# Association of Elevated Alanine Aminotransferase in Newly Detected Diabetes and Impaired Glucose Tolerance Patients

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*Summary: Objectives: Clinical evaluation and identification ofaetiology of asymptomatic raised serum alanine aminotransferase (ALT) level in newly detected adult diabetic and impaired glucose tolerance (IGT) patients.Methods: In this crosse-sectional study, newlydetected adult diabetic and IGT patients having asymptomatic raised serum ALT level of >1.5 times of upper limit of normal were evaluated clinically and by laboratory tests.Results: Total number of patients was 120, whichwas 3.1% of all newly registered diabetic and IGT patients over the study period. Male were 74 and female 46. Diabetes mellitus(DM) was found in 93.3% cases and IGT in 6.7%. Mean age was 43.1 years, mean body weight was 64.5kg and mean body mass index (BMI) was 25.5 kg/m². Central (abdominal) obesity was found in 61.5% cases. Increased waist hip ratio was found in 86.3% cases. Hypertension and hepatomegaly were present in 35% and 5.8% cases respectively. Dyslipidaemia was found in 98.3% cases and 45% patients fulfilled criteria for metabolic syndrome. Regarding etiology, 76.7% cases had non-alcoholic fatty liver disease(NAFLD), 8.3% had HBsAg seropositivity, 4.2% had anti-HCV seropositivity. In 7.5% cases no cause was found. Raised serum ALT level had a significant correlation with metabolic syndrome (p=0.016) and increasing age (p=0.008). Conclusion: Elevation of serum ALT is common inDM and IGT. NAFLD is the commonest cause followed by hepatitis B and C virus infection.*
*Keywords: alanine aminotransferase (ALT), Diabetes mellitus, impaired glucose tolerance (IGT)*
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## I.  Introduction

The prevalence of diabetes mellitus (DM) is increasing day by day. Patients with DM often have elevated levels of Alanine Aminotransferase (ALT). [1]Majority of them remain asymptomatic or have non-specific symptoms. The prevalence of asymptomatic elevated ALT is much higher In diabetic population then non-diabetic counterpart.[1]Elevated ALT is often a marker for non alcoholic fatty liver disease (NAFLD), chronic hepatitis B and C virus infection and metabolic syndrome. [2]Up to 70% of type 2 diabetic patients may have NAFLD. [3]A strong association remains between hepatitis C virus (HCV) infection and type 2 DM.[4]HCV related morbidity and mortality is higher in patients with DM than patients without DM.In a recent study, serum ALT concentrations were related to hepatic insulin resistance and later decreased hepatic insulin sensitivity[5,6]. In contrast, aspartate aminotransferase (AST) and gamma glutamyltransferase concentrations were  not related to changes in hepatic insulin sensitivity.[7]Chronic hepatitis B virus (HBV) infection is also significantly higher in diabetic population.[8,9] If inadequately addressed, the spectrum of NAFLD can pass through simple hepatic steatosis to non-alcoholic steatohepatitis (NASH) to cirrhosis to hepatocellular carcinoma and death. [10] In this study, we have tried to clinically evaluate adult newly detected patients with asymptomatic elevated ALT and to find out the Aetiology for raised ALT.

## II. Materials and Methods

In this prospective crosse-sectional study adult newly detected IGT and DM patients with elevated (>1.5 times of upper normal limit) ALT were evaluated at Rangpur Medical College, Rangpur, Bangladesh from July to December 2016. Patients with diagnosed chronic liver disease, acute hepatitis, congestive cardiac failure and history of regular alcohol or hepatotoxic drug intake were excluded from the study. The study was approved by the ethical review committee. Informed written consent was taken from every patient after explaining the purpose and procedure. A standard questionnaire was filled up. Every patient was clinically evaluated and supplemented by appropriate laboratory investigations.

**Study Design:** Prospective type of cross sectional study
**Study Location**: This was a tertiary care teaching hospital based study done in Department of Gastroenterology, at Rangpur Medical College Hospital, Rangpur, Bangladesh.
**Study Duration:** July 2016 to December 2016, over 06 months period.
**Sample size:** 120 newly detected IGT and DM patients.
**Subjects & selection method**: Adult newly detected IGT and DM patients with elevated (>1.5 times of upper normal limit) ALT.
**Inclusion criteria:** Apparently healthy newly detected IGT and DM patients with elevated (>1.5 times of upper normal limit) ALT admitted in the gastroenterology department of Rangpur Medical College Hospital, Rangpur.

**Exclusion criteria:**
1) chronic liver disease,
2) acute hepatitis
3) congestive cardiac failure,
4) alcohol intake,
5) hepatotoxic drug and
6) Diabetes mellitus with other known complcations.

