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TYPE II DIABETES MELLITUS;

FREQUENCY OF ASYMPTOMATIC ELEVATION OF LIVER FUNCTION ENZYMES IN TYPE II DIABETES MELLITUS PATIENTS USING STATINS.

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ABSTRACT… Objectives: To determine the frequency of asymptomatic elevation of liver function enzymes in type II diabetes mellitus patients using statins. **Study Design:** Cross sectional study. **Setting and Period:** Nishtar Hospital Multan, from February 2017 to February 2018. **Material and Methods:** A total of 335 patients were enrolled for this study. Sample size was calculated from the reference study.[9] Clinical and biographical data was obtained from each patient in the form of previous medical records and patient interview such as, sex, age, height, weight, age at onset of diabetes, family history of diabetes, duration of diabetes, family history of liver diseases, medication history. All the data was measured and recorded by the researcher himself. Data thus obtained was subjected to statistical analysis by using computer software SPSS version 23. Mean and standard deviation was calculated for continuous variables while frequency and percentage was calculated for categorical variables. A p value of less than or equal to 0.05 was taken as significant for univariate test. ANOVA test was utilized to evaluate the relationship ALT and AST and other metabolic parameters. **Results:** Although the prevalence of elevated ALT increased with the increasing age, duration of diabetes, BMI, FBS and TG, but it was not statistically significant with (p=0.634), (p=0.759), (p=0.844), (p=0.400) and (p=0.246) respectively. Similarly, the prevalence of elevated AST increased with the increasing age, duration of diabetes, BMI, FBS and TG, but it was not statistically significant with (p=0.779), (p=0.945), (p=0.987), (p=0.199) and (p=0.933) respectively. (Table II). **Conclusion:** From this study it can be concluded that use of statins does not alter the usual finding of elevated liver enzymes among the patients with type two diabetes mellitus.

Key words: Liver Function Enzymes, Statins, Type II Diabetes Mellitus.

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INTRODUCTION

Diabetes mellitus is a well-known cause of non-alcoholic steatohepatitis and screening for this disease is done by using liver enzymes like alanine transaminase and aspartate transaminase.[1] Risk of developing chronic liver disease like alcoholic fatty liver disease is doubled in patients with type II diabetes mellitus. Liver function enzymes like alanine aminotransferase and aspartate aminotransferase are biological markers of hepatocyte injury which leak into the blood circulation and provide a measure of concentration of intracellular enzymes of liver.[2]

Normal concentrations of these aminotransferases are 5-40 UL.[1-3] Mild elevation of alanine aminotransferase and aspartate aminotransferase is normally found in diabetic patients with type II. The mechanism of this rise in liver enzymes in patients with type II diabetes mellitus is not very well understood.

Diabetic patients suffering from type II diabetes mellitus are at increased risk of developing cardiovascular diseases [4] and as a result of large number of randomized control trails and studies it has been recommended that statins must be used in all the diabetic patients.[5] Use of statins in diabetes has its limitations in terms adherence to the drug. Lack of adherence to the use of statins by the diabetic patients is thought to be because of lack of involvement of the patients in decision making for the use of the drugs.[6]

Initially statins were reported to be associated with significant liver abnormalities. High doses of lovastatin have been shown to cause significant liver problems but lower doses are not significantly associated with liver injury.[7] Most of these trails were experimental performed on animals.

It has been previously discussed in literature that statins are very commonly associated with asymptomatic elevation of alanine aminotransferase and aspartate aminotransferase.[8] It is considered to be as a class effect of statins. In multiple clinical trials significant elevation in aminotransferases is used as end point for the safety of statin use. Asymptomatic elevation of these enzymes with the use of statins is dose related and has an incidence of less than 3% as has been evident from the previous studies.

Studies have shown that asymptomatic elevation of liver enzymes is not that much different in placebo treated patients and patients treated with statins. This concept states that this asymptomatic elevation in liver enzymes can be due to hyperlipidemic fluctuations in transaminases instead of depending upon statin use. In this study our rationale is to assess the frequency of asymptomatic elevation in liver enzymes in patients with type two diabetes mellitus using statins. There are no such previous studies regarding the evaluation of elevation in transaminases in diabetic patients using statins.

