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GENDER BASED ASSOCIATION OF CLINICAL AND ANTHROPOMETRIC VARIABLES WITH NAFLD –A CASE CONTROL STUDY

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ABSTRACT

Introduction: Non-alcoholic fatty liver disease (NAFLD) is emerging as an epidemic due to increasing prevalence of obesity and metabolic disease. **Objectives:** The study was undertaken to analyze the gender wise anthropometric and clinical characteristics in NAFLD cases and healthy controls and their association with NAFLD .**Materials and Methods:** A total of 160 Cases and 160 Controls with equal number of males and females in each group (n=80) were included. The subjects fulfilled the inclusion criteria for either or cases or controls. Socio demographic information, anthropometric measurements for BMI, WC, WHR WHtR, central (subscapular and suprailiac) and peripheral skin folds (biceps and triceps), percent body fat and clinical parameters (blood pressure)were recorded . **Results**: Males and females with NAFLD had significantly higher central obesity, body circumferences, central and peripheral skin folds, body fat, percent body fat, systolic blood pressure, diastolic blood pressure and pulse in both genders with NAFLD compared to the control group. Central obesity **(**WC, WHR and WHtR) were positively associated with NAFLD in both the genders, the magnitude of risk was however higher in males versus females. On regression analysis, waist circumference showed a positive and significant association with NAFLD after adjustment with co-variables. The risk of NAFLD increased by 8 times when the WC was >80 cm for females/90 cm for males (p<0.001).**Conclusion:** Anthropometric and clinical characteristics were significantly higher in both genders of NAFLD cases versus controls. Central obesity showed a significant association with NAFLD. Waist circumference was identified as a predictor of NAFLD.

Key Words: Non-alcoholic fatty liver disease, anthropometry, central obesity, gender

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is infiltration of fats in the liver (hepatic steatosis) in absence of alcohol intake and other known causes of CLD. (1). It is one of the leading causes of chronic liver disease and affects 25 % of the population globally (2). Its prevalence is reported as 9 % to 32% in India.(3).The prevalence of NAFLD varies across both developed and developing countries ,in both rural and urban areas. The spectrum of NAFLD ranges from simple steatosis (non-alcoholic fatty liver-(NAFL) to non-alcoholic steatohepatitis (NASH) and cirrhosis. NAFL requires the presence of > 5% hepatic steatosis without any evidence of hepatocyte injury compared to NASH which requires the presence of > 5% hepatic steatosis with evidence of inflammation and hepatocyte injury(ballooning (4).NASH may or may not be accompanied by fibrosis.

NAFLD may have equal gender distribution or male preponderance and is prevalent in all age groups (5). NAFLD is associated with risk factors of obesity. The anthropometric measures like Body Mass Index (BMI), Waist to Hip Ratio (WHR) and Weight Height Ratio (WHtR) and other methods of measuring thickness of subcutaneous fat layer at specific sites for estimating body fat percentage could play an important role in the prediction of NAFLD.

BMI is widely used to define obesity. However, it does not take into account the distribution of fat around the body (6).The distribution of body fat, rather than the whole body fat mass, plays a critical role in fat metabolism. Visceral fat is a better predictor than subcutaneous fat for NASH and is related to the severity of NAFLD (7).WC, WHR and WHtR have been considered as alternative indices for abdominal obesity in published studies (8).Hip circumference has a positive correlation with body fat percent, BMI and WC (9).MUAC has a correlation with body circumferences, total adipose tissues along with BMI and WHtR (10). Skin fold thickness measures subcutaneous adiposity which vary in sites like -biceps, triceps, sub-scapular, supra-iliac.

AIMS AND OBJECTIVES

Identification of anthropometric predictors of fatty liver is crucial in clinical practice, since it can be used as an easy and fast method in identifying the disease and improve early detection and management of chronic liver disease. The study was undertaken to analyze the gender wise anthropometric and clinical characteristics in NAFLD cases and healthy controls and their association with NAFLD.

MATERIALS AND METHODS

Study population

A case control study was undertaken in the period of September 2015 to September 2016 at AIIMS, hospital, N Delhi. NAFLD Cases (n=160) and Controls (without NAFLD) (n=160) constituted the study population. The participants were enrolled from the Gastroenterology & Medicine OPDs at AIIMS hospital.

Inclusion Criteria

Adults of both genders (18 - 60 years) who fulfilled the inclusion criteria for either or Cases or Controls were included in the study.

