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Comparison of Elevated Liver Enzymes in Type 2 Diabetic Patients in User and Non-User of Statin

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Abstract

Background
Type-2 diabetes is a risk factor for progressive non-alcoholic fatty liver disease and the majority of diabetic patients have blood lipid disorders, so they take statin drugs. Statins have the adverse effects such as liver dysfunction and increase in liver enzymes. The purpose of this study was to compare the liver enzymes in type 2 diabetic patients who are user and non-user of statin.

Materials and Methods
In a case-control study, increased liver enzymes (ALT and AST > 40 U/L) were measured in blood samples of 200 type II diabetic patients (with and without statin consumption) who referred to Mashhad Diabetes Clinic in Mashhad city (Iran), during May to November 2017. Levels of liver enzymes and anthropometric indices were measured for both groups. Liver enzymes were assessed at the baseline of two groups. The SPSS 20th software was used for data analysis.

Results
The mean of Body mass index in two groups of diabetic patients with and without statin consumption had a significant difference ($p < 0.05$). The mean of ALP in both groups was not statistically significant, but the mean of LDL, ALT, AST and cholesterol levels in two groups of patients was statistically significant ($p<0.05$).

Conclusion
Based on the results, cholesterol level in diabetic patients with statin consumption was higher than non-consuming group.

Key Words: ALT, AST, Diabetes Mellitus, Statins**.**

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1- INTRODUCTION

Liver disease (also called hepatic disease) is a type of damage to liver cell or disease of the liver. The symptoms related to liver dysfunction include both physical signs and a variety of symptoms related to digestive problems, blood sugar problems, Immune disorders, abnormal absorption of fats, and metabolism problems. Increased activities of liver enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and glutamyltranspeptidase (GGT) are indicators of hepatocellular injury. Increased activity of these markers is associated with insulin resistance (1), metabolic syndrome, and type 2 diabetes. AST (Serum glutamic oxaloacetic transaminase [SGOT]), and ALT (Serum glutamate pyruvate transaminase [SGPT]) are sensitive indicators of liver damage from different types of disease (2-9).

Tohidi et al.'s study showed that among the liver enzymes, only ALT has a significant relationship with type 2 diabetes (10). Mehar and Asija in a study showed that in diabetic patients, the normal level of SGPT and SGOT may be greater than the chance of liver disease. In liver disease patients, the normal level of SGPT and SGOT may be greater than the risk of diabetes (11). The increasing incidence of obesity and type-2 diabetes is a risk factor for progressive non-alcoholic fatty liver disease (NAFLD), as the most common cause of chronic liver disease worldwide (1, 2). Individuals with type-2 diabetes mellitus (T2DM) have a high prevalence (40% to 70%) of NAFLD (12-14), and liver disease is an important cause of death in these patients (15). Type 2 diabetes is characterized by hyperglycemia, insulin resistance, and insulin deficiency. The insulin resistance contributes to the abnormal lipid profile that dyslipidemia contributes to increased cardiovascular events in patients with type 2 diabetes (16). Studies suggested diabetes be considered as a risk factor for the development of NAFLD and its progression to more advanced liver disease including fibrosis, cirrhosis, and hepatocellular carcinoma (17). The 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors, also known as statins, such as atorvastatin and simvastatin are widely prescribed to achieve low-density lipoprotein cholesterol targets in NAFLD patients with T2DM and increasing numbers of these patients have received statins in recent decades in all developed countries (13, 18, 19). Statins have become the first-line therapy for reducing the risk of cardiovascular disease (CVD) mortality and morbidity as well as the need for coronary artery revascularization procedures (CARP) in people who have suboptimal lipid profile, with or without other risk factors.

Statins are the cornerstone of treatment for dyslipidemia, but a recent meta-analysis of randomized trials found an association between their use and incident diabetes (20). The role of statins in primary and secondary prevention of CVD, including among patients with type 2 diabetes, is well established. However, the relationship of statin therapy to incident type 2 diabetes is controversial. In the first study that evaluated this association using the West of Scotland Coronary Prevention Study (WOSCOPS) published in 2001, pravastatin (40mg/day) was reported to be associated with a 30% risk reduction for incident diabetes, although the upper bound of the 95% confidence interval (CI) for that observation was 0.99 (21). High-dose statin therapy is associated with more frequent abnormalities of liver function tests (LFTs), although they are generally still relatively infrequent. In the Treating to New Targets (TNT) trial, 20 patients with clinical cardiovascular disease (CVD) were randomized to 10 or 80 mg of atorvastatin. The incidence of persistent elevation in ALT, AST, or both (defined as

