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EFFECT OF OBESITY ON THE RELATIONSHIP BETWEEN NONALCOHOLIC FATTY LIVER DISEASE AND GLOMERULAR FILTRATION RATE

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ABSTRACT Background: Obesity is a significant risk factor for the incidence of NAFLD and also associated with the prevalence of CKD). In obesity, especially at the beginning, are related to the increase of GFR, in which GFR may increase 150-200% depending on the degree of obesity. This study was conducted to determine the effect of obesity on the relationship between NAFLD and GFR.

Method: This was an analytical study with a cross-sectional design. Subjects were men and women aged from 18-80 years with abdominal ultrasound indicated fatty liver in Wahidin Sudirohusodo Hospital, Makassar, Indonesia.

Result: The proportion of subjects with GFR <90 ml/min/1.73 m2 was found to be significantly higher in the NAFLD than in non NAFLD (59,6% vs 45,9%, p< 0.05) and subjects with stage 3-4 CKD (GFR <60 ml/min/1.73 m2) was found to be significantly higher in the NAFLD (34,0% vs 14,9%, p< 0.05). The proportion of subjects with GFR <90 ml/min/1.73 m2 was found to be significantly higher in non-obese than in obese (68,4% vs 51,0%, p< 0.05). In the NAFLD, it was found that the proportion of subjects with GFR < ml/min/1.73 m2 was significantly higher in non-obese than in obese (74,1% vs 54,45, p< 0.05). In the non NAFLD, the proportion of subjects with GFR < 90 was also higher in non-obese than in obese (56,0% vs 40,8%, p< 0.05).

Conclusion: Obese with NAFLD have higher GFR compared to non-obese subjects with NAFLD.

KEYWORDS Obesity, nonalcoholic fatty liver disease, glomerular filtration rate.

Introduction

Obesity is a significant health problem in the world and a multifactorial disease that occurs due to the accumulation of excessive fat tissue that can interfere with health status. Obesity is a complex abnormality in the regulation of appetite and energy metabolism which is controlled by several specific biological factors. Physiologically, obesity is defined as a condition with abnormal or excessive fat accumulation in adipose tissue and measured by body mass index (BMI) $\geq$ 30 kg/m2. [1,2] Obesity is associated with a spectrum of liver abnormalities, known as NAFLD, which is characterized by an increase in intra-hepatic triglyceride (IHTG) levels (e.g. steatosis) with or without inflammation and fibrosis (e.g. steatohepatitis). [3] Obesity is currently associated with the risk of NAFLD. In the USA, every 1 of 20 people are at risk of obesity and have BMI > 40 kg/m2. While in the UK, the prevalence of obesity is increasing with average reported cases approximately 23%. [4] Obesity and the risk of renal impairment are associated with several mechanisms; one of them is glomerular hyperfiltration. Glomerular

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Table 1 Subjects characteristic

Variable		n	%
Sex	Men	154	55,6
	Women	123	44,4
IMT	Underweight	5	1,8
	Normoweight	74	26,7
	Overweight	58	20,9
	Obese 1	98	35,4
	Obese 2	42	15,2
Obesity	Obese	198	71,5
	Non Obese	79	28,5
Stage CKD/GFR	Stage 1 (≥90)	122	44,0
(ml/min/1,73m2)	Stage 2 (60-89)	75	27,1
	Stage 3 (30-59)	71	25,6
	Stage 4 (15-29)	9	3,2
Stage CKD	Stage 3-4 (15-59)	80	28,9
	Stage 1-2 (60-≥90)	197	71,1

hyperfiltration is commonly found in obese subjects caused by increased sympathetic activity, increase angiotensin II levels and hyperinsulinemia. Glomerular hyperfiltration is a condition characterized by an increase in glomerular capillary pressure as a result of the rise of blood flow into the kidney. This condition in the short term will increase the GFR, but in the long term it may cause glomerulosclerosis and further renal impairment. Other factors that may cause renal impairment in obese subjects are lipotoxicity and chronic inflammation.

