ORIGINAL RESEARCH

The Effect of Metabolic Syndrome on Prostate-specific Antigen Levels: A Meta-analysis

Harris L. Lim, MD; Sigfred Ian R. Alpajaro, MD; Leonardo Arriola Zabala III, MD; Lizlane Roman Zamora, MD and Janine Mae Elaine Kua Zapata, MD

Section of Urology, Department of Surgery, University of Santo Tomas Hospital

It has been proposed that Metabolic Syndrome causes an inadvertent lowering of PSA levels in affected individuals.
Objective: This study aimed to determine the effect of metabolic syndrome on the serum PSA level.
Methods: Literature search was done using MEDLINE and Cochrane databases. The primary outcome measure was serum prostate-specific antigen (PSA) levels. Secondary outcome measures included prostate volume, plasma volume, and PSA mass density. Mean differences were computed using Review Manager 5.3 software.
Results: There were six articles available for analysis with a total of 33,775 in metabolic syndrome group (MS) and 70,305 in non-metabolic syndrome group (NM). Overall, there was no significant difference between the PSA levels between MS and NM group. The prostate and plasma volume were significantly higher in the MS compared with NM, having mean difference of 2.95 mL (95% CI, 1.41 to 4.49) and 162.68 mL (95% CI, 120.24 to 205.11), respectively. However, there were no significant difference in the PSA mass density between metabolic and non-metabolic syndrome.
Conclusion: Metabolic syndrome does not affect PSA levels and PSA mass density, despite increase in hemodilution.

Key words: prostate cancer, prostate-serum antigen, prostate cancer screening (non-MeSH), metabolic syndrome

Introduction

In the Philippines, prostate cancer is fifth most common cancer overall, accounting for 5.2% of all cancer cases, and the second most common cancer in males, as of 2018. It ranks seventh among the most common cancer-related deaths, accounting for 3.9% of all cancer mortality.[1] Several factors contribute to the mortality risk of prostate cancer, including age, genetic factors, such as race and family history, medical standards, and environmental factors, such as diet and exercise.[2] Prostate-specific antigen (PSA) is a serine protease that is almost exclusively secreted by prostate epithelial cells, both normal and pathologic prostate tissue. An elevation in its serum levels signifies anomaly in the prostate gland, making it an organ specific glycoprotein. It is most commonly implicated in prostate cancer, therefore fortifying its role in determining the prognosis of prostate cancer, screening for prostate cancer, and assessing treatment response.[2,3] The advent of serum PSA screening was able to decrease prostate cancer mortality rate by 20%. However, PSA has a low

specificity, as it is affected by age, race, prostate weight, recent history of prostate manipulation, prostatitis, and obesity.[3,4]

According to some studies, prognosis of several cancers, including prostate cancers, is affected by diet and obesity. Metabolic syndrome is caused by excess weight and dietary intake accompanied by sedentary lifestyle, and is especially seen in genetically susceptible patients.[5] It is a spectrum of at least three of the following conditions: hypertension, dyslipidemia, diabetes mellitus, and central obesity.[2,4,5] Age is a strong risk factor for metabolic syndrome, affecting 43.5% of the elderly population aged 60 to 69 years old.[4] Metabolic syndrome in itself is associated with high morbidity and mortality due to increased risk of cardiovascular diseases and stroke. It is also associated with the increased risk and aggressiveness of several malignancies, including prostate cancer.[2,5,6] The increasing prevalence of metabolic syndrome is related to the rising global obesity epidemic. In the Philippines, the national prevalence of obesity increased to 9.6% among adults from 20 to 59 years old, where 10% is found in Metro Manila.[7] Gathered data from peer-reviewed literature suggest that metabolic syndrome and obesity affects serum PSA levels, but with conflicting results. According to some studies, obesity was associated with the alteration of testosterone metabolism and hemodilution, causing significant decrease in serum PSA levels.[3,4] Contrarily, other studies found that metabolic syndrome does not affect serum PSA levels.[8] These conflicting results have negative implication on the use of serum PSA levels in detecting prostate cancers, especially in patients with metabolic syndrome.

The objective of this study was to determine the effect of metabolic syndrome on the serum PSA level. This is significant primarily because of the growing rate of metabolic syndrome and prostate cancer in the Philippines with little present study and data available. It is important to have the knowledge of the association between metabolic syndrome and serum PSA, and consequently understanding the condition as to its risks which may impact the clinical decision as to when patients should be started for screening of conditions that are commonly associated with elevated serum PSA like prostate cancer.

