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Relationship between Angiotensin Converting Enzyme (ACE) and Cellulite

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ABSTRACT

Introduction: Cellulite is a local metabolic disorder in subcutaneous tissue characterized by changes in skin topography, occurring in parts of the body with a large accumulation of fat tissue, especially thighs, buttocks, hips, and abdomen. Angiotensin converting enzyme is a zinc metallopeptidase, distributed on the surface of endothelial cells. Increased ACE levels cause microcirculation disorders, adipocyte hypertrophy, increased extracellular matrix, and stimulate the emergence of inflammatory cytokines which will cause an increase in the inflammatory response in the tissue, stimulate fibrogenic response and influences the appearance of cellulite. The aim of this study was too determine the relationship between ACE and cellulite.
Method: This study was an observational study with a cross-sectional design of 40 cellulite patients and 40 controls. Each patient underwent history, dermatological examination, and blood sampling to assess ACE levels by ELISA test. These data were analyzed statistically using the Chi square test.
Results: The mean ACE level in cellulite was 66.78±15.38 µg/ml. The highest age with cellulite was 26–35 years 17 subjects (42.5%). Most of them had a family history of cellulite from their mother 22 subjects (55%). The majority of cellulite are located on the femoral and gluteus regions by 27 subjects (67.5%). The result of this study showed that there was a relationship between high ACE levels causing a risk of 4.5 times for cellulite ($p = 0.002$).
Conclusion: There is a relationship between ACE levels and cellulite.

Keywords

Cellulite, Angiotensin Converting Enzyme, ACE levels, Gynoid lipodystrophy, Risk factors.

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INTRODUCTION

Cellulite is also known as gynecoid lipodystrophy, panniculosis, nodular liposclerosis, and edematofibrosclerotic panniculopathy or local lipodystrophy which is a local anatomical and metabolic disorder of the subcutaneous tissue that causes changes in body contour, characterized by irregular relief changes on the skin surface of the affected area, which presents an appearance like orange peel, cottage cheese, or mattress.[1-3] Cellulite is most often found on the upper thighs, buttocks, and abdomen.[4] Cellulite is painless and aesthetic problem characterized by raised skin surfaces and indentations on the skin surface.[1,5,6]

Cellulite occurs in around 85–90% of women aged over 20 years.[5] Cellulite can occur in all races but is more common in Caucasians than Asians.[5] The etiopathogenesis of cellulite is still not clearly understood and is multifactorial, but there are several hypotheses which state that cellulite can occur due to the influence

of genetic factors, differences in gender, age, race, diet, and hormonal factors.[1,6,7] There are several supporting factors, for the occurrence of cellulite, such as obesity, hormone intake, and metabolic changes.[8,9]

There are many theories that explain the pathophysiology of cellulite. Haxel et al. explains that the majority of theories involve modifications in adipose tissue and microcirculation, as a result of disruption of blood vessels and lymphatic vessels that cause fibrosclerosis of connective tissue.[10] Several hypotheses state that cellulite is multifactorial, namely there is a role in the number and type of fibrous septa, microvascular dysfunction, hypoxia, inflammation, subcutaneous fibrosis, decreased dermis thickness with age, and adipose tissue deposition.[11-13]

Angiotensin converting enzyme is a peptide hydrolase that mediates the conversion of angiotensin I to angiotensin II. This process is very important in the renin angiotensin system. Angiotensin II is a potent vasoconstrictor and will cause effects after binding to specific receptors, namely angiotensin II type 1 and type 2 receptors.[14,15] The increase in ACE is caused by damage to endothelial cells and also an increase in adipose tissue which causes dysregulation of blood flow which then causes microcirculation disorders, facilitates adipocyte hypertrophy, increases the extracellular matrix, and stimulates the emergence of inflammatory cytokines which will cause an increase in the inflammatory response in the tissue. Disruption of microcirculation, and increased inflammatory response will stimulate a fibrogenic response.[16–18]

Cellulite is related to the ACE gene. The female gene that carries the ACE allele can increase the risk of developing cellulite due to increased production of angiotensin II in subcutaneous adipose tissue, causing dysregulation of blood flow and tissue hypoxia which ultimately causes disruption of vascular microcirculation and the formation of subcutaneous fibrous tissue complexes.[16,19,20]

Based on the explanation above, there is a hypothesis that ACE has a role in the pathophysiology of cellulite, but it is still limited, so research is needed to determine the relationship between ACE levels and cellulite.

