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ORIGINAL ARTICLE

Comparative Study on Serum Hepatic Enzymes between Normal Healthy Adults and Obese People of Rajshahi City

Md. Rakib Rashed[1], Sumayra Jhumu,[2] Tania Sultana Zaman,[3] Fatema Khatun[4]

ABSTRACT

Background & objective: Obesity is rapidly emerging as one of the major causes of non-alcoholic fatty liver disease (NAFLD), the early sign of which is elevated liver enzymes. But very few studies have yet been done in our country to find the association between overweight and obesity and levels of serum hepatic enzymes. The present study was undertaken to determine the association between overweight/obesity determined by body mass index (BMI) and serum hepatic enzymes.

Methods: This cross-sectional analytical study was conducted in the Department of Physiology, Rajshahi Medical College, Rajshahi over a period of one year between July 2018 to June 2019 in collaboration with the Department of Biochemistry of the same Medical College. Based on certain predefined enrolment criteria, 33 overweight or obese (BMI ≥23 kg/m^2) individuals (case) and 33 sex-matched apparently healthy adults (BMI <23 kg/m^2) (control) were included from the Rajshahi City. All the study subjects were then tested for serum hepatic enzymes (ALT, AST, ALP and GGT). The investigation findings obtained were compared between case and control groups.

Result: The mean ages of the cases and controls were almost similar (31.1 and 29.4 years respectively, $p = 0.576$).All the serum hepatic enzymes but GGT were found to be significantly raised in the case group than those in the control group. The BMI was found to bear significantly linear relationship with serum ALT, AST and ALP ($r = 0.709$, $p < 0.001$, $r = 0.718$, $p < 0.001$ and $r = 0.545$, $p < 0.001$ respectively) indicating that more than 70% of the variations in ALT and AST and 55% of the variations in ALP might be due to variation in BMI. When waist circumference was correlated with hepatic enzymes, it was found to correlate better than the BMI did with 70.3% of the variations in ALT, 77.2% of variations in AST and 57.4% variation in ALP being explained by waist circumference. However, WHR did not correlate well with hepatic enzymes. AST alone bears a weekly significant correlation with WHR, with only 28% of the variations in AST could be explained by WHR.

Conclusion: The study concluded that all the serum hepatic enzymes but GGT are significantly raised in the overweight and obese individuals than those in individuals with normal BMI. The BMI bears significantly linear relationships with serum ALT, AST and ALP. A substantial proportion of the variations in ALT and AST could be explained by BMI. Waist circumference correlates even better than the BMI does. However, WHR is not a good predictor of serum hepatic enzymes.

Key words: Non-alcoholic fatty liver disease, ALP, ALT, AST, GGT, BMI, WHR, etc.

Authors' information:

[1] ***Dr. Md. Rakib Rashed,*** *MBBS, M. Phil (Physiology), Assistant Professor (C.C.), Department of Physiology, Rajshahi Medical College, Rajshahi.*

[2] ***Dr. Sumayra Jhumu,*** *M.Phil (Physiology), Lecturer, Department of Physiology, Rajshahi Medical College, Rajshahi.*

[3] ***Dr.Tania Sultana Zaman,*** *M.Phil (Physiology),Lecturer, Department of Pathology, Islami Bank Medical College, Rajshahi.*

[4] ***Dr. Mst. Fatema Khatun,*** *M.Phil (Physiology), Senior Lecturer, Department of Physiology, TMSS Medical College and Rafatullah Community Hospital, Bogura.*

Correspondence: ***Dr. Md. Rakib Rashed,*** *Phone: +8801711427240, E-mail:drrakibrashed1@gmail.com*

INTRODUCTION:

Overweight and obesity has become a public health problem all over the world[1] including Sub Saharan Africa and South Asia.[2] In 2016, more than 1.9 billion adults, 18 years and older, were overweight, of these over 650 million were obese. Most of the World's population live in countries where overweight and obesity kills more people than underweight.[1] The WHO estimates that about 5% global deaths in 2015 were attributable to overweight and obesity. Asia and the pacific region is now the home to the largest absolute number of overweight and obese people, equivalent to about 1 billion. The latest available data indicates that over 40% of adults in this region are overweight and obese compared to 34.6% in 1990. In Bangladesh, prevalence of overweight and obesity has increased from 8% in 1990 to 16.9% in 2013.[2]

