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ARTIKEL PENELITIAN

Angiotensin Converting Enzyme (ACE) Gene Polymorphism and Random Blood Sugar Levels In Obese

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Abstrack: Background: Obesity is a condition where there is excessive accumulation of fat that can pose a risk to health in the form of the risk of chronic diseases such as type 2 diabetes mellitus (DM). Current blood sugar levels are one of the diagnoses of type 2 DM (T2DM) which is a standard test that describes blood glucose homeostasis. Angiotensin Converting Enzyme (ACE) is an important enzyme in the renin-angiotensin system (RAS) because it catalyzes the conversion of angiotensin I to angiotensin II (Ang II). The RAS component of adipose tissue provides a potential pathway by which obesity can lead to insulin resistance where ACE gene polymorphisms can raise blood sugar levels.
Objectives: To analyse the relationship of ACE gene polymorphism with random blood sugar levels as a predictor of type 2 DM risk in obesity.
Materials and Methods: The design of this study was observational analytic with a cross-sectional approach. The sample in this study were blood from 35 obesity people in Universitas Muhammadiyah Sumatera Utara and then carried out PCR examination to identify ACE gene polymorphisms and random blood sugar levels. The data were analyzed with the Kruskal Wallis Test.
Results: The major samples were in 26-35 years old (42,86%). The most types of ACE gene polymorphisms were type II 51,4%, followedby the type of *ID* polymorphisms (32,4%), and the least was the type of *DD* polymorphisms (10,8%). The random blood sugar levels was normal level 80-140mg/dl (74,29%). The Kruskal Wallis test of ACE gene polymorphism and blood sugar levels with $p = 0.119$ ($p > 0.05$).
Conclusion: There was no correlation of ACE gene polymorphism with random blood sugar levels in obesity.

Keywords: ACE gene polymorphism, random blood sugar levels, obese

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BACKGROUND

Obesity has become a global public health problem whose incidence continues to increase and can occur at almost any age. Obesity is an excessive accumulation of fat that can pose a risk to health in the form of the risk of degenerative diseases such as T2DM triggered by chronic inflammation. A person can be said to be obese with various methods and standards of measuring body fat distribution, one of which is anthropometric measurements.(1)

The Asia Pacific international classification states obesity if the body mass index (BMI) is greater than 25kg/m2. Obesity is associated with the accumulation of pro-inflammatory cells in visceral adipose tissue which is an important underlying cause of insulin resistance and the development of T2DM. T2DM is characterized by high blood sugar levels, which is a direct result of reduced systemic sensitivity to the anabolic hormone insulin(2) and high blood sugar levels.(3)

Currently, several major causative genes of human obesity have been identified, and it is speculated that there are genes involved in the process of adipogenesis or in the regulation of adipose tissue metabolism that may result in susceptibility to the incidence of obesity.(4) Angiotensin Converting Enzyme (ACE) is involved in adipocyte growth and function and angiotensin II inhibits adipocyte differentiation. A meta-analysis showed that ACE I/D gene polymorphisms are closely related to susceptibility to metabolic syndrome, a disorder closely linked to central obesity.(4) ACE is an important enzyme in the renin-angiotensin system (RAS) because it catalyzes the conversion of angiotensin I to angiotensin II (Ang II). Due to the main role of ACEs in RAS, changes in their activity will significantly affect RAS. The RAS component of adipose tissue provides a potential pathway by which obesity can lead to insulin resistance where ACE I/D polymorphisms may be associated with this state. ACE is an important enzyme in the renin-angiotensin system (RAS) because it catalyzes the conversion of angiotensin I to angiotensin II (Ang II). Due to the main role of ACEs in RAS, changes in their activity will significantly affect RAS. The RAS component of adipose tissue provides a potential pathway through which obesity can lead to insulin resistance where ACE I/D polymorphisms may be associated with this condition where ACE D/D genotypic polymorphisms are significantly associated with insulin resistance and BMI. ACE I/D polymorphisms are also associated with obesity and insulin resistance in Egyptian subject populations.(5) RAS activation can also contribute to insulin resistance in Ang II-responsive tissues through 2 pathways: (1) reducing the percentage of insulin-sensitive immature adipose compared to relatively

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insulin-resistant adipose mature cells, (2) decreasing blood flow which can reduce the delivery of insulin and glucose to insulin-sensitive tissues.(6)

