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Abnormal Liver Parameters among Individuals with Type 2 Diabetes Mellitus Nepalese Population

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Abstract

Background: Diabetes Mellitus (DM) is one of the major lifestyle-related metabolic disorders with emerging high incidence around the globe. The prevalence of type 2 Diabetes Mellitus is around 4.5% among Nepalese population as per the data of 2013 and the trend is just increasing yearly. Among various complications associated with DM, different patterns of liver diseases like fatty liver, cirrhosis and acute liver failure also count to be crucial ones. Early assessment of liver profile parameters provides better information for the management and cure of possible liver damages in type 2 diabetic population. The present study aimed to assess and compare liver parameters in Nepalese type 2 diabetic population.

Methods: A total number of 300 patients were included in descriptive cross-sectional study conducted at Manmohan Memorial Teaching Hospital. Among them, 162 were type 2 Diabetic and 138 were non- Diabetic control population. Fasting blood sugar (FBS) and HbA1c were estimated to diagnose Diabetes Mellitus and Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), total protein and albumin were estimated to assess liver function by using standard methods. The parameters were analyzed with SPSS version 20.0 and data with p-value less than 0.05 was considered as statistically significant.

Results: We observed increased level of ALT (57%) and AST (46%) among patients with diabetes mellitus. Moreover, a significant level of elevation in AST and ALT was observed among the patients with DM compared to non-diabetic controls ($p<0.001$). Although not significant statistically, the level of ALP was also high among the diabetic group of patients. However, total protein, albumin and A/G ratio were significantly decreased in diabetic group of patients compared to non-diabetic controls. In addition, transaminases were also significantly associated with duration of diabetes. The levels of HbA1c were positively correlated with transaminases at significant level.

Conclusion: Type 2 DM is associated with mild chronic changes in transaminases and decrease hepatic functions. Routine assessment of liver parameters in those populations may prevent further complications associated with liver due to insulin resistance.

Keywords: Type 2 DM; Transaminases; Insulin resistance; Nepal

Abbreviations: DM: Diabetes Mellitus; FBS: Fasting Blood Sugar; PP: Post Prandial Blood Sugar; BMI: Body Mass Index; HbA1c: Glycated Hemoglobin; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; ALP: Alkaline Phosphatase; TP: Total Protein; A/G: Albumin Globulin ratio; GGT: Gamma Glutamyl Transpeptidase; NIDM: Non-Insulin Dependent Diabetes Mellitus; IDF: International Diabetes Federation; LFTs: Liver Function Tests; NAFLD: Non-Alcoholic Fatty Liver Diseases

Background

One of the oldest diseases known to humankind is diabetes mellitus. It is a chronic metabolic disorder resulting either from insulin insufficiency (Insulin insufficiency results in Type 1 Diabetes Mellitus - T1DM) or insulin insensitivity (Type 2 Diabetes Mellitus - T2DM). T2DM resulting from interaction between genetic, environmental and behavioral risk factors have characteristic features of hyperglycemia, insulin resistance and relative insulin deficiency [1].

T2DM, being the most common form of Diabetes Mellitus, accounts for 90% of all cases and the rate is rocketing [2]. Data reported by WHO showed a dramatic surge in the number of diabetes cases from 108 million in 1980 to 422 million in 2014. The global prevalence of diabetes among adults over 18 years of age has raised by 3.8% from 1980 (4.7%) to 2014 (8.5%) [3]. Among all the diabetic cases recorded, 80% is reported from low and middle income countries alone [1]. Approximately 1.2 million deaths were caused by diabetes in 2012. WHO has profiled that by 2030, diabetes will be the 7th leading cause of death.

T2DM, if uncontrolled and unmanaged in a timely way, may call for short and long term complications which are possibly fatal. There are numerous complications associated with T2DM which encircle diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, diabetic ketoacidosis, stroke, liver injury, fatty liver disease and many more [4]. Liver associated disorders detected in diabetes involve elevated liver enzymes, fatty liver disease, cirrhosis, hepato-cellular carcinoma and acute liver failure [5].

Chronic hyperinsulinemia and relative insulin resistance cause a cascade of reactions that lead to increase in lipogenesis and associated fatty changes. Accumulation of free fatty acid is known to be toxic to hepatocytes engendering disruption of cell membrane, mitochondrial dysfunction, oxidative stress and increase in pro-inflammatory cytokine – Tissue Necrotic Factor [6]. Moreover, accumulation of intracellular glycogen in hepatocytes lead to liver injury showing typical biochemical findings of mild to moderate

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rise in ALT, AST and normal synthetic function with or without ALP elevation [7].