The prevalence of obesity in the World has reached a pandemic level following industrialization and mechanized life during the recent century.[3] Obesity is rapidly overtaking alcohol as one of the major causes of fatty liver disease.[4] NAFLD, which encompasses a disease spectrum that starts with development of bland fatty liver (steatosis), silently progressing to non-alcoholic steato-hepatitis (NASH), characterized by steatosis, inflammation, degeneration & some degree of fibrosis and may progress to cryptogenic irreversible liver cirrhosis, culminating in organ failure with a predisposition to development of hepatocellular carcinoma.[5,6] Majority (70-80%) of obese subjects has the first stage of NAFLD[7] and the risk increases with increases in BMI.[1]

In early stages of NAFLD, as patients remain asymptomatic, it is incidentally diagnosed by 1) persistent elevation of liver enzymes, particularly ALT in liver enzyme studies, which often increases up to three times its normal value[8], 2) ultrasonography of abdomen revealing increased echogenicity with respect to kidney and macro-vesicular fat accumulation increasing the liver weight by 5-10% (fatty liver) and 3) liver biopsy, the gold standard to confirm the diagnosis, determining the severity of NAFLD. Mass screening for significant liver injury in NAFLD patients will be a daunting medical challenge in the years to come because of the epidemics of obesity and diabetes. Our inability to face this challenge makes the noninvasive, readily available and easy to perform serum markers a high priority. Evaluation of aminotransferases enzymes in daily practice may serve as surrogate markers for screening of fatty liver disease.[9]

The serum enzymes those are most commonly used in evaluating liver function are ALT (alanine aminotransferase), AST (aspartate aminotransferase), ALP (Alkaline phosphatase) and GGT (γ-glutamyl transferase). The serum liver enzymes, ALT, AST and GGT are broadly used as indicators to assess the level of liver injury,[10,11] and ALP for biliary integrity.[12] Increased body weight and obesity are well-known risk factors for elevated serum liver enzyme values especially for ALT, both in adult and children irrespective of sexes.[13-16] Increased total body fat is associated with elevated serum ALT, AST and GGT activities in men and is associated with elevated ALT, GGT as well as ALP and LD activities in women.[17] By far very few studies have yet been done in our country to find the direct relation between obesity and levels of serum hepatic enzymes. The present study was, therefore, designed to evaluate the association between overweight/obesity and serum hepatic enzymes.

METHODS:

On obtaining approval from the Ethical Review Committee, Rajshahi Medical College, Rajshahi this cross-sectional analytical study was conducted in the Department of Physiology in collaboration with the Department of Biochemistry of the same Medical College over a period of one year between July 2018 to June 2019. A total of 33 overweight and obese individuals aged 18-65 years were consecutively included in the study as case, while an equal number sex-matched adult individuals from Rajshahi city was taken as control

group. As Asian tends to have high levels of body fat at low BMI[18] and at any given BMI above 25 kg/m^2, the respective mortality risk was higher among Asians in comparison to their US counterpart.[19-20] So, in 2000, the western pacific regional office of WHO (WPRO) proposed a lower cut-off definition of overweight (BMI 23-24.9 kg/m^2) and obesity (BMI ≥25 kg/m^2) for Asian populations. Accordingly, overweight and obese (BMI ≥23 kg/m^2) adult individuals from Rajshahi city as cases and healthy adults with normal BMI (18.5-22.9 kg/m^2) as control were included in the study. However, patients with known case of acute and chronic liver disease, individuals taking hepatotoxic/hepatic enzymes inducer drugs- Methotrax, paracetamol, NSAID, anti-TB drugs (e.g., INH), Antipsychotics (e.g., Chlorpromazine, Risperidone etc.), corticosteroids etc. and individuals with history of liver injuries including liver surgery, known alcoholics, diabetic patients and patients suffering from hypothyroidism or any known endocrine diseases, renal, cardiovascular or respiratory diseases were excluded. Pregnant women were also discouraged from participating in the study.

Physical examination was done at entry. Then after overnight fasting 5 ml of whole blood was collected from anterior cubital fossa by venipuncture, using 21-gauge hypodermic needle and was taken in a sterile container. It was allowed to clot and then centrifuged at 4000 rpm for about 10 minutes at room temperature (29^{0}C-31^{0}C) to separate serum. Serum ALT, AST and ALP were estimated using Kinetic test reagent (Agappe Diagnostics, Switzerland) Kits and GGT by Biolabo reagent kits, France on automatic Biochemical Analyzer (EMP-168, Hamburg, Germany) according to the manufacturer's recommendations.

