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Comparison of angiotensin converting enzyme 1 levels to the grading of knee osteoarthritis

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ABSTRACT

Background and aim. One of the most prevalent chronic joint illnesses is osteoarthritis (OA), which can impair a patient's quality of life by causing joint pain, stiffness, deformity, and narrowed joint spaces. Many factors influence the pathogenesis of Osteoarthritis such as age and body weight, as well as genetic factors that are reported to play a role in the occurrence and progression of Osteoarthritis. Recently, many studies have demonstrated that inflammatory variables contribute to osteoarthritis pathomechanisms. It is currently thought that inflammatory variables alone are an independent risk factor for osteoarthritis.

Methods. Observational sub-analysis with a cross-sectional approach to examine the relationship between Angiotensin Converting Enzyme 1 (ACE 1) levels and the grading of osteoarthritis at "Dr. Wahidin Sudirohusodo" Hospital from October 2020 to February 2021. ACE 1 levels were measured using the Elisa KIT and grading of osteoarthritis using the Kellgren and Lawrence criteria.

Results. Analysis of the relationship between ACE 1 levels and osteoarthritis grading using the ANOVA test and Post Hoc Bonferonni Test showed a significant relationship between ACE 1 levels and osteoarthritis grading, where high ACE 1 levels were related to osteoarthritis grading. Deficiency and insufficiency ($p<0.05$). The results of this study are in line with previous research.

Conclusion. The higher the ACE 1 level, the more severe the degree of knee osteoarthritis.

Keywords: ACE1, angiotensin, renin angiotensin system, osteoarthritis, knee osteoarthritis grading

INTRODUCTION

Among the most prevalent chronic joint illnesses, osteoarthritis (OA) can result in joint pain, stiffness, deformity, and narrowing of the joint space, all of which have a negative effect on the patient's quality of life [1]. Osteoarthritis occurs due to various etiologies resulting in biological and morphological abnormalities [2]. Osteoarthritis can affect joints, especially the knee, hand and hip joints [2].

Age, gender, ethnicity, genetics, food, obesity, muscle weakness, excessive physical activity, past trauma, reduced proprioceptive function, hereditary variables resulting in osteoarthritis, and mechanical factors are some of the risk factors for osteoarthritis [3]. These risk factors affect the development of abnormal bone growth, joint cartilage damage, and bone injury [4]. Based on etiology, osteoarthritis can occur primarily (idiopathic) or secondary [4].

The diagnosis of osteoarthritis is based on clinical symptoms. There are no specific supporting examinations that can determine the diagnosis of osteoarthritis [4]. Radiological examination can determine the presence of osteoarthritis, but it is not directly

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related to the clinical symptoms that appear [4]. Radiographic assessment of osteoarthritis relies primarily on the assessment of the narrowing of the joint space and osteophytes [5]. Osteophytes, namely bone growths at the edges of joints, usually show up earlier than joint space reducing. The primary factors determining the grading of osteoarthritis are joint space constriction and concurrent subchondral bone disease [5].

Genetic and environmental factors influence the pathophysiology of osteoarthritis by activating cellular and molecular pathways that contribute to joint damage [6]. Synovial inflammation, oxidative stress, chondrocyte death, cartilage extracellular matrix degradation, subchondral bone sclerosis, and osteophyte production are typical symptoms of affected joints, leading to discomfort, pain, and joint failure [6]. In recent years, studies have shown that the main components of RAS, including ACE, AT1R, and AT2R, are expressed in synovial tissue in humans and animals and participate in the pathogenesis of osteoarthritis; their expression levels are related to the degree of inflammation and severity of arthritis [7].

The Renin-Angotensin Aldosterone system influences bone density by participating in the regulation of bone resorption [8]. The major RAS proteins and receptors are expressed locally in bone tissue and majorly regulate bone remodeling and metabolism [9]. The enzyme Renin transforms angiotensinogen (AGT) into angiotensin I (Ang I), which is subsequently transformed into angiotensin II (Ang II) by Angiotensin Converting Enzyme 1 (ACE 1) [10]. Additionally, Ang 2 promotes inflammation and cell proliferation [10].