According to research that fat tissue is also one active endocrine tissue that can be associated with the liver and muscles (target insulin tissue) through the release of intermediaries that will affect insulin function and the increase in fat accumulation can lead to insulin resistance. Insulin resistance that occurs in obese patients will result in a decrease in insulin action in target tissues, causing glucose to be difficult to absorb by body cells.(7) An obese person has increased amounts of non-esterified fatty acids, glycerol, hormones, cytokines, proinflammatory markers, and other substances involved in the pathophysiology of insulin resistance. Obesity also impacts β-pancreatic cell dysfunction and leads to decreased glucose control. β cell dysfunction and insulin resistance induce hyperglycemia and hence also increase insulin demand. Dysfunction of pancreatic β cells leads to inadequate insulin secretion, leading to higher concentrations of glucose in circulation. Glucose concentrations that continue to rise above the physiological range result in manifestations of hyperglycemia and elevations in blood sugar levels.(8)

MATERIAL AND METHODS

The design of this study was observational analytic with a cross-sectional approach. We were used obese citivas academica in Universitas Muhammadiyah Sumatera Utara according to Asia Pacific BMI classification as our subjects that met the inclusion criteria. As for inclusion criteria were obese, have no type 2 diabetic history or not consumed antiglicemic oral. The total sample in this study being 35 people after exclusion, and then took the patient's blood and divided into two for examination of ACE gene polymorphism such as II, ID, DD and random blood sugar level.

Examination of ACE gene polymorphism levels is carried out by first isolating DNA using procedures and materials from the DNA purification kit genomic wizard. DNA sample was stored at a temperature of 2-8ºC and continued with the PCR (Polymerase Chain Reaction) method which primers 3 F 5'– GAT, GTG, GCC, ATC, ACA, TTCGTC, AGAT -3' and Primers 3, R 5' – CTG, GAC, ACC, ACT, CCC, ATC, CCT, TCT-3' and producing products in the form of DNA bands at 490 bp and 190 bp. The PCR method used is with a thermal cycler tool with the first order of 2 minutes at a temperature of 98 º C then carried out 31 cycles at a temperature of 98 º C for 15 seconds, 58 º C for 1 minute and 75 º C for 30 seconds. After 31 cycles entered a temperature of 75ºC for 5 minutes and the results were stored at 4ºC. PCR results were read using 2% agarose gel electrophoresis stained with gel red. The interpretation of the

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results on this PCR result is polymorphism II when only one DNA band is found at 490 bp, DD polymorphism when there is only one DNA band at 190 bp and ID polymorphism when2 DNA bands are found, namely at 490 bp and 190 bp.[9]

Examination of random blood sugar level by using "easy touch" rapid glucocheck that was calibrated periodically before the examination carried out. Univariate analysis is seen to describe each variable studied, both dependent and independent variables. This analysis is used to look at the frequency distribution table to determine the number and percentage of each variable. Data analysis includes descriptive analysis and hypothesis testing. Kruskal Wallis bivariat test is used to determine the correlation between ACE gene polymorphism with random blood sugar level. Blood tests for ACE gene polymorphism and random blood sugar levels were examined at biochemistry laboratory at the Faculty of Medicine, Universitas Muhammadiyah Sumatera Utara.

RESULTS

This research has received approval from the ethics commission of Faculty ofMedicine, Universitas Muhammadiyah Sumatera Utara for the implementation ofresearch activities with letter number 1043/KEPK/FKUMSU/2023. Data collection in August 2023.

Table 1. Frequency distribution of characteristic of samples

Characteristic	N (%)
Age (years old)	
18-25	7 (20)
26-35	15 (42,86)
>36	13 (37,14)
Gender	
Male	21 (56,8)
Female	14 (37,8)
Gene ACE Polymorphism	
Insertion/Insertion (I/I)	19 (51,4)
Insertion/Deletion (I/D)	12 (32,4)
Deletion/Deletion (D/D)	4 (10,8)
Random Blood Sugar Level (mg/dl)	
<80	2 (5,71)
80-140	26 (74,29)
>140	7 (20)
Total	**35 (100)**

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Based on table 1, It can be seen that of the 35 samples collected, the most sample were 26-35 years old (42,86%), with male in large portion than female (56,8%). The most type of ACE gene polymorphism is I/I (51,4%) with normal random blood sugar level (74,29%). And the correlation of ACE gene polymorphism and random blood sugar level with p value 0,119 with Kruskal wallis test (table 2.). It means there is no correlation between ACE gene polymorphism and random blood sugar level in this study.