Eligibility Criteria for Cases were (i) Fatty liver on radiological examination (ultrasound) in the previous month (ii) By interview-cum-questionnaire method that the current /recent alcohol consumption (in last six months) is less than 21 drinks on average per week in males and less than 14 drinks on average in females per week.

Eligibility Criteria for Controls were (i) Healthy volunteers who were attendants of participants from the OPD, having similar age & BMI as that of cases (ii) No evidence of fatty liver on radiological examination (ultrasound) in the previous month and (iii) By interview-cum-questionnaire method that the current /recent alcohol consumption (in last six months) is less than 21 drinks on average per week in males and less than 14 drinks on average in females per week (11).

Exclusion criteria for both Cases and controls were (i) Past history of CLD (Chronic Liver Disease) and (ii) history of intake of drugs leading to fatty liver like steroids, tetracycline, tomoxifen, valproic acid, oral contraceptives or corticosteroids (iii) Patients with Type 2 Diabetes, CVD,IBD, HIV infection, pregnant and lactating women (iv) Patients with presence of HBs Ag (Hepatitis B Surface Antigen),anti-HCV (Antibody to Hepatitis C Virus) and anti HIV antibody (vi) Any use of medications for weight loss /participation in weight loss programs. (vii) Providing no consent for the study.

Detailed sample size calculation is published in study by Chaturvedi et al (12).Further the gender based association was done using above referred study data. Equal number of males (n=80) and equal number of females (n=80) comprised the NAFLD Cases and Controls

Sociodemographic data

A pretested questionnaire cum interview schedule was used to collect demographic and household information, based on educational status, occupation and income. (13)

Anthropometric assessment was undertaken by using standard WHO techniques (14) . The height was measured to the nearest 0.1 cm using a stadiometer. Weight was measured to the nearest 100 grams with electronic scale (Seca Model 803). Waist circumference and hip circumference were measured to the nearest 0.1 cm and at a level midway between the lowest rib and the iliac crest and at the level of the great trochanter. Quetelet's ratio was used for calculation of BMI (Weight in kilograms divided by the square of height in meters). Cut offs as per Asian Indian population were used for BMI and Waist - Hip Ratio (15). Body circumferences were measured by non elastic, non stretchable fiber glass tape. Central (sub scapular and supra iliac) and peripheral skin folds (biceps and triceps) were measured by standard techniques. Skin fold thicknesses were measured by using calipers on the right hand side of the body to the nearest millimeter. All skinfold and circumference measurements were repeated 3 times and the 3 values were averaged. Percent body fat of the subjects was estimated by using body composition analyser.

Clinical assessment

It included measurement of Systolic blood pressures (SBP) and Diastolic blood pressures (DBP) which were recorded in a sitting position. An average of three readings was noted after a gap of 5 minutes using an automated blood pressure instrument (Omron HEM-7203, Kyoto, Japan).

Radiological examination

Trained radiologist performed trans-abdominal ultra sonography of the liver using a 1-5 MHz curvilinear transducer (iU22, Philips, Netherlands) after an overnight fast. Based on ultrasound findings of the presence or absence of fatty liver, the study population was divided into cases and controls, respectively In cases, the fatty liver was graded according to standard definition. Brightness and posterior attenuation were considered indices of the extent of fatty infiltration. The diagnosis of fatty liver was be made based on findings of echogenicity: graded as: grade 0: normal echogenicity ; grade 1: slight, diffuse increase in fine echoes in liver parenchyma with normal visualization of diaphragm and intrahepatic vessel borders; grade 2: moderate, diffuse increase in fine echoes with slightly impaired visualization of intrahepatic vessels and diaphragm; and grade 3: marked increase in fine echoes with poor or non-visualization of the intrahepatic vessel borders, diaphragm, and posterior right lobe of the liver (16) **.**

Ethical Considerations

The study was approved by the Institutional Ethics Committee of Lady Irwin College and AIIMS.

Statistical Analysis

Data was analyzed with help of statistical software STATA 14.0.

The continuous descriptive data is presented as means and standard deviation for normally distributed data and as medians and Interquartile range (IQR) for non normally distributed data. Categorical variables are reported as percentages. The main outcome variable was presence or absence of NAFLD. Differences in continuous variables were between both genders was computed with independent t test for normally distributed data and with nonparametric analysis (Mann Whitney U test) for non normally distributed data. Differences between categorical variables were determined by Pearson chi square test or Fishers exact test. All p values were interpreted at the 5 % level of significance. Logistic regression analysis was used to estimate Odds by adjusting confounding factors.