An essential component of RAS, ACE preserves water, electrolytes, and the internal environment of the organisms balanced [8]. By converting Ang 1 into Ang 2, ACE may constrict blood vessels, release aldosterone, and contribute to the inflammatory process of osteoarthritis [7].

On osteoblasts and osteoclasts, angiotensin receptor types 1 and 2 (AT1R and AT2R) are expressed. Furthermore, renin and ACE have also been expressed in bone cells [7].The function of angiotensin II in the skeletal system is to stimulate the proliferation of osteoblast cells in the calvaria via AT1R, apart from that, angiotensin II can also reduce calcium absorption in the bones. Additionally, it has been noted that improving metabolism and bone structure can be achieved by blocking AT1R with losartan [8].

MATERIALS AND METHODS

Patient population

The Study population was all patients diagnosed with Osteoarthritis at "Dr. Wahidin Sudirohusodo" Hospital Makassar from October 2020 to February 2021. Samples are individuals who match all criteria for inclusion.

Inclusion and exclusion criteria

The Inclusion criteria: Patients diagnosed with osteoarthritis according to ACR and Kellgren-Lawrence criteria at "Dr. Wahidin Sudirohusodo" Hospital Makassar were then examined for ACE 1 levels. The Exclusion criteria: Participants who could not agree to be part of the study sample, Secondary osteoarthritis patients, and patients who are temporarily taking ACE inhibitor drugs.

Clinical data and sample collection

Sampling was carried out by consecutive sampling.

Statistical analysis

The data was analyzed using SPSS version 25. Statistical tests and descriptive approaches made up the analysis approach. The goal of the cross-sectional design approach, also known as the cross-sectional study, is to gather broad details on the research sample. The mean value, standard deviation (SB), and frequency distribution are calculated using a statistical method. The ANOVA statistical test is employed. If the test p value is less than 0.05, the findings of the statistical test are deemed significant. Complete with tables and figures, the collected results, will be presented narratively.

RESULTS

Study population

This research collected 80 subjects who were grouped based on the Kellgren-Lawrence (KL) criteria into groups KL 1 (20 subjects), KL 2 (20 subjects), KL 3 (20 subjects) and KL 4 (20 subjects) with characteristic as displayed in Table 1.

TABLE 5. Characteristics of research subjects (N:80)

Characteristics	
Variable	**Mean (SD)**
BMI(kg/m^2)	27.9±4.72
Age (Year)	63.2±8.84
Waist size (cm)	100.4±14.7
ACE 1	136±81.9
Osteoarthritis (%)	80
Grade 1	20 (25%)
Grade 2	20 (25%)
Grade 3	20 (25%)
Grade 4	20 (25%)

SD= standard deviation; BMI = Body Mass Index; ACE1=Angiotensin Converting Enzyme 1

Considering on Table 1, the average age found in this study was 63.2 ± 8.84. The mean Body Mass Index found was 27.9 ± 4.72. The mean waist circumference was 100.4 ± 14.7.

The relationship between angiotensin converting enzyme levels and the severity of knee osteoarthritis

The relationship between angiotensin converting enzyme levels and the severity of knee osteoarthritis can be seen in Table 3. In this study, to see the relationship between ACE and the severity of knee osteoarthritis, a bivariate analysis using the ANOVA test was carried out, showing a significant relationship between the severity of osteoarthritis and ACE-1 levels (**P** = 0.048) and it was found that the ACE 1 levels found in 80 samples had values with osteoarthritis grade 1 (108.3 ± 25.3), grade 2 (119.6 ± 38.1), grade 3 (145.0 ±59.7) and grade 4 (109.2±139.6) (Table 2).