Data were processed and analyzed using SPSS (Statistical Package of Social Sciences) software program for windows, version 25.0. Test statistics used to analyze the data were descriptive statistics, Chi-square (χ^2) and Unpaired t-Test. While categorical data were compared between case and control groups using Chi-square (χ^2) or Fisher's Exact Probability Test, continuous data were compared between groups using Unpaired t-Test. The risk of having elevated liver enzymes in overweight/obese individuals was estimated with Odds Ratio (OR) along with its 95% confidence interval. The level of significance was set at 0.05 and p-value less than 0.05 was taken as significant.

RESULT:

Demographic characteristics between case and control groups:

Age distribution shows that one-third (33.3%) of the cases was 21 – 30 years old and 27.3% 31- 40 years old. Together they constitute over 60% of the cases. In contrast 36.4% of the controls were formed of subjects of < 20 years old and 27.3% with subjects of 21-30 years old. The cases were somewhat older than the controls, although the difference between the two groups was not statistically significant (p=0.576). Over one-quarter of the cases (27.3%) was service- holder, another one-quarter (27.3%) housewife and 36.3% were students. In the control group, students formed the main bulk (45.5%) followed by service-holder (30.3%), other occupants (15.1%) and housewife (9.1%). The two groups were almost homogeneous in terms of occupation (p = 0.339). The lower middle class was predominant in the control group (60.6%) compared to that in the cases (45.5%). Around one-quarter of both cases and control were poor. The two groups were almost identical with respect to social class (p = 0.287). Nearly half (45.5%) of both cases and controls were higher secondary level educated followed by primary and secondary level (30.3% & 45.5% respectively) and graduate plus (18.1 and 24.2% respectively). No difference was observed between the groups with respect to level of education (p = 0.174) (Table I).

Association between overweight/obesity and serum hepatic enzymes:

All the serum hepatic enzymes except GGT were found to be significantly elevated in the case group than those in the control group ($p < 0.001$) (Table II). The cases invariably exhibited elevated serum ALT and AST as opposed to 3 and 9.1% of the controls respectively ($p < 0.001$) (Table III).

Correlation between BMI and serum hepatic enzymes:

Fig. 1 to Fig. 4 shows the correlations between BMI and serum hepatic enzymes. The BMI and serum ALT bear a significantly linear relationship ($r = 0.709$, $p < 0.001$) (Fig. 1). Similarly, BMI and AST and BMI and ALP exhibit significantly positive correlation ($r = 0.718$, $p < 0.001$ and $r = 0.545$, $p < 0.001$ respectively) (Fig. 2 & Fig. 3). However, BMI and GGT does not bear any significant correlation ($r = 0.092$, $p = 0.467$) (Fig. 4).

Correlation between waist circumference and serum hepatic enzymes:

Fig. 5 to 8 depict the correlations between waist circumference and serum hepatic enzymes. The waist circumference and serum ALT exhibit a significantly linear relationship ($r = 0.703$, $p < 0.001$) (Fig. 5). Similarly, waist circumference demonstrated its significantly linear relationship with AST and ALP ($r = 0.772$, $p < 0.001$ and $r = 0.574$, $p < 0.001$ respectively) (Fig. 6 & Fig. 7). However, waist circumference and GGT does not bear any significant correlation ($r=0.065$, $p=0.606$) (Fig. 8).

Correlation between WHR and serum hepatic enzymes:

Fig. 9 to Fig. 12 demonstrate the correlations between waist to hip ratio and serum hepatic enzymes. The WHR did not bear any significant correlations with serum ALT, ALP and GGT ($r = 0.221$, $p = 0.074$, $r = 0.229$, $p = 0.065$ and $r = -0.002$, $p = 0.988$ respectively) (Fig. 9, 11& 12). However, WHR was observed to be significantly correlated with serum AST ($r = 0.281$, $p = 0.022$) (Fig. 10).

