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THE CORRELATION BETWEEN TNF-α SERUM LEVEL AND ANDROPAUSE WITH QUALITY OF LIFE ON ELDERLY

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ABSTRACT
As the population of elderly increases, the number of andropause also increases. Andropause is characterized by the decrease of testosteron level which is accompanied by hypogonadism symptoms. Many studies mentioned that decreased testosterone level will contribute to inflammation state, one of the cytokine is TNF-α, which then lead to many chronic inflammation disorders and influence the quality of life. Understanding the significant correlation between androgen and inflammation allows accurate consideration making in using androgen replacement therapy, therefore the quality of life will be improved significantly.This research was an analytical cross-sectional study. Subjects were recruited through random sampling at Denpasar in 2019. TNF-α serum level was measured by human immunoassay method. Andropause was measured by ADAM questionnaire and confirmed by total decreased testosterone serum level. Quality of life was measured by WHOQOL-BREF questionnaire which was then continued by bivariate and multivariate analysis to control the confounding variables. It was considered statistically significant if P value is more than 0.05. There were 60 elderly involved as research subjects consisting of 43 andropause cases and 17 non andropause cases. There was significant correlation between TNF-α serum and quality of life. This study also found that there was significant difference in quality of life between andropause and non andropause group. This study shows that there was significant correlation between TNF-α serum level and andropause with quality of life in elderly.

Keywords: andropause; elderly; quality of life; TNF-α serum

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INTRODUCTION

According to the Law of Republic of Indonesia Number 13 of 1998 concerning Elderly Welfare, an elderly person is someone who has reached the age of 60 years and over. Indonesia is one of the countries which has aging population (Ministry of Health RI, 2017). As the elderly population increases, the number of andropause case also increases. Andropause is defined by the gradual decreased testosterone level by age which is accompanied by hypogonadism symptoms such as sexual dysfunction, fatigue, insomnia, loss of motivation, mood disorder and others (Pangkahila, 2017). Study in USA showed that 54% males showed hypogonadism symptoms in group of age

between 60-90 years old (Taher, 2005). In 2020, andropause cases were estimated about 24.7 million cases in Indonesia (Soewondo, 2006).

Production and bioavailability of testosterone will decrease as the aging process occured. Many studies showed that decreased of sexual hormones will lead to chronic inflammation state. A study on elderly males shows decreased testosteron level and increased interleukin-6, tumor necrosis factor-α and interleukin-1β, which contribute to many conditions such as sarcopenia, osteoporosis, arthritis, cardiovascular diseases, and frailty (Chin & Ima-Nirwana, 2017). TNF-α is more reliable than IL-1β (Koelman et al, 2019) and not affected by hypoxic condition in elderly, unlike IL-6 (Gonzalo-Calvo et al, 2010). Understanding the correlation between androgen and inflammation is really important because inflammation contributes to many diseases' pathogenesis. Significant correlation will give us accurate consideration in using androgen replacement therapy and will give good effect to the quality of life (Mohammad et al, 2018).

Quality of life in elderly also plays important role for evaluating the success of healthcare intervention, both in terms of prevention and treatment (Nugroho, 2008). Decreased testosterone related to aging is one of major factors that can decrease the quality of life (Moncada, 2006). Andropause can be confirmed by total low testosteron or free testosterone level, but this research studied about andropause in elderly, in which many comorbid conditions can contribute to andropause, so total testosterone correlates better in elderly than free testosterone, because free testosterone only specific about hypogonadism etiology (Liu et al, 2017).

However, study on the correlation between inflammation and andropause, also quality of life is limited and inconsistent. Therefore, this study is needed to confirm the correlation between inflammation with andropause and quality of life. This study was conducted as a consideration for clinicians in using hormone replacement therapy to improve inflammatory conditions and quality of life on the elderly.

METHOD

This study was conducted using analytical cross-sectional study. Elderly male subjects were recruited using random sampling technique in a community centre located at Banjar Busung Yeh Kangin and Banjar Busung Yeh Kauh in 2019. Subjects with infection, clinically showed active lung tuberculosis symptoms, history of corticosteroid, psychoactive agent, and herbal supplement consumption, as well as history of using testosterone replacement therapy and severe cognitive impairment were excluded. History taking, anthropometry data, laboratory results and diagnosis data were recorded. Andropause was screened by ADAM questionnaire and confirmed by total low testosteron serum (below 475 ng/dL). TNF-α serum levels were measured by human immunoassay method.