Methods

Published articles were acquired using MEDLINE and Cochrane databases from the time of inception until September 2020, using the following MeSH terms: [metabolic syndrome] AND [[prostate specific antigen level] OR [PSA level]] AND [prostate cancer screening]. Supplementary articles were acquired from the list of references of selected published articles. Chosen articles met the following inclusion criteria: 1) the study was published in English language, 2) the study is a cohort or case control study, and 3) the study included subjects who were healthy males for routine check-up. Exclusion criteria are as follows: 1) studies that included subjects with urologic pathology, such as urethritis, prostatitis, urethral stricture, neurogenic bladder, prostatic cancer, benign prostatic hyperplasia (BPH), history of prostatic trauma, history of surgery involving the prostate; 2) studies that included patients with elevated PSA levels; 3) non-human trials; and 4) incomplete data for analysis.

The primary outcome measure used in this study was the serum PSA level of patients undergoing routine physical examination, measured in ng/mL. Secondary outcome measures included prostate volume, plasma volume, and PSA mass density. Prostate volume was measured through imaging by a certified radiologist. Plasma volume was computed by multiplying body surface area with 1670. To adjust for the effect of plasma and prostate volume on PSA levels, PSA mass density was computed by dividing PSA mass by prostate volume. PSA mass was computed by multiplying PSA by plasma volume.[10,14] Mean difference between the Metabolic syndrome (MS) group and the Non-metabolic syndrome (NM) group were computed and analyzed using Review Manager 5.3 software. A negative mean difference meant that the effect favors the MS group over the NM group.

Results

Initial literature search found 43 articles screened for this study. A review of the abstracts of each article was done, and 34 articles failed to meet the inclusion criteria. Contents of each remaining 9 articles were reviewed. Three articles were excluded due to the

exclusion criteria. There was a total of six articles that were available for analysis (Figure 1).[9-14] This study has a total of 33,775 subjects in the MS group and 70,305 subjects in NM group. The details of each included study is summarized in Table 1. To ensure the quality of each included article, a risk of bias analysis was done (Table 2).

Quantitative analysis using the data of each article was done to compute the mean differences of PSA levels, prostate volume, plasma volume, and PSA mass density between MS and NM group. Overall, there was no significant difference between the PSA levels between MS and NM group (Figure 2). The prostate and plasma volume are significantly higher in the MS compared with NM, having mean difference of 2.95 mL (95% CI, 1.41 to 4.49) and 162.68 mL (95% CI, 120.24 to 205.11), respectively (Figures 3 & 4). There was no significant difference in the PSA mass density between metabolic and non-metabolic syndrome (Figure 5).

Table 1. Summary of included articles

Study Title	Authors	Date	Patients (MS/NM)	Inclusion criteria	Results
The illusion of prostate-specific antigen decline in patients with metabolic syndrome and insulin resistance	Choi, H., Park, J., Cho, B., Son, K., Yoo, Y., Kwon, H.	2011	8985/ 19330	Korean men who underwent routine health check-ups	PSA level could be underestimated in patients with MS or insulin resistance due to hemodilution
Prostate-specific antigen lowering effect of metabolic syndrome is influenced by prostate volume	Choi, W., Heo, N., Paick, J.,Son, H.	2016	1242/2869	Men who underwent routine check-ups	The presence of MS was a significant independent factor for lower PSA (decrease by 4.1%)
The association of metabolic syndrome and its components with serum prostate-specific antigen levels in a Korean-screened population	Jeong, I., Hwang, S., Kim, H., Ahn, H., Kim, C.	2010	8325/ 15276	Korean men 40 years and older who underwent routing health check-ups	MS was not associated with PSA level
The association between metabolic syndrome and prostate-specific antigen levels	Kim, Y., Cho, Y., Oh, J., Jeon, Y., Lee, S., Kim, W.	2008	348/1659	Healthy Korean men aged 30 to 79 years old	MS is associated with decreased PSA levels. It should be considered as factor associated w/ reduced PSA
The association of pathogenic factors of metabolic syndrome on serum prostate-specific antigen levels: a pilot study	Xia, B., Zhao, S., Chen, Z., Chen, C., Liu, T., Yang, F., Yan, Y.	2019	190/316	Men over 45 years old who underwent routine physical examination	Insulin resistance and sexual hormone changes may be the most significant contributors to the decline in serum PSA levels
Actual lowering effect of metabolic syndrome on serum prostate-specific antigen levels is partly concealed by enlarged prostate: results from a large-scale population-based study	Zhao, S., Xia, M., Tan, J., Yan, Y.	2016	14685/ 30855	Healthy men from 55 to 60 years old, who underwent routine health check-ups	Actual lowering effect of MS on PSA was partly concealed by enlarged prostate in men w/ MS, and presence of MS was independently associated w/ lower serum PSA levels

