Original Article

Obesity Measures and Elevated Levels of Alanine Aminotransferase: A Population Based Study

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ABSTRACT

Background:
Obesity may lead to various morbidity including liver diseases. The present study was done to determine which obesity indices, including body mass index (BMI), waist circumference (WC), waist to hip ratio (WHR), and waist to height ratio (WHtR) have the stronger association with rising levels of alanine aminotransferase (ALT).

Materials and Methods:
Of 6143 subjects aged ≥ 10 years of a cohort study in northern Iran, the data of 5052 subjects were analyzed. We performed multivariate logistic regression analyses for data of men and women, separately. In multivariate analyses the obesity measures were separately included in model in addition to other potential confounders. A high value of ALT was considered as outcome. The capability of obesity indices to discriminate an elevated level of ALT was evaluated using receiver operating characteristic (ROC).

Results:
Based on our results, men and women with obesity showed significantly higher values of liver enzymes for all obesity indices. In multivariate analysis, while WHtR showed the strongest association with a high value of ALT in men [Wald=91.44; OR=3.348, 95%CI (2.613-4.289); *P*<0.001], WC showed the strongest association in women [Wald=26.76; OR=1.724, 95%CI (1.402-2.119)].

Conclusion:
WHtR in men and WC in women have more independent association with elevated levels of ALT.

Keywords: Obesity indices, Alanine aminotransferase, Non-alcoholic fatty liverdisease

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INTRODUCTION

The prevalence of obesity has critically increased worldwide in recent decades(1). Reports show that 74% of men and 65% of women in US are obese or at least overweight(2). Although a reprehensive data in Middle East is rare, the available data emphasize an extremely high prevalence of obesity in this region (3). Moreover, a critical high and rising trend of obesity was reported in Iran (4). Obesity may lead to various comorbidities including, diabetes type 2, cardiovascular

diseases, gastroesophageal reflux disease (GERD), non-alcoholic fatty liver disease (NAFLD), and some malignancies(5-8). Several popular indices were developed to evaluate the obesity, such as body mass index (BMI), waist circumference (WC), waist to hip ratio (WHR), and waist to height ratio (WHtR). Of the mentioned indices, BMI is considered as a general index of obesity while others are utilized as indicators of central obesity.

A close association was reported between obesity and some liver conditions, particularly NAFLD and non-alcoholic stomatohepatitis (NASH). Furthermore, alanine aminotransferase (ALT), aspartate aminotransferase (AST),and gemma-glutamyltransferase (GGT) are usually used as the most important laboratory tests in the diagnosis of liver diseases. Of the above mentioned liver enzymes, ALT is considered as a specific indicator of the pathologies of liver tissue.

Because obesity is considered as an etiology of some liver diseases including NAFLD and NASH, it is expected that there might be an association between obesity and an elevated level of liver enzymes. On the other hand, the population of northern Iran has a high prevalence of metabolic disorders and liver diseases (9-11). Consequently the present study was done to determine which obesity indices, including BMI, WC, WHR, and WHtR have the stronger association with rising levels of ALT and also to determine the discriminatory ability of each of the mentioned indices in the diagnosis of elevated levels of ALT.

MATERIALS AND METHODS

Study participants

Of 6143 subjects aged 10 years and over who were included in a cohort study in northern Iran, the data of 5052 subjects were analyzed. The baseline cohort study was done in Amol, a populated city in northern Iran. Primary health centers were used to collect the data. Sampling method of the cohort study and the schematic diagram of the study participants, as well as study population and design of the study similar to the present study, were explained elsewhere (12,13).

Data collection

Trained healthcare staff measured the weight, height, WC, hip circumference, and blood pressure in health care centers. Assessors measured the height while the participants were standing with their heels and buttocks pressed up against a wall. The midpoint between the lowest costal ridge and the upper border of the iliac crest was determined as WC. The largest circumference between waist and knee was determined as hip circumference.

Blood pressure was measured using a fitted cuff and when the participants were in the sitting position with supported back and uncrossing legs following a minimum 5-minute rest in a quiet room.