It knows that obesity is a significant risk factor for the incidence of NAFLD and also CKD, in this case, the decrease of GFR. On the other hand, obese subjects, especially at the beginning, are associated with the increase of GFR, in which GFR may increase 150-200% depending on the degree of obesity. This study was conducted to determine the effect of obesity on the relationship between NAFLD and GFR.

Method

This was an analytical study with a cross-sectional design. The study was conducted in Wahidin Sudirohusodo Hospital, Makassar, Indonesia from July-December 2018.

It has been approved by the ethics committee of the Faculty of Medicine of Hasanuddin Univesity with reference number: 17 / UN4.6.4.5.3.1 / PP36-KOMETIK / 2019

Population

Subjects were men and women aged from 18 - 80 years with the results of abdominal ultrasound indicate fatty liver. Abdominal ultrasound performed by the hepatologist makes the diagnosis of fatty liver. While the exclusion criteria are subjects with hepatitis B, hepatitis C, hepatic cirrhosis, hepatoma, malignancy, and alcoholism.

Method and data collecting

Subjects underwent anamnesis, physical examination, laboratory tests and abdominal ultrasound. A retrospective analysis was conducted to identify risk factors that could influence GFR changes

Statistic analysis

Using SPSS version 22. Statistical calculations are given in descriptive, frequency distribution and using Paired-t-test, Independent-t-test and Chi-Square. The results are significant if $p < 0.05$.

Result

The subjects studied were between 18-86 years old with a mean age of 49.1 ± 12.6 years, men subjects (55.6%) and individuals with obese (71.5%). Table 2 shows the proportion of NAFLD found to be higher in obese (75.3%) than in non-obese (68.4%), but not statistically significant ($p > 0.05$). Because it was not significant, the OR value was assumed to be 1 (which means that the risk of suffering from NAFLD in obese is substantial, not significantly different from non-obese).

Table 3 shows the proportion of subjects with GFR < 90 ml/min/1.73 m2 found to be significantly higher in non-obese subjects than in obese subjects, (68.4% vs 51.0%, $p < 0.05$). This shows that there is a significant relationship between obesity (non-obese) and GFR reduce < 90 ml/min/1.73 m2. Based on the OR value, obese subjects have a risk lower than non-obese to suffer from GFR reduce < 90 ml/min/1.73 m2 or it could also be said that non-obese subjects have a greater risk 2 times than obese subjects for suffering GFR reduce < 90 ml/min/1.73 m2.

In the NAFLD group, the proportion of subjects with GFR < 90 ml/min/1.73 m2 was significantly higher in non-obese subjects compared to obese subjects (74.1% vs 54.4%, $p < 0.05$). In the non-NAFLD group, the proportion of subjects with GFR < 90 ml/min/1.73 m2 was also higher in non-obese subjects (56.0%) than in obese subjects (40.8%), but statistically not significant ($p > 0.05$). Based on the above, it can be concluded that non-obese NAFLD subjects were more at risk for suffering GFR reduce < 90 ml/min/1.73 m2 compared to non-NAFLD subjects or obese subjects (table 4).

Discussion

Subject included in this study were from the obese and non-obese group and also from NAFLD and non-NAFLD group. A total of 277 patients with NAFLD, 154 subjects (55,6%) were men. From CKD staging, in this study found 122 (44%) subjects with GFR > 90 ml/min/1.73 m2 (stage 1), 75 (27,1%) subjects with GFR 60-89 ml/min/1.73 m2 (stage 2), 71 (25,6%) subjects with GFR 40-59 ml/min/1.73 m2 (stage 3) and 9 (3,2%) subjects with GFR 15-29 ml/min/1.73 m2 (stage 4). Obese subjects found to be higher in the NAFLD group (73.4%) than non-NAFLD (66.2%), but not statistically significant ($p > 0.05$). This showed that obese subjects have a high risk of NAFLD, even though non-obese subjects can also cause NAFLD. This research is in line with the research conducted by Patell et al. [7] about the association of NAFLD and obesity conducted in 60 obese subjects who had BMI > 30 kg/m2 and showed a significant result in which NAFLD subjects had BMI 36.15 ± 4.20 weather in non-NAFLD subjects 33.54 ± 4.19. This study showed that the risk of NAFLD was greater in obese subjects. BMI has been used to correlate the risk among obese patients. Higher BMI means

