

## The Role Of Adiponectin Gene Polymorphism On The Change Of Adiponectin Content In Individuals Overweight And Obesity After Aerobic Exercise In Combination Diet OCD

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### ABSTRACT

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**Background:** The Indonesian obesity study group examined more than 6000 people from almost all provinces and obtained obesity rates with a body mass index (BMI) > 30 kg / m<sup>2</sup> in men at 9.16% and women 11.02%. Obesity has been known to be associated with Adiponectin and insulin resistance even from an early age. Wiecek (2012) compared adiponectin, lipid and proinsulin levels between obese and normal adolescents. From these studies, it is known that obese adolescents have adiponectin up to 50% lower compared to teens with normal weight. **Aim:** To Find Out The Role Of Adiponectin Gene Polymorphism On The Change Of Adiponectin Content In Overweight Individual And Obesity After Aerobic Exercise In Diet OCD Combination. **Methods:** The research method used is pre-experimental design precisely quasi-experimental research design with one group pre-post test design. The research subjects were 36 women with more than normal body weight. **Results:** man Whitney test results differed significantly between adiponectin levels with variations in the TT genotype with a p-value of 0.001 and GT with a p-value of 0.038 after doing aerobic exercise for 6 weeks or 18 times of exercise, but the Spearman correlation test obtained a sig value of 0.301 which showed that the correlation was not significant between adiponectin levels and adiponectin genes. The spearman correlation value of 0.074 indicates that the direction of the positive correlation with the strength of the correlation is very weak meaning that there is an increase in adiponectin levels after aerobic exercise for 6 weeks or 18 times of exercise but adiponectin levels are not related to variations in the adiponectin gene after aerobic exercise for 6 weeks or 18 practice times.. **Conclusion:** There was a significant increase in adiponectin levels in the GT and TT genotypes after aerobic exercise combined with the OCD diet, but adiponectin levels were not related to variations in the adiponectin gene after aerobic exercise for 6 weeks or 18 times.

**Key words:** Aerobic exercise; adiponectin levels; overweight; obesity.

### INTRODUCTION

Obesity has become a global pandemic worldwide and is declared by the World Health Organization (WHO) as the biggest chronic health problem in adults. The World Health Organization (WHO) estimates that around one billion men are overweight (BMI > 25 kg / m<sup>2</sup>) and around 300 million women are defined as obese (BMI > 30 kg / m<sup>2</sup>). The

WHO further said that more than 1.4 billion adults over the age of 20 were overweight and at least 2.8 million adults died as a result of obesity. Where 44% of them have diabetes, 23% have heart disease, ischemic, 7 - 41% have cancer all of which are caused by obesity. (WHO, 2013) Overweight and obesity are now ranked fifth as a global risk of death. There are 44% of diabetes cases, 23% of ischemic heart disease and 7% -41% of cancers are caused by overweight/obesity. The estimated prevalence of overweight and obesity in children is estimated at 35 million in developing countries compared to 8 million in developed countries (Blüher, 2019).

The Indonesian Obesity Study Group Examined More Than 6000 People From Almost All Provinces And Obtained Obesity Rates With A Body Mass Index (Bmi) > 30 Kg / M<sup>2</sup> In Men At 9.16% And Women 11.02%. In indonesia, the national basic health research (riskesdas) study reported an increase in the national prevalence of obesity (combined overweight and obese categories) of age over 15 years from 19.1% in 2007 to 23.1% in 2010. Increased prevalence of national age obesity above 15 years according to sex in 2007-2010, in men by 13.9% to 17.6% in women increased from 23.8% to 28.4%. Of the 33 provinces in indonesia in 2007, the highest obesity prevalence was north sulawesi at 33.2%, which increased to 39.2% in 2010. In particular, the prevalence of central obesity according to the 2013 national riskesdas was 31.5%. And in the year 2010-2013 according to gender that in men in 2010 amounted to 15% and in 2013 increased to 20%, women in 2010 amounted to 26% and in 2013 increased to 35% (ministry of health 2010 and 2013). If this trend continues as it is now, then in 2025 the indonesian population will carry the title of obesogenic.(blüher, 2019).

