Effects of 8-Week Vitamin E (α Tocopherol) Supplementation on Reduced Insulin Resistance in Non-diabetic Obese Subjects

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Abstract: Obesity is a risk factor for diabetes mellitus (DM) and coronary heart disease. In obesity, oxidative stress and adipokine hormone increase, leading to insulin resistance (IR) which can develop into DM. Vitamin E is an antioxidant that is expected to lower IR. This study aims to determine the effects of 8-week supplementation of vitamin E on reducing IR in non-diabetic obese subjects. The design was PROBE (Prospective Randomized Open Blinded End-point). The subjects were ≥18 years old with ≥25 kg/m^2 body mass index and HOMA-IR value >2.7 The exclusion criteria were DM patients and those taking metformin or antioxidants. Twenty subjects in group A received 800 IU Vitamin E supplementation while 20 subjects in group B received placebo, both for 8 weeks. Reduced IR was measured from the decreasing HOMA-IR value after 8 weeks. The difference in decreasing HOMA-IR value between both groups was analyzed using independent t-test. The mean in group A was 0.199 ± 0.336, while group B had - 0.078 ± 0.271. The between both groups was statistically significant, with p = 0.004, 95% CI (0.096-0.457. Supplementation of 800 UI Vitamin E for 8 weeks could decrease IR in obese non-diabetic subjects.

1 INTRODUCTION

The prevalence of obesity has increased rapidly due to lifestyle and diet changes, making it a global problem in developed and developing countries. Obesity is a complex, multifactorial, and mostly preventable disease. The population with obesity and overweight problems currently reaches more than a third of the world's population. If secular trends continue, it is estimated that 38% of the world's adult population will be overweight, and another 20% will be obese by 2030 (Chooi *et al*., 2019). Obesity represents a significant health challenge because it substantially increases the risk of diseases, such as type-2 diabetes mellitus, fatty liver disease, and cardiovascular disease, thereby contributing to a decline in quality of life and life expectancy (González-Muniesa *et al*., 2017). The risk of type-2 diabetes mellitus will increase significantly and progressively in line with the increase in body mass index and the duration of obesity (Cederberg & Laakso, 2014).

World Health Organization (WHO) defines overweight as BMI (body mass index) of 23-24.9 kg/m^2 and obesity as BMI of ≥25 kg/m^2 in the Asia-Pacific population (Purnamasari *et al*., 2014). In obesity, oxidative stress and adipokines increase, and they are responsible for the incidence of insulin resistance (Hurrle & Hsu, 2017). A previous study found that the prevalence of insulin resistance in obese people was 59.6%. Insulin resistance, a process of decreasing insulin sensitivity, is determined using HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) values of >2.7. Insulin resistance is a metabolic disorder with a negative impact of underlying diabetes mellitus and cardiovascular disorders (Reynolds & He, 2005). In obese people, an increase in non-esterified fatty acids, glycerol, adipokine hormones, cytokines, pro-inflammatory markers, and other substances are associated with insulin resistance.

Epidemiological, clinical, and animal studies have reported the role of oxidative stress in the pathogenesis of obesity and its associated related

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conditions, including insulin resistance. Obesity can also induce systemic oxidative stress through multiple biochemical mechanisms, such as superoxide generation from NADPH oxidases (NOX), oxidative phosphorylation, glyceraldehyde auto-oxidation, and protein kinase C (PKC) activation (Savini *et al*., 2013). Other factors contributing to oxidative stress due to obesity include increased free fatty acid, hyperleptinemia, tissue dysfunction, low antioxidant defence, and chronic inflammation (Serra *et al*., 2013). In obesity, free fatty acids that enter the target organs are stored as triglycerides or used as a substrate for the oxidation of mitochondrial cells to produce ROS (Reactive Oxygen Species). Reactive Oxygen Species causes oxidative stress which has the potential to damage cellular functions. To prevent these damaging effects, the cells create a complex antioxidant system to eliminate ROS (Serra *et al*., 2013). In obese people, however, antioxidants' concentration decreases, causing an imbalance in ROS production and antioxidants that prevent oxidative stress (Manna & Jain, 2015). Deficiencies in vitamins and minerals can also contribute to the development of an impaired antioxidant defence in obesity. Increased BMI is found to be correlated with lower levels of carotenoids, vitamin C, and vitamin E. In obesity, oxidative stress is thought to be one of the factors causing insulin resistance and developing diabetes mellitus (McMurray *et al*., 2016).

