Acta Biomed 2024; Vol. 95, N. 2: e2024024 DOI: 10.23750/abm.v95i2.15323

Original article

Obesity's impact on metabolic syndrome clusters and fatty liver incidence in millennial subjects

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Abstract. *Background and Aim:* The expanding mass of adipose tissue amplifies the release of free fatty acids, leading to insulin resistance and the onset of metabolic syndrome. In addition to obesity, metabolic syndrome encompasses four other key components. Metabolic Associated Fatty Liver Disease (MAFLD) is a condition characterized by fatty liver occurring in conjunction with metabolic syndrome. However, research into the influence of obesity within metabolic syndrome on the development of fatty liver, particularly in Indonesia, remains limited. This study seeks to elucidate the impact of obesity on the clustering of metabolic syndrome components in millennials and its role in the development of fatty liver. *Methods:* This cross-sectional study enlisted 91 subjects, subjecting them to screening for metabolic syndrome components and fibroscan examinations to evaluate fatty liver. Statistical analysis encompassed the chi-squared test and multivariate analysis using multiple logistic regression. *Results:* Among the metabolic syndrome components, obesity emerged as the most significant factor associated with fatty liver (P: 0.002; OR 4.7; 95% CI 1.76 – 12.70). The obese group with metabolic syndrome exhibited a significantly higher incidence of fatty liver (75.0%; P: < 0.001) compared to the non-obese group (69.8%). In an analysis comparing central obesity with general obesity, it was revealed that general obesity bore a more substantial relationship with the development of fatty liver than central obesity (P: 0.003 vs. 0.102). *Conclusions:* Obesity represents a substantial risk factor for fatty liver development, especially when combined with metabolic syndrome. Furthermore, general obesity exhibits a more pronounced association with the degree of fatty liver compared to central obesity. (www.actabiomedica.it)

Key words: fatty liver, central obesity, general obesity, metabolic syndrome

Introduction

Fatty liver encompasses a spectrum of liver damage that ranges from simple steatosis to steatohepatitis, advanced fibrosis, and cirrhosis (1). Recently, a panel of 22 international experts proposed diagnostic criteria for Metabolism-Associated Fatty Liver Disease (MAFLD) (2). MAFLD is defined by the presence of hepatic steatosis, which can be evidenced through hisgical examination, imaging studies, or blood biomarkers, in conjunction with at least one of three metabolic criteria: overweight/obesity, established type 2 Diabetes Mellitus, or the presence of metabolic dysregulation characterized by at least two metabolic abnormalities (2–5).

Metabolic syndrome is characterized as a cluster of metabolic disorders that include abdominal obesity, hypertension, dyslipidemia, and glycemic abnormalities (5,6). Based on the Adult Treatment Panel III (2005 revision), metabolic syndrome is established if three or more of the following five criteria are met: (1) Waist circumference >102 cm (men) or > 88 cm (women) (2). Fasting blood glucose > 100 mg/dL (5.6 mmol/L) or diagnosed diabetes (3). HDL cholesterol <40 mg/

dL (1.0 mmol/L) in men, <50 mg/dL (1.3 mmol/L) in women, or taking certain medications (4). Plasma triglyceride levels >150 mg/dL (1.7 mmol/L) or taking certain medications (5). Blood pressure >130/85 mmHg or taking certain medications. Metabolic syndrome is diagnosed based on ATP III, and one of its criteria is waist circumference (WC) as an indicator of obesity as well as body mass index (BMI). In addition, elevated BMI is associated with an increased risk of developing metabolic syndrome and its components, such as insulin resistance, high blood pressure, abnormal lipid levels, and glucose intolerance (7).

Fatty liver is known to be closely associated with various components of metabolic syndrome, as supported by research findings. Approximately 90% of patients with fatty liver exhibit more than one characteristic of metabolic syndrome, and around 33% meet three or more criteria for metabolic syndrome (8,9).

Research conducted by Varanasi et al. identified central obesity and central obesity in combination with diabetes mellitus as the highest risk factors for fatty liver. This underscores that individuals associated with central obesity, either alone or in combination with diabetes mellitus, face a significantly higher risk of developing fatty liver compared to other metabolic combinations (10). However, studies examining the influence of obesity on other components of metabolic syndrome in millennials remain limited. Furthermore, research exploring the relationship between metabolic syndrome clusters and fatty liver remains relatively scarce, especially in the context of the Indonesian population.