Obesity has been known to be associated with Adiponectin and insulin resistance even from an early age. Compared adiponectin, lipid and proinsulin levels between obese and normal adolescents. From these studies, it is known that obese adolescents have adiponectin up to 50% lower compared to teens with normal weight. Plasma adiponectin concentrations were found to be lower in obese subjects. The mechanism underlying the reduction in plasma adiponectin concentration is unclear, one of which is the inhibition of the synthesis and secretion of tumor necrosis factor-alpha (TNF-alpha), which is produced locally in large quantities in visceral obesity, beginning with the entry of macrophages into adipose tissue. The activity of alpha TNF can be measured by measuring the soluble tumor necrosis factor-alpha receptor 2 associated with an increase in insulin resistance(Nikolić et al., 2019).

Other studies have revealed that adiponectin, insulin resistance and especially leptin, play a role in the occurrence of glomerular hyperfiltration in central obese subjects (Nikolić et al., 2019). Genetic variations of the adiponectin gene that are widely reported are related to insulin resistance, obesity and the risk of type 2 diabetes on intron 2, G276T and exon 2, T45G (Ahmed et al., 2019). In research conducted in Japan, it was found that subjects with GG genotype had lower plasma adiponectin levels than TT genotype. The odd ratio in this condition is more than 2 (Iwabu et al., 2019).

Adiponectin is an anti-inflammatory adipocytokine that modulates the effects of insulin. Adiponectin is a 30 kDa molecular weight. In normal humans, adiponectin expression is limited in adipose tissue. Adiponectin levels are negatively correlated with BMI, fasting sugar levels, fasting insulin, insulin resistance and triglycerides (Li et al., 2019). Molecularly, adiponectin can increase insulin sensitivity by increasing the effectiveness of insulin suppression on gluconeogenesis and increasing the oxidation of fatty acids in liver cells and muscle cells through AMP-kinase and PPAR mechanisms. The anti-inflammatory and antiatherogenic effects of adiponectin are thought to be mediated by inhibition of TNF- $\alpha$  induced by NF- $\kappa$ B activation, inhibiting the expression of adhesion molecules, decreasing smooth muscle cell proliferation, and reducing foam cell formation (Potenza et al., 2019).

Alpha TNF is a cytokine molecule that links inflammation with obesity, where this molecule is found to be very abundant in the adipose tissue of obese rats. Several studies have shown that overproduction of alpha TNF or TNF receptors in adipose tissue is an important marker in obese people and contributes to insulin resistance. Alpha TNF works by suppressing the transcription of adiponectin in 3T3-L1 in adipocyte cells, which is a mechanism of low adiponectin levels in obese people. Studies conducted by Shimamura et al show that mice with adiponectin are characterized by high TNF mRNA expression in adipose tissue. and high levels of TNF in the plasma (Tilg et al., 2020). Adiponectin will affect the sensitivity of insulin which will cause triglycerides in adipose cells to break down into excessive FFA will cause the number of free radicals and oxidation of fatty acids to decrease so that it will reduce the levels of adiponectin and triglycerides that are formed will be more. Excessive formation of triglycerides will cause the accumulation of liver cells that can be detected by ultrasound as a fatty liver.

Adiponectin is influenced by several factors including environmental factors (nutritional excess and lack of adequate physical activity) and genetic factors (SNPs

[I164T])(Iwabu et al., 2019). Adiponectin may be a protective factor in the incidence of non-alcoholic fatty liver disease in obese children and that examination of adiponectin levels should be a standard examination in obese children to evaluate the presence of non-alcoholic fatty liver disease(ZOU et al., 2005).