Table I. Comparison of demographic characteristics between case and control groups

Demographic characteristics	Group		p-value
	Case (n = 33)	Control (n = 33)	
Age* (yrs.)			
< 20	7(21.2)	12(36.4)	
21 – 30	11(33.3)	9(27.3)	
31 – 40	9(27.3)	7(21.2)	
41 – 50	5(15.2)	2(6.1)	
> 50	1(3.0)	3(9.1)	
Mean ± SD	31.1 ± 11.1	29.4 ± 12.8	0.576
Occupation*			
Service	9(27.3)	10(30.3)	
Housewife	9(27.3)	3(9.1)	0.339
Student	12(36.3)	15(45.5)	
Others	3(9.1)	5(15.1)	
Socioeconomic status**			
Poor	8(24.2)	9(27.3)	
Lower middle class	15(45.5)	20(60.6)	0.287
Middle class	9(27.3)	3(9.1)	
Upper middle class	1(3.0)	1(3.0)	
Level of education**			
Illiterate	2(6.1)	1(3.0)	
Primary and secondary	10(30.3)	9(27.3)	0.174
Higher secondary	15(45.5)	15(45.5)	
Graduate plus	6(18.1)	8(24.2)	

*Data were analyzed using **Unpaired t-Test** and were presented **as mean ± SD**. **Data were analyzed using **Chi-squared** (χ^2) **Test.** Figures in the parentheses denote corresponding percentage

Table II. Comparison of levels of serum hepatic enzymes between groups

Hepatic enzymes	Group		p-value
	Case (n = 33)	Control (n = 33)	
Serum ALT (U/L)	64.7 ± 12.4	40.5 ± 7.9	< 0.001
Serum AST (U/L)	56.8 ± 6.7	40.7 ± 6.4	< 0.001
Serum ALP (U/L)	196.1 ± 19.1	169.2 ± 18.5	< 0.001
Serum GGT (U/L)	5.8 ± 1.9	5.7 ± 1.7	0.957

*Data were analyzed using **Unpaired t-Test** and were presented **as mean ± SD**.

Table III. Association between overweight/obesity and hepatic enzymes

Hepatic enzymes	Group		p-value
	Case (n = 33)	Control (n = 33)	
Serum ALT* (U/L)			
Elevated (> 49)	33(100.0)	1(3.0)	< 0.001
Normal (≤ 49)	0(0.0)	32(97.0)	
Serum AST* (U/L)			
Elevated (> 46)	33(100.0)	3(9.1)	< 0.001
Normal (≤ 46)	0(0.0)	30(91.9)	

*Data were analyzed using **Fisher's Exact Test**. Figures in the parenthesis denote corresponding percentage.

