

# Levels of Adiponectin and Soluble Tumor Necrosis Factor- $\alpha$ Receptor 2 (sTNF $\alpha$ R2) in Obese Males with or without Fatty Liver

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## ABSTRACT

**Background:** Increased lipolysis in obese patients will cause elevated free-fatty acid level leading to insulin resistance. There are varied inflammatory cytokines (sTNF $\alpha$ R2) and anti-inflammatory cytokines (adiponectin) in obese patients, with and without fatty liver (FL). The aim of this study was to determine sTNF $\alpha$ R2 and adiponectin levels in obese patients with and without fatty liver.

**Method:** This study was an observational study with cross-sectional approach, which was conducted between September 2008 and August 2009. The patients were 94 obese male with waist circumference  $\geq 90$  cm based on criteria of the International Diabetes Federation. Fatty liver was detected by ultrasonography; while adiponectin and sTNF $\alpha$ R2 levels in blood were analyzed by using ELISA method and blood examination at the clinical laboratory.

**Results:** Levels of adiponectin and sTNF $\alpha$ R2 were different between obese patients with and without FL. The adiponectin level was  $3.10 \pm 1.14$  in patients with FL and was  $3.52 \pm 1.07$  in patients without FL; while the sTNF $\alpha$ R2 were  $23.92 \pm 6.00$  (FL) and  $20.61 \pm 5.29$  (without FL). In patients with low adiponectin level ( $< 3.33$   $\mu\text{g/L}$ ) and high sTNF $\alpha$ R2 level ( $> 21.78$  pg/dL), there was relatively higher occurrence of fatty liver compared to the other patients.

**Conclusion:** Obese patients with fatty liver have higher sTNF $\alpha$ R2 level than patients without fatty liver. Moreover, obese patients with fatty liver have lower adiponectin level compared to patients without fatty liver. Patients with low adiponectin level and high sTNF $\alpha$ R2 level have higher incidence of fatty liver than subjects with high adiponectin level and low sTNF $\alpha$ R2 level.

**Keywords:** adiponectin, soluble tumor necrosis factor  $\alpha$  receptor 2 (sTNF $\alpha$ R2), obese, fatty liver

## ABSTRAK

**Latar Belakang:** Lipolisis yang meningkat pada pasien dengan obesitas akan meningkatkan kadar asam lemak bebas dan menyebabkan resistensi insulin. Sitokin inflamasi (sTNF $\alpha$ R2) dan sitokin anti-inflamasi (adiponektin) bervariasi pada pasien obesitas dengan dan tanpa perlemakan hati (PH). Tujuan penelitian ini adalah menentukan kadar sTNF $\alpha$ R2 dan adiponektin pada pasien obesitas dengan dan tanpa perlemakan hati.

**Metode:** Desain penelitian ini adalah studi observasi dengan pendekatan potong lintang pada bulan September 2008 – Agustus 2009. Subjek penelitian yaitu pasien laki-laki obesitas sebanyak 94 orang dengan lingkaran pinggang  $\geq 90$  cm (kriteria International Diabetes Federation untuk orang Asia). Perlemakan hati dideteksi dengan ultrasonografi. Kadar adiponektin dan sTNF $\alpha$ R2 darah dianalisis menggunakan metode ELISA. Pemeriksaan darah dilakukan di laboratorium klinik.

**Hasil:** Kadar adiponektin dan sTNF $\alpha$ R berbeda antara pasien dengan obesitas dan tanpa perlemakan hati. Kadar adiponektin pada pasien sebesar  $3,10 \pm 1,14$  (PH) dan  $3,52 \pm 1,07$  (tanpa PH), sedangkan kadar sTNF $\alpha$ R2 sebesar  $23,92 \pm 6,00$  (PH) dan  $20,61 \pm 5,29$  (tanpa PH). Pada pasien dengan kadar adiponektin rendah ( $< 3,33 \mu\text{g/L}$ ) dan kadar sTNF $\alpha$ R2 tinggi ( $> 21,78 \text{ pg/dL}$ ) kejadian perlemakan hati ditemukan lebih tinggi dibanding yang lainnya.