A venous blood sample was drawn from each participant after 12-hour fasting to assess fasting blood sugar (FBS) and lipid profiles. All tests, including FBS, triglycerides (TGs), high-density lipoprotein (HDL), low-density lipoprotein, and cholesterol levels were assessed enzymatically using the BS200 Auto analyzer (Mindray, China). For all the participants viral markers for hepatitis B and C along with autoimmune hepatitis screening tests were performed.

Non-alcoholic fatty liver disease (NAFLD) was determined by evidence of hepatic steatosis in sonography without existence of other causes of acute or chronic hepatitis, secondary hepatic fat accumulation such as significant alcohol intake, consumption of steatogenic medication and/or hereditary disorders.

All ultrasound examinations were carried out by a single sonographer who was expert in the field of radiology.

Homeostasis model assessment-insulin resistance (HOMA-IR) was computed using the following formula:

$$\text{HOMA-R}=[\text{insulin}(\mu\text{U/mL}) \times \text{Glucose(mg/dL)}]/405$$

Mean arterial pressure was computed using the following equation: $\text{MAP}=\text{DBP}+\frac{1}{3}(\text{SBP-DBP})$

Ethics

All the participants gave informed consent to participate in the study. The study protocol was approved by the Ethics Committee of Iran University of Medical Sciences, according to Helsinki rules.

Statistical analyses

We performed univariate and multivariate logistic regression analyses for data of men and women, separately. In multivariate analyses, the obesity measures were separately included in model in addition to age, MAP, HDL, TG, HOMA-IR values

Table 1: Mean values of liver enzymes based on age group and sex

	Mean ±SD		
Variable	**Male**	**Female**	***P* value**
18-39			
ALT	29.05±22.54	18.62±14.24	0.001
AST	24.63±10.92	19.44±9.87	0.001
GGT	26.69±16.69	20.91±11.67	0.001
40-64			
ALT	26.24±17.01	20.75±14.24	<0.001
AST	23.92±13.45	20.45±9.96	0.001
GGT	32.69±32.78	28.48±23.70	0.001
≥65			
ALT	19.65±11.10	17.81±11.43	0.039
AST	23.31±14.28	19.86±7.34	0.003
GGT	30.31±39.27	31.87±35.64	0.651

ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma-glutamyltransferase, SD: standard deviation

and NAFLD as independent variables. A high value of ALT was considered as outcome. We considered two versions of high ALT levels as the outcome. Firstly, the western population cutoff points (updated criteria) including ALT≥30 in men and ≥19 in women was considered as the outcome (14). Secondly, ALT values ≥31 in women and ≥41 in men, based on recommendations of related manufacturer accounted as an elevated level of ALT (outcome).

Moreover, the values of obesity indices were categorized to binary variables according to the data of the related literature. Thus, BMI was categorized to a binary variable according to a threshold of 30 Kg/m^2 in women and men, WC according to a threshold of 90 cm in men and women, WHR according to thresholds of 0.85 in women and 0.9 in men, and finally WHtR according to a threshold of 0.5 in women and men (15-18).

The odds ratio and related confidence intervals along with P values were reported. The capability of obesity indices to discriminate an elevated level of ALT was evaluated using receiver operating characteristic (ROC) curve for which the sensitivity of infinite decision thresholds of obesity indices was plotted against their false positive rates. Thus, the related areas under the curves (AUCs) were calculated. The lower boundary line for AUC was considered 0.5. A significantly greater area than 0.5 showed some ability of indices to discriminate patients with an elevated level of ALT. The statistically significant level for all analyses was considered as 0.05. All statistical analyses were conducted using SPSS software version 21(SPSS Inc, Chicago, USA) and STATA software, version 12 (StataCorp, Texas, USA.

RESULT

Of our participants, 56.6% were male. The basic characteristics of the study population were reported elsewhere (13).

Table 1 shows the mean values of liver enzymes based on age group and sex. Except for AST in the age group of 40-64 years and GGT in the age group of ≥65 years, the men had significantly higher values of liver enzymes than women.