METHOD

This study is an analytic observational study with a cross sectional design involving 18-45 years old of 40 cellulite patients and 40 controls at the Dermatology and Venereology polyclinic in Universitas Sumatera Utara, Medan. Every research subject who informed consent was included in this study. The exclusion criteria were pregnant and lactating women, menopause, obesity, cancer, hypertension, coronary heart disease, pulmonary tuberculosis, diabetes mellitus, hyperthyroidism, psoriasis, keloid, alopecia areata, deep vein thrombosis, and taking ACE inhibitor drugs. The ethical license was granted by the Health Research Ethics Committee, Faculty of Medicine, Universitas Sumatera Utara.

This study was conducted after obtaining ethical clearance from the Research Ethics Committee of the University of Sumatera Utara (No. 270/KEPK/USU/2023) and from the Prof. Chairuddin P Lubis Universitas Sumatera Utara Hospital Research Permit (No. 1571/UN5.4. 1.1.3/KPM/2023).

The data collected by researchers at the work location of patients who come to Dermatology and Venereology polyclinic in Universitas Sumatera Utara, Medan. Researchers is taking a careful history, clinical examination, and blood sample tests to check serum ACE. Serum ACE levels were measured by using Human ACE Elisa Kit. The data collected were analyzed using Chi-square test to determine the relationship between serum ACE levels with cellulite which $p < 0.05$ was considered a significant result.

RESULT

In this study, the subjects were divided into cellulite and control groups (with no cellulite). The characteristics of the subjects based on age and family history were presented in Table 1. Most of the research subjects in the cellulite group were 26–35 years old (42.5%), while most of the control group were 26–35 years old (37.5%). According to family history, the majority of the cellulite group had a family history, from their mother was 22 subjects (55%) and most of the control group had no family history was 18 subjects (45%).

According to the location, we observed that 27 subjects (67.5%) had their cellulite on gluteus and femoral areas, while 11 subjects (27.5%) had it on the femoral, gluteus, and abdominal areas, and 2 subjects (5%) on gluteus areas (Table 2).

Table 1. Distribution of research subjects by age and family history

	Cellulite patients		Control	
	n=40	%	n=40	%
Age (years)				
18–25	12	30	14	35
26–35	17	42.5	15	37.5
36–45	11	27.5	11	27.5
Family History				
Mother	22	55	9	22.5
Sibling	1	2.5	2	5
Mother and sibling	11	27.5	11	27.5
No family history	6	15	18	45

Table 2. Distribution of research subjects by location of cellulite

Cellulite Locations	Cellulite patients	
	n	%
Gluteus	2	5
Femoral and gluteus	27	67.5
Femoral, gluteus, and abdomen	11	27.5
Total	40	100

Then the ACE level was measured using ELISA. The ELISA showed that ACE level in the cellulite group was higher than in the control group (66,78±15,38 vs. 46,68±10,97µg/ml) (Table 3). Assessing the relationship between ACE and cellulite, we found that the OR value at 4.5 (p = 0.002) means that subjects with high serum ACE have 4.5 times higher risk of cellulite than those who have a lower level of ACE (Table 4).

Table 3. Average ACE levels in study subjects

Group	ACE levels		
	n	Mean	SD
Cellulite	40	66.78	15.38
Control	40	46.68	10.97

Table 4. Relationship between ACE levels and cellulite

ACE levels	Group			
	Cellulite	Control	Odd	p value*
Low	16 (40%)	30 (75%)	4.5	0.002
High	24 (60%)	10 (25%)		
Total	40 (100%)	40 (100%)		

**Chi square*

DISCUSSION

This study found that most of the research subjects in the cellulite group were 26–35 years old (42.5%), while most of the control group were 26–35 years old (37.5%). Research conducted by Indriayani S, Putra IB, and Jusuf NK in Dermatology and Venereology Polyclinic, Universitas Sumatera Utara Hospital, the highest distribution of cellulite was found in women aged 20–30 years.[7] The results of this study are in line with the results conducted by Hexsel et al. in Brazil with the results obtained in the form of a mean age of cellulite patients of 32 years, with an age range between 18–45 years.[21] Cellulite occurs very often (85%–98%) in post-pubertal women.[22] The thickness of the dermis decreases with age due to a decrease in the amount of

collagen and elastin, causing fat to protrude into the dermis. Fat globules also become more hypertrophic with age. This explains the potential for cellulite to occur more frequently with increasing age, but because young women can also experience cellulite, so age-related changes in dermis thickness are not the main contributor to cellulite.[5,23]

According to family history, this study found that the majority of the cellulite group had a family history, from their mother was 55% and most of the control group had no family history was 45%. In research conducted by Mirrashed et al. In Canada, it has been found that daughters of mothers with cellulite also tend to have cellulite.[24] In research conducted by Lubis, Jusuf NK, and Putra in this study found that 82.5% of patients with cellulite had a family history of suffering from cellulite.[25] There is a genetic element in individuals who are susceptible to cellulite. Research conducted by Emanuele et al. found that there is a genetic component related to cellulite. The clinical appearance and severity of cellulite are often similar between women in the same family due to the similarity on the distribution of subcutaneous fat.[26,27] The degree of cellulite severity is related to structural changes such as the thickness of the subcutaneous fat, the thickness of the dermis, the invagination percentage of the hypodermis into the dermis, and the percentage of adipose tissue to connective tissue in the hypodermis.[28]