**Kesimpulan:** Pasien obesitas dengan perlemakan hati mempunyai kadar sTNF $\alpha$ R2 lebih tinggi dibandingkan dengan pasien tanpa perlemakan hati. Disisi lain pada pasien obesitas dengan perlemakan hati mempunyai kadar adiponektin yang rendah dibandingkan dengan tanpa perlemakan hati. Pasien dengan kadar adiponektin yang rendah dan kadar sTNF $\alpha$ R2 tinggi mengalami kejadian perlemakan hati lebih tinggi dibandingkan dengan kadar adiponektin yang tinggi dan sTNF $\alpha$ R2 rendah.

**Kata kunci:** adiponektin, soluble tumor necrosis factor  $\alpha$  receptor 2 (sTNF $\alpha$ R2), obesitas, perlemakan hati

## INTRODUCTION

Fatty liver is a condition characterized by steatosis hepatis or fat accumulation in liver cells, which occur as excessive amounts of triglycerides and other fats inside the liver cells caused by imbalance between triglycerides production and secretion by the liver.<sup>1</sup> Fatty liver may develop into steatohepatitis, liver fibrosis and liver cancer which is usually initiated by steatosis hepatis.<sup>2</sup> The condition of steatosis hepatis is categorized into macrovesicular and microvesicular steatosis.<sup>3</sup> The prevalence of fatty liver in obese patients ranges from 25% to 90%; while in diabetic patients, it ranges from 21 to 55% and 3 to 92% in patients with dyslipidemia.<sup>4</sup> A study conducted by Hasan et al, found 30% prevalence of fatty liver in Indonesia.<sup>5</sup> The causes of fatty liver include alcoholic and non-alcoholic etiologies. One of the non-alcoholic causes is obesity. Fatty liver caused by obesity has been known as the non-alcoholic fatty liver disease (NAFLD).<sup>2</sup>

The correlation between fatty liver and obesity could be explained by several mechanisms including increased free fatty acid level and insulin resistance. Type-2 diabetes and central obesity have been enormously reported in association with both NAFLD and non-alcoholic steatohepatitis (NASH). Insulin resistance is the key component in obesity and has been known as the risk factor of NAFLD pathogenesis.<sup>6</sup> Liver fat accumulation and insulin resistance have been correlated to the activity of some cytokines, including the adipokine. A study conducted by Dyck et al, in mouse models found that resistin and tumor nucleus factor- $\alpha$  (TNF- $\alpha$ ) or the adipokine have been implicated in impairing insulin sensitivity in rodents; while the other adipokines, including leptin and adiponectin increase insulin sensitivity in lean and obese rodents. Adiponectin and leptin have each been demonstrated to increase the rate of fatty acid oxidation and decrease muscle lipid content, which may become the underlying mechanism in improving the insulin effect.<sup>7</sup>

Adiponectin plays roles as anti-diabetic, anti-inflammatory and anti-teratogenic agent. There are significantly reduced plasma adiponectin levels in subjects with obesity, insulin resistance, metabolic syndrome, type-2 diabetes and coronary heart disease.<sup>8</sup> Plasma adiponectin concentration was found lower in patients with obesity compare to the non-obese patients. The underlying mechanism for reduced plasma adiponectin concentration is still vague, but one of them may include inhibition of TNF- $\alpha$  synthesis and secretion, which is produced locally in large amount in visceral obesity. It is initiated by macrophage invasion into adipose tissue.<sup>9,10</sup> Thus, based on such principles, we would like to conduct a study to recognize the occurrence of fatty liver in obese patients through the interaction of balanced work of adiponectin and soluble TNF  $\alpha$  receptor 2 (sTNF $\alpha$ R2).

## METHOD

This study was an observational study with cross-sectional approach. The study subjects were adult male patients who had their general medical check-up at Prodia clinical laboratory in Makassar between September 2008 and August 2009. Female patients were excluded as study subjects to prevent the effect of women's hormone on the adiponectin levels. The number of sample that required for the differential test was 24 patients per group with 80% of power and significance level of ( $\alpha$ ) 5%; while for the correlation test, about 65 patients were required. Of 120 patients, 94 patients were eligible who were categorized further into 2 groups, i.e 49 obese patients with fatty liver and 45 obese patients without fatty liver.