Quality of life was measured by WHOQOL-BREF questionnaire. The collected data were analyzed by SPSS 21.0 including descriptive analysis for age, age group, comorbid score, cognitive score, body mass index, nutritional status, and body weight; kolmogorov-smirnov test was used to determine the data distribution; bivariate analysis including Spearman test was carried out for analyzing the correlation between TNF-α serum level and quality of life in elderly. Furthermore, this research also conducted

independent t-test for analyzing the quality of life difference in andropause and non-andropause group and multivariate analysis including multiple linear regression test and ANCOVA for controlling the risk factors, such as age, body mass index, and comorbidities.

RESULTS

There were 60 elderly involved as subjects consisting of 43 andropause cases and 17 non andropause cases. The mean of TNF-α serum level was 85.72 ± 99.08 ng/dL. The median of total testosterone serum level was 396 (5-1263) ng/dL.

Table 1.
Characteristic of the sample

Characteristics	Mean ± SD	Median	Frequency
Age (years)	69.33±7.21		
Age group			
60 – 74 years old			50 (83.3%)
≥ 75 years old			10 (16.7%)
Comorbid score (CACI)		3 (2-5)	
Cognitive score (AMT)			
Normal			47 (78.3%)
Moderate cognitive impairment			13 (21.7%)
Body mass index (kg/m^2)	23.80 ± 3.57		
Nutritional status based on BMI			
Obesity			9 (15.0%)
Overweight			13 (21.7%)
Normal			33 (55.0%)
Underweight			5 (8.3%)
Body weight (kg)	64,78 ± 10,51		

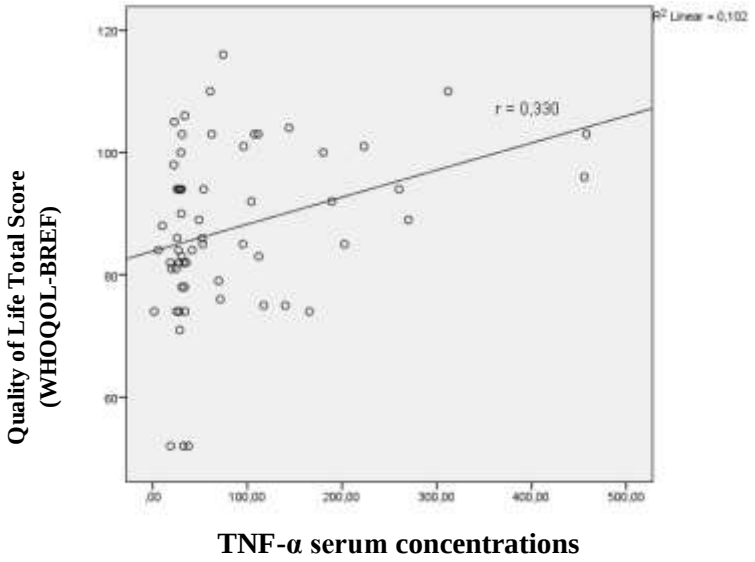

Figure 1. Scatter plot of correlation between TNF-α and quality of life

Spearman test showed weak positives correlation between TNF-α concentrations and quality of life (r=0.330; p=0.01).

Table 2.
Multivariate analysis for confounding variables that affect the quality of life on elderly

Variables	B	SE	p value
TNF-α	0.045	0.017	0.012*
Age	0.482	0.296	0.109
Body mass index	0.703	0.500	0.165
Comorbid score (CACI)	-1.176	1.949	0.549

TNF-α = Tumor Necrosis Factor-Alpha
CACI = Charlson Age Comorbidity Index

General linear model test showed TNF-α independently affected the quality of life on elderly.