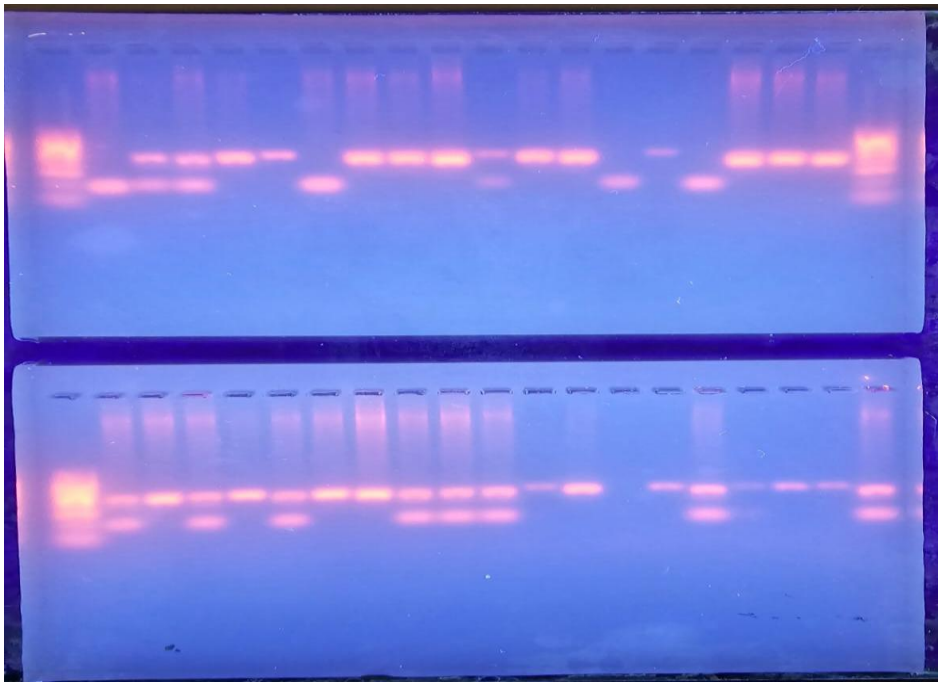

Figure 1. PCR of Gene ACE Polymorphism

Gene ACE Polymorphism; Insertion/Insertion (I/I); one band on the top, Insertion/Deletion (I/D); two bands on the top and bottom, Deletion/Deletion (D/D): one band at the bottom

Table 2. Correlation of ACE Gene Polymorphism with Random Blood Sugar level

	Random Blood Sugar level	P value
Gene ACE Polymorphism	35	0,119

DISCUSSION

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Many risk factors can cause T2DM, one of which is obesity. Earlier studies reported significant association of obesity, hypertension and T2DM. Genetic and many disease-associated alleles have been identified through the genome-wide association studies (GWAS) and applied to T2DM and indicated roles of renin-angiotensin system (RAS) in insulin signaling pathway and insulin resistance has been well documented.[10]

The roles of renin-angiotensin system (RAS) in insulin signaling pathway and insulin resistance has been well documented.[11] The blockade of the system has been found to have beneficial effects in the prevention of T2DM.[12] Angiotensin converting enzyme (ACE) gene is a potent vasoconstrictor and directly involved in the process of cell proliferation, differentiation, apoptosis and angiogenesis. Positive association of obesity with T2DM has been established repeatedly in many cross-sectional and prospective studies.[13,14]

This study found the most type of ACE gene polymorphism is I/I and suggest no correlation between ACE gene polymorphism and random blood sugar level. The role of ACE I/I carriers showed higher systolic blood pressure than those of D/D and I/D carriers.[15] They reported that children carrying the I/I genotype were demonstrated to have higher blood pressure and greater early growth acceleration compared to those with the other ACE genotypes.[16] The controversies may be attributed to clinical characteristics of subjects, such as patient's age, racial difference and sample size.

In addition, based on earlier study that an inevitable gene of RAAS is ACE and its I/D polymorphism has been frequently reported to be associated with T2DM, HT and CKD in different ethnic population.[15,17,18] The ACE D allele is associated with higher serum ACE levels and increased conversion of angiotensin I (Ang I) to angiotensin II (Ang II). Elevated serum ACE levels diminish glucose utilization in skeletal muscles during exercise and ACE inhibitor (ACEI) reduces the ACE levels and increases insulin sensitivity, GLUT-4 synthase and hexokinase activity and also suppresses hepatic glucose production. As a result of these previous reports, high ACE activity, namely the ACE D/D genotype, seems to increase the risk of impaired glucose metabolism or T2DM.[19] The ACE I/D polymorphism in physiological has association with plasma ACE activity. The presence of DD genotype of this polymorphism is associated with 2-fold increased ACE activity, whereas those with the I/I genotype have the lowest ACE expression.[20]

Most studies confirmed that ACE I/D polymorphism is involved in the susceptibility to overt nephropathy with protective role of ACE II genotype against the disease in both type 1 and 2 diabetes mellitus. The relationship of ACE gene I/D polymorphism with BMI-defined obesity is insignificant in Chinese patients with T2DM;

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the obese group obtained higher ratio of hypertension. Furthermore, we also strengthened the fact that BMI is associated with hyperglycemia, hypertension, and dyslipidemia in T2DM patients.

CONCLUSION

This study confirmed the most type of ACE gene polymorphism in obese subject is I/I polymorphism and have no correlation with random blood sugar level, based on most earlier study that I/I polymorphism correlated with blood pressure and renal.

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