We aim to further investigate the differences in the occurrence of fatty liver in obese individuals when using waist circumference criteria compared to BMI. This study is designed to enhance our understanding of the impact of obesity on the clustering of metabolic syndrome components and its role in the development of fatty liver, particularly in the context of millennials in Indonesia.

Materials and methods

Patient population

This research employed a cross-sectional study design conducted from September to October 2023 at Hasanuddin University Teaching Hospital and Dr. Wahidin Sudirohusodo Hospital, Makassar, South Sulawesi. The research population comprised all participants enrolled in the Internal Medicine specialist education program at Hasanuddin University Teaching Hospital (RSP), Central General Hospital (RSUP) and Dr. Wahidin Sudirohusodo. We employed a purposive sampling method, wherein all samples meeting the predetermined inclusion and exclusion criteria were selected from the entire population. A total of 91 subjects meeting both inclusion and exclusion criteria were included in this study.

Eligibility criteria

Inclusion criteria for this study were as follows: participants in the Internal Medicine specialist education program, aged between 25 and 40 years considered as millennials in a previous study (11), non-pregnant females, absence of a history of jaundice, negative HBsAg, and negative Hepatitis C status, and willingness to participate in the study.

Exclusion criteria encompassed the following: history of treatment with steroids, synthetic estrogens, heparin, calcium channel blockers, amiodarone, valproic acid, arsenic, mercury, homeopathic drugs, and antiviral agents; presence of autoimmune hepatitis and coronary artery disease; history of alcohol consumption and drug abuse, including opium and nicotine.

Clinical data and sample collection

The study participants were individuals enrolled in the Internal Medicine specialist education program at Hasanuddin University Teaching Hospital and Dr. Wahidin Sudirohusodo Central General Hospital, Makassar. Eligible participants who met the study criteria and provided informed consent were included. Anthropometric assessments were conducted, and fasting blood samples were collected to measure fasting blood glucose, triglycerides, and HDL cholesterol levels. Subsequently, fibroscan examinations were performed to assess the fatty liver indicator CAP using a dB/m examination unit value.

Statistical analysis

Data analysis was conducted using SPSS version 25. Descriptive statistics and frequency distributions were computed, and statistical tests, including the Chi-square test, were employed. Furthermore, multivariate analysis was performed using Multiple Logistic Regression. Statistical significance was determined with a threshold of P:< 0.05.

Results

Study population

The study encompassed a total of 91 millennial participants who met the research criteria, consisting of 46 males (50.5%) and 45 females (49.5%). The age distribution revealed that the majority, 73 individuals (80.2%), were aged 35 years or younger, with 18 individuals (19.8%) being older than 35 years. The average age of the participants was 32.5 ± 3.2 years. Of the subjects, 5 individuals (5.5%) had a history of disease, while 86 individuals (94.5%) did not have a history of disease (Table 1).

Table 2 presents the frequency distribution of various variables studied according to BMI. Among the participants, the highest number, 33 individuals (36.3%), had an obese BMI. The assessment of obesity based on waist circumference identified 57 individuals (62.6%) as obese. Regarding fasting blood glucose levels, the majority, 88 individuals (96.7%), fell within the normal range. Similarly, 72 individuals (79.1%) had normal HDL cholesterol levels. Concerning triglyceride levels, 77 individuals (84.6%) had normotriglycerides. In terms of blood pressure, 39 individuals (42.9%) exhibited normal readings. When evaluating metabolic syndrome, 15 individuals (16.5%) met the criteria for metabolic syndrome, while 76 individuals (83.5%) did not. In terms of the degree of steatosis, 42 individuals (46.2%) showed no signs of fatty liver, while 21 individuals (23.1%) exhibited a severe degree.