two consecutive measurements obtained 4–10 days apart that were more than three times the upper limit of the normal range) was 0.2 and 1.2%, respectively ($P < 0.001$) (22). Efficacy and safety of statins in significantly reducing cardiovascular events in moderate-to-high-risk patients has been well documented, both in primary and secondary prevention (23, 24), however, diabetes increases the risk of cardiovascular mortality by two- to four-fold, hence, use of statins appears to be paradoxical (23). The prescribed statins challenges and adverse effects such as liver dysfunction, myopathy, cognitive impairment and increases in liver enzymes are commonly reported, but, in general, statins are well tolerated with a low incidence of side-effect (23, 25, 26). The management of diabetes patients is theoretically complicated by liver-related alterations and requires attention and precision in the use of medications. In this study, we aimed to investigate the prevalence of elevated liver enzymes in type 2 diabetic patients who were user and non-user of statin.

2- MATERIALS AND METHODS

2-1. Method

This cross-sectional study was conducted on 200 type-2 diabetic patients who were user (n=100), and non-user (n=100) of statin who referred to Mashhad Diabetes Clinic in Mashhad city (Iran), from May to November 2017.

2-2. Anthropometric characteristics

Weight and height were measured using standard procedures in all subjects. Body mass index (BMI) was calculated as weight divided by height squared (kg/m2). Waist circumference was measured at the superior border of the iliac crest and values >102 cm for men and >88 cm for women were considered central obesity.

2-3. Biochemical characteristics

Blood samples were collected during each visit from the antecubital vein between 8 a.m. and 10 a.m. in a sitting position after 12 h of fasting. Total cholesterol, high-density lipoprotein cholesterol (HDL), triglycerides (TGL) and blood glucose were measured in all participants using colorimetric enzymatic method in a Technicon automatic analyzer RA-1000 (Dade-Behring Marburg GmbH, Marburg, Germany). LDL cholesterol was calculated using the Friedewald formula: total cholesterol—HDL cholesterol—1/5 × (triglycerides), (valid when triglycerides <400 mg/dl). All biochemical measurements were carried out in the same laboratory that followed the criteria of the World Health Organization Lipid Reference Laboratories. Determination of the frequency of liver enzymes in two groups (user and non-user of statin in diabetic patients) was done using USA, Cobas® 6000 analyzer series. For each participant, 5 ml of serum was kept at -70 °C for measuring liver enzymes. The most sensitive and widely used liver enzymes include: Aspartate Aminotransferase (AST or SGOT), Alanine Aminotransferase (ALT or SGPT). These enzymes are normally contained within liver cells. AST and ALT were measured by photometric enzyme method. In the measurement of the above analysis, commercial kits (Parsazmun Co., Tehran, Iran) were used.

2-4. AST and ALT the Normal Range

AST (SGOT) is from 5 to 40 units per liter of serum (the liquid part of the blood). ALT (SGPT) is from 7 to 56 units per liter of serum (27).

2-5. Ethics

The study was voluntary. All participants signed a research consent form.

2-6. Data analysis

Blood samples were obtained from patients and a self-made questionnaire was used to collect data. Increased liver

enzymes (ALT and AST > 40 U/L) were measured in blood samples of 200 diabetic subjects who were user and non-user of statin. For doing the study, the second researcher referred to Mashhad Diabetes Clinic and after obtaining informed consent from the patients, questionnaires were completed and the blood samples were taken. Data were analyzed using SPSS software version 20.0 and descriptive and analytic statistic tests, and P<0.05 was considered significant.

3- RESULTS

In this study 200 type 2 diabetes patients with and without statin consumption participated. There was no statistical significant difference between the two groups in baseline characteristics (p>0.05). The mean of waist circumference in both groups was not statistically significant. The mean of BMI in two groups with and without statin consumption had a significant difference (p <0.05). The mean of ALP in both groups was not statistically significant, but the mean of LDL, ALT, AST and cholesterol levels in two groups of patients was statistically significant (p = 0.00). **Table.1** represents mean of indicated variables in diabetic patients with and without statin consumption. In terms of equalization of variances and having independent samples, the Levene's test was used. According to the mean age, BMI, LDL and cholesterol in the two groups of diabetic patients with and without statin consumption had a significant difference (p<0.05). Mann-Whitney test was used for non-normal distribution of the data. There was a significant difference between the mean liver enzymes of AST and ALT and triglyceride in the two groups of diabetic patients with and without statin consumption (p<0.05).