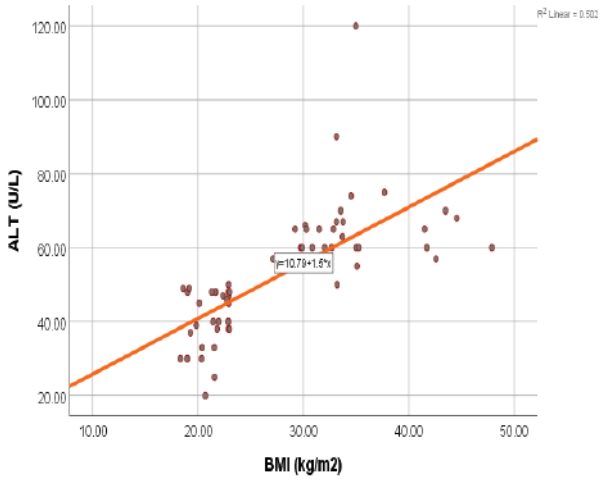

Fig. 1: Correlation between BMI and ALT

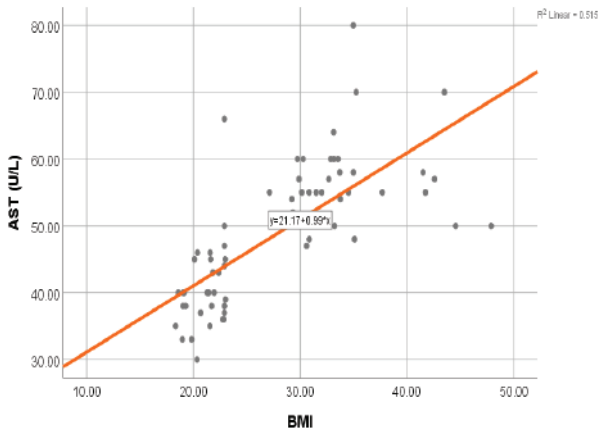

Fig. 2: Correlation between BMI and AST

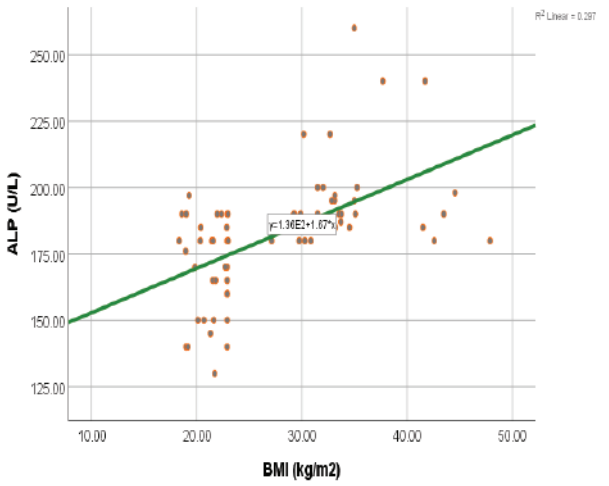

Fig. 3: Correlation between BMI and ALP

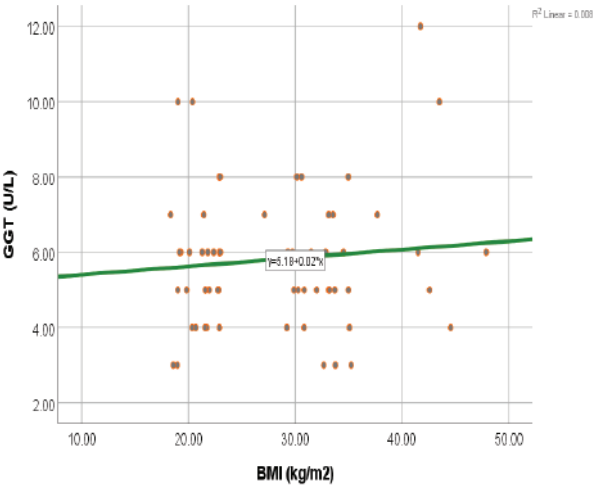

Fig. 4: Correlation between BMI and GGT

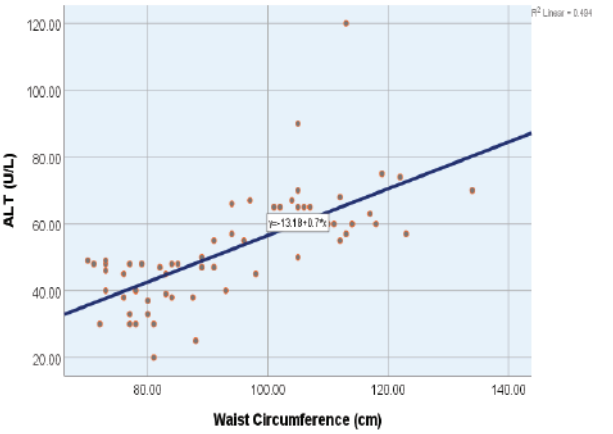

Fig. 5: Correlation between waist circumference and ALT

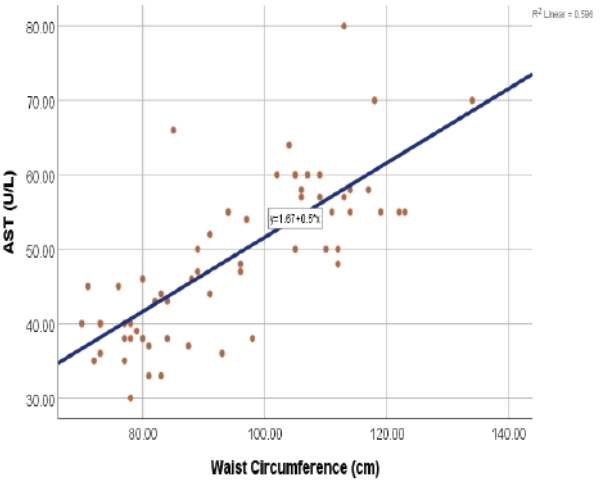

Fig. 6: Correlation between waist circumference and AST

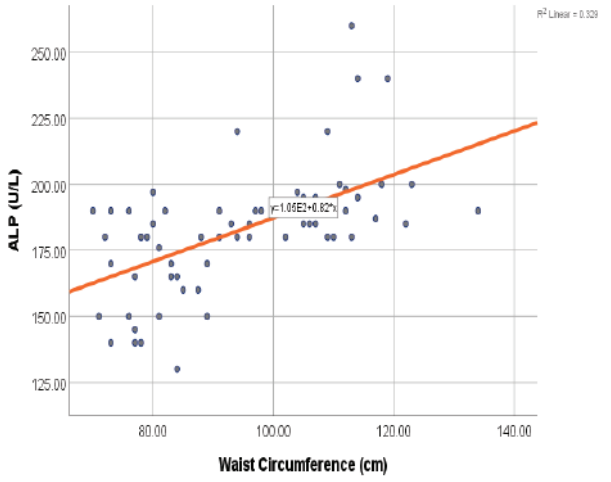

Fig. 7: Correlation between waist circumference and ALP

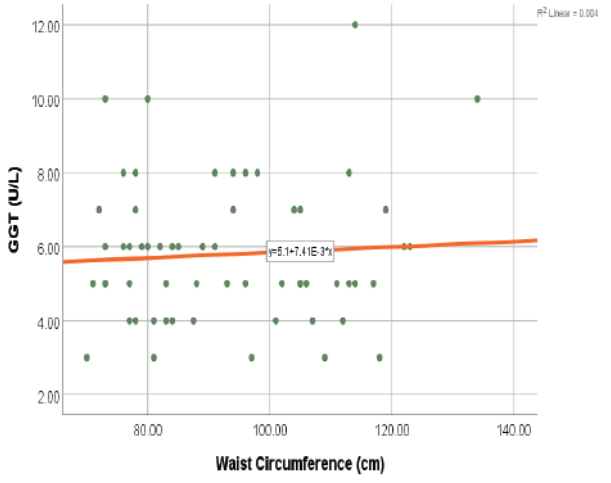

Fig. 8: Correlation between waist circumference and GGT

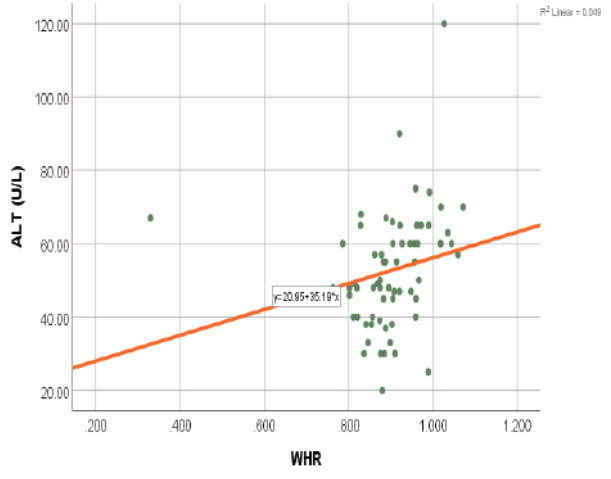

Fig. 9: Correlation between waist to hip ratio (WHR) and ALT

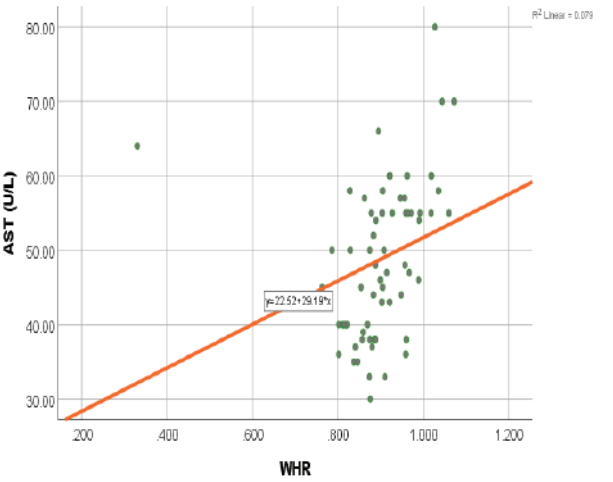

Fig. 10: Correlation between WHR and AST

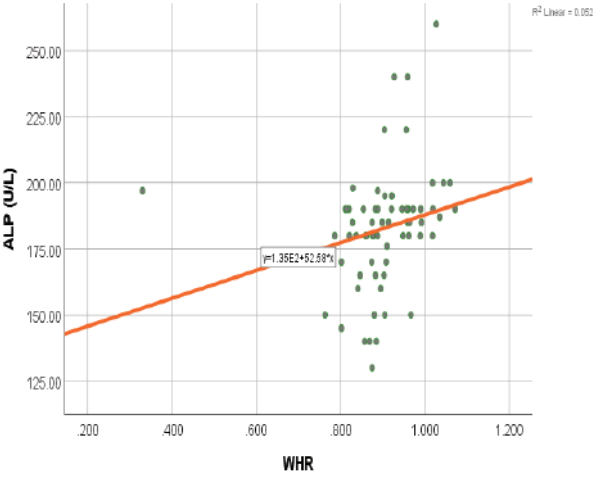

Fig. 11: Correlation between WHR and ALP

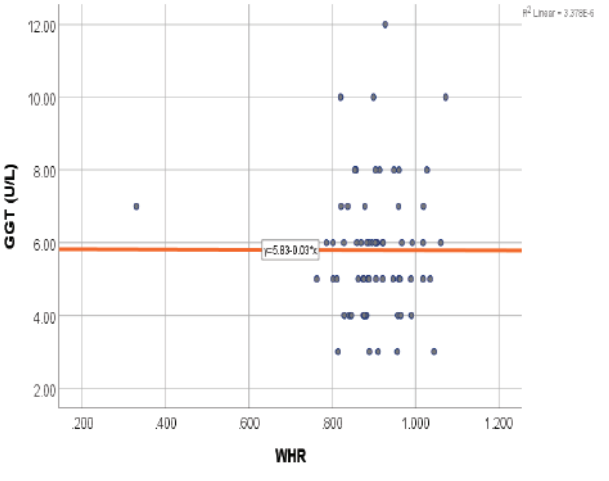

Fig. 12: Correlation between WHR and GGT

DISCUSSION:

Obesity causes liver cell injury causing intracellular enzymes to come out into the circulation and found in increased amount in obese individuals. The present study intended to evaluate the association between overweight/obesity and serum hepatic enzymes showed that all