RESULTS

Table 1 shows that males and females with NAFLD had significantly higher adiposity (WC, WHR and WHtR, hip circumference, MUAC, skin folds-biceps, triceps, subscapular, suprailiac, body fat, percent body fat) systolic blood pressure , diastolic blood pressure and pulse compared to the control group ($p< 0.05$).

Table 1 Gender wise comparison of anthropometric variables between NAFLD cases & controls

	Males			**Females**		
Variable	**NAFLD Cases (n=80) Mean ± SD**	**Controls (n=80) Mean ± SD**	**p value**	**NAFLD Cases (n=80) Mean ± SD**	**Controls (n=80) Mean ± SD**	**p value**
Age(years)	40.0 ± 7.82	39.6±7.84		39.5 ±8.98	39.26±9.42	
Height(cm)	167.91±6.37 (153.4-183.5)	164.99±7.74 (150.0-181.4)	**0.013**	156.09±6.25 (139.5-172.5)	154.13±5.75 (142.3-167.4)	0.075
Weight(kgs)	75.11±11.12 (53.5-102.3)	72.26±11.28 (51.8-101.7)	0.112	66.67±10.68 (44.7-96.5)	64.77±10.72 (39-88)	0.248

	Males			**Females**		
Variable	**NAFLD Cases (n=80) Mean ± SD**	**Controls (n=80) Mean ± SD**	**p value**	**NAFLD Cases (n=80) Mean ± SD**	**Controls (n=80) Mean ± SD**	**p value**
BMI (kg/m^2)	26.56±2.92 (20-32.3)	26.53±3.25 (19.1-33.5)	0.855	27.40±3.93 (19.6-37.1)	27.24±4.03 (18-36.1)	0.766
WC (cm)	90.91±7.36 (65.5-112.0)	84.91±6.43 (72-106)	**<0.001**	82.23±8.14 (64-102)	77.18±7.26 (52-93)	**<0.001**
WHR	0.91±0.05 (0.77-1.08)	0.89±0.04 (0.81-0.98)	**0.001**	0.80±0.09 (0.68-1.3)	0.77±0.05 (0.64-0.9)	**0.011**
WHtR	0.54±0.04 (0.39-0.66)	0.51±0.044 (0.38-0.65)	**<0.001**	0.52±0.05 (0.38-0.67)	0.50±0.0.04 (0.36-0.63)	**<0.001**
Hip Circumference (cms)	98.51±6.77 (82-113)	94.27±6.31 (82-110)	**<0.001**	102.55±10.24 (56-120)	99.5±9.00 (74-119)	**0.012**
MUAC (cms)	31.14±3.63 (23-46)	28.73±2.61 (24-36)	**<0.001**	31.43±6.22 (24-61)	29.18±5.14 (18-56)	**<0.001**
Mid thigh (cms)	50.16±5.31 (29-60)	49.18±4.30 (41-61)	0.063	52.13±6.58 (30-64)	51.08±6.45 (31-62)	0.295
Biceps(mm)	12.67±4.26 (4.6-22.4)	9.65±3.58 (3.8-21)	**<0.001**	17.37±6.21 (4.9-32.4)	14.72±6.90 (5-33)	**<0.001**
Triceps (mm)	19.33±5.75 (6-33.4)	16.67±4.66 (7-31)	**0.002**	26.20±5.12 (9.2-38)	24.13±5.74 (9.4-35.4)	**0.010**
Sub scapular (mm)	26.60±7.27 (5-39.6)	22.70±6.20 (10-38)	**<0.001**	30.54±6.13 (12.4-40)	26.78±6.47 (8.2-38.2)	**<0.001**
Supra iliac (mm)	22.50±8.42 (5.4-40)	16.57±5.65 (5.4-32)	**<0.001**	26.18±6.92 (11-39.2)	23.48±7.21 (4.4-39.8)	**0.014**
Body Fat (kgs)	19.75±4.90 (8.3-31.0)	17.95±6.00 (7.5-34)	**0.021**	24.55±6.51 (12.7-41.0)	21.04±5.93 (6.6-35.2)	**0.002**
Percent Body fat	26.05±3.70 (13.8-34.8)	25.08±5.00 (13.6-34.9)	0.080	36.47±4.51 (23.7-45.7)	34.25±5.36 (18.8-45.9)	**0.010**
FFM	52.55±7.31 (38.4-73.9)	55.37±7.11 (43.9-74.8)	**0.015**	39.18±4.53 (28.3-50.2)	41.87±5.11 (29.8-56.1)	**<0.001**
Systolic BP (mmHg) (SBP)	129.3±10.3 (104-166)	121.3±3.6 (112-137.5)	**<0.001**	124.7±5.8 (110-138)	116.5±6.7 (98-128)	**<0.001**
Diastolic BP (mmHg) (DBP)	81.6±6.5 (63-104)	80.1±4.4 (56.5-97)	**<0.001**	81.3±2.8 (70.5-86)	76.6±5.8 (62-85)	**0.001**
Pulse (beats/minute)	81.1±5.2 (69-102)	73.8±4.1 (61-90)	**<0.001**	78.55±5.3 (68-102)	72.2±4.3 (64-96)	**<0.001**