Table 2 Distribution of NAFLD according to Obesity

Obesity			Group		Total		
			NAFLD	Non NAFLD		p	OR (95% CI)
	Obese	n	149	49	198		
		%	75,3%	24,7%	100,0%		
	Non	n	54	25	79		
	Obese	%	68,4%	31,6%	100,0%	0,241	1,4 (0,8 – 2,5)
Total		n	203	74	277		
		%	73,3%	26,7%	100,0%		

Table 3 Distribution of GFR according to Obesity

Obesity			GFR		Total		
			<90	≥90		p	OR (95% CI)
	Obese	n	101	97	198		
		%	51,0%	49,0%	100,0%		
	Non	n	54	25	79		
	Obese	%	68,4%	31,6%	100,0%	0,009	0,5 (0,3 – 0,8)
Total		N	155	122	277		
		%	56,0%	44,0%	100,0%		

that more fat in the body and can directly correlate with higher risk of complications from obesity including DM, hypertension and dyslipidemia. According to our study, obese patients were known as risk factors for NAFLD.

Loomis et al. [8] showed that the risk of NAFLD /NASH increased linearly with BMI, so the risk of NAFLD/NASH was 5-9 times higher in BMI 30-32.5 kg/m2, 10-14 times higher with BMI 37.5-40 kg/m2 compared to patients with BMI of 20-22.5 kg /m2. This study divided into two large groups which involved two centres in their study, the results of the study showed that obese patients with a mean BMI 28.14 ± 6.43 kg /m2 had a higher risk of NAFLD compared with mean BMI 26.81 ± 5.57 kg /m2.

The increasing prevalence of obesity is associated with risk of morbidity and mortality. Therefore, in addition to measuring BMI, waist circumference was also measured to assess obesity. The presence of intra-abdominal fat has been proven to be the main cause of insulin resistance. Insulin resistance is also a major mechanism in the pathogenesis of NAFLD/ NASH. [9]

In this study, the GFR value was higher (60.6 ± 28 ml/min/1.73 m2) in patients with obese compared with patients with non-obese (53.3 ± 22 ml/min/1.73 m2) and showed that the proportion of subjects with GFR <90 ml/min/1.73 m2 was found to be significantly higher in non-obese subjects than in obese subjects (68.4 % vs 51.0%, p < 0.05) with OR 0.5 (0.3 - 0.8). In this study, it showed that non-obese subjects have two times risk greater than obese subjects to suffer from GFR reduce < 90 ml/min/1.73 m2. Lemoine et al. [10] in their study conducting 209 obese subjects showed a mean BMI of 34.86 ± 4.6 kg /m2 and were associated with an increase in GFR values. The increasing prevalence of obesity, especially in the Western, is associated with risks for the development of kidney disease. Hormonal factors, oxidative stress, inflammation, and endothelial dysfunction are closely related to obesity and CKD.

Friedman et al. [11] showed that GFR values were linearly associated with total weight (r = 0.59, p < 0.001), lean body mass (r = 0.65, p < 0.001), BMI (r = 0.47, p < 0.001), and BSA (r = 0.60, p < 0.001), and not related to height (r = 0.35, p=0.067) or fat mass (r = 0.14, p = 0.46). While serum creatinine value is inversely associated with fat mass (r = -0.54, p < 0.002) and positively associated with height (r = 0.43, p = 0.021). Obese patients will experience glomerulosclerosis related to obesity, segmental glomerulonephropathy associated with proteinuria and can develop into CKD.