Table-1: The comparison of the variables in diabetic patients with and without statin consumption.

Variables		Mean (SD)	P-value
Waist (cm)	Statin users	99.9 (7.10)	0.116
	Non-user	97.73 (10.36)	
BMI (kg/m2)	Statin users	29.56 (4.76)	0.048
	Non-user	28.164 (5.21)	
ALP (U/L)	Statin users	209.27 (62.39)	0.80
	Non-user	209 (62.83)	
HCT (gr/ dl)	Statin users	40.213 (4.32)	0.675
	Non-user	39.96 (4.04)	
BUN (mg/dl)	Statin users	27.64 (4.04)	0.842
	Non-user	27.28 (13.25)	
LDL (mg/dl)	Statin users	129.08 (12.13)	0.00
	Non-user	82.37 (15.69)	
HDL (mg/dl)	Statin users	51.33 (21.36)	0.337
	Non-user	51.33 (13.92)	
Cholesterol (mg/dl)	Statin users	237.44 (29.09)	0.00
	Non-user	157.43 (21.60)	
ALT (U/L)	Statin users	1.32 (0.47)	0.019
	Non-user	1.17 (0.384)	
AST (U/L)	Statin users	1.32 (0.47)	0.014
	Non-user	1.16 (0.37)	

SD: Standard deviation; HCT: Hematocrit; BUN: blood urea nitrogen; LDL: Low-density lipoprotein; HDL: high-density lipoprotein; BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

4- DISCUSSION

The purpose of this study was to compare the liver enzymes in type 2 diabetic patients with and without statin consumption. Based on the results of this study, the mean AST and ALT liver enzymes in the two groups of diabetic patients with and without statin consumption was significantly different; the results showed a significant increase in AST and ALT in diabetic patients with statin consumption ($p<0.01$). Westerbacka et al. (28) had demonstrated that ALT was closely associated with liver fat unlike Aspartate transaminase (AST), and gamma-glutamyl transferase (GGT), and hence, ALT is used as a surrogate marker for many epidemiological studies. AST (SGOT) and ALT (SGPT) are sensitive indicators of liver damage from different types of disease. But it must be emphasized that higher-than-normal levels of these liver enzymes should not be automatically equated with liver disease. They may indicate liver problems. The interpretation of elevated AST and ALT levels depends upon the whole clinical picture and so it is best done by doctors experienced in evaluating liver disease. The precise levels of these enzymes do not correlate well with the extent of liver damage or the prognosis. Thus, the exact levels of AST (SGOT) and ALT (SGPT) cannot be used to determine the degree of liver disease or predict the future.

Our study showed a high incidence of elevated ALT and AST levels in diabetic patients with statin consumption. Strong epidemiological, biochemical, and therapeutic evidence support the premise that the primary pathophysiological derangement, in most patients with NAFLD, is insulin resistance (29). Insulin resistance leads to increased lipolysis, triglyceride synthesis, increased hepatic uptake of free fatty acids, and accumulation of hepatic triglyceride (30-32); our data demonstrates higher serum cholesterol in the patients with statin consumption. Several factors could explain the increased risk of new onset diabetes among patients receiving certain statins (33-35). The increased production of plasma derived low density lipoprotein (LDL) cholesterol as a compensatory response to de novo cholesterol synthesis inhibition might result in direct inflammation and oxidation within the β cell. Consequently, the functional and structural integrity of β cells is compromised, impairing insulin secretion as a result of cellular apoptosis (35). Additionally, metabolic receptor effects interfere with cellular glucose uptake, energy production, and insulin secretion (33-36). Statins can also inhibit calcium mediated pancreatic insulin release and decrease expression of the β cell glucose transporters GLUT-2 and GLUT-4 (35). Also, statins are known to interfere with the synthesis of ubiquinone (CoQ10), which could independently alter insulin secretion (35, 36). The degree to which statins are involved in these respective mechanisms of diabetes onset is variable and supports why some statins pose a higher risk than pravastatin (34).

A meta-analysis by Sattar et al. of 13 trials that included both WOSCOPS (West of Scotland Coronary Prevention Study), and JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial) studies, with 91,140 participants, revealed 9% increased risk of new-onset diabetes in the statin group compared to placebo group (37). With reference to the overall significant beneficial potential of statin in the management of hyperlipidemia and reduction in the cardiovascular risk and all-cause mortality in diabetic patients, family doctors or general practitioners should discuss with their patients in details about the role of lipid-lowering medications in their long-

term management plan. In the interim, the role of lifestyle modifications, including healthy diet, regular exercise, and weight control, are equally important as patients with chronic diseases are now encouraged towards being more self-empowered and self-enabled (38). Nonetheless, patients should be warned about any statin-related side-effects such as liver impairment or allergic reaction.