the serum hepatic enzymes except GGT were found to be significantly raised in the overweight and obese individuals than those in individuals with normal BMI. The BMI was found to bear significantly linear relationship with serum ALT, AST and ALP. The correlation coefficients (r-values) indicate that more than 70% of the variations in ALT and AST might be due to changes in BMI, while 54.5% of the variations in ALP might be due to variation in BMI. When waist circumference was correlated with hepatic enzymes, it was found to correlate better than the BMI did with 70.3% of the variations in ALT, 77.2% of variations in AST and 57.4% of variations in ALT being explained by waist circumference. Although limited similar studies were found on online literature search, their findings were compared and contrasted with the findings of the present study to arrive at a conclusion.

Cases & controls were categorized according to their age, religion, occupation, socio-economic status & level of education to reveal the influence of these baseline characteristics on the study. Then the baseline characteristics were compared and found no statistically significant difference of them between two groups or any significant association of them with the groups which might influence the study. So those were not determinants of obesity. But if it was, we used to do regression whether the determinants were independent predictor or not. Whatever, then the estimated hepatic enzymes were compared between the two almost identical groups.

There were significant differences in ALT, AST & ALP levels ($p < 0.001$) between cases and controls. Consistent with the findings of the present study, Strauss et al[21] demonstrated that 60% of adolescents with elevated ALT levels were either overweight or obese with approximately 1% having ALT levels more than 2-fold of the normal level. In another study, the mean levels of serum ALT and AST in men with high fatness were significantly higher than those in men with low fatness ($p < 0.01$).[17] In a group of treatment-seeking obese patients, Marchesini et al[22] divided the study subjects into two groups – Class-I (BMI 25.0 – 29.9 kg/m^2) and Class-II (≥ 30 kg/m^2). Median ALT & AST were observed to be increased with increasing obesity class ($p = 0.001$ and $p = 0.005$) and exceeded normal limits in 21.0% of cases. Sull et al[23] found that across the range of BMI values (<18.5 to ≥ 32 kg/m^2) in man, ALT was estimated to increase by 18.8 U/L and AST by 7.1 U/L. In men, interaction between BMI and alcohol consumption was significant ($p < 0.001$) for ALT & AST, but after adjustment by multiple regression, BMI emerged as independent predictor of increased ALT and AST activities.