In subgroup analysis, a significant relationship was found between ACE1 levels and the severity of osteoarthritis grades 1 and 3 (*P* = 0.016) and grades 1 and 4 (*P* = 0.044).

In the study, it was found that there were differences in Body Mass Index in OA grade 1, grade 2, grade 3, grade 4 (*P* = 0.002). However, there was no difference in waist circumference between OA grade 1, grade 2, grade 3, grade 4 (*P* = 0.548). There was no difference in age between OA grade 1, grade 2, grade 3, grade 4 (*P* = 0.991) (Table 3).

TABLE 2. The relationship between Angiotensin Converting Enzyme levels and the severity of knee osteoarthritis (N=80)

	Grading of knee osteoarthritis				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**P Value**
ACE 1	108.3±25.3	119.6±38.1	145.0±59.7	174±139.6	0.048

** ANOVA test, significant if P<0.05*

TABLE 3. Relationship of confounding variables to the grading of knee OA (N=80)

	Grading of knee osteoarthritis				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**P Value**
BMI	25.5±4.55	28.9±5.33	24.8±3.82	30.6±3.51	0.002
Waist Size	96.5±15.6	100.4±12.2	102.7±14.4	102.2±16.7	0.548
Age	63.4±7.04	63.6±10.4	58.4±9.82	62.8±8.38	0.991

This study also found that there was a relationship between BMI and the severity of OA with a P value of (0.002), so we continued to carry out further analysis to assess the relationship between OA and BMI.

A positive association was found between ACE levels and OA grade, with OR 1.019 (1.005-1.033) *P* = 0.007, and after being corrected for BMI. This relationship remains significant with OR 1.02 (1.006-1.035), *P* = 0.005 (Figure 2).

DISCUSSION

This study examines the relationship between ACE levels and the severity of knee osteoarthritis in Wahidin Sudirohusodo and his network. The 80 research subjects were grouped based on the Kellgren-Lawrence