Vitamin E is a major fat-soluble component in the cell's antioxidant defence system and is obtained exclusively from food. It has many essential roles in the metabolic system due to its antioxidant activity. Vitamin E is also a potent chain-breaking antioxidant that inhibits molecules of reactive oxygen species' production when fat is oxidized (Rizvi *et al*., 2014). Such antioxidant is known to have the effect of preventing free radicals that can adversely affect and damage cells (Han, 2016)

Previous studies of vitamin E's effects to reduce insulin resistance have been controversial as the results were inconsistent. A study by Manning *et al.* (2004) showed that the effects of high doses of vitamin E are associated with decreased insulin resistance and several inflammatory parameters, including FFA, in the overweight population (Manning *et al*., 2004). Another study by Balbi *et al.* (2018) found that Vitamin E correlates with a significant reduction in blood glucose and glycated hemoglobin compared to placebo in Type-2 DM patients (Balbi *et al*., 2018). A previous study indicated that the combination of vitamins C, E, and β-carotene during an 8-week supplementation moderately reduces HOMA-IR values in overweight young adults. Oxidative stress also decreases and may become a potential mechanism underlying such favorable changes in cardiovascular disease and precursors of diabetes (Vincent *et al*., 2009). Several studies, however, do not support the role of vitamin E in improving insulin sensitivity. An animal study found that vitamin E supplementation in obese rodents does not improve insulin sensitivity but changes mitochondrial biogenesis and mitochondrial protein expression (Picklo & Thyfault, 2015). Since vitamin E's role in insulin resistance remains unclear, this study aims to determine the effects of vitamin E on reduced insulin resistance in the obese population without diabetes mellitus.

2 MATERIAL AND METHODS

2.1 Research Design

This study was conducted with a clinical trial design of prospective randomized open and blinded endpoint evaluation (PROBE). In PROBE, the researcher knows the patients' medication but not the patients' final evaluation (laboratory results).

2.2 Subjects and Methods

Forty subjects aged 18-65 with a BMI of ≥25 kg/m2 and HOMA-IR of >2.7 (insulin resistance) were recruited from community populations using an open recruitment method. The exclusion criteria were diabetes mellitus patients and candidates using metformin or TZD drugs and antioxidant supplements during the last one month. The independent variable was the vitamin E therapy, and the dependent variable was HOMA-IR. The required number of subjects was calculated using the formula for unpaired numerical analytic research (Dahlan, 2010).

The subjects received a clinical examination, and the anthropometric, health, and lifestyle information was collected. The participants agreed and signed informed consent, and they were randomized into two groups, namely group A that received 800 IU Vitamin E supplementation, and group B, that received placebo.

The subjects were instructed to take vitamin E and placebo with meals. Vitamin E at a dose of 800 IU was given twice a day in a capsule form containing Vitamin E (alpha-tocopherol) maleate. The placebo used was a capsule containing flour with a shape similar to a capsule containing Vitamin E and also given twice a day. The supplementation was carried

out for 8 weeks, and HOMA-IR was measured before and after 8 weeks of 800 IU Vitamin E supplementation or placebo. The participants were instructed not to make lifestyle changes during the study. In the course of the supplementation, the participants reported their conditions and complaints to the researcher.

2.3 Blood Sampling

Fasting blood samples were collected using a catheter from an antecubital vein into heparinized vacutainer tubes before and after supplementation. The blood samples were then analyzed for glucose, insulin, cholesterol, and triglycerides of pre-supplementation and glucose and insulin of post-supplementation. All of the samples were batched within each subject and run in the same assay. The homeostasis model assessment (HOMA) was calculated from the fasting glucose (G_0) and insulin (I_0) concentrations using the following formula: (G_0 X I_0)/ 22.5.

2.4 Statistics

All of the data were expressed in mean ± standard error (SE) and analyzed using a Statistical Package for Social Sciences. The differences in the mean reduced HOMA-IR values (insulin resistance reduction) after 8 weeks of treatment in the two groups were analyzed using the independent t-test with a significance level of $p < 0.05$. and a 95% confidence level.

2.5 Ethical Consideration

This study kept the confidentiality of the patients and performed all procedures according to the study ethics. The research approval was obtained from the ethical review committee of Faculty of Medicine Universitas Islam Indonesia for biomedical studies involving human subjects and written informed consent was taken from the subjects.

3 RESULTS

Forty subjects who met the inclusion and exclusion criteria were randomized into two groups: twenty subjects in group A (Vitamin E) and 20 subjects in group B (placebo). The subjects consisted of 17 men and 23 women. Table 1 shows the baseline characteristics of the 40 subjects in this study. No significant differences existed in the variables of age, weight, BMI, systolic blood pressure, diastolic blood pressure, fasting glucose levels, fasting insulin levels, HOMA-IR, and cholesterol levels between the two groups at the baseline.

Table 2 shows the HOMA-IR levels before and after supplementation in the two groups. HOMA IR-values after the supplementation of 800 IU vitamin E for 8 weeks decreased significantly ($p = 0.04$). Meanwhile, Group B had increased HOMA-IR after receiving the placebo, although it was not significant with $p = 0.08$. A decrease in HOMA-IR values indicates insulin resistance reduction. Table 3 shows the mean HOMA-IR reduction differences after 800 IU vitamin E and placebo supplementation for 8 weeks between the two groups.