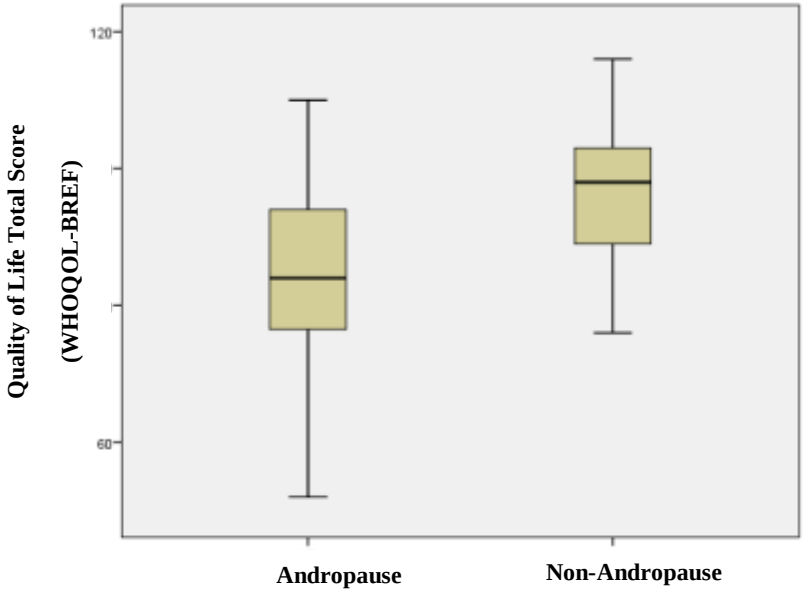

Figure 2. Box plot of quality of life difference between andropause and non-andropause group on elderly.

Table 3.
Multivariate analysis for confounding variables that affect the quality of life on elderly

Variables	F	p value
Andropause	0.008	0.929
Age	5.334	0.025*
Body mass index	4.439	0.040*
Comorbid score (CACI)	0.129	0.721

Independent T-test showed significant different quality of life between andropause group and non-andropause group on elderly with Sig. (2-tailed) of 0.002. ANCOVA showed age and body mass index independently affected the quality of life on elderly.

DISCUSSION

The rate at which total testosterone decreases by age was at the average of 0.4-1% per year. Thus, for men over 60 years, about 20% of healthy men have total testosterone serum levels below the reference value for younger men (<320 ng / dl or 11 nmol/ liter). Between the age of 40 and 79, 17% of men had total testosterone level below 320 ng/dl. The prevalence of andropause itself from a population study in Europe was estimated to be at the average of 2.1%, where there was an increase in the prevalence at older ages, which is 3.2% at 60-69 years and 5.1% at 70-79 years (Samaras et al, 2012).

In Indonesia, there was no studies explaining prevalence, however, total testosterone levels were far above the lowest levels in the general range used by laboratories compared to studies in Caucasians, with many contributing causes including nutrition (Pangkahila, 2017). In addition, differences in the method of examining andropause also affect prevalence, such as a questionnaire for screening the andropause symptoms (Samaras et al, 2012).

In this study, among 60 samples, it was found that the mean age of the subjects was 69 years with a median total testosterone level of 396 ng/dl. These samples were confirmed by Andropause (based on the ADAM questionnaire screening and total testosterone levels <475 ng/dl) of 72%. The median value of total testosterone levels in this study was quite high for the elderly. Not all studies showed that older men have lower testosterone levels than younger men. In old age, the function of the testes and hypothalamus decreases. The number of Leydig cells is 44% lower in men aged 50-76 years compared to men aged 20-48 years. The secretory ability of the testes is indeed lower in old age. Although decreased testicular function is the main cause of low testosterone levels in the elderly, GnRH secretion in the hypothalamus (but not in the pituitary LH reserve) is lower in older men. This indicates a dysregulation of the hypothalamus-pituitary-testis axis in old age. The symptoms of andropause are also nonspecific and overlap with other symptoms related to the normal or natural aging process. (Ahern & Frederik, 2015)

The range of total testosterone levels in this study was also extreme, with the lowest levels being 5 ng/dL and the highest levels being 1263 ng/dL. A study explained the factors that affect the variability of testosterone levels, namely chronic disease and high drug use, age, testing techniques (immunoassay and mass spectrometry yielded variability of 14.1% to 19.2% and ± 40% in total testosterone levels < 100 ng / dl), specimen handling, preparation, replacement, calibration methods and matrix disturbances, diurnal variation in testosterone levels, morning peak testosterone concentrations that can drop dramatically after waking up, genetics contribute to 42-65% variability, geographic factors, and it was found that testosterone levels on repeated measurements varied from 65% to 153%. Nearly 50% of men with total testosterone levels <300 ng/dl to >300 ng/dL was at the next measurement. Repeating two to three tests reduced the variability by 30 to 43%. Lifestyle factors also affect the variability, such as obesity, intensity and duration of physical activity, and smoking (although still unclear). Weather is considered to be a factor in variability of testosterone levels but the data are conflicting (Trost & Mulhall, 2016).