Table 2. Risk of bias of included articles

Type of bias	Choi 2011	Choi 2016	Jeong 2010	Kim 2008	Xia 2019	Zhao 2016
Random sequence generation (selection bias)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Allocation concealment (selection bias)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Blinding of participants and personnel (performance bias)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Blinding of outcome assessment (detection bias)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Incomplete outcome data (attrition bias)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Selective reporting (reporting bias)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

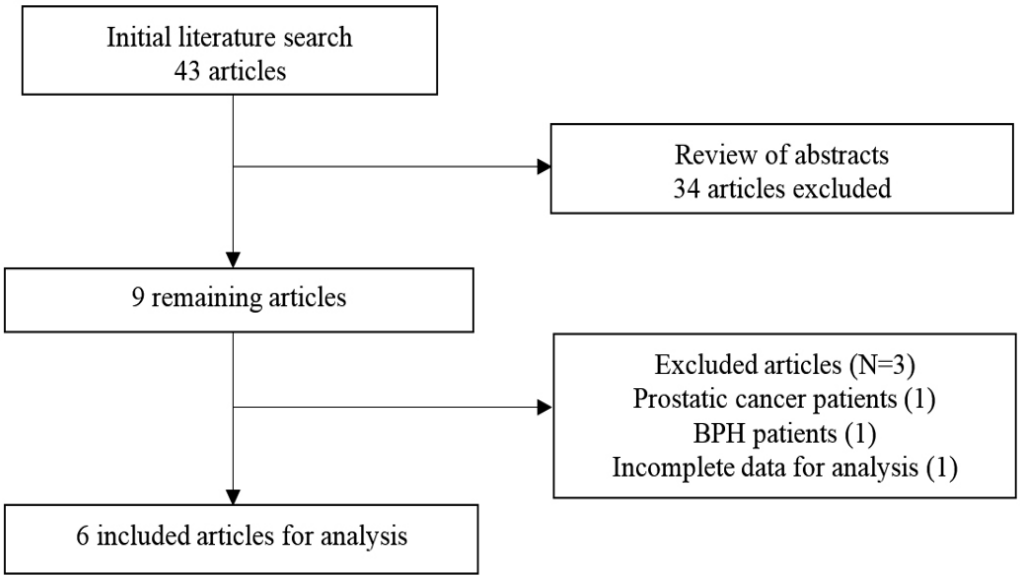

Figure 1. Diagrammatic flowchart of literature search

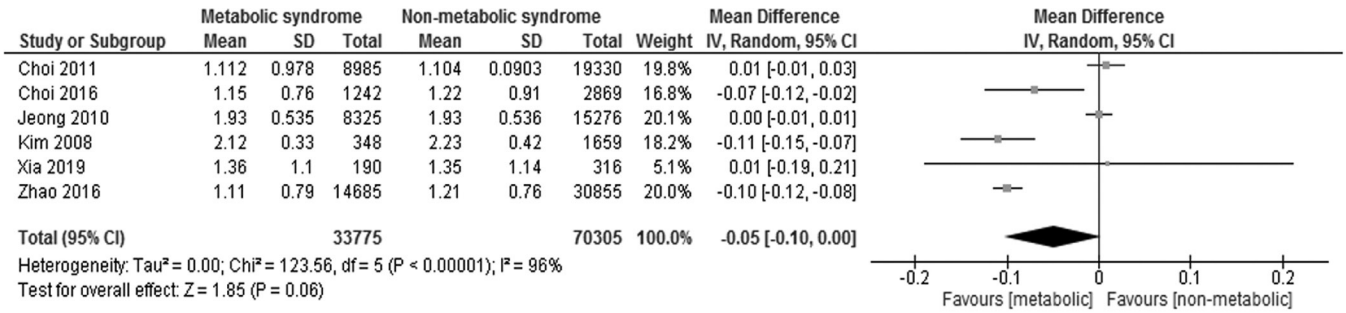

Figure 2. Comparison of PSA levels between metabolic and non-metabolic syndrome

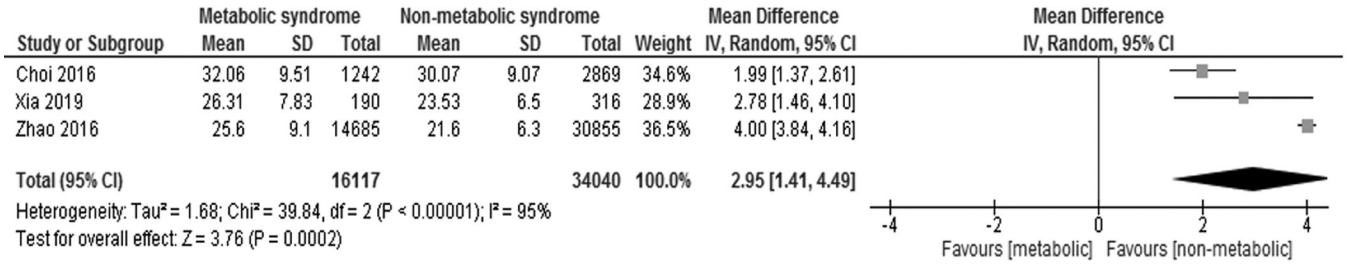

Figure 3. Comparison of prostate volume between metabolic and non-metabolic syndrome

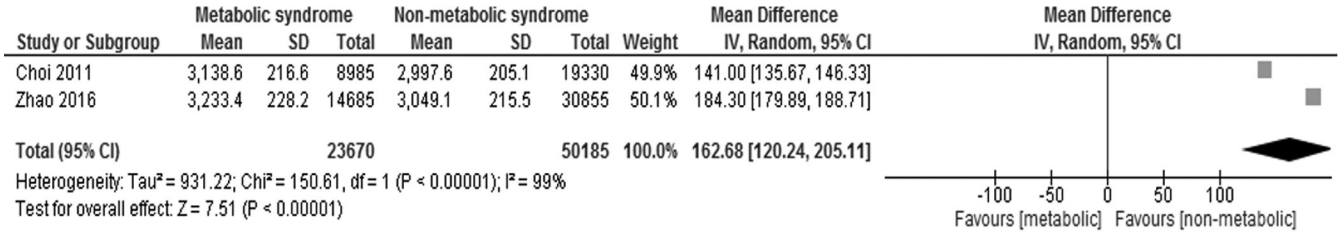

Figure 4. Comparison of plasma volume between metabolic and non-metabolic syndrome

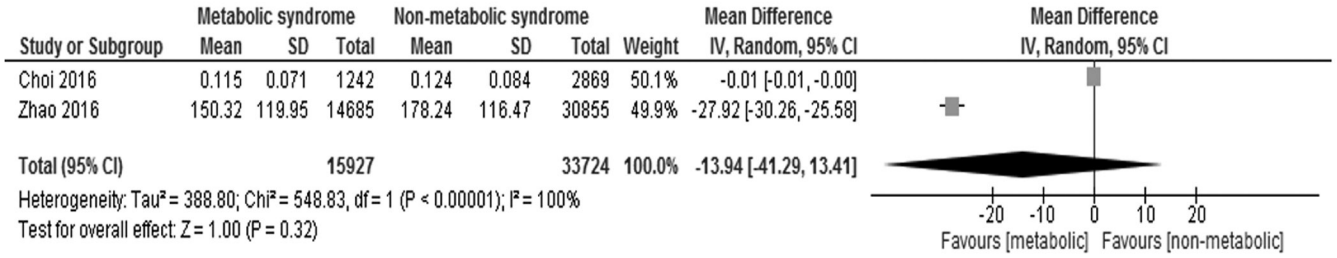

Figure 5. Comparison of PSA mass density between metabolic and non-metabolic syndrome

