Conclusion: Liver injury in diabetes is a long term process and the use of metformin can offer protection against liver injury through keeping liver enzymes within normal limits.

Keywords: Liver function test. ALT, AST, Albumin, Metformin, Diabetes.

Corresponding Author: Jaafar Abu Abeeleh
Tel: 00962772047577
E-mail address: ayhamjafar@yahoo.com

Indian Research Journal of Pharmacy and Science; 13(2017)1009-1014;
Journal Home Page: https://www.irjps.in
DOI: 10.21276/irjps.2017.4.2.8

INTRODUCTION:

Diabetes mellitus is considered as the most non-communicable diseases affecting human, with increasing prevalence at global level[1]. Type 2 diabetes is the most prevalent form of diabetes, about 90% of all cases[2]. At global level, it has been estimated that the prevalence of diabetes was 2.8% in 2000 and expected to increase to 4.4% in 2030[3].

Diabetes and liver injury have well established association[1]. The metabolism of carbohydrates is mainly controlled by liver. In case, glycogen has accumulated within the liver, it is expected to develop hepatomegaly and alterations in liver enzymes such as mild to moderately elevated aminotransferases[4].

Amino transferases include aspartatealanine aminotransferase (ALT) and aspartate aminotransferase (AST) reflect the magnitude of liver injury and can be good indicators for non-alcoholic steatohepatitis(NASH)[5].

Usually, diabetes is associated with increased levels of ALT and AST[1]. In their study, Erbey et al[6] reported that there were elevated levels of ALT in diabetic patients 7.8% compared to 3.8% in control subjects. Salmela et al[7] reported the findings of their study as increased levels of ALT among diabetics to be associated with increased BMI and poor glycemic control.

Belcher and Schernthaner[8]conducted a study to explore the hepatic influences of medicines used to treat diabetics. The authors depended on published randomized, double-blind studies which compared the impacts of metformin or a sulphonylurea, gliclazide, in the treatment of over 3700 patients with Type 2 diabetes. Study findings showed that pioglitazone lowered the mean levels of liver enzymesbetween 3 and 18%, gliclazidelower liver enzymes from 3 to 13%. Metformin treatment induced slight differences in liver enzymes.

The study of Ni et al[1] aimed to explore the differences in the means of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin in diabetics compared with control subjects. The levels of these proteins were within normal range in control groups. Diabetic group participants exhibited increased levels of ALT (18.5%), AST (14.8%)and bilirubin (4.9%). The results showed that the levels of ALT and AST were not significantly correlated with other study variables including age, family history of diabetes, mode of therapy or type of diabetes.

Dango *et.al.*[9] conducted a study to investigate the differences in the levels of liver function test among type 2 diabetic patients who are treating with metformin. The results showed that the level of AST and ALT were lower in study group compared with control group. The mean value differences between the study group and control of total bilirubin(TB) were not statistically significant. In another study, Lebovitz et al[10] showed no significant differences in the incidence of liver enzymes in patients treated with metformin in trials with 5000 patients. Another study conducted by Al-Mola and Ahmed[12] showed that the level of ALT was higher ($p<0.05$)in metformin treated diabetics, while the levels of AST and bilirubin did not show any changes. On the other hand, the study of Desiletset al[12]showed increased level of bilirubin in diabetic patient treated by metformin.

STUDY OBJECTIVES: To explore the potential of metformin treatment in reducing the level of liver injury.

METHODS AND SUBJECTS:

The present study employed the retrospective study design to review the files of diabetic patients. Files were considered eligible for revision if liver function tests were included. Study variables included, but not restricted to, gender, age, duration of diabetes, metformin treatment, and liver function tests. Data were gathered from each file and entered to excel sheet. After all data had been gathered, data were analyzed using SPSS version 21. Several styles of statistical analyses were involved including descriptive statistics. The relationship between variables was examined using Chi-square test, and T test. Significance was considered if $p\leq 0.05$.

RESULTS:

Demographic and clinical characteristics of participants

As shown in table 1, the mean age of study participants was 62.95$\pm$ 11.98 years, a total of 33 (53.22%) of study participants were males (figure 1); duration of diabetes was 7.51$\pm$5.86 years, metformin was used as a diabetic therapeutic option by 41 (66.13%) (Figure 2), the mean dose of metformin was 1617.32+694.49 mg, the mean level of AST was 16.01+7.79, the mean level of ALT was 18.500+8.89,

and the mean level of bilirubin was 0.38+0.18 (figure 3).