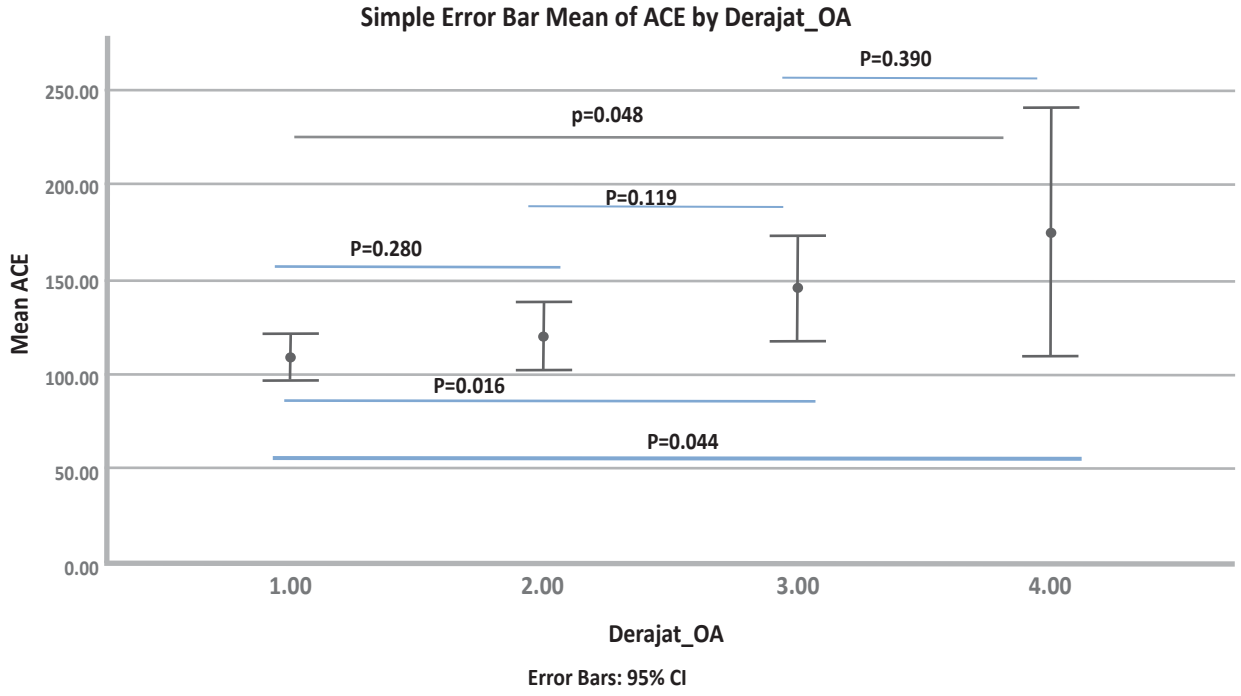

FIGURE 1. Relationship between Angiotensin Converting Enzyme Levels and Severity of Knee Osteoarthritis
*Post Hoc Bonferonni Test, significant if *P* < 0.05

TABLE 4. Variable in the equation

		B	S.E	Wald	def	Sig.	Exp(B)	95% C.I for EXP (B)	
								Lower	Upper
Step 1	**ACE 1**	0.020	0.007	7.900	1	0.005	1.020	1.006	1.035
	BMI	0.082	0.054	2.288	1	0.130	1.085	0.976	1.206
	Konstan	-4.887	1.897	6.634	1	0.010	0.008		