Table 2 shows the liver enzymes values based on obesity measures including BMI (BMI<30 and BMI ≥ 30), WC (WC <90 and WC ≥ 90), WHR (WHR < 0.90 and WHR ≥ 0.90 in men and also WHR <0.85 and WHR ≥ 0.85) and (WHtR <0.5 and WHtR ≥ 0.5) in men and women, separately. Based on our results, men and women with obesity showed significantly higher values of liver enzymes for all obesity indices.

Table 3 shows the results of univariate and multivariate logistic regression analyses in men and women separately. In multivariate analyses the obesity measures were separately included in model in addition to age, MAP, HDL, TG, and HOMA-IR values as independent variables. A high value of ALT was considered as outcome. In multivariate analysis, while WHtR showed the strongest association with a high value of ALT in men [Wald =91.44; OR =3.348, 95%CI (2.613-4.289); P<0.001], WC showed the strongest association in women [Wald =26.76; OR =1.724, 95%CI (1.402-2.119)].

Figure 1 shows the discriminatory ability of different obesity measures for diagnosis of a high value of ALT. Based on our findings, while in women different indices almost had the similar ability, in men BMI showed higher ability than other indices.

DISCUSSION

In this study, we evaluated the association between obesity indices and elevated levels of ALT. BMI, WC, WHR, and WHtR were used to evaluate the obesity. Two thresholds of elevated ALT levels were considered

Table 2: Liver enzymes values based on different obesity measures

Obesity measure	Mean ±SD		p-value	Mean ±SD		P value
	Male			Female		
BMI	**BMI<30**	**BMI≥30**	**P value**	**BMI<30**	**BMI≥30**	**P value**
ALT	24.30±16.89	34.04±22.88	<۰,۰۰۱	17.69±11.35	21.63±16.27	<0.001
AST	23.35±12.31	26.18±13.42	<۰,۰۰۱	18.93±6.46	21.13±12.27	<0.001
GGT	27.74±24.44	36.67±30.02	<۰,۰۰۱	22.75±18.19	28.85±24.61	<0.001
WC	**WC<90**	**WC≥90**	**P value**	**WC<90**	**WC≥90**	**P value**
ALT	21.95±15.30	30.22±20.91	<۰,۰۰۱	17.13±11.80	21.41±15.23	<0.001
AST	23.14±13.10	24.69±12.21	۰,۰۰۱	18.92±8.72	20.76±10.32	<0.001
GGT	23.96±14.73	34.76±35.45	<0.001	21.16±15.04	28.72±24.77	<0.001
WHR	**WHR <0.90**	**WHR ≥0.90**	**P value**	**WHR <0.85**	**WHR ≥0.85**	**P value**
ALT	23.38±15.71	29.41±21.32	<۰,۰۰۱	17.62±11.66	21.42±15.72	<0.001
AST	23.36±11.98	24.57±13.24	0.006	19.02±8.80	20.87±10.42	<0.001
GGT	24.44±14.67	35.33±36.86	<۰,۰۰۱	21.55±12.78	29.50±27.00	<0.001
WHtR	**WHtR <0.5**	**WHtR ≥0.5**	**P value**	**WHtR <0.5**	**WHtR ≥0.5**	**P value**
ALT	21.18±15.08	28.97±20.15	<۰,۰۰۱	16.42±13.37	20.27±14.08	<0.001
AST	22.75±10.86	24.57±13.38	0.007	18.86±7.28	20.22±10.15	<0.001
GGT	21.89±11.34	33.74±33.22	<۰,۰۰۱	18.52±8.87	27.15±23.22	<0.001

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, GGT: gamma-glutamyltransferase, SD: standard deviation, WC: waist circumference, WHR: waist to hip ratio, WHtR: waist to height ratio.

as the outcome. Firstly, the western population cutoff points (updated criteria) including ALT ≥30 in men and ≥19 in women. Secondly, ALT values ≥31 in women and ≥41 in men, based on recommendations of related manufacturer. Accordingly, our study showed that obesity had a significant association with elevated levels of ALT. This association was confirmed by applying all obesity indices to evaluate the obesity in our participants. When we evaluated the relationships by removing the confounding effects of age, blood pressure, lipid profiles, and insulin resistance in a multivariate statistical analyses, the associations were confirmed again. Our results also confirmed the associations both in men and women. However, the associations were not identical using different obesity measures or in men and women. While WHtR showed a stronger independent association with elevated values of ALT in men compared with women in multivariate model, WC had a stronger association in women.