The questionnaire for this study included a history of using herbal medicines of which the composition is unknown (whether they contain testosterone or not). All samples with a history of using herbal or herbal medicines were excluded, but the openness and understanding of the samples regarding this question were still uncertain.

Testosterone is the dominant gonadal androgen in men. Low testosterone levels are correlated with an increased risk of metabolic syndrome and systemic inflammation. Since adipose tissue is a source of inflammatory cytokines, testosterone can play a role in inflammation regulation by acting on adipose tissue. From some literatures, both animal and human studies, it was stated that testosterone deficiency is correlated with an increase in pro-inflammatory cytokines and testosterone replacement therapy to reduce pro-inflammatory cytokines. This suppression of inflammation by testosterone was observed in patients with coronary artery disease and diabetes mellitus through increased anti-inflammatory cytokines and decreased proinflammatory cytokines (IL-1β, IL-6 and TNF-α). However, several studies also reported an insignificant relationship. (Mohammad et al, 2018).

There are several aspects in determining the quality of human life, which according to WHO is divided into four domains, those are physical health (pain and discomfort, energy and fatigue, sleep and rest, dependence on drugs, mobility, daily activities and work capacity), psychological aspect (positive feelings, negative feelings, self-esteem, ability to concentrate, body image and appearance, spirituality, religion, and personal beliefs), social relationships (personal relationships, sexual life, and social support from friends), and the environment (safety in everyday life -day, the physical environment in the form of pollution, noise, traffic, weather, as well as sources of funds, opportunities to get new information, participation and opportunities for recreation, housing conditions, health and social security, and transportation) (Pangkahila, 2017).

In this study, the measurement of quality of life used WHOQOL-BREF questionnaire which was declared valid and reliable to measure the quality of life in the elderly, where the cross-cultural ability of this instrument is an advantage and has been widely used in various industrial and developing countries (Salim et al, 2007). From this study, it was found that there was a significant relationship between TNF-α serum level and quality of life in elderly men. This is consistent with previous studies that studied the correlation between inflammation and quality of life, although there were still many shortcomings in previous studies due to the lack of longitudinal data and narrow generalizations (Roediger et al, 2019).

Tumor Necrosis Factor-α, a cytokine secreted by activated macrophages, has shown the ability to modulate Leydig cell steroidogenesis. The effects of TNF-α on basal testosterone production and stimulated by 8-Br-cAMP, as well as side-chain cleavage cholesterol enzymes (P450scc) and 17α-hydroxylase/C17.20 lyase (P450c17) have been studied in previous studies (Hong et al, 2004). Apart from its main function as a male sexual hormone, testosterone also has an important role in modulating inflammation. Chronic inflammation is the cause of many pathological conditions, such as heart disease and cancer, endogenous testosterone can predict many diseases. Excessive inflammation can affect the function of Leydig cells and decrease testosterone production due to their sensitivity to inflammation. (Mohammad et al, 2018).

The multidirectional correlation between testosterone, inflammatory processes, and various metabolic diseases is strongly affected by fatty tissue, which increases the activity of aromatase (an enzyme that converts testosterone to estradiol). This conversion directly inhibits the hypothalamus-pituitary axis and decreases testosterone production. Visceral fat is an active secretory tissue that produces cytokines, adipokines, biochemical modulators, and other proinflammatory factors including IL-6, IL-1β, and TNF-α, which act as a contributing factor in inflammation and systemic and peripheral vascular dysfunction. Adipose tissue also produces leptin which has a negative reciprocal effect on the hypothalamic-pituitary-gonadal axis via inhibition of gonadotropins in the Leydig cells of the testes, which results in androgen production. Decreased levels of testosterone in the tissues help store triglycerides in adipocytes by increasing lipoprotein lipase activity. Elevated triglycerides are an important risk factor that contributes to various conditions such as metabolic syndrome, type 2 diabetes mellitus, and cardiovascular disease. Inflammation also plays a major role in other diseases, including cancer, bleeding, infection and tuberculosis (Mohammad et al, 2018).