**Overall Percentage 63.7 ; R Squere 0.214 ; Sig 0.001*

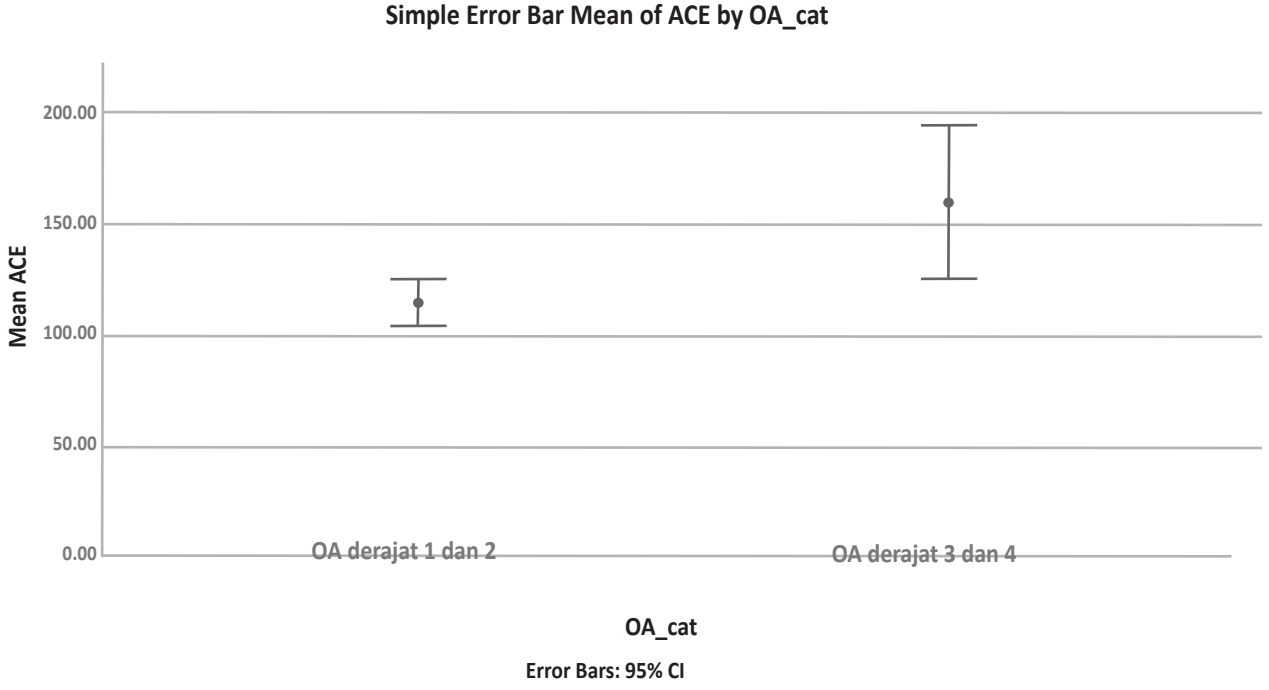

FIGURE 2. Relationship between Grading Osteoatrtitis and BMI

(KL) criteria into groups KL 1 (20 subjects), KL 2 (20 subjects), KL 3 (20 subjects) and KL 4 (20 subjects). All research samples were female. The majority of the sample was aged between 40 – 84 years. Body Mass Index is between 44 kg to 99 kg on average.

It is known that ACE-1 changes Angiotensin I to Angiotensin II so that high levels of ACE-1 will cause high levels of Angiotensin II. We know that Angiotensin II is a pro-inflammatory agent which is thought to play a role in increasing the severity of osteoarthritis.

Bivariate analysis using ANOVA test in this study found that A correlation was seen between the severity of knee osteoarthritis and ACE levels, including ACE-1 levels (P = 0.048) and Body Mass Index (P = 0.002), and a non-significant relationship with age (P = 0.991), Waist Circumference (P = 0.548). In accordance with research by Wu et al. (2019) which states that ACE components, Angiotensi I and Angiotensi II, are found in humans synovial tissue, can contribute to the etiology of several inflammatory joint conditions, including osteoarthritis [7]. From research by Yan et al. (2017) it is found relationship between increased levels of components of the renin angiotensin system with the severity of inflammation and severity of Osteoathrtitis [11].

Research by Raud et al. (2020) shows a correlation between increasing body weight and the severity of knee Osteoathrtitis [12]. Lee et al. (2012) researched that biomechanical changes are patho-mechanisms that play a role in the relationship between obesity and the incidence and severity of knee OA [13]. In this case, there is an increase in the load on the knee joint cartilage which acts as a joint cushion, This results in surface erosion of the joint cartilage and changes the hyaline cartilage's composition, structure, and mechanics [14].

Individuals with a BMI > 30 kg/m^2 have a 6.8 times greater risk of suffering from knee OA compared to normal individuals with a normal BMI [9]. The prevalence and severity of knee OA is also associated with obesity [9]. A study reported an increase of one level of KL in knee OA sufferers with a BMI > 27.5 kg/m^2 or an increase of > 1.5 mm in joint space narrowing [15].

CONCLUSION

The degree of progression of knee osteoarthritis increases with ACE 1 level. The strength of this study is that it can be considered giving ace inhibitor as a treatment for hypertensive patients with osteoarthritis. This research has the limitation that ACE 1 levels were measured from blood, so for further research, ACE 1 levels in joint fluid can be examined.

Ethics committee approval

The Ethics Committee for Biomedical Research on Humans at Hasanuddin University's Faculty of Medicine in Makassar, South Sulawesi, Indonesia, approved for this study. Based on recommendation letter number 942/UN4.6.4.5.31/PP36/2023, dated December 11, 2023; protocol number UH23110824; study approval term, December 11, 2023–December 11, 2024.

Author's contributions:

FE (concept, design, materials, sources,data processing, interpretation and analysis, literature research, and manuscript editing); FS (concept, planning, guidance, interpretation and analysis); HR (concept, planning, guidance, evaluation, and literature research); SB (concept, planning, guidance, evaluation, and literature research); HI (concept, critical review, design); NM (concept, evaluation, critical review); GW (concept, design, editing); AZ (concept, analysis and interpretation, critical review)

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Conflict of interest:

The authors certify that they have no financial relationships that could create a conflict of interest about the submitted manuscript.