**Anthropometric measurement:**This included weight and height. Body mass index (BMI) was calculated as body weight in kilogram divided by height in meters square. Waist circumference was measured at the horizontal plane mid-way between anterior superior iliac spine and lower costal margin at the narrowest part of the waist line while the patient was standing and at the end of normal expiration. Hip circumference was measured at a horizontal plane passed through greater trochanter of femur on both side in standing position.

**Blood Pressure:**Blood pressure (BP) was measured by using a standard sphygmomanometer in the supine position after rest for at least 15 minutes. Hypertension was considered with blood pressure >130/85mmHg and / or patient on regular use of anti-hypertensive medication.

**Biochemical tests:**All patients underwent the following tests: oral glucose tolerance test (OGTT), fasting lipid profile,serum ALT level, HBsAg, anti-HCV, ultrasonography of hepatobiliary system and pancreas. Additional investigations were done as required. Plasma glucose was measured by glucose oxidase method. Fasting plasma triglycerides (TG), high density lipoprotein cholesterol (LDL-c) were measured by enzymetic colorimetric endpoint method using reagents of Randox Laboratories Ltd.,UK. HBsAg was measured by micro-particle enzyme immune-assay (MELA) method and anti-HCV was measured by ELISA.
**Dyslipidemia:**Dyslipidemia was defined according to National Cholesterol Education Programme (NCEP) Adult Treatments Panel (ATP) III criteria-plasma triglyceride (TG)>150mg/dl, plasma total cholesterol>200mg/dl, plasma HDL-c<40 mg/dl in male/<50 mg/dl in female or plasma LDL-c>100 mg/dl.
**Metabolic syndrome:**Metabolic syndrome was defined according to international Diabetic Federation (IDF) criteria-central obesity (waist circumference> 90cm for male and >80 cm for female as for Asian) plus any two of the followings four criteria: (1) Raised plasma TG level> 150 mg/dl or >1.7 mmol/L or specific treatment for this lipid abnormality. (2) Low plasma HDL-c <40mg/dl or <1.03 mmol/L for males or <50mg/dl or <1.29mmol/L for females or specific treatment for lipid abnormality, (3) Rasied BP: systolic blood pressure>130 mmHg or diastolic blood pressure>85mmHg, (5) Fasting plasma glucose ≥6.1mmol/L.
**Abdominal ultrasound examination:**This was performed in all enrolled patients fasting for at least 10 hours by a single sonographer using SIEMENS Sonoline antares. Liver echo pattern was graded as follow:
**Grade I (mild):** A single diffuse increase in fineechoes in the hepatic parenchyma with normal visualization of the diaphragm and intrahepatic vessel borders.
**Grade II (moderate):** A moderate diffuse increasein fine echoes with slightly impaired visualization of the intrahepatic vassels and diaphragm.

Grade III (marked): A marked increase in fine echoes with poor or no visualization of the intra-hepatic vessel borders, diaphragm and posterior portion of the right lobe of the liver.

**Statistical Analysis:** Analysis was performed using statistical package for social science (SPSS) version 12. Data were expressed as mean, standard deviation (SD), percentage etc. Chi- square test ($x^2$) was used for the comparison of qualitative data. Results were considered statistically significant at p<0.05. Statistical analysis for association between raised serum ALT level and clinical parameter, biochemical parameter as well as ultrasonographic findings or hepatobilliary system were perfomed using univariate analysis with SPSS windows programme.

## III. Results

Over the study period a total of 3871 adult newly detected IGT and DM patients were found to have asymptomatic elevated ALT of > 1.5 times of upper normal limit (UNL) (considering exclusion criteria) which was 3.1%. Sixty (50%) of study subjects had ALT between 2-5 times of UNL, 52 (43%) had <2 times of UNL and 8 (7%) had > 5 times of UNL. Central obesity, increased waist hip ratio, hypertension, hepatomegaly, dyslipidaemia, fatty liver and metabolic syndrome were present in 61.5%, 86.3%, 35%,5.8%, 98.3%, 76.7% and 45% cases respectively. Base-line demographic, clinical and biochemical characteristic of the study subjects are shown in table I and II.

Rasied serum ALT level had a significant correlation with the age of the study subjects (P 0.008) and metabolic syndrome (P 0.016), but not with BMI (P 0.891) (Table III).

NAFLD was the commonest aetiology for raised ALT in this study (Table IV). Other causes included hepatitis B and C virus infection. In 7.5% cases no cause could be identified.