Table 1: Demographic and clinical characteristics of participants

Variable	Description
Age (M±SD) years	62.95±11.98
Gender (N, %): - Males - Females	 33 (53.22%) 29 (46.78%)
Duration of diabetes (M±SD) years	7.51±5.86
Metformin use (N, %): - Yes - No	 41(66.13%) 21(33.87%)
Metformin dose (M±SD) mg	1617.32±694.49
AST(M±SD)	16.01±7.79
ALT (M±SD)	18.500±8.89
Bilirubin (M±SD)	0.38±0.18

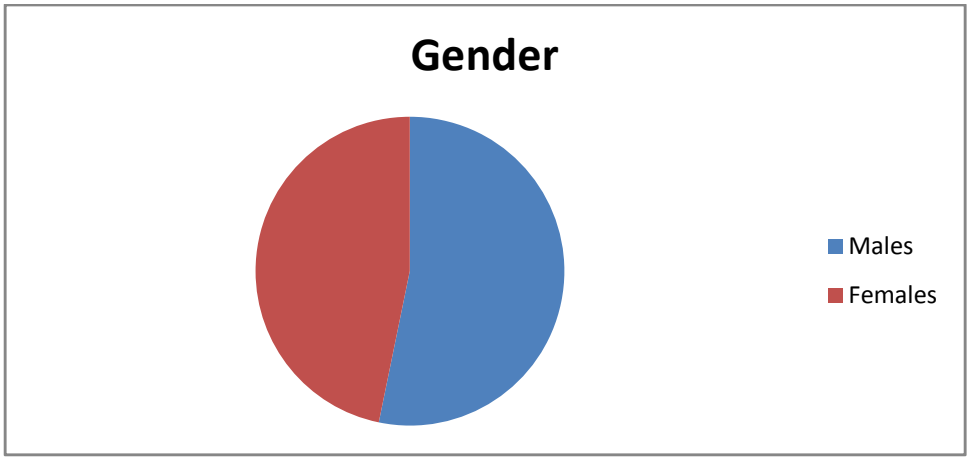

Figure 1: The distribution of gender by study participants

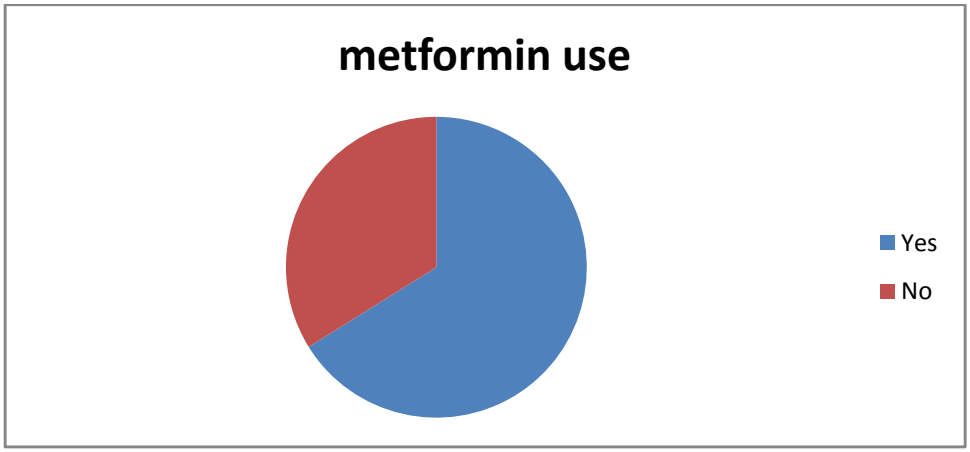

Figure 2: The frequency of using metformin by diabetic patients.