Table 3 indicates a significant difference in the decreased HOMA-IR values between group A receiving vitamin E supplementation and group B receiving placebo. In Group B, the HOMA-IR value increased as opposed to the baseline. This significant difference in decreased HOMA-IR values indicates that Vitamin E supplementation can lower insulin resistance than placebo.

4 DISCUSSION

Oxidative stress has been implicated in the development of insulin resistance, and in some studies, antioxidant therapy has proved to reduce ROS and improve glycemic control in people with type-2 diabetes. Besides, antioxidant concentrations significantly decrease in individuals with obesity (Manning *et al*., 2004).

Table 2: HOMA-IR Levels before and after Supplementation Vitamin E and Placebo

Variable	Group A (Vitamin E)			Group B (Plasebo)		
	Before	After	p*	Before	After	p*
HOMA IR	3.070±0.630	2.871±0.430	0,04	3.081±0.856	3.158±0.534	0,08

* analysis of differences in the mean levels before and after therapy using paired t-test

However, it remains unknown whether antioxidant therapy improves insulin sensitivity in non-diabetic obese individuals. Our results suggest that 800 IU vitamin E supplementation for 8 weeks can reduce insulin resistance condition in obese people in conjunction with decreased HOMA-IR.

This study is in line with some findings of previous studies. Research by Manning *et al.* (2004) showed the effects of high doses of vitamin E on reducing insulin resistance and several inflammatory parameters, including FFA in the overweight population. The reduced insulin resistance after the administration of high doses of vitamin E has an 18% difference from placebo treatment. A meta-analysis study by Balbi *et al.* (2018) indicated that Vitamin E is associated with a significant decrease in blood glucose as well as glycated hemoglobin compared to placebo. Supplementation of vitamin E can be a valuable strategy for controlling diabetes complications and enhancing antioxidant capacity.

Supplementation of vitamin E in obesity and type-2 diabetes mellitus can significantly impact the parameters of antioxidant status and glycemic control, which may positively benefit patients. The beneficial effects of vitamin E can be explained by the reduced damaging effects of free radicals on the structural and functional components of cells and vessel walls. Type-2 diabetes mellitus patients have a high risk of experiencing microvascular and macrovascular complications, and daily vitamin E supplementation provides an alternative strategy for metabolic control, in addition to the combination of diet, exercise, and medication (Balbi *et al*., 2018).

A previous study also showed that a combination of vitamins C, E, and β-carotene during an 8-week supplementation period moderately reduces HOMA-IR values in overweight young adults (Vincent *et al*., 2009). In animal subjects studies, vitamin E supplementation can improve adipose tissue expansion through a reduction in the fibrotic process. This improvement, in turn, reduces steatosis and inflammation, thereby restoring insulin sensitivity. The mechanism may involve, although not exclusively, vitamin E antioxidant activity, thus reducing ROS-mediated collagen deposition and inflammation (Alcalá *et al*., 2015). A review by Wong *et al.* (2017) summarized the findings in animal and human studies of the effects of vitamin E and articulated the contrasting potential of vitamin E in preventing the medical conditions associated with obesity and metabolic syndrome. It suggests that vitamin E may be a promising agent for attenuating obesity and metabolic syndrome (Wong *et al*., 2017). These previous studies support our findings that vitamin E has a potential mechanism in vitamin E-induced metabolic improvement, including insulin resistance reduction in obesity.

Table 3: Mean levels of reduction in plasma HOMA-IR after supplementation

	Group A (Vitamin E)	Group B (Plasebo)	p*
HOMA IR	3.070±0.630	2.871±0.430	0,04

*analysis using independent t test

However, some previous research had different results, such as a study by Picklo *et al.* (2015) which showed that vitamin E and vitamin C supplementation in obese rodents do not modify exercise-induced insulin sensitivity improvement. Changes in mitochondrial biogenesis and mitochondrial protein expression may be modified by antioxidant supplementation (Picklo & Thyfault, 2015). A study of obese adolescents by Hendarto *et al.* (2019) found that vitamin E supplementation at a dose of 400 IU/day for two months does not significantly affect lipid profiles and adiponectin levels (Hendarto *et al*., 2019).

This study has limitations in terms of a limited number of subjects and design. In addition, the confounding factors that could affect the level of HOMA-IR in the study samples were not fully controlled, thereby suggesting the importance of performing a study with a larger number of samples and a better study design. We strongly recommend that further well-designed, large-scale, long-term, head-to-head controlled trials and meta-analyses be carried out to demonstrate the effects of vitamin E supplementation on non-diabetes mellitus obesity. Further studies should also be conducted to strengthen this evidence, especially for defining the appropriate doses and regimen of vitamin E and supporting its use in daily practice.

5 CONCLUSION

The supplementation of 800 UI Vitamin E for 8 weeks can reduce insulin resistance in obese people without diabetes mellitus. This finding may represent a step forward in disease management.

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