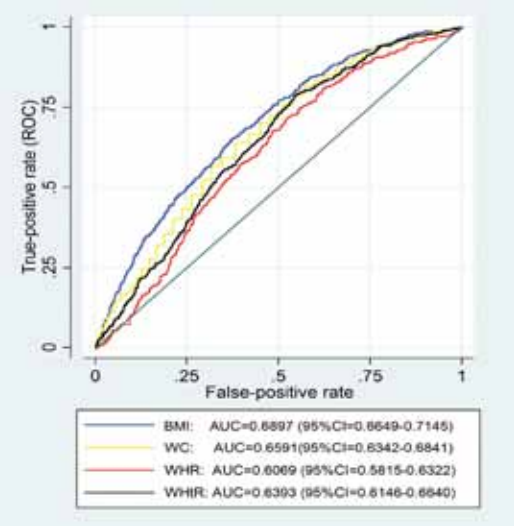
On the other hand, we evaluated the discriminatory ability of obesity indices in the diagnosis of elevated values of ALT. Although all obesity indices showed some degrees of discriminatory ability, these abilities were not good enough. Among obesity measures, BMI showed the best ability in men, while in women the abilities were approximately similar. A part of these differences can be referred to difference in statistical analysis approaches because, we evaluated the discriminatory ability in a univariate model without removing the effects of other confounding variables in ROC analyses. In fact, we aimed to evaluate the discriminatory abilities of obesity indices in whole and consequently an independent discriminatory ability of indices did not matter to us.

As mentioned above, the central obesity indices showed stronger association with elevated levels of ALT than BMI in multivariate analyses. Central obesity may lead to insulin resistance and consequently the related outcomes including, MetS (Metabolic Syndrome) and NAFLD. Obesity and particularly central obesity can lead to predominantly elevated levels of ALT through mediating NAFLD. This issue was confirmed by our study findings, where the association between obesity and elevated levels of ALT was critically diluted in multivariate models when NAFLD was added to the multivariate model, as a confounding variable, compared with

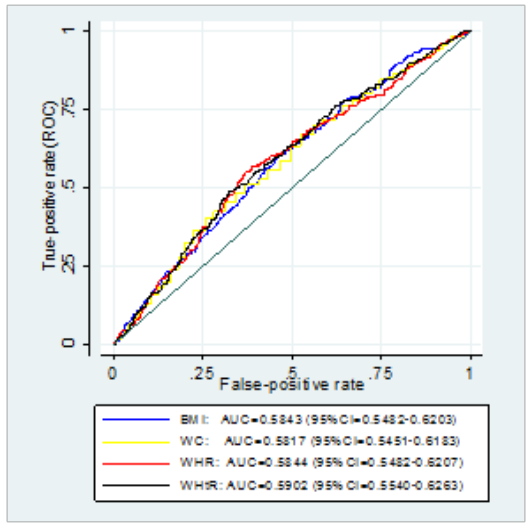
Table 3: The results of univariate and multivariate logistic regression analyses in men and women