**Table-1**
Demographic and clinical characteristics of the study subjects (N=120)

| Male: Female | 74 (61.7%): 46 (38.3%) | |
|---|---|---|
| Mean age (years) | 43.1 | ± 11.1 |
| Mean body weight (kg) | 64.5 | ± 11.1 |
| Mean BMI (kg/m$^2$) | 25.5 | ± 4.0 |
| Mean systolic blood pressure (mm of Hg) | 122.0 ± 15.3 | |
| Mean diastolic blood pressure (mm of Hg) | 79.4 | ± 7.7 |
| Mean waist circumference (cm) | 89.2 | ± 9.8 |
| Mean hip circumference (cm) | 90.7 | ± 6.8 |
| Mean waist hip ratio | 0.97 | ± 0.07 |

**Table-II:** Biochemical characteristics of the study subjects (N=120)

| Mean fasting plasma glucose (m.mol/L) | 11.9 | ±4.9 |
|---|---|---|
| Mean 2 hours after 75 gm glucose (m.mol/L) | 19.2 | ± 7.2 |
| Mean ALT (U/L) | 103.1 ± 54.1 | |
| Mean total cholesterol (mg/dl) | 196.3 ± 44.9 | |
| Mean triglycerides (mg/dl) | 187.9 ± 99.9 | |
| Mean HDL-c (mg/dl) | 36.8 | ± 8.2 |
| Mean LDL-c (mg/dl) | 125.8 ± 36.6 | |

**Table-III:** Frequency of raised ALT for different risk factors among the study subjects (N=120)

| Risk factors | ALT<2XUNL (52.43%) | ALT>2XUNL (68.57%) | Total (120) | P value |
|---|---|---|---|---|
| **Age (years)** | | | | |
| <35 | 7(5.8%) | 26(21.7%) | 33(27.5%) | |
| 35-50 | 29(24.7%) | 30(25%) | 59(49.2%) | 0.008 |
| >50 | 16(13.3%) | 12(10%) | 28(23.3%) | |
| **Sex** | | | | |
| Male | 34(28.3%) | 40(33.3%) | 74(61.7%) | 0.464 |
| Female | 18(15%) | 28(23.3%) | 46(38.3%) | |
| **BMI (kg/m$^2$)** | | | | |
| 18.5-24.9 | 23(19.2%) | 31(25.8%) | 54(45%) | |
| 25-29.9 | 23(19.2%) | 28(23.3%) | 51(42.5%) | 0.891 |
| e"30 | 6(5%) | 9(7.5%) | 15(12.5%) | |
| **Metabolic syndrome** | | | | |
| Present | 30(25%) | 24(20%) | 54(45%) | 0.016 |
| Absent | 22(18.3%) | 44(26.7%) | 66(55%) | |
| **Fatty liver (on USG)** | | | | |
| Present | 42(35%) | 50(41.7%) | 92(76.7%) | 0.681 |
| Absent | 10(8.3%) | 18(15%) | 28(23.3%) | |

**Table-IV:** Aetiology of raised ALT in newly detected DM and IGT patients

| Aetiology | Total (N=120) | DM(n=112) | IGT (n=8) |
|---|---|---|---|
| NAFLD | 92(76.7%) | 89(74.2%) | 3(2.5%) |
| HBV infection | 10(8.3%) | 8(6.7%) | 2(1.7%) |
| HCV infection | 5(4.2%) | 5(4.2%) | 0(0%) |
| NAFLD and HBV infection | 4(3.3%) | 4(3.3%) | 0(0%) |
| Unidentified | 9(7.5%) | 6(5%) | 3(2.5%) |

## IV. Discussion

Persistent elevation of ALT in asymptomatic patient accounts much of the challenge in clinical practice. In the United States, NAFLD is replacing alcoholic hepatitis and viral hepatitis as the most common etiology of chronically elevated serum ALT in both diabetic and non-diabetic individuals and 60-95% of them are obese[7]. In two different studies the prevalence of elevated ALT was considerable higher the in general population.[8,9] In the current study the prevalence of elevated ALT(>1.5 times of UNL) in newly detected IGT and DM was 3.1%. NAFLD as the cause of raised ALT in our study was much higher than other studies, which may indicate insulin resistance as an important contributory factor in Bangladeshi diabetic and IGT population.[9,10] It was seen that the prevalence of HBV infection was higher among persons with diabetes than without diabetes. [8]In different studies HBV sero-positivity was found 2-4% but in our study it was much higher.[9,10] The frequency of anti-HCV sero-positivity was lower in our study than two other studies. [9,10] In different studies, male gender, younger age, greater waist circumference, presence of type 2 DM, poor glycaemic control, BMI>25 kg/m$^2$, long duration of DM were significant factors associated with an elevated serum ALT level.[8,9,10] On the other hand, high activity of ALT independent of age and obesity is associated with the occurrence of type 2 DM and metabolic syndrome.[9,10] In our study, elevated ALT had a significant correlation with the age and metabolic syndrome. Our study had some limitations. Study sample was small and study period was short. Fibro-scan and liver biopsy was not done and NAFLD was diagnosed by USG only. Age and sex matched large-scale propective study may provide more detail information. Liver biopsy should be considered for histological confirmation of etiology of raised serum ALT level. In conclusion it could be said that mild to moderate elevation of serum ALT is a common in IGT and DM. So, serum ALT level should be checked in every diabetic patient at diagnosis and at regular intervals thereafter. NAFLD is the most common etiological factor followed by HBV and HCV infection.

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