According to the location, we observed that 67.5% subject had their cellulite on gluteus and femoral areas, while 27.5% subject had it on the femoral, gluteus, and abdominal areas. The same condition was found in a study by Fovina, Jusuf NK, and Putra IB which cellulite most often occurs on the thighs and buttocks by 62.5%.[29] However, this was different from Uebel et al. stated that the most cellulite locations were on thighs by 88.8%.[27] A greater percentage of women's body fat is stored in the thighs and buttocks, this type of fat deposition is typically called gynoid or pear-shaped.[30] Cellulite can occur in any anatomical area with subcutaneous adipose tissue but most often occurs on the thighs, buttocks, hips and can also be found on the breasts, lower abdomen, upper arms, and nape.[30,31]

The mean serum ACE level in the cellulite group from our study were 66,78±15,38 and 46,68±10,97 µg/ml in the control group. Until now, there is no research on ACE levels in cellulite patients. Research by Fahim et al. the average ACE level in alopecia areata patients was 52.1±9 and in controls 55.3±14.7 µg/ml.[30] Research by Huskie et al. the ACE level in psoriasis patients was 35.02 ± 2.07 µg/ml, in lichen planus patients 35.90±2.09 µg/ml, and in seborrheic dermatitis patients before therapy 31.44±2.79 µg/ml.[31] This was different from our findings because associated variations in each study. Factors which can affect ACE levels in the blood can be affected in other diseases such as cancer, hypertension, coronary heart disease, pulmonary tuberculosis, diabetes mellitus, hyperthyroidism, psoriasis, keloid, alopecia areata, deep vein thrombosis, and taking ACE inhibitor drugs.[32-34] In this study, all of these things were excluded in the research subjects.

In this study, there were 24 subjects (60%) with high ACE levels in the cellulite group and 16 subjects (40%) with low ACE levels in the cellulite group. Based on the Chi square test, there is a statistically significant relationship between ACE levels and cellulite. High ACE levels causing a risk of 4.5 times for cellulite ($p = 0.002$).

The increase in ACE is caused by damage to endothelial cells and also an increase in adipose tissue which causes dysregulation of blood flow which then causes microcirculation disorders, facilitates adipocyte hypertrophy, increases the extracellular matrix, and stimulates the emergence of inflammatory cytokines which will cause an increase in the inflammatory response in the tissue. Disruption of microcirculation, increased inflammatory response will later stimulate a fibrogenic response.[16-18]

Research by Emanuele et al. stated that there is a genetic variant of ACE associated with the occurrence of cellulite. The ACE gene can modulate ACE activity which catalyzes the conversion of angiotensin I to angiotensin II (vasoconstriction peptide), and also the catabolism of bradykinin (vasodilation peptide) resulting in cellular hypertrophy and stimulating extracellular matrix deposits which ultimately induces dysregulation of blood flow in adipose subcutaneous tissue, adipocyte hyperplasia, and structural abnormalities in adipose subcutaneous tissue. Structural abnormalities in adipose tissue will cause adipose tissue hypoxia due to

decreased blood flow, thereby initiating adipose tissue fibrosis and causing local inflammation as seen in cellulite.[20,33,34]

Carriers of the D allele of ACE rs1799752 can cause vasoconstriction even in normal healthy people, with consequent impairment of tissue oxygenation. Some evidence shows that adipocyte tissue has a local angiotensin II producing system, which suggests that this vasoactive molecule can be produced in adipocyte tissue.[35] Differences in connective tissue anatomy between women and men cause cellulite to occur more often in women, in addition to the presence of the hormone estrogen in women, making it easier for lipogenesis to occur.[36] Women have more adipocyte cells, adipocyte cells can also secrete ACE, which contributes to an increase in ACE.[35,37]

CONCLUSION

Based on the analysis of the data obtained from this study can be concluded that there was a relationship between ACE and cellulite. High ACE levels cause a 4.5 times risk of cellulite.

DECLARATIONS

The research has received approval from the Universitas Sumatera Utara and RSUP Haji Adam Malik Health Research and Ethics Committee with Number. All participants were informed about subject of the study.

CONSENT FOR PUBLICATION

The Authors agree to publication in Journal of Society Medicine.

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COMPETING INTERESTS

The authors declare that there is no conflict of interest in this research.

AUTHORS' CONTRIBUTIONS

All authors are responsible for conceptualization, manuscript preparation, manuscript editing, and manuscript assurance.

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