MATERIAL AND METHOD

It is a cross sectional study which was conducted in Nishtar Hospital Multan from February 2017 to February 2018. A total of 335 patients were enrolled for this study. Sample size was calculated from the reference study.[9] Non probability consecutive sampling technique was used to collect the sampling size. Inclusion criterion was set as diabetic patients with type II diabetes mellitus using statins for more than two years. Exclusion was done on the basis of presence of one of the following conditions; history of known liver diseases, other problems which could possibly be the cause of raised transaminases, considerable amount alcohol consumption, viral hepatitis, history of use of medicine other than statins which may cause elevation of liver enzymes for example steroids, Bleomycin, Tamoxifen, Methotrexate, Amiodarone and sodium valporate etc. Other patients presenting with gestational diabetes, maturity onset diabetes of young or uncertain type of diabetes were also excluded from this study. Ethical approval for the study was obtained from Hospital Ethics Committee of Nishtar hospital Multan. Informed consent was taken from each patient before including them into our current study. Clinical and biographical data was obtained from each patient in the form of previous medical records and patient interview such as, sex, age, height, weight, age at onset of diabetes, family history of diabetes, duration of diabetes, family history of liver diseases, medication history.

Blood sample was obtained after an overnight fast and parameters like, plasma glucose, glycated hemoglobin, triglycerides, AST and ALT were measured and estimated by enzymatic methods. AST and ALT more than 40 U L^{-1} was taken as abnormal. In patients showing asymptomatic elevation of liver enzymes a complementary viral test was preformed. Ultrasonography and other investigations were performed in patients with enzyme levels two times more than normal. All the data was measured and recorded by the researcher himself. Data thus obtained was subjected to statistical analysis by using computer software SPSS version 23. Mean and standard deviation was calculated for continuous variables while frequency and percentage was calculated for categorical variables. A p value of less than or equal to 0.05 was taken as significant for univariate test. ANOVA test was utilized to evaluate the relationship ALT and AST and other metabolic parameters.

RESULTS

A total number of n=335 type 2 diabetic patients using statins for more than two years were included, in this study. The mean age, duration of diabetes, BMI, FBS, ALT, AST and TG was 54.55±10.99 years, 8.88±5.68 years, 26.86±4.43 kg/m^2, 198.75±68.56, 26.82±12.60, 30.03±19.77 and 279.86±142.04 respectively.

Gender distribution revealed as (63.9%) n=214 males and (36.1%) n=121 females. (Table-I).

Although the prevalence of elevated ALT increased with the increasing age, duration of diabetes, BMI, FBS and TG, but it was not statistically significant with (p=0.634), (p=0.759), (p=0.844), (p=0.400) and (p=0.246) respectively. Similarly, the prevalence of elevated AST increased with the increasing age, duration of diabetes, BMI, FBS and TG, but it was not statistically significant with (p=0.779), (p=0.945), (p=0.987), (p=0.199) and (p=0.933) respectively. (Table-II).

Characteristics	Mean±S.D
Age (Years)	54.55±10.99
Gender	
Male	(63.9%) n=214
Female	(36.1%) n=121
Duration of diabetes (years)	8.88±5.68
BMI (kg/m^2)	26.86±4.43
FBS	198.75±68.56
ALT	26.82±12.60
AST	30.03±19.77
TG	279.86±142.04

