ORIGINAL RESEARCH

Differences of Serum Total Antioxidant Capacity Levels in Women with Early Menopause and Normal Menopause

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Abstract

Introduction: Antioxidant can be defined as any substance that significantly delays and prevents the oxidation of an oxidizable substrate (oxidant). So that the causal relationship of menopause and the imbalance of oxidant–antioxidant becomes a reciprocal relationship and influences each other, decreases in antioxidant levels have been researched can cause oxidative stress, which triggers apoptosis in ovarian reserves.

Objective: The purpose of this study is to compare the serum total antioxidant capacity (TAC) levels between early-menopausal and normal-menopausal women.

Methods: This is an observational analytic study with a case–control design with 20 women with early menopause and normal menopause were included according to the inclusion and exclusion criteria by consecutive sampling, then the characteristic data were collected and grouped according to the study group. A blood test was done to assess serum TAC in the participants. Data were collected and processed, and statistical analysis was carried out.

Results: It was found that there were differences in age at menopause in the group of participants who experienced early menopause and normal menopause. There were differences in TAC levels based on body mass index and TAC levels in early menopause and normal menopause.

Conclusion: There are differences in serum TAC levels between early menopausal and normal menopausal women.

Keywords: Early menopause, Normal menopause, Total antioxidant capacity.

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Introduction

Menopause is one of the physiological phases experienced by every woman where there has been a decline in physiological functions in the human body. On the basis of the classification of the World Health Organization, menopause can be divided into premenopause, perimenopause, and postmenopausal.[1] At menopause there are several major changes in women caused by a decrease in estrogen levels, which reflects the depletion of the ovarian follicles.[2,3]

The prevalence of menopausal women in the city of Medan in 2018 with an average age of menopause ranged from 49 to 50 years, with normal menopause in 66.70%, early menopause in 15.4%, late menopause in 13%, and premature menopause in 4.9%.[3] Factors that influence the occurrence of early menopause include genetic factors, autoimmune diseases, infections, and iatrogenic factors, such as chemotherapy, surgery, and radiation therapy,[4] where these factors cause the balance of oxidants and antioxidants to be disturbed (oxidative stress).

The antioxidant can be defined as any substance that significantly delays and prevents the oxidation of an oxidizable substrate (oxidant).[5] So that the causal relationship of menopause and the imbalance of oxidant–antioxidant becomes a reciprocal relationship and influences each other. The antioxidant activity of the "nonspecific" antioxidant pool is often referred to as the total antioxidant capacity (TAC).[4] Decreased level of these antioxidants can cause oxidative stress conditions that can induce inflammation of the ovaries, the shortening of telomeres, mitochondrial dysfunction, apoptosis of granulosa cells, and accelerated degeneration of the corpus luteum, thereby accelerating cell death in ovarian and shortening of ovarian age.[6,7]

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Ethical consideration: The Committee has approved all study protocols of Ethics, Universitas Sumatera Utara, Medan, Indonesia (NO: 211/KEP/USU/2021). All study procedures are following Helsinki's declaration of human rights.

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Conflict of interest: None

Methods

This research is an observational analytic study with a method of case–control conducted to assess differences in levels of

TAC in women with early menopause and normal menopause. This research was conducted in Medan City, North Sumatra, Indonesia, and through laboratory, examinations carried out at the Prodia Laboratory from March 2021 to September 2021. There were 10 participants in each group of early menopause and normal menopause, so the total sample size was 20 participants who met the inclusion criteria, namely women who had not menstruated for 12 consecutive months without contraception who agreed to the informed consent of the study, while women who were active smokers and drinkers of alcohol, which used regular antioxidant supplementation in the past 1 month, who used hormonal therapy, and pregnant women were excluded from the study.

This research was conducted after obtaining approval from the ethics committee of the Faculty of Medicine, University of North Sumatra. The participants who met the inclusion and exclusion criteria were given *informed consent* and have agreed as research subject. Data on the characteristics of the participants were obtained by history taking and physical examination in the form of name, date of birth, current age, education, occupation, parity, weight, height, body mass index (BMI), exercise status, history of surgery, history of contraception, age of menarche, age menopause, duration of menopause, and contact subjects who can be contacted to confirm laboratory results. From the anamnesis results, the participants were grouped into case group (early menopause) and controls (normal menopause) after being homogenized from the history taking the form of menopause to reduce bias. Furthermore, the participants were scheduled for blood sampling at the Medan Prodia Laboratory. Blood samples were taken from the median cubital vein as much as 5 cc to determine the level of TAC *of* serum using the colorimetric method (ELISA). Then the data were collected and processed, and then statistical analysis was carried out through SPSS.

Results

The results of this study were followed by 10 participants who experienced early menopause and 10 participants who experienced normal menopause who had met the inclusion and exclusion criteria (Table 1).