One study showed that testosterone levels significantly decreased the expression of TNF-α both physiologically and pharmacologically in monocyte-derived macrophages. Several other studies have also shown that there was an inverse correlation between testosterone and inflammation. Testosterone replacement therapy has been speculated to modulate inflammation and improve the patient's condition. Giving testosterone therapy to andropausal men is considered to reduce mortality by 39% with a hazard ratio of 0.61 (0.42-0.88) compared to those who do not receive the therapy (Corcoran et al, 2010).

Fat tissue is strongly correlated with increased levels of inflammatory mediators, considering that cytokines play a major role in the metabolism of fat tissue. Cross-sectional data and prospective studies show an increase in acute phase proteins such as CRP, fibrinogen, plasminogen activator inhibitors, serum amyloid A, and some cytokines and chemokines (such as IL-6 and IL-1β, as a sign of chronic inflammation in obesity and diabetes mellitus). Plasma CRP levels reflect the amount and activity of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6. The increase in fat mass correlated with the release of adipocytokines and other proinflammatory cytokines is considered to have an inhibitory effect on the hypothalamus-pituitary-gonad axis, which may contribute to andropause. These proinflammatory mediators are not only produced by macrophages on the white fat tissue, but also in the hypothalamus directly (Ebrahimi & Christ-Crain, 2016).

Testosterone has long been recognized as a property that modulates the immune system. Cell culture of monocytes, macrophages and human endothelial cells incubated with testosterone showed production of proinflammatory cytokines (TNF-α, IL-1β, and IL-6). In a trial of male patients with hypogonadism, testosterone supplementation showed a significant reduction in the proinflammatory mediators TNF-α and IL-1β, accompanied by an increase in the anti-inflammatory cytokine, IL-10. In another randomized controlled trial (Moscow study) involving 184 men with metabolic syndrome and hypogonadism, 30 weeks of testosterone therapy significantly reduced inflammatory markers IL-1β, TNF-α, and CRP. (Ebrahimi & Christ-Crain, 2016)

From the research conducted, it was found that there were significant differences in the quality of life between the Andropause group and those without Andropause, where after controlling for confounding variables, age and testosterone levels had a significant effect on the quality of life in the elderly. In the previous literature, it was also explained that decreased energy and impaired sexual performance are the worst aspects in which andropause have as the greatest effect on quality of life. (Novak et al, 2002).

Various psychological and physical symptoms due to decreased testosterone can interfere the quality of life. Frequent sadness, stress, difficulty sleeping, feeling inferior, often tired, and erectile disorders are symptoms that, among others, occur in andropause. When the hormone testosterone decreases significantly, then the energy is reduced, sex drive is inhibited, and erectile function is also hampered. This means that sexual activity, which is one aspect of social relations, becomes disturbed. This means that one of the aspects that determines the value of the quality of life decreases (Pangkahila, 2017).

This is also consistent with the literature that studies the multidirectional relationship between age, testosterone, inflammation, and metabolic syndrome (Ebrahimi & Christ Crain, 2016). However, there are still some studies that show an insignificant relationship between all of these variables, which is research conducted by Huang et al., Zhao et al., and Maggio et al (Mohammad et al, 2018).

The limitation of this study is the lack of openness and understanding of the sample in the interpretation of the research questionnaire. This study does not examine causal correlation because it takes a long time to conduct longitudinal studies. Measurement of TNF-α serum level and total testosterone serum level are still quite challenging in various studies because TNF-α tends to be unstable and testosterone variability is still affected by many factors.

This significant correlation hopefully can give consideration for giving testosterone replacement therapy to treat andropause and many chronic inflammatory disease that leads to better quality of life in elderly and longitudinal study is needed to confirm the causality of this relationship.

CONCLUSION

This study shows that there is a weak positive correlation between TNF-α levels with quality of life in elderly and there was significant quality of life difference between andropause and non andropause group in elderly.

REFERENCES

Ahern, T., Frederik, C. W. W. (2015). New horizons in testosterone and the ageing male. *Age and Ageing*; 44(2): 188-195.