Obesity measure	Univariate			Mean ±SD		
	Wald	OR (%95CI)	p-value	Wald	OR (%95CI)	P value
Outcome: ALT ≥30 in men and ALT ≥19 in women						
Men						
BMI	126.62	2.723 (2.287-3.242)	<0.001	33.26	1.837 (1.494-2.258)	<0.001
				4.21*	1.260 (1.010-1.570)*	0.040*
WC	148.35	2.798 (2.371-3.302)	<0.001	73.28	2.500 (2.027-3.083)	<0.001
				21.91*	1.727 (1.374-2.170) *	<0.001*
WHR	65.43	1.909 (1.632-2.233)	<0.001	54.39	2.232 (1.803-2.763)	<0.001
				19.47*	1.657 (1.324-2.073) *	<0.001*
WHtR	112.73	2.774 (2.298-3.350)	<0.001	91.44	3.348 (2.613-4.289)	<0.001
				43.84*	2.411(1.858-3.128) *	<0.001*
Women						
BMI	56.73	1.876 (1.593-2.210)	<0.001	18.91	1.503 (1.251-1.807)	<0.001
				3.63*	1.213(0.994-1.480) *	<0.057*
WC	81.84	2.190 (1.848-2.595)	<0.001	26.76	1.724 (1.402-2.119)	<0.001
				8.83*	1.396 (1.120-1.740) *	<0.003*
WHR	51.25	1.822 (1.546-2.147)	<0.001	10.90	1.419 (1.153-1.746)	<0.001
				4.83*	1.269 (1.026-1.569) *	<0.008*
WHtR	42.81	2.193 (1.733-2.774)	<0.001	9.10	1.556 (1.167-2.073)	<0.003
				3.05*	1.300 (0.969-1.745) *	<0.081*
Outcome: ALT ≥41 in men and ALT ≥31 in women						
Men						
BMI	102.52	3.025 (2.442-3.748)	<0.001	28.24	1.983 (1.540-2.552)	<0.001
				2.81*	1.259 (0.962-1.647) *	0.093*
WC	85.93	3.005 (2.381-3.792)	<٠.<0.001	44.70	2.619 (1.975-3.473)	<0.001
				7.74*	1.562 (1.141-2.139) *	0.005*
WHR	51.55	2.193 (1.770-2.717)	<0.001	56.43	2.961 (2.231-3.931)	<0.001
				21.88*	2.034 (1.511-2.739) *	<0.001*
WHtR	58.26	2.865 (2.186-3.754)	<0.001	48.50	3.272 (2.344-4.568)	<0.001
				14.50*	2.019 (1.406-2.898) *	<0.001*
Outcome: ALT ≥41 in men and ALT ≥31 in women						
Women						
BMI	17.49	1.717 (1.333-2.213)	<0.001	9.15	1.553 (1.168-2.066)	0.002
				1.33*	1.199 (0.881-1.630) *	0.248*
WC	20.82	1.874 (1.431-2.454)	<0.001	9.88	1.688 (1.218-2.339)	0.002
				1.74*	1.267 (0.891-1.802) *	0.187*
WHR	21.59	1.849 (1.427-2.396)	<0.001	13.34	1.840 (1.327-2.552)	<0.001
				7.52*	1.591 (1.141-2.217) *	0.006*
WHtR	7.426	1.693 (1.159-2.473)	0.006	1.655	1.345(0.856-2.113)	0.198
				1.016	1.031 (0.642-1.655) *	0.901*

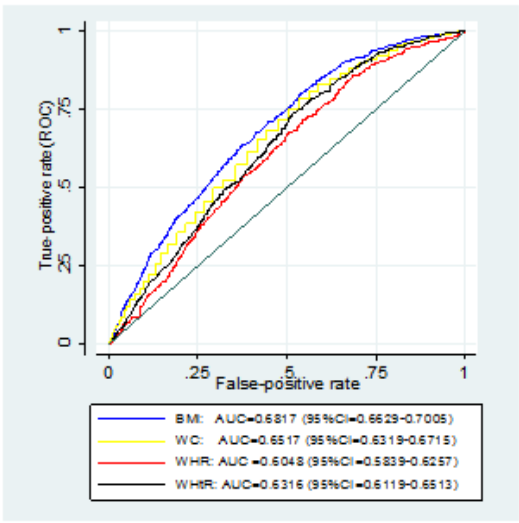
ALT: alanine aminotransferase, BMI: body mass index, WC: waist circumference, WHR: waist to hip ratio, WHtR: waist to height ratio.
*Results of multivariate analysis when NAFLD was added to the model in addition to age, MAP, HDL, TG, and HOMA-IR values as independent variables