The criteria of obesity were determined based on the International Diabetes Federation (IDF) for Asian population, i.e. male patients would be categorized as obese if their waist circumferences were  $\geq 90$  cm. Fatty liver was identified through ultrasonographic examination using Medison SA-606<sup>®</sup> ultrasonography (Medison Co LTD, Korea); the criteria for ultrasound

diagnosis of fatty liver were homogenously increased echogenicity and deep posterior attenuation of the beam. The inclusion criteria were male aged  $\geq 30$  years, obese patient with fatty liver, obese patient without fatty liver, non-alcoholic patients, had no consumption of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase agents, angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), aspirin; were not undergoing any treatment to prevent bias due to the inflammatory drugs effect. Moreover, the exclusion criteria were hsCRP level  $> 10$  mg/L indicating chronic inflammation, including the obesity; patients with hepatitis B and C; patients who had blood glucose level of  $> 126$  mg/dL, which had been determined to reduce the inflammatory factor, restricting only from obesity cause; and patients who were on diet program for losing their weight, with or without drug treatment.

Adiponectin levels were measured in the fasting serum sample through the Sandwich ELISA method by using Daiichi Sekisui® reagent (lot number 004RKCED 2006-06, Japan). sTNF $\alpha$ R2 levels were evaluated in the fasting serum sample through Sandwich ELISA method by using reagent of Quantikine® catalog (number DRT 200; R&D system Inc).

The study has been approved by the Ethics Committee of Faculty of Medicine, University of Hasanuddin, Makassar. The statistics were performed using SPSS software version 16.0 for Windows.

The statistic test performed were univariate analysis including the frequency distribution test and bivariate analysis. To observe the patient characteristics with and without fatty liver, the frequency distribution test was performed in each group. To recognize differences between two groups, we performed Mann Whitney U test; while to evaluate the correlation between variables, we performed the Spearman test. Moreover, cross-tabulation was performed to evaluate the correlation between adiponectin and sTNF $\alpha$ R2 levels. Subsequently, we obtained OR value indicating the prevalence of fatty liver. The cut-off points for adiponectin and sTNF $\alpha$ R2 level were determined based on median value of the obtained data with significance level of ( $\alpha$ ) 5%.

## RESULTS

Of 94 eligible male obese patients, the patients were categorized into two groups, i.e. 49 male obese patients with fatty liver and 45 male obese patients without fatty liver. The general characteristics of patients are presented on Table 1; while the characteristics of both groups could be seen on Table 2.

On Table 2, we present characteristics of age, systolic and diastolic blood pressure and no significant difference between both groups. Waist circumference, fasting blood glucose level, insulin level, homeostatic model assessment of insulin resistance (HOMA IR), sTNF $\alpha$ R2 were significantly higher in the fatty

**Table 1. Clinical and biochemical patient characteristics**

Parameter	Minimum	Maximum	Mean $\pm$ SD
Age (years)	30.00	84.00	43.00 $\pm$ 10.00
Waist circumference (cm)	90.00	121.00	99.00 $\pm$ 7.00
Systolic blood pressure (mmHg)	90.00	130.00	114.00 $\pm$ 9.00
Diastolic blood pressure (mmHg)	70.00	90.00	79.00 $\pm$ 4.00
Fasting blood glucose (mg/dL)	77.00	133.00	94.00 $\pm$ 11.00
Insulin (mU/mL)	1.99	38.60	8.27 $\pm$ 6.45
HOMA IR (mmol $\mu$ g/MI dL)	0.39	8.86	1.98 $\pm$ 1.68
sTNF $\alpha$ R2 level (pg/mL)	12.19	39.99	22.33 $\pm$ 5.88
Adiponectin level ( $\mu$ g/mL)	1.07	7.60	3.30 $\pm$ 1.12