There are several previous reports from various parts of world revealing altered liver parameters among the diabetic subjects. However, such evidences from Nepalese people are scarce in the literature. Therefore, this report aimed to investigate and compare the various liver parameters among people living with type 2 diabetes and non-diabetic control subjects attending a tertiary care hospital in Kathmandu, Nepal.

Methods

This was a descriptive cross-sectional study conducted among a total of 300 patients aged above 40 years visiting Manmohan Memorial Teaching Hospital, a tertiary care referral center in Kathmandu during the period of six months. Among total patients, 162 were type 2 Diabetic and 138 were healthy control subjects. The apparently healthy individuals attending for general health checkup purpose was selected and was grouped as control while population with diabetic history and suspected individuals were accounted by International Diabetes Federation (IDF) guideline 2012 and grouped as type 2 diabetic populations. Information regarding the patients' demography (age, sex), family history, history of disease, duration of diabetes and anti-diabetic therapy were collected and recorded in a clinical profile form.

About 5ml of venous blood was collected from every diabetic and non-diabetic patient for the estimation of biochemical parameters. Fasting blood glucose, postprandial blood glucose and HbA1c were estimated to diagnose Diabetes Mellitus. For categorization of type 2 DM from total population, the type 2 DM diagnostic criteria provided by the IDF was used [8]. AST, ALT, ALP, total protein and albumin were estimated in total population to assess liver function by using standard methods as per the guideline provided by the reagent manufacturer (Human GmBh, Germany). ALT and AST were estimated at 37°C flow cell temperature and normal range for both was considered up to 42 U/L in male and up to 32 U/L in female as provided by SOP [9]. HbA1c was estimated by ion exchange resin method colorimetrically and all other parameters were analyzed by HumaStar 300 fully automated analyzer following manufacturers' instructions.

Inclusion and exclusion criteria

Patients above 40 years of age attending MMTH were included in the study. The apparently healthy individuals attending for whole body checkup purpose were selected and were grouped into control while population with diabetic history and suspected individuals were accounted by IDF guideline 2012 were grouped as type 2 diabetic populations. The population with history of alcohol intake, liver cirrhosis, kidney disease, evidence of bone diseases and evidence of prescribed hepatotoxic drugs (methotrexate) were excluded from this study. Patients were screened for Hepatitis B surface antigen and presence antibody of Hepatitis C virus and patients with positive test were excluded from study.

Ethical approval

Written permission was taken from Institutional Review Committee (IRC) of Manmohan Memorial Institute of Health Sciences (MMIHS) and informed consent was taken from each individual included in the study.

Data analysis

Data were analyzed using SPSSversion20.0and Microsoft Excel 2013. Student's t-test was used to analyze the differences in liver profile parameters between control and diabetic population. Pearson correlation coefficient was used to evaluate the association of HbA1c with liver parameters in diabetic population.

Results

The study was carried out in 300 populations between age group 40-85 years in Manmohan Memorial Teaching Hospital among which 166 were male and 134 were female. The mean age of study population was 56±10, in which the number of type 2 diabetic patients was 162 and that of non-diabetic control was 138.

We observed an increased level of AST (46%), ALT (57%), ALP (7%) and decreased level of albumin (8.2%) and total protein (3.5%) in the patients with Diabetes Mellitus (Table 1).

Liver transaminases (both AST and ALT) were found to be statistically significant between early diabetic population (age ≤ 55 years) and prolonged diabetic population (age>55 years).

However, the differences in transaminases level for male and female diabetic population, in relation to family history of disease, was not statistically significant (Table 2).

A significant level of elevation in AST and ALT was observed among the patients with diabetes mellitus compared to non-diabetic control ($p < 0.001$). Although not significant statistically, the level of ALP was also high among the diabetic group of patients compared to non-diabetic control ($p=0.17$). However, total protein, albumin and A/G ratio were significantly decreased in diabetic group of patients compared to non-diabetic controls ($P<0.001$). Body Mass Index (BMI) was significantly high in diabetic population compared to control (Table 3).

HbA1c was positively correlated at significant level with transaminases and ALP in diabetic population whereas there was significant negative correlation of HbA1c with albumin in diabetic population. Besides, no significant correlation between HbA1c and total protein in diabetic population was observed (Table 4).

Discussion

Whole world is in the peril of non-communicable diseases which is almost half of the total disease burden. The prevalence rate of type-II Diabetes Mellitus is around 4.5% in adult population as per the data reported by IDF atlas 2013 in Nepal and the trend is escalating [10]. A higher incidence of liver function test (LFT) abnormalities has been associated with individuals suffering from type 2 diabetes than individuals without diabetes [11]. In support to this statement, many studies around the globe have reported a varied frequency of derangements in LFTs among diabetic population. Studies conducted by Bora et al. in India [12] and Balogun et al. in Nigeria [13] reported a high prevalence of deranged LFTs of about 71.2% and 70% respectively among the diabetic population. Present study also showed high rate of abnormal liver parameter with relatively lower rate of 62.3% in compare to above studies. The higher prevalence is especially true

Variables	Mean± SD	No. of patients outside the references range (%)
ALP (IU/L)	93 ± 34	7
ALT (IU/L)	58 ± 40	57
AST (IU/L)	51 ± 34	46
TP (g/dl)	7.3 ± 0.6	3.5
Albumin (g/dl)	4.2 ± 0.6	8.2

Table 1: Mean value of biochemical parameters among Diabetic population (N = 162).