Discussion

Since its development in 1986, serum PSA measurement has been used for screening prostate cancer. Initially, a rise in the serum PSA level was thought to be associated only with an increased malignant tumor size in large prostate glands or with increased tumor volume regardless of prostatic size. However, later, it was discovered that other conditions, such as prostatitis, urinary retention, and benign prostatic hyperplasia (BPH), as well as procedures like prostate biopsy and digital rectal examination, can also elevate PSA values. Serum PSA level test is organ specific, but not disease specific. Aside from being a screening tool, it is also used as a marker for treatment response of prostatic diseases, such as BPH and prostate cancer.[14,15] Given its low specificity, several factors can influence the levels of PSA—age, race, body mass index (BMI), and prostate volume.[14,16] A study done by Chia, et al. showed higher PSA levels per unit volume among Korean, Japanese, Chinese, Malay, Indian and Arab men, but lower blood PSA levels and smaller prostate volumes compared to the western population. Nonetheless, clinical values used in the diagnosis of prostatic diseases utilize western cutoff scores.[17]

Metabolic syndrome describes a group of risk factors that raise the probability of getting heart disease and other health problems, such as diabetes and stroke.[4] Based on the US National Cholesterol

Education Programme Adult Treatement Panel III (NCEP ATP III), current definitions of metabolic syndrome may be distilled into four central features—insulin resistance, visceral obesity, atherogenic dyslipidemia and endothelial dysfunction. Of these, the first two appear to be absolutely required for metabolic syndrome, which makes it a complex, highly prevalent disorder and a worldwide epidemic.[19] Metabolic syndrome is difficult to diagnose, because of its varying presentation of the different components.

The production of PSA levels is affected by several hormones—androgens, insulin-like growth factors (IGF), sex-hormone binding globulin (SHBG), and insulin. Each component of metabolic syndrome plays a role in the alteration of these hormones, consequently affecting PSA levels. Obesity is associated with endocrine and metabolic changes that cause low testosterone and high IGF-1, insulin, and estrogen levels. Insulin resistance seen in diabetes mellitus, sometimes accompanied by concomitant compensatory hyperinsulinemia, stimulates IGF-1 production and suppresses SHBG and insulin-like growth factor binding protein 1 and 2.[12] These metabolic and endocrine aberrations may lead to the development of BPH and lower urinary tract symptoms (LUTS) in men.[18]

It is suggested that metabolic syndrome is an independent risk factor for decreased PSA levels.[13] Study performed by Zhao, et al. has found decreased serum PSA levels of 11.3% among men with metabolic syndrome compared to the control group, with a linear relationship present between the decrease of PSA and the associated number of metabolic syndrome components.[14] Similarly, a study conducted by Han, et al., looking into the components of metabolic syndrome and effect on PSA levels, showed a positive association between older age, diastolic blood pressure, and the serum PSA level, whereas BMI, high-density lipoprotein (HDL), and fasting blood glucose correlated negatively with the serum PSA level.[4] Metabolic syndrome decreases PSA levels by 0.06 ng/mL in general, and by 0.2 to 0.55 ng/mL if the PSA is approximately 4.0 ng/mL.[10,12] Contrarily, in a study conducted by Zorba, et al., patients with metabolic syndrome have higher PSA levels, prostate volume, and International Prostate Symptom Score (IPSS)—storage and voiding symptom scores; while studies done by De Nunzio, et al. and Dong, et al. reported similar PSA values in patients with metabolic syndrome compared to normal counterparts.[20-22] In this study, metabolic syndrome also failed to show any significant lowering effect on PSA levels and PSA mass density.

In some studies, BMI was shown to be negatively correlated with serum PSA levels.[4] Jeong, et al. found that central obesity, specifically waist circumference of more than 90 cm, is negatively associated with serum PSA level after adjusting for age, overall adiposity, and BMI. Waist circumference is the best anthropometric measure of total body fat and intra-abdominal fat mass. It is a stronger predictor of low endogenous testosterone levels as compared to BMI.[11] BMI is associated with in increased estrogen levels and decreased androgen levels, with a resultant decrease in PSA levels.[4] Moreover, the inverse relationship of PSA and BMI could be a result of hemodilution caused by increased plasma volume.[9] To account for the effect of hemodilution on PSA values, PSA mass density was computed. However, this study also failed to show any significant differences in the PSA mass density between the two groups despite having a significantly higher plasma volume in the MS group. This may indicate that hemodilution is not the only reason for the decrease in the PSA levels found in other studies.