Table-I. Characteristics of the patients

		ALT			AST		
Risk Factors		**Normal**	**Abnormal**	**Test of sig.**	**Normal**	**Abnormal**	**Test of sig.**
Gender	Male	(63.1%) n=176	(67.9%) n=38	χ^2 =0.461,p=0.497	(65.9%) n=162	(58.4%) n=52	χ^2 =1.56,p=0.211
	Female	(36.9%) n=103	(32.1%) n=18		(34.1%) n=84	(41.6%) N=37	
Age (years)	<45 years	(20.4%) n=57	(17.8%) n=10	χ^2 =0.913,p=0.634	(19.9%) n=49	(20.2%) n=18	χ^2 =0.498,p=0.779
	45-55 years	(34.4%) n=96	(41.1%) n=23		(36.6%) n=90	(32.6%) n=29	
	>55 years	(45.2%) n=126	(41.1%) n=23		(43.5%) n=107	(47.2%) n=42	
Diabetes	<5 years	(34.8%) n=97	(32.1%) n=18	χ^2 =0.55,p=0.759	(34.6%) n=85	(33.7%) n=30	χ^2 =0.113,p=0.945
	5-10 years	(29.4%) n=82	(26.8%) n=15		(28.5%) n=70	(30.3%) n=27	
	>10 years	(35.8%) n=100	(41.1%) n=23		(37%) n=91	(36%) n=32	
BMI	<25	(40.5%) n=113	(19.6%) n=11	χ^2 =0.34,p=0.844	(40.7%) n=100	(16.9%) n=15	χ^2 =0.026,p=0.987
	25-30	(42.7%) n=119	(39.3%) n=22		(41.9%) n=103	(40.4%) n=36	
	>30	(16.8%) n=47	(41.1%) n=23		(17.5%) n=43	(42.7%) n=38	
FBS	<140	(20.1%) n=56	(19.6%) n=11	χ^2 =1.84,p=0.400	(22.4%) n=55	(13.5%) n=12	χ^2 =3.22,p=0.199
	140-200	(29.7%) n=83	(21.4%) n=12		(27.6%) n=68	(30.3%) n=27	
	>200	(50.2%) n=140	(58.9%) n=33		(50%) n=123	(56.2%) n=50	
TG	<150	(18.3%) n=51	(25%) n=14	χ^2 =1.34,p=0.246	(19.5%) n=48	(19.1%) n=17	χ^2 =0.007,p=0.933
	>150	(81.7%) n=228	(75%) n=42		(80.5%) n=198	(80.9%) n=72	

Table-II. Frequency of ALT and AST in type 2 diabetic patients for various risk factors

DISCUSSION

It has been well established that asymptomatic elevation of liver enzymes has higher incidence in people with type two diabetes mellitus as compared to the people who do not have type two diabetes mellitus.[10] In current study we assessed changes in elevation of liver enzymes in patients using statins for more than 2 years who were also suffering from type 2 diabetes mellitus and the results show that use of statins did not affect the incidence of elevation of liver enzymes among the patients with type 2 diabetes mellitus by the use of statins therapy for their cardiovascular risks.

Most common abnormality found in asynmptomatic elevation of liver enzymes is the elevation of ALT. In another study it was found that asymptomatic elevation of ALT, GGT and AST had a greater frequency in type 2 diabetes mellitus. Thus it was concluded that these enzymes can be used as a biomarker for evaluation of type 2 diabetes.[11] Belay Z et al performed a similar study and found that not only ALT and AST but ALP, total bilirubin, direct bilirubin and serum glucose were significantly higher in incidence among patients of type 2 diabetes mellitus.[12]

Statins as a drug are quite useful in medical field and there is no way they can be stopped from being used. Although current available data suggests that statins are significantly safe from hepatic point of view, but further research is required to understand multiple aspects regarding their usage in humans. Studies are required to assess the effects of statins on hepatic histology when used in patients suffering from fatty liver disease and NASH. Few studies have suggested beneficial effects of statins on hepatic histology and have reported that statins show improvements in histology of the liver. There is need of further studies on epidmeological and effect of different statins and their doses on liver histology, as with the passage of time early in age and long term use of statins has increased.[13]

In a study like this one where they studied the effect of statins in patients who had elevated baseline liver enzymes and results showed that there was no higher risk of hepatotoxicity with the use of statins. In that study they compared two groups, in one groups there were patients with elevated liver enzymes and were treated with statins while in second group there patients with elevated liver enzymes but were not on statin therapy. The results showed that there was no significant difference among the two groups regarding the mild to moderate or severe elevations. It showed that people with elevated liver enzymes as it happens in type two diabetes mellitus are not susceptible to changes in liver histology or hepatotoxicity from use of statins. Some other studies had similar results.[14,15&16]

In few studies use of statins in patients with type 2 diabetes mellitus was associated with reduction of cardiovascular abnormalities risk. In a study use of statins for 5.4 years showed marked reduction in cardiovascular events among patients of diabetes mellitus type 2 with increased serum cholesterol levels.[17,18]

CONCLUSION

From this study it can be concluded that use of statins does not alter the usual finding of elevated liver enzymes among the patients with type two diabetes mellitus.

Conflict of Interest

There was no conflict of interest.

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