Chin, K., Ima-Nirwana, S. (2017). The effects of testosteron deficiency and its replacement on inflammatory markers in rats: a pilot study. *Int J Endocrinol Metab*;15(1):e43053.

Corcoran, M., Meydani, M., Lichtenstein, A., Schaefer, E., Dillard, A., Lamon-Fava, S. (2010). Sex Hormone Modulation of Proinflammatory Cytokine and C-reactive

Protein Expression in Macrophages from Older Men and Postmenopausal Women. *J Endocrinol;* 206(2):217-224.

Ebrahimi, F., Christ-Crain, M. (2016). Metabolic syndrome and hypogonadism – two peas in a pod. *Swiss Med Wkly*;146:w14283.

Gonzalo-Calvo, D., Neitzert, K., Fernandez, M., Vega-Naredo, I. (2010). Differential inflammatory responses in aging and diseases: TNF-α and IL-6 as possible biomarkers. *Free Radical Biology & Medicine;* 49:733-737.

Hong, C. Y., Park, J. H., Ahn, R. S., Im, S. Y., Choi, H., Soh, J., Mellon, S. H., et al. (2004). Molecular Mechanism of Suppression of Testicular Steroidogenesis by Proinflammatory Cytokine Tumor Necrosis Factor Alpha. *Mol Cell Biol;* 24(7):2593-2604.

Kementrian Kesehatan RI. Pusat Data dan Informasi. (2017). Analisis Lansia di Indonesia. [cited 2018, Agustus 10]. Available at: http://www.depkes.go.id/download.php?file.../Analisis%20Lansia%20Indonesia%202017

Koelman, L., Pivovarova-Ramich, O., Pfeiffer, A., Grune, T., Aleksandrova, K. (2019). Cytokines for evaluation of chronic inflammatory status in ageing research: reliability and phenotypic characterisation. *Immunity & Ageing*; 16: 11.

Liu, Z., Liu, J., Fu, Q. (2017). Comparing calculated free testosterone with total testosterone for screening and diagnosing late-onset hypogonadism in aged males: A cross-sectional study. *J Clin Lab Anal*; 31(5): e22073.

Mohammad, N., Wong, S.K., Hasan, W.N.W., Jolly, J.J., Nur-Farhana, M.F., Ima-Nirwana, S., Chin, K. (2018). The relationship between circulating testosterone and inflammatory cytokines in men. *Aging Male*; 1-21.

Moncada, I. (2006). Testosterone and men's quality of life. *The Aging Male*; 9(4):189-193.

Novak, A., Brod, M., Elbers, J. (2002). Andropause and quality of life: findings from patient groups and clinical experts. *Maturitas*;43:231-237.

Nugroho, W. (2008). Keperawatan Gerontik dan Geriatrik. Edisi 3. Jakarta: Balai Penerbit EGC.

Pangkahila, W. (2017). Tetap Muda, Sehat, dan Berkualitas Konsep Anti-Aging Medicine. Jakarta: Penerbit Buku Kompas.

Roediger, A., Marucci, M., Duim, E., Santos, J., Duarte, Y., Oliveira, C. (2019). Inflammation and quality of life in later life: findings from the health, well-being, and aging study (SABE). *Health and Quality of Life Outcomes;* (17)26:1-7.

Salim, O.C., Sudharma, N.I., Kusumaratna, R.K., Hidayat, A. (2007). Validitas dan reliabilitas World Health Organization Quality of Life-BREF untuk mengukur kualitas hidup lanjut usia. *Universa Medicina*;26:27-38.

Samaras, N., Frangos, E., Forster, A. (2012). Andropause: A review of the definition and treatment. *European Geriatric Medicine*;3:368-373.

Soewondo, P. (2006). Menopause, andropause, dan somatopause: perubahan hormonal pada proses menua. In: Sudoyo, A.W. (eds). Buku Ajar Ilmu Penyakit Dalam Jilid III Edisi IV. Jakarta: FKUI, hal:1989-1992.

Taher, A. (2005). Proportion and Acceptance of Andropause Symptoms Among Elderly Men: A Study in Jakarta. *Indones J Intern Med;* 37: 82-86.

Trost, L. W., Mulhall, J. P. (2016). Challenges in Testosterone Measurement, Data, Interpretation, and Methodological Appraisal of Interventional Trials. *J Sex Med;* 13(7): 1029-1046.