According to Choi, et al., decrease in PSA levels may be secondary to metabolic disturbances, such as secondary hyperinsulinemia due to insulin resistance.[9] Furthermore, high fasting blood glucose also has a significant inverse linear relationship with serum PSA. Patients with diabetes has 21.6% lower PSA levels than those without; and overweight men who was diagnosed for more than 10 years had 40.8% lower PSA than those without.[4] Similarly, patients who are taking anti-diabetic medications were shown to have 13% lower PSA levels, than patients with normal fasting blood glucose (<100 mg/dL).[10,11] This may be caused by the effect of insulin on the SHBG, testosterone, free testosterone, and aromatase levels.[9] In metabolic syndrome, there is lower SHBG, enhanced activity of aromatase, and low-grade inflammation; all of which, directly influence the synthesis, clearance, and conversion of testosterone.[14] SHBG binds to testosterone to prolong its metabolic clearance – the more the SHBG, the more the plasma

testosterone level is.[4] PSA levels was shown to have a positive correlation with the total and free serum testosterone, even after adjusting for age, BMI, prostate volume, HDL levels.[11,13] Aromatase, on the other hand, is increased in obesity; and it facilitates conversion of testosterone to estradiol.[4] According to Xia, et al. SHBG is a better indicator when assessing metabolic syndrome- PSA relationship, compared to testosterone and estrogen.[13]

A positive correlation between hypertension and PSA levels is demonstrated in some studies.[4,11] Elevated diastolic blood pressure is associated with carotid atherosclerosis, and this, in turn, decreases the endogenous androgen concentration.[4] Androgens cause upregulation of thromboxane A2 expression, neuropeptide Y, norepinephrine synthesis, angiotensin II expression, and endothelin-1 action.[11]

Furthermore, metabolic syndrome is also associated with increased prostatic size, in particular, of the transitional zone, supporting a positive role for metabolic derangements in the progression of benign prostatic enlargement. Meta-regression analysis suggested that metabolic syndrome-induced differences in prostate volumes were almost equally weighted as a factor of age, waist circumference or serum HDL concentration.[23] Larger prostate gland may decrease the sensitivity of prostate biopsy and delay detection of prostatic cancer.[12] According to Ozden, et al., there was significant correlation between annual total prostate and transitional zone growth and insulin levels. Hyperinsulinemia stimulates sympathetic nervous system by increased intake of glucose to the ventromedial hypothalamic neurons, which consequently cause BPH. Furthermore, IGF-1, which is a strong mitogen for increasing cell proliferation and suppressing apoptosis in prostatic stroma and epithelium, is increased as well.[24,25] Enlarged prostate gland in the presence of hemodilution may be the reason for the lack of significant difference in the PSA result of this study.

Notwithstanding all the attempts made to correctly define metabolic syndrome, a major problem related to most definitions remains the applicability to different populations and ethnic groups. Although there are growing evidences of the association of metabolic syndrome with the initiation and clinical progression of prostatic diseases, such as BPH and prostatic cancer, molecular mechanisms and effects on treatment efficacy remain unclear.[21] Furthermore, previous study has shown the involvement of metabolic syndrome in the onset and progression of cancer involving the liver, colon, breast, bladder, and prostate.[26] Patients with metabolic syndrome has been shown to increase the risk of prostate cancer, having high grade tumors (T2c to T4) or Gleason score 8-10 or PSA of more than 20 ng/mL upon diagnosis.[2,10] Prostate cancer is more aggressive with higher risk of biochemical recurrence and mortality even after radical prostatectomy in the presence of metabolic syndrome.[2,14] Metabolic syndrome components, such as BMI, high waist-to-hip ratio, and high serum insulin levels, are all positively correlated higher risk of prostate cancer.[12] According to Lebdai, et al., metabolic syndrome is an independent predictor for positive margins, extra-prostatic spread, and International Society of Urological Pathology (ISUP) group 4 or more. The low HDL component of metabolic syndrome is associated with positive margins, locally advanced cancer, and high grade tumors, while the high serum cholesterol is associated with the aggressiveness of the tumor. Intracellular cholesterol is a substrate for the de novo androgen synthesis and likewise regulates AKT signaling. HDL is a reverse cholesterol transport that transports cholesterol from prostate tissues back to the liver.[5] Other factors that is responsible for cancer aggressiveness are elevated IGF-1, leptin, adiponectin, chronic inflammation, and oxidative stress.[2,27]

In conclusion, metabolic syndrome does not affect PSA levels and PSA mass density, despite increase in hemodilution. However, extra precautionary measures must still be undertaken in these sets of patients, because metabolic syndrome can still conceal early prostate cancer, and at the same time, promote prostate cancer aggressiveness.

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