Correlation of BMI with serum ALT, AST & ALP exhibit a significantly positive linear relationship ($p <0.05$). However, BMI and GGT does not bear any significant correlation ($p =0.467$) (Fig. 4). Choi[17] also found serum ALT, AST and GGT activities to be correlated significantly with total body fat (TBF) in both overweight men and women. Stranges colleagues[24] evaluated the relation between central fat accumulations, as assessed by BMI and liver function tests (assessed by ALT, AST & GGT). They found waist circumference to correlate better with ALT & GGT levels than do the BMI in both sexes. Their findings supported a role for central adiposity independent of BMI in predicting levels of hepatic enzymes, more likely as a result of unrecognized fatty liver.

The present study demonstrated waist circumference to linearly correlate with serum ALT, AST & ALP ($p <0.05$) even better than BMI does. But waist circumference and GGT did not do so ($p =0.606$) (Fig. 8). Adams et al[25] demonstrated that BMI and waist circumference were strongly associated with ALT and GGT ($p<0.0001$). The risk of an elevated ALT was seven-fold higher with obesity but only two-fold higher with moderate or heavy alcohol use. However, in the present study, WHR did not correlate well with hepatic enzymes (Fig. 9, 11& 12). Only AST

demonstrated a weekly significant correlation with WHR ($r = 0.281$, $p = 0.022$) (Fig. 10). Rhul and associates[26] in their study reported that 65% of the overweight and obese individuals (BMI ≥ 25 kg/m^2) had elevated ALT activity. Although ALT activity was most strongly associated with higher WHR, BMI was not independently related. Contrasting with the findings of the present study and those presented above, Das et al[27] demonstrated no significant association between obesity status and hepatic enzymes (ALT, AST & GGT). They divided the study subjects into normal (BMI 18.5 to 24.9 kg/m^2), overweight (BMI 25.0 to 29.9 kg/m^2) and obese (BMI >30 kg/m^2) and compared the levels of ALT, AST & GGT among the groups and found no significant difference among them in terms of these enzyme activities. However, an increasing trend of these enzymes was evident with increasing obesity.

Normal levels of liver transaminases have been demonstrated in several studies with the entire spectrum of NAFLD, and therefore ALT and AST activity are not supposed to be very useful in predicting NASH.[28-30] Current standards of normal liver enzymes were defined 2 decades ago by using general populations that may have included covert liver pathological conditions such as nonalcoholic liver disease. Prati and colleagues[31] have recently proposed a new normal upper limit of ALT for healthy males and females to be 30 U/L and 19 U/L, respectively revising the previous ones. Therefore, it is of particular interest in investigating the application of the new guidelines. Thence, in order to understand the complex interaction between liver enzymes and obesity, there is a need for undertaking a larger cross-section of the population to elucidate the association.

Strengths and Limitations of the study:

One of the strengths of this study was that we had correlated BMI, waist circumference and also WHR with four serum hepatic enzymes which highlighted the detailed nature of relationship between obesity and serum hepatic enzymes. The limitations of this study were that we had done a cross-sectional study on a smaller sample size. So, a longitudinal study, on a large sample size should be done and effect of gradual weight reduction on hepatic enzymes should be monitored to confirm our findings. Moreover, many other clinical parameters such as fasting lipid profile, ultrasonography of the hepatobiliary system, liver biopsy, blood sugar level etc. could have been correlated.

The overall results of our study presented that serum hepatic enzyme levels are significantly raised in overweight and obese. So, a regular periodic screening program is recommended to work out the reference range of these hepatic enzymes in normal, overweight and obese individuals to establish their relation with the severity of NAFLD.

CONCLUSION:

The study concluded that all the serum hepatic enzymes but GGT, are significantly raised in the overweight and obese individuals than those in individuals with normal BMI. The BMI bears significantly linear relationships with serum ALT, AST and ALP. A substantial proportion of the variations in ALT and AST could be explained by BMI. However, the waist circumference correlates far better than the BMI does, while WHR is not a good predictor of serum hepatic enzymes.

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