### **MATERIAL AND METHODS**

This research is experimental research or experimental design (quasi-experiment) which is a study used to find the relationship of causes where randomization was not carried out and did not use a control group. The study design uses a Pre-posttest group design. In this study, selected subjects or experimental units. Before being given treatment, a measurement (pre-test) is then given care and in the end the activity or after giving a gift, is measured again (post-test). The results of the measurement of pre and post-test will be compared to see differences in the value of the variable after being given a replacement. With the following program:

- a. Aerobic exercise program which is followed by aerobic exercise with a frequency of exercise 3 x / week for 6 weeks or 18 times of exercise with light intensity 60-70% of maximum ability, duration of exercise 30-40 minutes for 1 set. Aerobic exercise is carried out alternately with the OCD diet for 6 weeks. The sample is divided into the first 2 parts of the afternoon training schedule and the second group is held at night. Aerobic exercise is carried out alternately with fasting, with Monday's schedule aerobic gymnastic pain then on Tuesday the fasting pain continues to change for 6 weeks.
- b. The OCD diet program is from 7:00 AM to 3:00 PM to consume anything and starts from 16:00 to 7:00 AM fasting but may drink, this is done for 6 weeks. As for how to control the sample by providing an aerobic and fasting training schedule, providing 24-hour food recall format and daily activity format or ADL to be filled every day and collected every Saturday to calculate the number of calories consumed and the energy requirements needed every day then weigh weight every week. The control is by contacting all respondents during the training schedule and fasting schedule by telephone and enumerators from each institution to supervise.
- c. After aerobics and fasting for 6 weeks then within 24 hours or one day after the exercise program is complete, blood samples are taken for examination of adiponectin levels.

#### **Methods for registration of outcomes**

Aerobic exercise program that follows aerobics with a frequency of exercise 3 x /

week for 6 weeks or 18 times gymnastics with light intensity 60-70% of maximum ability, duration of exercise 30-40 minutes for 1 set. Aerobic exercise is carried out alternately with the OCD diet for 6 weeks. The sample is divided into 2 parts: the first group is the afternoon training schedule and the second group is held at night. Aerobic exercise is carried out alternately with fasting, with a schedule of Monday afternoon aerobics and then Tuesday afternoon fasting and so on alternately for 6 weeks, while the OCD diet program is from 7:00 in the morning until 3:00 in the afternoon to consume anything and from 16:00 to 7:00 in the morning fasting but may drink, this is done for 6 weeks. As for how to control the sample by providing an aerobic and fasting training schedule, providing a 24-hour food record format and daily activity format or ADL to be filled every day and collected every Saturday to calculate the number of calories consumed and the energy requirements needed every day then weigh weight every week. The control is by contacting all respondents when the training schedule and schedule is satisfied by telephone and enumerators from each institution to supervise.

How to check adiponectin genes using PCR while checking adiponectin levels using Elisa in the NHCR laboratory of the Hasanuddin University Hospital. As for how to check DNA extraction methods.

#### **DNA Extraction (GENEID)**

A total of 200 µl of serum sample was put into a sterile 1.5 ml microcentrifuge tube and then added 20 µl proteinase K, homogenized by pipetting, then incubated at 60 °C for 5 minutes. Add 200µl of GSB buffer (Geneid) then the vortex is then re-incubated at the same temperature for 2 minutes. Furthermore, absolute ethanol (96%) and vortex are added for 10 seconds. Move all the mixture into the rotary column, sent at 14,000 xg for 1 minute. Discard the collection of tubes that are higher than the spin column replaced with the new collection of tubes. Add 400µl buffer W1 then centrifuge for 30 seconds at the same speed then remove the liquid in the collection tube. Add 600 µl wash buffer (genid) centrifuge for 3 seconds, then remove the liquid in the tube collection and centrifuge again for 3 minutes Remove the collection tube and place a sterile microcentrifuge at the bottom of the spin column. Next add 100µl of elution buffer let stand for 3 minutes then centrifuge at the same speed for 30 seconds. Liquids containing DNA stored in microcentrifuge tubes were stored at -4 °C for use as a PCR template. The application is done using a PCR (DNA thermal cycler) machine. For the amplification of the T45G region of adiponectin gene, the initial stage of denaturation at a temperature of

95 °C for 15 minutes, then 94 °C for 1 minute, annealing at 55 °C for 30 seconds, extension 72 °C for 1.5 minutes 45 cycles followed by a final extension of 72 °C for 10 minutes and 12 °C + 30 minutes for storage.