Table 3 displays the mean values of metabolic syndrome components and fatty liver indicators among the study participants. BMI values ranged from 19 to 59 kg/m^2, with an average of 26.3 ± 5.8 kg/m^2. Abdominal circumference measurements ranged from 63 to 130 cm, with an average of 89.4 ± 13.2 cm. Fasting glucose levels varied from 69 to 115 mg/dL, with an average of 88.2 ± 6.9 mg/dL. HDL cholesterol levels ranged from 27 to 95 mg/dL, with an average of 53.7 ± 13.1 mg/dL. Triglyceride levels spanned from 39 to 286 mg/dL, with an average of 95.3 ± 53.3 mg/dL. The CAP values ranged from 100 to 361 dB/m, with an average of 243.7 ± 57.3 dB/m

Relationship of Metabolic Syndrome Components to Fatty Liver

Significant associations with fatty liver were observed in individuals with obesity, as measured by both BMI and waist circumference, hypertension, and low

Table 1. Characteristics of research subjects.

Variable	Frequency	Presentation (%)	Mean ± SD
Gender			
Male	46	50,5	
Female	45	49,5	
Age			32,5±3,2
≤ 35 years old	73	80,2	
>35 years old	18	19,8	
Disease History			
Yes	5	5,5	
No	86	94,5	
Total	91	100%	

Table 2. Frequency distribution of research variables.

Variable	Frequency	Presentation (%)
BMI		
Normal	19	20,9
Overweight	24	26,4
Obese 1	33	36,3
Obese 2	15	16,5
Waist circumference		
Obese	57	62,6
Non Obese	34	37,4
FBG		
Disturbed	3	3,3
Normal	88	96,7
HDL		
Low	19	20,9
Normal	72	79,1
Tryglicerides		
Hypertriglyceridemia	14	15,4
Normal triglyceridemia	77	84,6
Blood pressure		
Normal	39	42,9
Pre hypertension	22	24,2
Hypertension grade 1	25	27,5
Hypertension grade 2	5	5,5
Metabolic Syndrome		
Yes	15	16,5
No	76	83,5
Steatosis		
Absent	42	46,2
Mild	14	15,4
Moderate	14	15,4
Severe	21	23,1

Abbreviations: BMI: body mass index; WC: waist circumference; FBG: fasting blood glucose; HDL: High Density Lipoprotein; TG: Triglycerides.

HDL cholesterol levels (P: <0.001, <0.001, 0.002, and 0.014, respectively). However, there were no statistically significant differences in relation to fasting blood glucose and triglyceride levels (P:0.651 and 0.788, respectively) (Table 4).

Multivariate analysis of the relationship between the metabolic syndrome cluster and fatty liver

The investigation revealed a substantial association between the metabolic syndrome cluster and fatty liver, with obesity determined by both BMI and waist circumference emerging as the most significant component. The Odds Ratio (OR) indicated that individuals classified as obese by BMI had a 4.7 times higher risk of developing fatty liver compared to their non-obese counterparts. Similarly, those classified as obese by waist circumference had a 2.9 times higher risk of experiencing fatty liver compared to non-obese individuals based on waist circumference. The R-squared (R^2) value demonstrated that obesity, as measured by both BMI and waist circumference, contributes to approximately 30% of the incidence of fatty liver (Table 5).

Comparison of fatty liver incidence with obesity limiters

A notable disparity in the incidence of fatty liver was observed between individuals in the obese group with metabolic syndrome (75.0%) and those in the non-obese group with metabolic syndrome (69.8%), as indicated by BMI calculations. This difference was statistically significant with a p-value of <0.001. Similar findings were observed in waist circumference calculations (Table 6).

Comparison of the relationship between obesity and the degree of steatosis based on bmi and waist circumference

Statistical analyses of the obese group revealed a significant difference within the general obese subgroup, with a substantial proportion of individuals, totaling 20 samples (55.6%), exhibiting severe degrees of fatty liver. In contrast, within the non-obese subgroup, comprising 12 samples (92.3%), mild to moderate degrees of fatty liver were predominant. The statistical significance of this difference was evident with a p-value of 0.003. Conversely, in the central obese group, no significant difference was observed (P: 0.102) (Table 7).

Table 3. Descriptive statistical values of metabolic syndrome and fatty liver components from research subjects.

Variable	Minimum	Maximum	Mean	SD
BMI (kg/m^2)	19	59	26,3	5,8
WC (cm)	63	130	89,4	13,2
FBG (mg/dL)	69	115	88,2	6,9
HDL (mg/dL)	27	95	53,7	13,1
TG (mg/dL)	39	286	95,3	53,3
CAP Median (dB/m)	100	361	243,7	57,3

Abbreviations: BMI: body mass index; WC: waist circumference; FBG: fasting blood glucose; HDL: High Density Lipoprotein; TG: Triglycerides; CAP: controlled attenuation parameter.