Independent t test applied. Figures in parenthesis denote ranges.
All bold styling expressions are statistically significant (p<0.05).
Abbreviations: WC, waist circumference; WHR , waist hip ratio; WHtR; waist height ratio; FFM, fat free mass; BP, blood pressure

Table 2 shows**,** the prevalence and association of Central obesity and high blood pressure with NAFLD. The prevalence of Central obesity in NAFLD Cases was significantly high when compared to controls .For Waist Circumference the prevalence was 51.2 % in males and 57.5 % in females. For WHR it was 92.5 % in males and 70.0 % in females. Similarly for WHtR it was 86.2 % in males and 68.7 % in females (p<0.05 for all).For high blood pressure the prevalence was 38.7 % in males and 12.5 % in females(p<0.05 for all).

WC, WHR and WHtR were positively associated with NAFLD in both the genders ,however WC ,WHR and WHtR revealed a higher magnitude of risk for males as compared to females. On gender wise analysis there is significant and positive association of high blood pressure with NAFLD in both the genders, however a higher magnitude of risk for males as compared to females was observed.

TABLE 2 Association of Metabolic Risk Factors GENDERWISE with NAFLD using Logistic Regression

Variables	Males				Females			
	Cases (n=80)	Controls (n=80)	p Value	Unadjusted Odds Ratio (CI)	Cases (n=80)	Controls (n=80)	p Value	Unadjusted Odds Ratio(CI)
No	39(48.8)	70(87.5)			34(42.5)	52(65.0)		
Yes	41(51.2)	10(12.5)	0.001	7.3 (3.32-16.28)	46(57.5)	28(35.0)	0.004	2.5(1.32-4.75)
No	6(7.5)	17(21.3)			24(30.0)	42(52.5)		
Yes	74(92.5)	63(78.7)	0.013	3.3(1.23 -8.95)	56(70.0)	38(47.5)	0.004	2.5(1.34-4.93)
No	11(13.7)	28(35.0)			25(31.3)	39(48.7)		
Yes	69(86.3)	52(65.0)	0.002	3.3(1.54 -7.40)	55(68.7)	41(51.3)	0.025	2.09(1.09-3.98)
No	49(61.3)	75(93.7)			70(87.5)	76(95.0)		
Yes	31(38.7)	5(6.3)	0.001	7.2(3.36 -15.79)	10(12.5)	4(5.0)	0.044	2.7 (1.24-4.96)

Categorical variables are presented as sum and percentages/ Data are presented as n (%).

Table 3 shows the regression analysis of anthropometric &clinical variables (high blood pressure) with NAFLD. The anthropometric and clinical parameters variables, namely waist circumference and high blood pressure were found to be the significant risk factors on univariate logistic regression(p<0.05). Due to the co linearity between waist circumference, WHR and WHtR , WC was selected in the regression model. On regression analysis, waist circumference showed a positive and significant association with NAFLD after adjustment with co-variables like age, gender & BMI in the first model and after adjustment of co variables like energy, SFA percent, edible oils, physical activity, parent DM and alcohol intake in addition to age, gender & BMI in the second model. High blood pressure showed no significant association with NAFLD as compared to WC (p>0.05). It was analyzed that the risk of NAFLD increased by 8 times when the WC was >80 cm for females/90 cm for males (p<0.001).