Table 2 shows values of TAC based on age, parity, BMI, and exercise status. The mean TAC in subjects aged > 45 years was 1.47 (SD = 0.16), while in subjects aged 45 years, the mean TAC was 1.43 (SD = 0.16). By using the test Mann–Whitney, it was found that there was no difference in the mean levels of TAC based on age ($p = 0.421$).

Differences in serum TAC levels in early menopause and normal menopause were found to be significantly different with a p value of 0.004 (Table 3).

Table 1: Characteristics of participants

Characteristics of participants	*Early menopause (n = 10)*	*Normal menopause (n = 10)*	*p-value*
Age, years	46.8 (4.26)	53.10 (2.69)	0.001[a]
Mean (SD)	46 (40–52)	53 (48–57)	
Median (min–max)			
Menarche age, years	13.10 (1.52)	13.80 (1.32)	0.286[a]
Mean (SD)	13 (11–16)	14 (12–16)	
Median (min–max)			
Menopause Age, years	41 (2.31)	50.2 (1.81)	<0.001[b]
Mean (SD)	42.50 (36–44)	50.5 (47–53)	
Median (min–max)			
Menopause Length, months	49.8 (35.65)	43.8 (24.39)	0.666[a]
Mean (SD)	38 (12–110)	39 (18–94)	
Median (min–max)			
Education, *n* (%)			
SMP	1 (10)	1 (10)	0.890[c]
SMA	6 (60)	5 (50)	
College	3 (30)	4 (40)	
Occupation, *n* (%)			
Entrepreneur	1 (10)	2 (20)	0.582[c]
Teacher/midwife/nurse	1 (10)	2 (20)	
Peg. BUMD/PNS/TNI	2 (20)	3 (30)	
Helper/farmers	2 (20)	0	
Housewife	4 (40)	3 (30)	
Parity, *n* (%)	2 (20)	0	0.343[c]
Nullipara	2 (20)	1 (10)	
Primipara	1 (10)	3 (30)	
Secundipara	4 (40)	6 (60)	
Grandmultipara	1 (10)	0	
Body mass index, *n* (%)			
Normoweight	7 (70)	4 (40)	0.092[c]
Overweight	3 (30)	2 (20)	
Obese	0	4 (40)	
Sports status, *n* (%)			
No	7 (70)	8 (80)	1.000[d]
Yes	3 (30)	2 (20)	
Operation history, *n* (%)			
Cystectomy	1 (10)	0	0.516[c]
Myomectomy	1 (10)	0	
Cesarean section	1 (10)	2 (20)	
None	7 (70)	8 (80)	
Contraceptive history, *n* (%)			
Implant	1 (10)	1 (10)	0.583[c]
Spiral	1 (10)	3 (30)	
Injections per month	1 (10)	0	
Tubectomy	1 (10)	0	
None	6 (60)	6 (60)	

[a]T Independent, [b]Mann–Whitney, [c]Kruskal–Wallis, and [d]Fisher's exact test

Discussion

The hypothesis postulates that the ovaries age more rapidly than other body systems and establish a progressive decline in the amount and quality of their follicles. Reduced fertility can result not just from a loss in follicle quantity, but also from a decline in follicular quality.[8] There are a number of theories that have been established to explain the origins of aging-related changes.

Another study entitled "The Timing of the Age at Which Natural Menopause Occurs" found that an earlier occurrence of menopause was linked to smoking, lower parity, and poorer socioeconomic status.[9] Approximately 50% of the age variance at a normal menopause is caused by genetic factors. Being a child of multiple pregnancies, having a family history of early menopause, and certain genetics have all been recognized as risk factors for premature menopause and early menopause. Reproductive and

Table 2: Differences in serum TAC levels based on age, parity, BMI, and exercise status[8]

		TAC		
Variables	*n*	*Mean, SD*	*Median (min–max)*	*p*
Age (years)				
> 45	16	1.47 (0.16)	1.45 (1.21–1.85)	0.421[a]
45	4	1.43 (0.16)	1.35 (1.34–1.66)	
Parity				
Nullipara	2	1.4 (0.08)	1.4 (1.34–1.45)	0.390[b]
Primipara	3	1.44 (0.15)	1.36 (1.34–1.61)	
Secundipara	4	1.50 (0.14)	1.51 (1.36–1.64)	
Multipara	10	1.50 (0.17)	1.48 (1.30–1.85)	
Grandmultipara	1	1.21		
BMI				
Normoweight	11	1.48 (0.17)	1.4 (1.34–1.85)	0.047[b]; 0.078[aa];
Overweight	5	1.35 (0.11)	1.34 (1.21–1.51)	0.190[ab]; 0.027[ac]
Obese	4	1.56 (0.08)	1.58 (1.45–1.64)	
Sports status				
No	15	1.46 (0.16)	1.45 (1.21–1.85)	0.793[a]
Yes	5	1.47 (0.16)	1.37 (1.34–1.66)	