Table 4. Relationship between metabolic syndrome component clusters and fatty liver incidence.

Variable	Fatty Liver		P value*
	Yes	No	
Obesity (BMI)			
Obese	36 (75,0%)	12 (25,0%)	*<0,001*
Non Obese	13 (30,2%)	30 (69,8%)	
Obesity (WC)			
Obese	39 (68,4%)	18 (31,6%)	*<0,001*
Non Obese	10 (29,4%)	24 (70,6%)	
FBG			
Disturbed	2 (66,7%)	1 (33,3%)	*0,651*
Normal	47 (53,4%)	41 (46,6%)	
Hypertension			
Yes	23 (76,7%)	7 (23,3%)	*0,002*
No	26 (42,6%)	35 (57,4%)	
HDL			
Low	15 (78,9%)	4 (21,1%)	*0,014*
Normal	34 (47,2%)	38 (52,8%)	
Triglycerides			
High	8 (57,1%)	6 (42,9%)	*0,788*
Normal	41 (53,2%)	36 (46,8%)	

*Chi Square test. Abbreviations: BMI: body mass index; WC: waist circumference; FBG: fasting blood glucose; HDL: High Density Lipoprotein; TG: Triglycerides; CAP: controlled attenuation parameter.

Discussion

This study sought to compare the incidence of fatty liver between individuals with central obesity and general obesity. The analysis revealed no significant difference in gender distribution between the two groups. However, multivariate analysis unveiled a substantial association between both central and general obesity and an increased risk of fatty liver (P: 0.002; OR 4.7; 95% CI 1.76 – 12.70) compared to other components of metabolic syndrome. Notably, the clusters of central obesity and general obesity, when combined with metabolic syndrome, exhibited a pronounced association with the incidence of fatty liver (75.0% and 68.4%, respectively; P: <0.001 for both). Furthermore, an analysis comparing central obesity with general obesity demonstrated that general obesity had a more significant relationship with the occurrence of fatty liver (P: 0.003 vs. 0.102).

Overweight and obesity play pivotal roles in both metabolic syndrome and the development of fatty liver. The limited capacity of adipose tissue to store lipids results in lipid accumulation in ectopic sites, such as the liver and muscle, leading to insulin resistance through lipotoxic effects (5). Central obesity may exacerbate this situation by impairing the secretion of adipose tissue-derived adipokines, resulting in increased pro-inflammatory cytokines and reduced protective adipocytokines, thus accelerating the development of fatty liver (12).

The accumulation of excess unesterified fatty acids and intracellular lipid content is closely associated with insulin resistance. Normally, adipocytes act as lipid reservoirs during periods of caloric excess and release stored lipids when needed. However, when this storage capacity is exceeded, fatty acids accumulate in

Table 5. Relationship between metabolic syndrome component clusters and fatty liver based on multivariate analysis adjusted by FBG, HDL, hypertension and TG.

Variabel	B	S.E.	Wald	P*	OR	95% C.I	
						Lower	Upper
Obesity (BMI)	1,553	0,504	9,486	0,002	4,7	1,76	12,70
Obesity (WC)	1,071	0,523	4,190	0,041	2,9	1,05	8,13

*Multiple Logistic Regression – Backward Method adjusted by FBG, HDL, Hypertension, and TG. R^2 = 0,300. Abbreviations: BMI: body mass index; WC: waist circumference; FBG: fasting blood glucose; HDL: High Density Lipoprotein; TG: Triglycerides.

Table 6. Comparison of fatty liver incidence with obesity limiters.

Variable	Obese with metabolic syndrome		Non obese with metabolic syndrome		P value*
	Fatty liver		Fatty liver		
	Yes	No	Yes	No	
BMI	36 (75,0%)	12 (25,0%)	13 (30,2%)	30 (69,8%)	<0,001
WC	39 (68,4%)	18 (31,6%)	10 (29,4%)	24 (70,6%)	<0,001

*Chi Square test. Abbreviations: BMI: body mass index; WC: waist circumference.