TABLE 3 Regression Analyses of Anthropometric & Clinical Variables with NAFLD

Variable	Unadjusted OR (95% CI)	p value	MODEL 1 OR (95% CI)	p value	MODEL 2 OR (95% CI)	p value
Waist Circumference (>80 cms for Females/90 cms for Males)						
No	1		1		1	
Yes	3.6 (2.25-5.92)	<0.001	8.5 (4.3-16.76)	<0.001	8.0 (3.92-16.47)	<0.001
High BP Systolic ≥130 (mmHg)/85 (mmHg)						
No	1		1		1	
Yes	1.5 (0.93-2.53)	<0.091	1.5 (0.92-2.60)	0.095	1.3 (0.79-2.42)	0.244

Model 1- Adjusted for age, gender, BMI.
Model 2- Adjusted for physical activity, energy, saturated fatty acids (%), edible oils, parent DM & alcohol intake in addition to variables in Model 1.

DISCUSSION

In the present study males and females with NAFLD had greater adiposity (WC, WHR and WHtR, hip circumference, MUAC, skin folds-biceps, triceps, subscapular, suprailiac, body fat, and percent body fat compared to the controls. Similar results with gender differences in WHR were reported (17). Waist circumference was positively correlated with NAFLD severity in women.(18). The findings also revealed that the indicators of central obesity are better predictors of NAFLD risk, however a higher magnitude of risk for males as compared to females was observed. The possible reason could be that body composition differs between males and females. Females are protected from accumulation of fatty tissues in the visceral compartment due to higher leptin levels and higher subcutaneous adipose tissue, along with estrogen production. This is in contrast to males where distribution of adipose tissue is basically visceral, which is associated with insulin resistance along with higher influx of free fatty acids in the portal system, promoting NAFLD formation (19,20).

Waist circumference had the highest association with NAFLD on regression analysis.
WC is considered an alternative marker for the visceral fat and the visceral fat is strongly associated with triglyceride accumulation in liver cells, liver inflammation and liver fibrosis (21).
The mean of hip circumference was found to be significantly higher in NAFLD subjects versus controls in both males and females. Significantly higher values of hip circumference in NAFLD females, not in males have been reported (22). The mean of MUAC was found to be significantly higher in NAFLD cases versus controls in both males and females. Males with NAFLD are at an increased risk of having advanced stage of fibrosis with small peripheral adipose depots (sum of z scores of MUAC & hip circumference) (23). Risk of NAFLD was increased in female subjects with increase in MUAC levels, but this correlation was not reported in males (24). The mean of peripheral skin folds (biceps and triceps), central skin folds (subscapular and suprailiac), mean body fat and percent body fat was found to be significantly higher in both genders of the NAFLD cases compared to controls.

However Malavolti et al. reported significantly higher values of biceps, triceps, subscapular and suprailiac body fat and percent body fat values in NAFLD females, not in males, demonstrating the physiological differences in fat distribution between the two genders.

The mean of SBP, DBP was found to be significantly higher in both genders of the NAFLD cases compared to controls. An increase in BMI and WC was associated with increased risk of developing hypertension in a dose dependent manner, with the highest risk in males, with greatest increase in BMI (25).

In a meta analysis on hypertension it was concluded that there is a 30% risk of increase in HT and pre hypertension with NAFLD (26).

The strength of the study is that findings of present study support the association between anthropometric characteristics and NAFLD after controlling for the potential confounders.
The first limitation included the use of ultrasound, which is the conventional method, non invasive and of low cost for screening of NAFLD as against the liver biopsy which is considered as the gold standard method of screening for NAFLD. Secondly the present study had a retrospective design which is below the prospective study on the evidence hierarchy and presently there are no available prospective studies. Thirdly the effect of poorly measured confounding variables attributable to NAFLD could not be excluded and which may influence the observed associations.

According to the findings of the present study, central obesity (WC, WHR and WHtR) revealed higher magnitude of risk for males as compared to females of the NAFLD group and amongst all anthropometric indicators waist circumference was the predictor of NAFLD. Waist circumference is a simple and accessible index to detect the increased risk of steatosis and can be used in clinical settings for screening of NAFLD patients. More population based studies need to be undertaken gender wise for definitive associations with various anthropometric and clinical characteristics in Indian scenario due to regional variations. NAFLD patients need counseling for reducing weight and to maintain BMI and waist circumference through lifestyle changes (diet and physical activity).

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There are no conflicts of interest

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