	AST				ALT			
Variables	**Mean±SD**	**T**	**95% CI**	**P**	**Mean± SD**	**T**	**95%CI**	**P**
Age ≤55 years(70) >55 years(92)	 60.7 ± 36.3 45.5 ± 32.7	1.98	-0.97 - 30.56	0.04*	 71.7 ± 42.3 51.3 ± 38.2	2.27	2.48 - 38.24	0.02*
Gender Male(88) Female(74)	 57.7 ± 38.4 47.3 ± 31.4	-1.34	-25.82 - 5.06	0.18	 57.7 ± 35.3 63.0 ± 47.3	-0.58	-23.6 - 12.96	0.56
Family history Absent (58) Present(104)	 45.3 ± 33.1 58.7 ±36.4	-1.65	-26.39 - 6.25	0.23	 58.9 ± 33.3 62.6 ± 23.4	-0.98	-12.0 - 14.32	0.69
**represents p value at significant level*								

Table 2: Relationship between demographic, clinical characteristics and liver function tests (AST, ALT) among diabetes patients (N = 162).

	Non-Diabetic control Mean ±SD (N = 138)	Diabetic population Mean ± SD (N = 162)	P VALUE
BMI (kg/m^2)	22.6±5.2	25.2±4.6	0.001*
FBS(mg/dl)	101 ± 15	172 ± 94	0.001*
PP(mg/dl)	124 ± 20	249 ± 133	0.001*
HbA$_1$c (%)	5.5 ± 0.3	8.4 ± 2.2	0.001*
ALP(U/L)	86 ± 23	93 ± 34	0.17
AST(U/L)	33 ± 9.5	51 ± 34	0.001*
ALT(U/L)	38 ± 16	58 ± 40	0.001*
TP(g/dl)	7.6 ± 0.5	7.3 ± 0.6	0.001*
Albumin(g/dl)	4.5 ± 0.3	4.2 ± 0.6	0.001*
A/G ratio	1.5 ± 0.3	1.4 ± 0.3	0.001*
**represents p value at significant level*			

Table 3: Comparison of risk factors and biochemical parameters associated with liver diseases between control and diabetic population (N = 300).

	HbA$_1$c	
	r value	**p value**
ALT	0.368	0.001*
AST	0.347	0.001*
ALP	0.323	0.003*
TP	-0.172	0.10
Albumin	-0.237	0.02**

*Correlation being significant at 0.01 levels
**Correlation being significant at 0.05 level.

Table 4: Correlation of HbA$_1$c with liver profile parameters among Diabetic population (N=162).

for low and middle economy countries where a high frequency of abnormal liver profiles are reported in 50-70% of diabetic subjects [14] but it falls down to about 7.8-22.9% in Europe and US [11]. There is lack of established fact for the decreased rate of abnormal liver profiles in developed countries like Europe and US. However, the possible reason for such minimal rate of abnormal liver profile in T2DM might be because of better health care system and health awareness among the people. Therefore, it is crucial to update the liver function profiles in diabetic population in developing country like Nepal to prevent them from having further hepatic complications.

This study aimed to find out incidence of variations in liver profile among people with type 2 diabetes from our country. As a result, increased transaminases activity was observed in diabetic population as compared to healthy control. Level of ALT was increased in 57% of diabetic population while AST was increased in 45% of the subject but ALP was increased only in 7% of diabetic population. Similar finding was observed in a study conducted from western part of our country by Thanpari et al. in 2013. This study also reported higher derangements in liver enzymes in female diabetic subjects than that of diabetic males [15]. Similarly, study conducted by Ni H et al. from Malaysia illustrated identical pattern of report but with this relatively lower frequency for LFTs; 18%, 12% and 5% for ALT, AST and ALP respectively in diabetic population [2]. Hence, many other studies support increased levels of transaminases in diabetic population including the present study. However, the controversy relied in different increased pattern of LFTs in different research. Study conducted by Bora k et al. [12] reported ALP as the most increased parameter (41.2%) than AST and ALT. In contrast to this, researcher from Malaysia and India [2,16] described rise in ALP with lower frequency as compared to transaminases in diabetic subjects which agrees to the present result. In addition, few studies showed AST [15] and some other studies reported GGT [16] as the most deranged parameter in diabetic population.