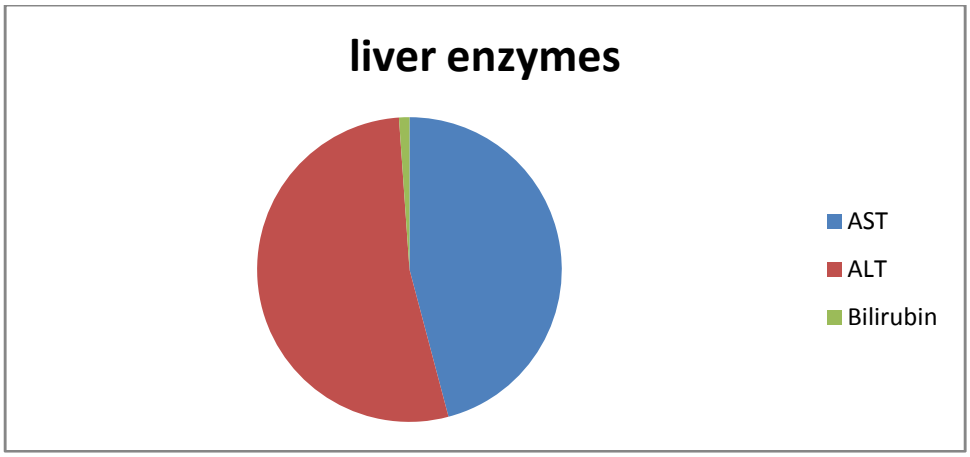

Figure 3: The mean of liver enzymes in diabetic patients

The impact of metformin dose on study variables: As shown in table 2, using T test showed that metformin dose was associated significantly with the mean level of AST (p=0.001), ALT (p=0.001), bilirubin (p=0.001), duration of diabetes (p=0.001), and age (p=0.001).

Table 2: The impact of metformin dose on study variables

Pairs		Mean	N	Std. Deviation	P value
	Metformin dose	1074.9839	41	948.65612	0.001
	AST	16.0065	62	7.79161	
	Metformindose	1074.9839	41	948.65612	0.001
	ALT	18.5000	62	8.88681	
	Metformin dose	1074.9839	41	948.65612	0.001
	Bilirubin	.3839	62	.18394	
	Metformin dose	1074.9839	41	948.65612	0.001
	Duration	7.5081	62	5.86074	
	Metformindose	1074.9839	41	948.65612	0.001
	Age	56.9516	62	11.97597	

The differences in liver enzymes in groups without metformin and with metformin treatment: As shown in table 3 and figure 4, we used independent T test to examine the differences in the means of liver enzymes. No statistical differences were observed (p>0.05).

Table 3: The differences in liver enzymes in groups without metformin and with metformin treatment

	Mean	SD	P value
ALT-no metformin	17.86	10.14	0.951
ALT-metformin	17.70	5.65	
Bilirubin-no metformin	0.381	0.19	0.653
Bilirubin-metformin	0.357	0.18	
AST-no metformin	16.14	6.64	0.952
AST-metformin	14.97	8.54	

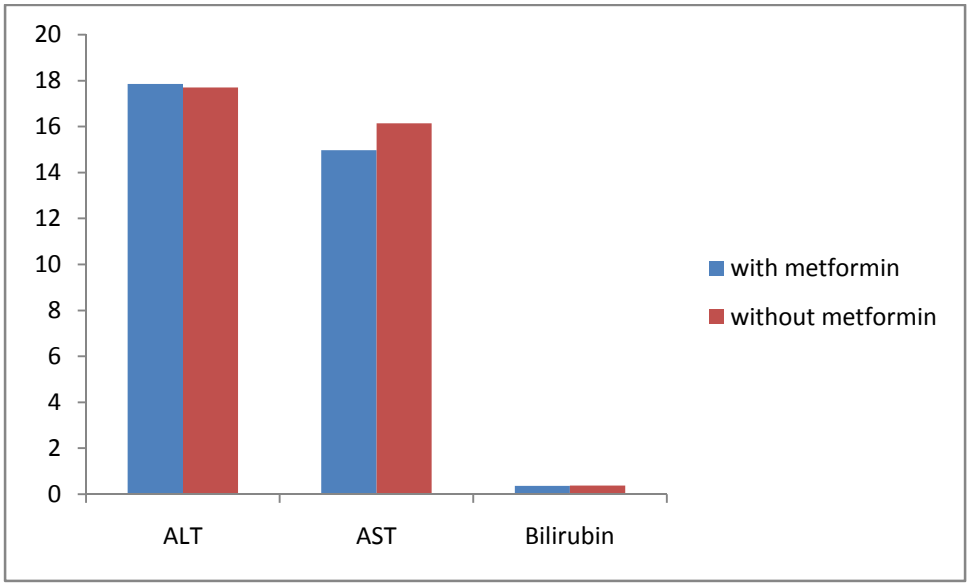

Figure 4: The frequency of liver enzymes according to metformin use

DISCUSSION:

Diabetes is a chronic disease and has been associated with liver injury[1]. Liver injury is reflected through several parameters including liver enzymes[4]. The present study was conducted to explore the potential of metformin treatment in reducing the level of liver injury. The levels of AST, ALT, and bilirubin were within normal range. This implies that measures of liver injury among diabetic patients do not indicate injured liver, and this may reflect the protective role of metformin. In this context, the findings of this study support previous studies which showed positive role of metformin in reducing liver injury[8]. However, other studies reported increased levels of liver enzymes among diabetic patients who were treated with metformin[1, 6, 7]. On the other hand, other studies reported decreased levels of liver enzymes in diabetic patients treated with metformin[9]. Taken together, no agreements in studies about the impact of metformin in liver injury, it seems that population variations in studies play an important role.

In another step of analysis, we examined the relationship between metformin dose and liver enzymes and found significant relationships ($p=0.001$) for all. It means that as the level of metformin increases, the level of liver injury is likely to decrease and this confirmed a protective role of metformin. Larger studies are required to confirm this finding.

No significant differences in the levels of liver enzymes were obtained when the liver enzymes were compared in groups with metformin and without metformin treatment. This is again confirmed that metformin may act on long term to maintain the function of liver.

CONCLUSION: liver injury in diabetes is a long term process and the use of metformin can offer protection against liver injury through keeping liver enzymes within normal limits.

REFERENCES:

1- Han Ni, HtooHtooKyawSoe, AungHtet, Determinants of abnormal liver function tests in diabetes patients in Myanmar. International Journal of Diabetes Research, 2012, 1(3): 36-41.
2- Amos AF, McCarty DJ, Zimmet P, The rising global burden of diabetes and its complications: estimates and projections to the year 2010. Diabetes Med, 1997, 14(5): 81–85.
3- Wild S, Roglic G, Green A, Sicree R, King H, Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care, 2004, 27(5):1047–1053.

4- Chatila R, West AB, Hepatomegaly and abnormal liver tests due to glycogenosis in adults with diabetes. Medicine, 1996, 75(6):327-33.
5- Meybodi M A, Afkhami-Ardekani M, Rashidi M, Prevalence of Abnormal Serum Alanine Aminotransferase Levels in Type 2 Diabetic Patients in Iran. Pakistan Journal of Biological Sciences, 2008, 11: 2274-2277.
6- Erbey JR, Silberman C, Lydick E, Prevalence of abnormal serum alanine aminotransferase levels in obese patients and patients with type 2 diabetes. Am. J. Med.2000, 109: 588–590.
7- Salmela PI, Sotaniemi EA, Niemi M, Maentausta O, Liver function tests in diabetic patients. Diabetes Care, 1984, 7: 248–254.
8- Belcher G, Schernthaner G, Changes in liver tests during 1-year treatment of patients with Type 2 diabetes with pioglitazone, metformin or gliclazide. Diabet Med., 2005, 22(8):973-9.
9- Dango D, Umeta M, Genet S, Menon M, Kebede T, et al, Profiles of Liver Function Tests among Type 2 Diabetic Patients Who are Receiving Different Anti-Diabetic Drugs Attending TikurAnbessa Specialized Hospitals. J Pharmacogenomics Pharmacoproteomics, 2016, 7: 163.
10- Lebovitz HE, Kreider M, Freed MI, Evaluation of liver function in type 2 diabetic patients during clinical trials: evidence that rosiglitazone does not cause hepatic dysfunction. Diabetes Care, 2002, 25: 815-821.
11- AI-Mola I, Ahmed P, The effect of metformin on some liver function tests in type 2 diabetic patients. Irq J pharm, 2006, 6: 25-27.
12- Desilets DJ, Shorr AF, Moran KA, Holtzmuller KC, Cholestatic jaundice associated with the use of metformin. Am J Gastroentero, 2000, l 96: 2257.

CONFLICT OF INTEREST REPORTED: NIL; SOURCE OF FUNDING: NONE REPORTED