HOMA IR: homeostatis model assesment of insulin resistance

**Table 2. Clinical and biochemical characteristics in fatty liver and non-fatty liver groups**

Parameter	Fatty liver (mean $\pm$ SD)	Non-fatty liver (mean $\pm$ SD)	P*
Age (years)	42.00 $\pm$ 9.00	44.00 $\pm$ 11.00	0.527
Waist circumference (cm)	101.00 $\pm$ 8.00	95.00 $\pm$ 5.00	0.000
Systolic blood pressure (mmHg)	113.00 $\pm$ 8.00	115.00 $\pm$ 9.00	0.299
Diastolic blood pressure (mmHg)	80.00 $\pm$ 3.00	78.00 $\pm$ 5.00	0.169
Fasting blood glucose (mg/dL)	95.00 $\pm$ 11.00	91.00 $\pm$ 10.00	0.048
Insulin (mU/mL)	10.39 $\pm$ 7.49	5.97 $\pm$ 4.04	0.000
HOMA IR (mmol $\mu$ g/MI dL)	2.55 $\pm$ 2.00	1.35 $\pm$ 0.92	0.000
sTNF $\alpha$ R2 level (pg/mL)	23.90 $\pm$ 6.00	20.61 $\pm$ 5.29	0.004
Adiponectin level ( $\mu$ g/mL)	3.10 $\pm$ 1.14	3.52 $\pm$ 1.07	0.050

HOMA IR: homeostatis model assesment of insulin resistance; \* Mann Whitney U test

liver group compared to the non-fatty liver group. Adiponectin level in fatty liver group was significantly lower than the non-fatty liver group.

The correlation of variables to incidence of fatty liver and the partial correlation in controlling waist circumference, blood glucose level, insulin and HOMA IR to evaluate the independency of those parameters to the incidence of fatty liver could be seen on Table 3.

The Table 3 shows that waist circumference, HOMA IR and sTNF $\alpha$ R2 have negative correlation to the non-occurrence of fatty liver, which means that low value of waist circumference, HOMA IR and sTNF $\alpha$ R2 plays role in the non-occurrence of fatty liver; while adiponectin has positive correlation indicating that high adiponectin level has important role in the non-occurrence of fatty liver.

Table 3 also demonstrates that sTNF $\alpha$ R2 is independent factor that affect the occurrence of fatty liver in this study. Such condition indicates that a

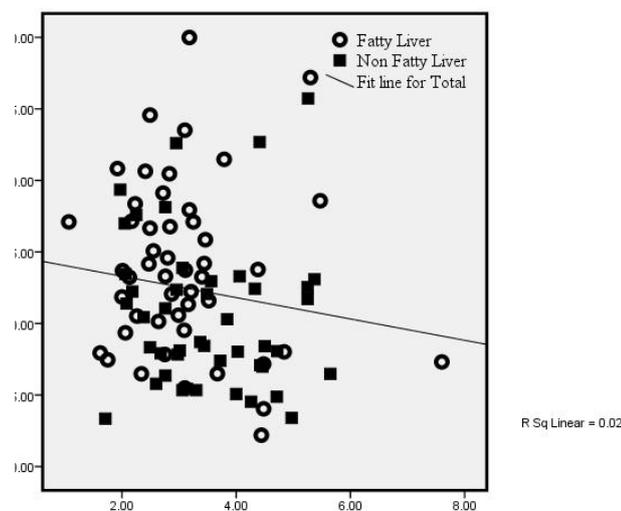
relatively important role of inflammation may affect the process of developing inflammation itself. This study also demonstrated the dynamic features of adiponectin and sTNF $\alpha$ R2 levels; while the distribution of adiponectin and sTNF $\alpha$ R2 levels could be seen on Figure 1. The figure shows that some patients with low adiponectin levels apparently also have higher sTNF $\alpha$ R2 level. Figure 1 also implies that incidence of fatty liver is more highly distributed in patients with low adiponectin and TNF $\alpha$ R2 levels.