4-1. Limitations of the study

The lack of patients' follow-up, and low sample size were among the limitations of this study.

5- CONCLUSION

In summary, this study demonstrates a high incidence of elevated ALT in patients with newly diagnosed T2DM, suggesting that the onset of the liver abnormalities associated with dysglycemia may precede the diagnosis of T2DM itself. These abnormal ALT levels are associated with features of the metabolic syndrome, but not glycemic control. Individuals with type 2 diabetes have a higher incidence of LFT abnormalities than individuals who do not have diabetes.

6- CONFLICT OF INTEREST: None.

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8- REFERENCES

1. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Bugianesi E, Lenzi M, McCullough AJ, Natale S, Forlani G, Melchionda N:Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. Diabetes 50:1844–1850, 2001.

2. Wannamethee SG, Shaper AG, Lennon L, Whincup PH: Hepatic enzymes, the metabolic syndrome, and the risk of type 2 diabetes in older men. Diabetes Care.2005; 28:2913–18.

3. Sattar N, Scherbakova O, Ford I, O'Reilly DS, Stanley A, Forrest E, et al. Elevated alanine aminotransferase predicts new-onset type 2 diabetes independently of classical risk factors, metabolic syndrome, and C-reactive protein in the West of Scotland Coronary Prevention Study. Diabetes.2004; 53:2855–60.

4. Vozarova B, Stefan N, Lindsay RS, Saremi A, Pratley RE, Bogardus C, Tataranni PA: High alanine aminotransferase is associated with decreased hepatic insulin sensitivity and predicts the development of type 2 diabetes. Diabetes.2002; 51:1889–95.

5. Perry IJ, Wannamethee SG, Shaper AG. Prospective study of serum -glutamyltransferase and risk of NIDDM. Diabetes Care.1998; 21:732–37.

6. Nakanishi N, Suzuki K, Tatara K. Serum -glutamyltransferase and risk of metabolic syndrome and type 2 diabetes in middle-aged Japanese men. Diabetes Care.2004; 27:1427–32.

7. Nannipieri M, Gonzales C, Baldi S, Posadas R, Williams K, Haffner SM, Stern MP, Ferrannini E: Liver enzymes, the metabolic syndrome, and incident diabetes: the Mexico City Diabetes Study. Diabetes Care.2005; 28:1757–62.

8. Lee DH, Ha MH, Kim JH, Christiani DC, Gross MD, Steffes M, et al. Gamma-glutamyltransferase and diabetes: a 4 year follow-up study. Diabetologia.2003; 46:359–64.

9. Hanley AJ, Williams K, Festa A, Wagenknecht LE, D'Agostino RB Jr, Haffner SM. Liver markers and development of the metabolic syndrome: the insulin resistance atherosclerosis study. Diabetes.2005; 54:3140–47.

10. Tohidi M, Harati H, Hadaegh F, Mehrabi Y, Azizi F. Association of Liver Enzymes with Incident Type 2 Diabetes: Tehran Lipid And Glucose Study. IJDLD. 2007; 7 (2):167-76.

11. Govind Mehar, Rajesh Asija. Relation of liver diseases in type II diabetes patients: an overview. Journal of Drug Discovery and Therapeutics. 2015; 3(27): 10-14.

12. Leite NC, Salles GF, Araujo AL, Villela-Nogueira CA, Cardoso CR. Prevalence and associated factors of non-alcoholic fatty liver disease in patients with type-2 diabetes mellitus. Liver International. 2009; 29(1):113-9.

13. Nascimbeni F, Aron-Wisnewsky J, Pais R, Tordjman J, Poitou C, Charlotte F, et al. Statins, antidiabetic medications and liver histology in patients with diabetes with non-alcoholic fatty liver disease. BMJ open gastroenterology. 2016; 3(1):e000075.

14. Abbas AM, El-Houfey AA, Abdelbadee AY, Ali MK, Ali SS, Abdelrahman RM, et al. Effects of Listening to Quran on Maternal and Neonatal Outcomes among Mothers Undergoes Cesarean Section. International Journal of Nursing, Midwife and Health Related Cases.2016; 2(2):39-50.