Approval of training and blood sampling was obtained after getting permission from the Hasanuddin University ethics commission unit.

## RESULTS

Characteristics of research subjects include gender, age, education. The sex of the respondent is 100% female, the respondent is 17-20 years old with an average respondent being 18 years old with a percentage of 47.2%, 100% student education.

**Table 1. Characteristics of research subjects**

Age	Frequency	Percentage (%)
17	5	13,9
18	17	47,2
19	9	25
20	5	13,9
<b>Total</b>	<b>36</b>	<b>100</b>

The average respondents had genetic variation in TT with a percentage of 75.0%, genotype GT 22.2%, GG 2.8%.

**Table 2. Genetic variations of the adiponectin gene in research subjects**

Gene Variation	Frequency	Percentage (%)
TT	27	75
GT	8	22,2
GG	1	2,8
<b>Amount</b>	<b>36</b>	<b>100</b>

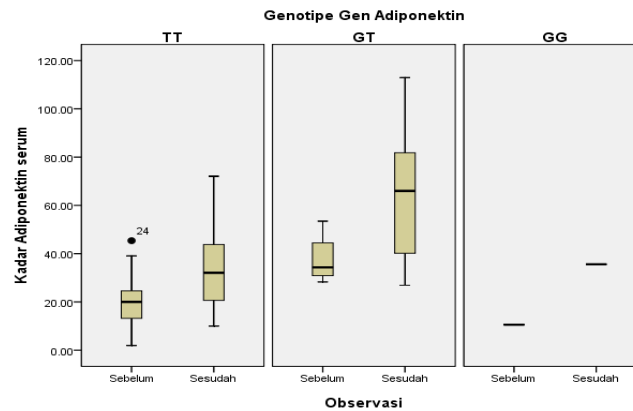
**Table 3. The role of the adiponectin gene for changes in adiponectin levels after undergoing an aerobic exercise program combined with OCD for 6 weeks or 18 exercises.**

Genotype genome	Mean (SD) Serum adiponectin levels			
	Pre	Post	The amount of improvement	
TT (n=27)	20,59 (10,38)	32,82 (17,35)	12,24	0,001
GT (n=8)	37,63 (9,75)	64,46 (28,76)	26,83	0,038
GG (n=1)	10,57	35,58		

The table shows that the results of the man Whitney test were significantly different between adiponectin levels and variations in the TT genotype with p values of 0.001 and GT with p values of 0.038 after doing aerobic exercise for 6 weeks or 18 times exercise. There is an increase in the level of adiponectin after aerobic exercise for 6 weeks or 18 times the exercise but the level of adiponectin is not related to the variation of the

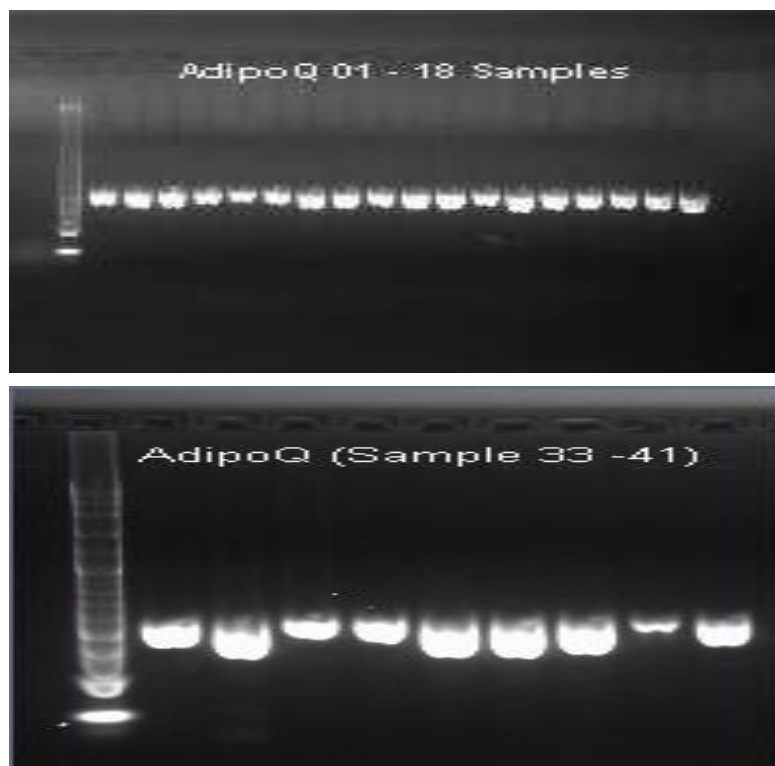
adiponectin gene after doing aerobic exercise for 6 weeks or 18 times the exercise can be shown in the figure below:

Figure 1



Adiponectin genotypic polymorphisms provide 3 forms of genotypes namely TT, GT, and GG genotypes.

Figure 2



## DISCUSSION

The results of this study indicate that there is an increase in adiponectin levels in the variation of the TT genotype than GT after aerobic exercise for 6 weeks or 18 times exercise. However, the magnitude of the increase in adiponectin levels was greater in the

GT genotype, which was 26.83  $\mu\text{g} / \text{ml}$ , the magnitude of the increase compared to the TT genotype of 12.24  $\mu\text{g} / \text{ml}$  after combination aerobic exercise training. This can be because the average respondent is not obese in the heavy category but the average respondent is in the category of overweight and mild obesity so that the heterozygote GT genotype which tends to be more expressed after aerobic exercise or aerobic exercise combination OCD diet which is known that the GT genotype carries two alleles namely T alleles and G alleles are known that T alleles tend to be normal carriers and G alleles are not normal so that it is possible that after an OCD dietary intervention this T allele is more expressed to increase adiponectin levels and G allele is less expressed so that the GT genotype is dominant rather than the TT that can increase adiponectin levels. This can also be caused by decreased levels of fat in adipose tissue affected by regular aerobic activity and calorie restriction causing an increase in the metabolic process of visceral and intraabdominal fat (triglycerides) in adipose tissue which is broken down into free fatty acids and glycerol which then fatty acids free turns into beta-oxidation which decomposes into energy-producing ATP while glycerol is converted to glucose and pyruvic acid is converted to energy-producing ATP (McArdle et al., 2010).

Messenger RNA transcribes adipocyte cells to produce more adiponectin levels so that adiponectin levels increase and visceral fat decreases abdominal circumference and body weight decreases. Then when adiponectin levels increase will increase the production of anti-inflammatory in the body so that the body's immune system increases. When adiponectin levels are increased by the adiposity signal on adiposity, pressing the central regulator of the hypothalamus to feel full so that appetite decreases and food intake decreases, body weight can be controlled (Hall & Guyton, 2013).

Adiponectin decreases the number of triglycerides in tissues and increases signaling in skeletal muscles, adiponectin increases the expression of molecules involved in the transport of fatty acids such as CD36, which are involved in burning fatty acids such as acyl-coenzyme A oxidase, and in energy use. This change causes a reduction in the number of triglycerides in the skeletal muscle and will inhibit the activation of phosphatidylinositol 3-kinase because the reduced amount of triglycerides in muscle tissue will improve insulin signal transduction (Yamauchi, 2001).

Changes in adiponectin levels in obesity have lower adiponectin levels in the GG genotype than in the TT genotype. This means that after aerobic exercise intervention is expected to be higher in the adiponectin TT level compared to the GG and GT genotypes,



this can be due to the basic principles of training, namely the individual principle because basically, respondents have different characteristics both physically and psychologically, where psychologically each respondent has different encouragement or motivation in participating in aerobic exercise and diet as well as stress that is different as well as movements during exercise that are not the same flexibility of muscles so that the response the results vary (Stern et al., n.d.)