REFERENCES

1. Morris JL, Letson HL, Gillman R, Hazratwala K, Wilkinson M, McEwen P, Dobson GP. The CNS theory of osteoarthritis: Opportunities beyond the joint. *Semin Arthritis Rheum.* 2019 Dec;49(3):331-336. doi: 10.1016/j.semarthrit.2019.03.008.
2. Perhimpunan Reumatologi Indonesia. Diagnosis dan Pengelolaan Osteoartritis. Vol 1. Jakarta: Perhimpunan Reumatologi Indonesia; 2021. p. 1– 48.
3. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis Rheumatol.* 2020 Feb;72(2):220-233. doi: 10.1002/art.41142.
4. Perhimpunan Reumatologi Indonesia. Rekomendasi IRA untuk Diagnosis dan Penatalaksanaan Osteoartritis. Jakarta: Divisi Reumatologi Departemen Ilmu Penyakit Dalam FKUI/RSCM; 2014. p. 1–3.
5. Roemer FW, Guermazi A, Demehri S, Wirth W, Kijowski R. Imaging in Osteoarthritis. *Osteoarthr Cartil.* 2022;30(7):913–34. doi: 10.1016/j.joca.2021.04.018.
6. Ansari MY, Ahmad N, Haqqi TM. Oxidative stress and inflammation in osteoarthritis pathogenesis: Role of polyphenols. *Biomed Pharmacother*. 2020;129:110452. doi: 10.1016/j.biopha.2020.110452.
7. Wu Y, Lu X, Li M, Zeng J, Zeng J, Shen B, Zeng Y. Renin-angiotensin system in osteoarthritis: A new potential therapy. *Int Immunopharmacol.* 2019 Oct;75:105796. doi: 10.1016/j.intimp.2019.105796.
8. Chen G, Hu S, Lai Z, Qiu B. Association between ACE gene I/D polymorphism and knee osteoarthritis in a Chinese population. *Biosci Rep.* 2019;39(2):1–10. doi: 10.1042/BSR20181713.
9. Mustari MN, Massi MN, Usman MA. Dynamic interaction of obesity, age, MCP-1 Level, and ACE-1 gene with the severity of knee osteoarthritis: a cross-sectional study. *Ann Med Surg.* 2023;3845–51. doi: 10.1097/MS9.0000000000000973.
10. de Sá GA, Dos Santos ACPM, Nogueira JM, Dos Santos DM, Amaral FA, Jorge EC, et al. Angiotensin II triggers knee joint lesions in experimental osteoarthritis. *Bone*. 2021 Apr;145:115842. doi: 10.1016/j.bone.2021.115842.
11. Yan K, Shen Y. Aliskiren has chondroprotective efficacy in a rat model of osteoarthritis through suppression of the local renin-angiotensin system. *Mol Med Rep.* 2017;16(4):3965–73. doi: 10.3892/mmr.2017.7110.
12. Raud B, Gay C, Guiguet-Auclair C, Bonnin A, Gerbaud L, Pereira B, et al. Level of obesity is directly associated with the clinical and functional consequences of knee osteoarthritis. *Sci Rep.* 2020;10(1):1–7. doi: 10.1038/s41598-020-60587-1.
13. Lee R, Kean WF. Obesity and knee osteoarthritis. *Inflammopharmacology*. 2012;20(2):53–8. doi: 10.1007/s10787-011-0118-0.
14. Yamagishi K, Tsukamoto I, Nakamura F, Hashimoto K, Ohtani K, Akagi M. Activation of the reninangiotensin system in mice aggravates mechanical loadinginduced knee osteoarthritis. *Eur J Histochem.* 2018;62(3):177–87. doi: 10.4081/ejh.2018.2930.
15. Houard X, Goldring MB, Berenbaum F. Homeostatic mechanisms in articular cartilage and role of inflammation in osteoarthritis. *Curr Rheumatol Rep.* 2013 Nov;15(11):375. doi: 10.1007/s11926-013-0375-6.