[a]Mann–Whitney, [b]Kruskal–Wallis, [aa]Mann–Whitney (normoweight vs overweight), [ab]Mann–Whitney (normoweight vs obese), [ac]Mann–Whitney (overweight vs obese)

Table 3: Differences in serum TAC levels between groups of subjects experiencing rapid manopause and normal menopause[8]

Characteristics of subjects with	*Early menopause (n = 10)*	*Normal menopause (n = 10)*	*p*
TAC levels			
Mean (SD)	1.38 (0.12)	1.55 (0.14)	0.004*
Median (min–max)	1.35 (1.21–1.66)	1.55 (1.37–1.85)	

*Mann–Whitney

lifestyle risk factors include early menarche, nulliparity or low parity, smoking, and being underweight are strongly associated with early menopause.[10]

It is also known that physical activity can induce oxidative stress conditions that increase enzymatic antioxidant activity, leading to increased resistance to oxidative defense, including various types of oxidative stress related to the disease.[11] The menarche and parity factors did not show a significant correlation. However, there was a very weak influence, while the factor of using non-hormonal contraception or not using contraception had a feeble effect but showed a significant correlation, the effect slowed the age of menopause by 0.02%.[12] TAC levels are significantly different between primiparity and multiparity, which found lower TAC levels in multiparity, this could be a complication of multiple parties such as hypertension, diabetes mellitus, preeclampsia, anemia, intrauterine fetal death, and the risk of premature birth, which can lead to premature birth caused by a decrease in the antioxidant defense system.[13]

These antioxidant parameters influence the value of TAC, which may be enhanced by improving the body's antioxidant level as well as compensatory response to combat increased oxidative stress. This suggests that being overweight or obese can increase TAC levels. The possibly high antioxidant value in overweight/obese people might be explained by a subsequent reaction to intense oxidative stress in those with more adipose tissue. As a result, in the early stages of metabolic disorders, but already in the presence of risk factors (obesity, high blood pressure), the antioxidant defense system may respond to sustained oxidative stress by increasing its activity, but at an advanced stage, the balance between free radicals and antioxidant defenses may be impaired due to decreased antioxidant levels or activity.[14]

Many studies have been conducted in response to Denham Harman's concept from 50 years ago about the role of free radicals in aging. High levels of endogenous reactive oxygen species (ROS) and low antioxidant activity during the aging process lead to a variety of oxidative injuries, including DNA damage, enzyme inactivation, protein oxidation, and lipid peroxidation in cell membranes. Antioxidant and oxidative stress may interfere with the ovaries' normal physiological functions, according to the existing evidence. Ovarian aging-related disorders, however, have not received enough investigation. The quantity and quality of follicles decline as the ovary ages, which is a protracted and intricate process. Ovarian aging-related changes in hormone production can have a number of negative health effects, such as vasomotor symptoms, cardiovascular disease, osteoporosis, cognitive decline, depression, and mood disorders, as well as effects on sexual function and vaginal atrophy.[15] Recent research has revealed that chromosomal aneuploidy, an age-related secondary malfunction, and increased mtDNA damage are present in low-quality oocytes. These mitochondrial alterations could be caused by an excess of ROS, which happens when ion channels open.[16]

Several theories, including the free radical hypothesis, apoptosis, telomere shortening, mitochondrial malfunction, and the inflammation hypothesis, have been presented to explain the mechanisms behind ovarian aging. According to the classical theory, oxidative stress caused by elevated amounts of ROS in intracellular is the primary cause of cellular senescence and aging in animals. Additionally, many studies have shown that oxidative stress is a key factor in progression of ovarian aging and development of various ovarian aging-related etiologies, such as telomere shortening, mitochondrial dysfunction, apoptosis, and inflammation. Antioxidants have been the focus of a lot of relevant studies because of the significant impact that oxidative stress plays in ovarian aging. The deterioration of ovarian function with aging is mostly caused by oxidative stress. Acts as an etiologic driver of ovarian aging. As a result, lowering oxidative stress in the ovaries is a key first step in postponing ovarian aging.[7] Process of ovarian aging is characterized by a decrease in the quantity and quality of follicles gradually. Ovarian quality is subsequently reduced as a result of increased amount of endogenous ROS and diminished antioxidant defenses, which also result in other types of cellular oxidative damage. Oxygen radicals, which increase with aging and become more prevalent, often promote cellular damage. Mitochondria are the first organelles to degenerate because they are the site of the production of oxygen radicals. Mitochondrial degeneration and loss of fertility confirms that the decline in follicle quality is the result of ROS-induced damage to the follicle mitochondria.[15]

Conclusion

This study found a significant difference in serum TAC levels in women with early menopause and normal menopause.

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