Besides other factors that can affect adiponectin levels are age and pregnancy, androgen and estrogen hormones have a negative role in the production of adiponectin levels (Andrzej W, et.al, 2007). In this study, respondents had an age between 17-21 years which entered the stage of old adolescents entering young adulthood, and the hormone estrogen plays an important role that can change adiponectin levels, in addition to the food intake that is assumed by each respondent can influence even in the calculation of the nutritional adequacy rate of the respondents the average has fewer categories so that adiponectin levels can quickly increase and body weight decreases, abdominal circumference decreases, and upper arm circumference also decreases.

This is in line with research Amir et.al (Rashidlamir et al., 2013) found that 20 women were divided into 2 groups of control and experimental groups, with the results of the experimental group being given aerobic exercise 4 times a week for 8 weeks with exercise intensity 70-80% of maximum ability, with the result that adiponectin levels increase significantly. Also by Elloumi et.al, (Elloumi et al., 2009), found in 21 obese adolescents (BMI = 30.8) dividing into 3 groups, low-calorie diet, exercise, the combination of diet and exercise, carried out for 2 months with results, all three groups showed an increase adiponectin levels and decreased leptin and were more significant in the combined diet sports group. The same thing showed that plasma adiponectin increased after 8 weeks of aerobic exercise, frequency 4 x / week with an intensity of 60-80% and an increase in adiponectin levels. Showing frequency of aerobic exercise 3 times / week for 12 weeks showed an increase in adiponectin levels ( $P = 0.002$ ), decreased leptin ( $P = 0.003$ ), IL-6 ( $P = 0.001$ ), CRP ( $P = 0.002$ ) (Akbarpour, 2013). The result of adiponectin levels rose 260% after 2-3 times of exercise per week with an average value of  $p = 0.001$ , even though body weight did not change and continued to increase  $p = .001$  (Hui et al., 2004). Found that there was no relationship with the amount of adiponectin, plasma lipid levels, and variable body composition. However, the 45T / + 276G haplotype analysis haplotype has lower adiponectin levels than noncarriers. And there are significant differences between

women who have higher body fat than normal (Melistas et al., 2009).

The results of the study found no significant differences in the frequency distribution of 45 T / G and 11391 G / A. with a p-value = 0.019 (Nomani et al., 2019). Another study result, found subjects with G alleles for SNP 276 had significantly higher triglyceride and LDL concentrations than T alleles, G / G subjects in SNP 276 had lower plasma adiponectin than on the T / T subject (Mohammadzadeh et al., 2016).

This can be caused by the average respondent having a mild obesity category so that it is easy to increase the level of adiponectin if fat decreases. This is in line with the results of the study that BMI, LP decreases after aerobic exercise, meaning that fat in the adipose tissue decreases so that adipokine is expressed to produce adiponectin which more so that adiponectin levels appear to increase after aerobic exercise combined OCD diet for 6 weeks or 18 times exercise. So that if the level of adiponectin increases, it can prevent inflammation or inflammation in the body as well when the level of adiponectin increases, the production of the hormone leptin will decrease which affects the hypothalamus to suppress the eating center so that the body weight can be balanced. Besides, if the level of adiponectin increases, it prevents atherosclerotic events that can cause heart disease.

Based on these results it can be concluded that the GT genotype is more likely to experience increased levels of adiponectin than TT. Because the average respondent of mild obesity is not severe obesity. Even though they have heterozygous genotype, there are abnormal and normal allele carriers, but if aerobic exercise and OCD diet are carried out regularly, the GT genotype will be expressed more dominantly in normal terms, meaning that genes influence adiponectin levels but the environment has a greater role or influence on changes in adiponectin levels.

### CONCLUSION

There was a significant increase in adiponectin levels in the GT and TT genotypes after aerobic exercise combined with the OCD diet, but adiponectin levels were not related to variations in the adiponectin gene after aerobic exercise for 6 weeks or 18 times.

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