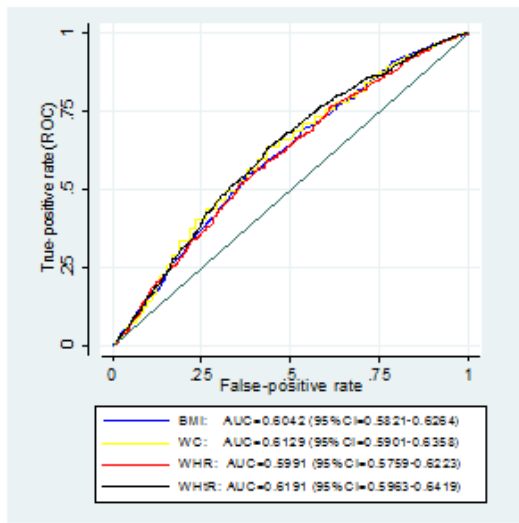
A: Men (outcome: ALT≥41)



B: Women (outcome: ALT≥31)



C: Men (outcome: ALT≥30)



D: Women (outcome: ALT≥19)

ALT: alanine aminotransferase, BMI: body mass index, WC: waist circumference, WHR: waist to hip ratio, WHtR: waist to height ratio.

Fig. 1: Discriminatory ability of obesity indices in the diagnosis of the elevated values of ALT

multivariate models without NAFLD. Elevated values of liver enzymes are related to liver damage and ALT is a specific marker for liver tissue damage. On the other hand adipocyte apoptosis can lead to insulin resistance and hepatic steatosis in both mice and humans (19). A more production of adipokines by adipose tissue in people with obesity and increasing levels of acute-phase proteins and inflammatory cytokines can generally result in low-grade chronic inflammation and consequently insulin resistance. In addition to inflammatory mediated mechanisms, dietary induced obesity can also lead to hepatic insulin resistance and consequently some related liver conditions such as NAFLD and NASH through insulin signaling mechanisms (20).

As mentioned above, a stronger association between obesity and ALT was detected in men than women. As we know NAFLD has more association with male gender than women as it was previously introduced as a male predominant disease (21). We

previously showed that although the prevalence of NAFLD was higher in female gender in northern Iranian population, in multivariate analysis male gender increased the chance of NAFLD (13). On the other hand as discussed above, NAFLD and related conditions have a critical role in elevated levels of ALT in people with obesity. Consequently, it is not too unexpected that we detected a stronger association between obesity and ALT in men than women.

Mean ALT in our study was 26.46±19.0 in men and 19.59±14.03 in women. Our values were critically higher than what reported by Kabir and colleagues particularly in men. It is worth remembering that we evaluated the mean ALT values in a population aged ≥18 years while Kabir and co-workers evaluated it in a population aged≥50 years (23). However, the ALT level was critically decreased in our old participants when we evaluated it in individuals aged 65 and over. Dong and colleagues suggest a close relationship between age and the ALT, so that ALT levels decrease with increasing age independent of adiposity signaling biomarkers, the effects of components of metabolic syndrome, and other liver function tests (24). The lower values of ALT in older individuals can be partially attributed to a lower prevalence of obesity and NAFLD in older individuals, and particularly a decrease in liver function in older people (25-26). On the one hand a progressive reduction in liver size and blood flow and on the other hand the determinant effects of oxidative stress can result in decrease in liver function and thus a lower level of liver enzymes in old people (25-26).

We evaluated the association between obesity and elevated levels of ALT applying four popular obesity measures in men and women separately in a large population based study. We showed all obesity measures had a relationship with elevated levels of ALT both in men and women. We also showed a stronger association between ALT and obesity measures in men than women. Our study also showed that WHtR in men and WC in women had more independently association with elevated levels of ALT. However, the present study had some limitations. Our study had a cross-sectional design, which does not account for an optimal design to evaluate the cause and effect relationships. However, since we evaluated the association between obesity and ALT in which a temporal relationship is determinable, it is not too inappropriate that we can conceptually claim to overcome this problem. On the other hand we used the cutoff points of ALT that are not optimal thresholds for our population. However, applying two different cutoff points of different perspectives and obtaining the similar results of them can certainly lead to a less bias from this aspect.

Our study showed that WHtR in men and WC in women have more independent association with elevated levels of ALT.

CONFLICT OF INTERESTS

Authors have declared that no conflicting interests exist.

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