The dynamic properties between adiponectin and sTNF $\alpha$ R2 were tested by determining the cut off point of each parameter. The cut off value of adiponectin level was determined at 3.33  $\mu$ g/mL ( $\geq 3.33$   $\mu$ g/mL = high adiponectin level;  $< 3.33$   $\mu$ g/mL = low adiponectin level); while the cut off value of sTNF $\alpha$ R2 level was 21.98 pg/mL ( $< 21.78$  pg/mL = low sTNF $\alpha$ R2 level,  $\geq 21.78$  pg/mL = high sTNF $\alpha$ R2 level). This study results demonstrated that there was higher occurrence of fatty liver on conditions

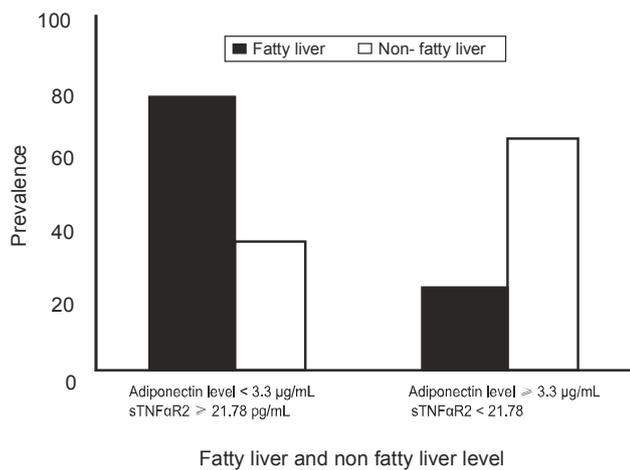
**Table 3. The correlation between fatty liver and some parameters**

Parameter	r	p*	Control			
			WC		WC, FBG, insulin, HOMA IR	
			r	p*	r	p*
Waist circumference (cm)	-0.409	0.000				
FBG (mg/dL)	-0.109	0.067	-0.122	0.242		
Insulin (mU/mL)	-0.344	0.001	-0.241	0.020		
HOMA IR (mmol $\mu$ g/MI dL)	-0.358	0.000	-0.252	0.015		
sTNF $\alpha$ R2 (pg/mL)	-0.282	0.006	-0.216	0.038	-0.251	0.017
Adiponectin ( $\mu$ g/mL)	0.188	0.070	0.190	0.068	0.120	0.259

WC: waist circumference; FBG: fasting blood glucose; HOMA IR= homeostatis model assesment of insulin resistance; r = correlation; \* Spearman correlation test



**Figure 1. Distribution of adiponectin level on sTNF $\alpha$ R2 level**



**Figure 2. Percentage of fatty liver and non-fatty liver occurrence in different levels of adiponectin and soluble tumor necrosis factor α receptor 2**

of adiponectin level < 3.33 µg/mL and sTNFαR2 level ≥ 21.78 compared to other condition with adiponectin level ≥ 3.33 µg/mL and sTNFαR2 < 21.78 pg/mL (Figure 2).

Dynamic characteristics between adiponectin and sTNFαR2 levels could be observed by performing the cross tabulation test on the dynamics of those levels with the occurrence of fatty liver (Table 4). This study results demonstrated significant correlation (p > 0.001) between the dynamic characteristics of adiponectin as well as sTNFαR2 and the occurrence of fatty liver with OR 6.43 (95% CI = 1.932–21.389) indicating that the occurrence of fatty liver in obese patients increased by

**Table 4. Correlation between varied adiponectin and sTNFαR2 level on the occurrence of fatty liver**

	Fatty liver n (%)	Non-fatty liver n (%)	p*	OR*
Low adiponectin level (µg/mL), High TNFR2 level (pg/mL)	24 (44)	7 (13)	0.002	6.43
High adiponectin level (µg/mL), Low sTNFR2 level (pg/mL)	8 (15)	15 (28)	0.002	

OR: odds ratio; \*chi square test

6.43 fold higher in patients who had low adiponectin level and high sTNFα2 level, compared to patients with high adiponectin level and low sTNFαR2 level.

## DISCUSSION

NAFLD is defined as a condition of steatorrheic liver on individual without alcohol intake yet still had liver injury. Although some drugs or genetic disorder may cause NAFLD, but the main causes in almost all cases include obesity, insulin resistance and type-2 diabetes.<sup>11,12</sup>

A study by Sulaeman et al, demonstrated that 50% of obesity patients and 66% patients with metabolic syndrome also experienced fatty liver.<sup>13</sup> The progressivity of fatty liver may occur from the

normal cell which will develop into steatorrheic cell, steatohepatitis and liver fibrosis. Such progressivity will be followed by varied adipokines produced by adipocytes. The adipokines will be further involved in the fatty liver process including adiponectin as anti-inflammatory agent and TNF as the pro-inflammatory agents.