In current study, though not in statistically significant level, values of both transaminases were higher in female than in a male diabetic patient which is akin to the finding reported from Nigeria [17]. Similar studies like by Bora et al. [12] highlighted significant differences in transaminases levels in gender wise distribution whereas findings by NI et al. [2] showed significant difference of AST level alone between the two gender in diabetic subjects.

Insulin resistance activates lipolysis resulting accumulation of non-esterified fatty acids. This enhanced fat accumulation in liver is known to be directly toxic to hepatocytes [18]. This attributes increase in transaminases and diminished synthetic capacity of liver [11]. One of the hepatic manifestation of diabetes mellitus with metabolic syndrome is NAFLD and more specifically ALT has been used as a marker of NAFLD [19]. In the study, data emphasizes statistically significant rise in transaminases and significantly lower levels of total protein and albumin in diabetic group than control population (P<0.001). Similarly, study conducted by Shrestha et al. in Kathmandu Nepal reported similar finding regarding transaminases with the only difference in the level of ALP, which was significantly higher in diabetic population as compared to control in their study [20]. In contrast to this, increase in ALP was not found to be statistically significant in our study. Furthermore, a similar research from western part of Nepal by Thanpari et al. described significant increase in ALT and ALP but AST did not elevate significantly in diabetic patients when compared to control group [15]. Most commonly, transaminases rise in any type of liver damages but ALP rise moderately or even it remains normal in liver damages [11]. These reports to increased ALP activity in diabetic population may be due to some hepato-toxicity induced by some drug therapy.

Type 2 DM is usually associated with chronic mild elevation of transaminases and downfall in hepatic functions [11]. However, some

study contrasts elevated levels of transaminases and GGT is associated with increased risk of type 2 DM [21,22]. In support to our study, many other studies conducted by Idris et al. in 2011, Atiba et al. in 2013, Elmahi et al. in 2014, Mathur et al. in 2016 reported similar trend of results where both the transaminases were significantly higher in diabetic patients than in control group [16,17,23,24].

Unfortunately, there are no any reports suggesting the liver diseases as a complication of DM from Nepal. In the study, we reported significantly lower level of total protein and albumin in diabetic population in comparison to control ($p<0.001$). In other hand, the decrease in plasma proteins is also associated with the diabetic nephropathy, which is the renal complication of DM [25]. Sadly, many studies around the world lack to exclude this confounding factor before reporting the diminished synthetic function of liver in DM. However, some studies from different part of globe disclose similar trend of biochemical findings to define lower synthetic activity of liver in diabetes [23,24].

Han Ma et al. from China reported increased HbA1c as an independent risk factor for NAFLD [26]. Findings of this study support to the promising effect of insulin resistance in the pathogenesis of liver diseases. In the study, we found a significant positive correlation of HbA1c with transaminases and ALP. Similarly, study conducted by Rajeswari et al. [27] reported AST and ALT having significant correlation with HbA1c in diabetic population. To the flip side, AST was not significantly correlated with HbA1c in a study conducted by AL-Jameil et al. in 2014 [28]. Many of the studies also have divulged the significant positive correlation of transaminases with duration of diabetes [24] and also with fasting blood glucose levels [17] in type 2 diabetes. Therefore, we believe this report would be helpful in encouraging the clinicians to give interest in monitoring this neglected diabetic hepatic complication in individuals suffering from type 2 DM. In addition, Liver parameters were significantly correlated with diabetes mellitus in our study population; hence, timely diagnosis and management of the abnormal liver parameters may help to minimize liver related morbidity and mortality in diabetic population.

Limitations

This study was time framed study, conducted during the period of six months in a tertiary care hospital, Kathmandu, Nepal, which limits the relatively larger sample size to establish causality of this descriptive cross-sectional study. This study could not rule out all possible risk factors associated with hepatic complications in patients with type 2 DM.

Ethics Approval and Consent to Participants

Written approval was taken from institutional review committee of MMIHS, after submitting and presenting the proposal to the committee and written informed consent was taken from every volunteer participant.

Consent for Publications

All subjects gave informed consent to participate in the study and to have their data used anonymously for publication and presentation purposes.

Availability of Data and Materials

All the data generated during this study are presented in this paper.The primary raw data will be made available to the interested researchers by the corresponding author of this article if requested.

Competing Interests

The authors declare that they have no competing interests.

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Not applicable.

Authors' Contributions

SG and BDP- conceived the design of the study, reviewed literature, performed necessary interventions including laboratory investigations and analyzed the data. SS, JS, and PA- participated in community data collection, laboratory procedure and data analysis. SG and BDP- prepared the manuscript. All authors read the final version of manuscript and approved for submission.

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