15. Tolman KG, Fonseca V, Dalpiaz A, Tan MH. Spectrum of liver disease in type 2 diabetes and management of patients with diabetes and liver disease. Diabetes care. 2007; 30(3):734-43.

16. Chogtu B, Magazine R, Bairy K. Statin use and risk of diabetes mellitus. World journal of diabetes. 2015; 6(2):352.

17. Williamson RM, Price JF, Glancy S, Perry E, Nee LD, Hayes PC, et al. Prevalence of and risk factors for hepatic steatosis and nonalcoholic Fatty liver disease in people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. Diabetes care. 2011:DC_102229.

18. Pastori D, Polimeni L, Baratta F, Pani A, Del Ben M, Angelico F. The efficacy and safety of statins for the treatment of non-alcoholic fatty liver disease. Digestive and Liver Disease. 2015; 47(1):4-11.

19. Chen MJ, Tsan YT, Liou JM, Lee YC, Wu MS, Chiu HM, et al. Statins and the risk of pancreatic cancer in Type 2 diabetic patients—A population-based cohort study. International journal of cancer. 2016; 138(3):594-603.

20. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010; 375:735-42.

21. Freeman DJ, Norrie J, Sattar N, Neely RD, Cobbe SM, Ford I, Isles C, Lorimer AR, Macfarlane PW, McKillop JH, Packard CJ, Shepherd J, Gaw A. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. Circulation 2001; 103: 357–62.

22. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al. The Treating to New Targets (TNT) Investigators: Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005; 352:1425–35.

23. Bhatia L, Byrne CD. There is a slight increase in incident diabetes risk with the use of statins, but benefits likely outweigh any adverse effects in those with moderate-to-high cardiovascular risk. Evidence-based medicine. 2010;15(3):84-5.

24. Chalasani N. Statins and hepatotoxicity: focus on patients with fatty liver. Hepatology. 2005;41(4):690-5.

25. Gao Y, Wang Y, Wu N-Q, Zhu C-G, Guo Y-L, Qing P, et al. Statins use and the risk of liver dysfunction: A Chinese cohort study in real world clinical practice. IJC Metabolic and Endocrine. 2017;16:16-20.

26. Calderon RM, Cubeddu LX, Goldberg RB, Schiff ER, editors. Statins in the treatment of dyslipidemia in the presence of elevated liver aminotransferase levels: a therapeutic dilemma. Mayo Clinic Proceedings; 2010: Elsevier.

27. Huupponen R, Viikari J. Statins and the risk of developing diabetes. BMJ. 2013; 346: f3156. doi: 10.1136/bmj.f3156.

28. Schindhelm RK, Diamant M, Dekker JM, Tushuizen ME, Teerlink T, Heine RJ. Alanine aminotransferase as a marker of non-alcoholic fatty liver disease in relation to type 2 diabetes mellitus and cardiovascular disease. Diabetes Metab Res Rev. 2006; 22: 437–43.

29. Polyzos SA, Kountouras J, Zavos C. Nonalcoholic Fatty liver disease: The pathogenetic roles of insulin resistance and adipocytokines. Curr Mol Med. 2009;9: 299–314.

30. Pagano G, Pacini G, Musso G, Gambino R, Mecca F, Depetris N, et al. Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrome: Further evidence for an etiologic association. Hepatology. 2002; 35: 367–72.

31. Sheth SB, Gordon FD, Chopra S. Non alcoholic steatohepatitis. Ann Intern Med. 1997; 126: 137–45.

32. Hamaguchi M, Kojima T, Takeda N, Nakagawa T, Taniguchi H, Fujii K, et al. The metabolic syndrome as a predictor of non-alcoholic fatty liver disease. Ann Intern Med. 2005;143: 722–8.

33. Preiss D, Sattar N. Statins and the risk of new-onset diabetes: a review of recent evidence. Curr Opin Lipidol 2011;22:460-6.

34. Koh KK, Sakuma I, Quon MJ. Differential metabolic effects of distinct statins. Atherosclerosis2011; 215:1-8.

35. Sampson UK, Linton MF, Fazio S. Are statins diabetogenic? Curr Opin Cardiol 2011; 26: 342-7.

36. Goldfine AB. Statins: is it really time to reassess benefits and risks? N Engl J Med 2012; 366: 1752-55.

37. N. Sattar, D. Preiss, H.M. Murray, et al.Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet. 2010; 375: 735-42.

38. American Diabetes Association Standards of medical care in diabetes-2015. Diabetes Care. 2015; 38(Suppl 1):S1–S93.