Adiponectin, an anti-inflammatory adipocytokine, may modulate the insulin effect. Adiponectin is a protein with 30 kDa molecular weight. In normal subject, the expression of adiponectin is limited to adipose tissue. Adiponectin level has negative correlation with body mass index (BMI), blood glucose level, fasting insulin level, insulin resistance and triglycerides.<sup>14</sup>

This study found lesser occurrence of fatty liver compared to non-fatty liver (Table 2). This study has been relevant to the study conducted by Yoon et al, which demonstrated that hypo adiponectinemia may occur in individuals with NAFLD. The experimental studies have demonstrated that adiponectin has protective effect both against alcohol and NAFLD. Yoon et al study has reported that hypo adiponectinemia is a feature of NASH independent of insulin resistance and lower adiponectin level is associated with the amount of necroinflammation and may have contribution on the development of necroinflammation in NAFLD.<sup>14</sup>

sTNFαR2 is a stable protein, which have been studied to be associated with BMI, waist hip ratio and insulin resistance; therefore, it could be used as a better predictor to demonstrate the activation of local TNF α system compared to the concentration of TNF-α in blood.<sup>15</sup> This study found that there were higher sTNFαR2 levels in patients with fatty liver than without fatty liver. It may be caused by the compensatory process in the body due to the low anti-inflammatory adipokines produced by lesser adipocytes number.

Adiponectin and TNF α may inhibit each other, which indicate that both adipocytokines have interaction in different metabolic pathway. A study by Kirsch et al, demonstrated that there were reduced adiponectin levels, increased soluble TNF receptor 2 levels in patients with NASH compared to the control group.<sup>16</sup>

TNF-α suppresses the transcription of 3T3-L1 in adipocytes, which is the basic mechanism of low adiponectin level in obese patients. A study conducted by Shimomura et al showed that in mouse models, the adiponectin characterized by high expression of TNF mRNA in adipose tissue and high TNF plasma level.<sup>17</sup>

On the other hand, the anti-inflammatory effect of adiponectin may inhibit the TNF regulation in affecting the expression of adhesion molecules on endothelial cells. Adiponectin inhibits the signaling endothelial nuclear factor kappa-β (NF-κβ) through

cyclic 3',5'-adenosine monophosphate, which may affect the macrophage function. The study conducted by Shimamura et al demonstrated that macrophage cultured with adiponectin had significantly inhibited the TNF synthesis as a response against endotoxin. The mouse model with adiponectin level showed increased production of both local and systemic TNF. It was assumed because of the suppressive effect of adiponectin on the synthesis and expression of TNF.<sup>18</sup>

Dynamic characteristics between anti-inflammatory cytokines and inflammatory cytokines may be illustrated by observing the adiponectin and sTNF $\alpha$ R2 levels. On Table 4, this study shows that the adiponectin level in obese patients with fatty liver is lower than patients without fatty liver. Moreover, the sTNF $\alpha$ R2 level is higher in obese patients with fatty liver compared to non-fatty liver patients. In this case, the dynamic characteristics of adiponectin and TNF  $\alpha$  includes sTNF $\alpha$ R2 showing alteration of inflammatory condition and reduced anti-inflammatory agent will develop higher occurrence of fatty liver; therefore, it can be assumed that the balance between inflammatory and anti-inflammatory agents may have important role in the development of fatty liver.

This study suggests the importance of considering balance between inflammatory and anti-inflammatory condition in obese patients to prevent the risk of developing fatty liver. We also expect that this study may enhance the basic approach of treatment for fatty liver by taking inflammatory condition into account in obese patients.

The weakness of this study includes the utilization of ultrasonography for detecting fatty liver which could not illustrate the cellular situation during the study. Further studies should be conducted based on the results of this study including the more sensitive detection for fatty liver which may provide more obvious evidence of clinical condition.

## CONCLUSION

There are reduced adiponectin level and increased sTNF $\alpha$ R2 level in obese patients who also have fatty liver. Such condition will also increase the occurrence of fatty liver.

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