Table 7. Comparison of the relationship between obesity and fatty liver degree based on BMI and waist circumference.

Variables	Fatty Liver		P value*
	Mild/ Moderate	Severe	
BMI			0,003
Obese	16 (44,4%)	20 (55,6%)	
Non Obese	12 (92,3%)	1 (7,7%)	
WC			0,102
Obese	20 (51,3%)	19 (48,7%)	
Non Obese	8 (80,0%)	2 (20,0%)	

*Chi Square test. Abbreviations: BMI: body mass index; WC: waist circumference.

ectopic sites like muscles, liver, and visceral fat, playing a pivotal role in the etiology of insulin resistance (8).

In this study, no significant differences were observed in blood glucose levels (P: 0.651), possibly due to limited variability among the samples. Only three out of 91 subjects displayed disturbed glucose levels, while the majority had normal glucose levels. However, previous research has indicated that fatty liver significantly contributes to insulin resistance by reducing adiponectin production, thereby limiting insulin sensitivity and glucose absorption (13–15).

A similar situation arose with triglyceride levels, where no significant differences were detected (P: 0.788). The relatively small number of samples with hypertriglyceridemia (14 out of 91) may have limited the ability to assess the relationship between triglycerides and fatty liver in this study. Previous investigations have highlighted that triglycerides play a central role in fatty liver, with stronger associations than other parameters such as blood glucose and HbA1c (16–19).

Several studies have explored metabolic syndrome component clusters as predictors of fatty liver (20–22). Bhargav et al. (10) identified the highest-risk groups as those including central obesity and central obesity with diabetes mellitus, emphasizing that central obesity, alone or in combination with diabetes mellitus, poses the greatest risk for fatty liver compared to other metabolic syndrome combinations. In contrast, Pang et al. (12) concluded that central obesity exerts a more substantial influence on fatty liver than general obesity. Our study, however, indicates that general obesity may have a more significant impact than central obesity. This difference could be attributed to the characteristics of the population under study.

A strength of this research lies in the utilization of fibroscan as a reliable and noninvasive method for assessing the degree of fatty liver. This approach offers

a convenient and expeditious means for clinicians to evaluate fatty liver in a clinical setting.

Nonetheless, the study is not without limitations. First, its cross-sectional design does not allow for the establishment of causal relationships. A cohort study would be more appropriate to investigate these relationships. Second, the exact onset of fatty liver and obesity among the participants remains unknown. Third, conducting Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) tests on the samples would have provided additional insight into insulin resistance.

Conclusions

The occurrence of fatty liver is notably higher in the obese group with metabolic syndrome than in the non-obese group with metabolic syndrome. In terms of the association with the degree of fatty liver, general obesity demonstrates a significant relationship compared to central obesity.

Based on these findings, the following recommendations are suggested: Healthcare providers should prioritize interventions aimed at obesity prevention and management as a means to reduce the risk of metabolic syndrome and fatty liver among individuals, particularly those in the millennial age group. Clinicians should consider assessing and monitoring individuals with metabolic syndrome for fatty liver, especially when obesity is present, in order to facilitate early detection and management. Public health campaigns should raise awareness about the potential health risks associated with obesity and the importance of maintaining a healthy weight through lifestyle modifications, including diet and physical activity.

Further research is warranted to explore the nuanced relationships between obesity, metabolic syndrome components, and fatty liver in diverse populations to better inform tailored preventive strategies and interventions.

Acknowledgements: This research was supported by the Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia.

Ethic Committee: This research was approved by the Ethics Committee of Biomedical Research on Humans, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia. Based on recommendation letter Number: 697/UN4.6.4.5.31/PP36/2023, September 15th, 2023 and duration of the study approval from 15 September 2023 to 15 September 2024 with protocol number: UH23080631

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

Authors Contribution: WPA (Concept, Design, Resources, Materials, Data Collection and Processing, Analysis and Interpretation, Literature Search, Writing Manuscript). HS Concept, Design, Supervision, Analysis and Interpretation, Literature Search). AMLP (Concept, Design, Supervision, Analysis and Interpretation, Literature Search). SB (Concept, Design, Critical Review). HI (Concept, Design, Critical Review). AS (Concept, Design, Analysis and Interpretation, Critical Review).

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Received: 22 October 2023
Accepted: 22 November 2023
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