Other studies in 597 men and 329 women in obese subjects showed that the risk of CKD increased threefold in patients with BMI ≥ 25 kg/m2. [12] Study in the US by Hsu, et al. [13] showed that obese subjects with BMI ≥ 30 kg/m2 had a higher risk of CKD compared to people with normal BMI. The risk is three times higher in class 1 obese, six times in class 2 obese, and seven times in class 3 obese. This can be caused by several comorbid factors that concomitant with obesity such as hypertension, diabetes, dyslipidemia and other factors that can trigger an inflammatory condition in the kidneys. The mechanism underlying kidney impairment in obese patients is suspected due to glomerular hyperfiltration and intraglomerular hypertension. This condition will cause glomerulosclerosis and fibrosis in tubulointerstitial and subsequently into CKD.

The cross-sectional study by Pacifico et al. [14] comparing kidney function in NAFLD and non-NAFLD patients with obesity. This study was conducted on 596 subjects consisting of 328 non-NAFLD subjects and 268 NAFLD subjects. The results

Table 4 Distribution of GFR according to Obesity and the NAFLD Group

Group	Obesity		GFR		Total		
			90	90		p	OR (95% CI)
NAFLD	Obese	n	81	68	149		
		%	54,4%	45,6%	100,0%		
	Non	n	40	14	54		
	Obese	%	74,1%	25,9%	100,0%	0,011	0,4 (0,2 – 0,8)
	Total	n	121	82	203		
		%	59,6%	40,4%	100,0%		
Non-NAFLD	Obese	n	20	29	49		
		%	40,8%	59,2%	100,0%		
	Non	n	14	11	25		
	Obese	%	56,0%	44,0%	100,0%	0,215	0,5 (0,2 – 1,4)
	Total	n	34	40	74		
		%	45,9%	54,1%	100,0%		

showed that GFR < 90 ml/min/1.73 m2 was found in 22 subjects (24.4%) in non-NAFLD and 46 subjects (17.5%) in NAFLD with p < 0,0001. These results are in line with our study which showed that in the NAFLD group, it was found that the proportion of subjects with GFR < 90 ml/min/1.73 m2 was significantly higher in non-obese subjects compared to obese subjects, (74.1% vs 54.4%, p < 0.05) and in the Non NAFLD group, the proportion of subjects with GFR < 90 ml/min/1.73 m2 was also higher in non-obese subjects (56.0%) than in obese subjects (40.8%), but not statistically significant (p > 0.05).

Higher BMI in obesity is the risk factors for CKD adjusted to multivariable models involving age, sex, race, education level, smoking status, history of myocardial infarction, serum cholesterol, proteinuria, hematuria, and serum creatinine. Hsu et al [1] comparing subjects who had normal body weight (BMI 18.5 - 24.9 kg/m2), the adjusted relative risk for CKD was 1.87 (1% CI, 1.64 to 2.14) for those who were overweight (BMI 25.0 - 29.9 kg/m2), 3.5 (CI, 3.05 to 4.18) for those who were class 1 obese (BMI, 30.0 - 34 , 9 kg/m2), 6.12 (CI, 4.97 to 7.54) for those who were class 2 obese (BMI 35.0 - 39.9 kg/m2) and 7.07 (CI, 5,37 to 9,31) for those who were class 3 obese (BMI ≥ 40 kg/m2). Higher initial BMI remains as an independent predictor for CKD after the next 15-35 years. Obesity may lead to some complications such as hypertension, DM, dyslipidemia and other factors that can trigger inflammatory condition in the kidneys. Based on these studies the mechanism underlying renal impairment in obese patients is suspected due to glomerular hyperfiltration and intraglomerular hypertension. This condition will cause glomerulosclerosis and fibrosis in tubulointerstitial and subsequently CKD. [13,15]

Conclusion

This study concluded that obese subjects with NAFLD have higher GFR compared to non-obese subjects with NAFLD, this was because obesity was associated with intraglomerular hypertension

Conflict of interest

The author states that there is no conflict of interest in this study.

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