Review Article

The impact of obesity towards prostate diseases

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ABSTRACT

Evidence has supported obesity as a risk factor for both benign prostate hyperplasia (BPH) and prostate cancer (PCa). Obesity causes several mechanisms including increased intra-abdominal pressure, altered endocrine status, increased sympathetic nervous activity, increased inflammation process, and oxidative stress, all of which are favorable in the development of BPH. In PCa, there are several different mechanisms, such as decreased serum testosterone, peripheral aromatization of androgens, insulin resistance, and altered adipokine secretion caused by inflammation, which may precipitate the development of and even cause high-grade PCa. The role of obesity in prostatitis still remains unclear. A greater understanding of the pathogenesis of prostate disease and adiposity could allow the development of new therapeutic markers, prognostic indicators, and drug targets. This review was made to help better understanding of the association between central obesity and prostate diseases, such as prostatitis, BPH, and PCa.

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1. Introduction

Obesity has risen alarmingly within the past few years, with an incidence of approximately one case in every three adults in the USA, compared with one in six adults 2 decades ago.[1] Global prevalence of obesity in men in Europe and Asia ranges from 4% to 30%.[2–6] According to the *Riset Kesehatan Dasar*[7] (Indonesia) in 2007, the prevalence of obesity in populations above 15 years of age was 10.3%. This number has grown approximately 20% within less than 5 years.[8] This geographic pattern can be explained, at least in part, by different socioeconomic conditions, as well as by lifestyle (sedentary lifestyle and lack of physical activity) and nutritional factors (western diet).

It is well known that obesity is associated with an increased risk of heart disease and diabetes. Most of these excess deaths were attributed to coronary artery disease, diabetes, and kidney disease. There are no clear indications that the obesity prevalence is returning back to healthier levels.[9] Recent studies have also looked into its relationship with prostate disease.[10–12] The aim of this study is to evaluate the association between central obesity and prostate disease [prostatitis, benign prostate hyperplasia (BPH), and prostate cancer (PCa)].

2. Definition of obesity

The World Health Organization and The National Institutes of Health define overweight as a body mass index (BMI) of greater than 25 kg/m^2, and obesity as BMI of greater than 30 kg/m^2, whilst in Indonesia, according to the *Riset Kesehatan Dasar*[7] by the Health Ministry in 2010, overweight is defined as a BMI of between 25 kg/m^2 and 27 kg/m^2 and obesity is more than 27.1 kg/m^2.[8] Though easy to determine, BMI has its limitations, such as the inability to both differentiate between fat and muscle, and measure fat distribution in the body (since fat in different regions may contribute different functions), especially in elderly individuals.[13–15]

Central obesity is known to be more dangerous than general obesity because it is able to produce hormonal and systemic modifications leading to inflammation. Waist circumference (WC) in determining visceral adiposity has been used in various studies as an alternative measurement and definition of central obesity.[16] WC can be measured either at the narrowest torso circumference or at the midpoint between the lower ribs and iliac crest.[17] This relatively practical application has led to the wide use of WC in many studies as a tool to measure central obesity.[18–20] The measurement of WC, which represents abdominal adipose tissue, has been reported to increase at a faster rate than BMI, which counts

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the body's entire weight including both adipose tissue and muscle mass. In addition, the adverse health consequences of obesity may be underestimated by trends of BMI.[21,22] Central obesity can be diagnosed if WC is larger than 90 cm in men and 80 cm in women.[23]

There is evidence linking the amount of adipose tissue to the level of both acute and chronic inflammation.[24–30] However, there are certain types of adipose tissue, which vary from different adipose tissue location and composition, that are strongly correlated with inflammation.[6,19,21,22,24,31,32] Adipose tissue is divided into two categories: visceral (abdominal/central) adipose tissue (VAT) and subcutaneous (peripheral) adipose tissue (SAT).[25] VAT has a distinct characteristic in terms of function and inflammation compared to SAT. VAT is mainly composed of omental, mesenteric fat, and retroperitoneal fat masses by delineation along the dorsal borderline of the intestines and the ventral surface of the kidney.[30] Adipocytes from VAT appear to have reduced capacity for lipogenesis and greater capacity for lipolysis than SAT cells, with VAT containing more proinflammatory and angiogenic cytokines than SAT.[21] Fox et al[24] demonstrated that the VAT compartment is metabolically active, secreting such vasoactive substances as inflammatory markers and adipocytokines, which may contribute to its role in the inflammation process. Alterations in plasma lipoprotein levels, particularly increased triglyceride and decreased high density lipoprotein levels, has also been associated with VAT distribution.[30] Because obesity often associates with a sedentary lifestyle, and physical activity decreases the risk of prostate problems, this could suggest novel prevention and treatment strategies through weight loss and lifestyle changes.[33]

3. Obesity and prostatitis

Prostatitis is a common but poorly defined condition, without clear diagnostic criteria and treatment approaches.[34] Age, race, and geographic region have been identified by several studies to be a significant risk factor for chronic prostatitis.[35–37] Prostatitis is found in approximately 10–14% of men of all ages and racial origin and nearly 50% of men at some point in their life encounter this condition.[5,19,37–42]

There is currently no evidence about the relationship between obesity and prostatitis. Although it still remains unclear, there are few studies reviewing this relationship between obesity and prostatitis using the BMI parameter. Wallner et al[12] showed that increased BMI has a protective effect on prostatitis risk after adjustment for age.[12] The odds of having a history of prostatitis were decreased by approximately 68% in obese men (BMI > 30 kg/m^2) when compared with men with a BMI of 25 kg/m^2. This result is likely due to the influence of physical activity on this relationship. This study revealed that the odds of developing prostatitis in men who were vigorously physically active were 67%. In the same study, a larger percentage (57.8%) of the men characterized as obese were found to engage in vigorous exercise compared with overweight (4.8%) and normal weight men (22.4%). Unfortunately, this particular study did not state the type of exercise performed by their participants. Studies regarding this subject are paramount in determining the risk of prostatitis in people with obesity. Thus many studies relating obesity and prostatitis are still needed and might be enlightening.

4. Obesity and BPH

BPH is the most common nonmalignant medical condition of the prostate occurring in middle aged and older men.[43] BPH is a histological diagnosis associated with unregulated proliferation of connective tissue, smooth muscle, and glandular epithelium within the prostatic transition zone. Cellular proliferation leads to increased prostate volume and increased stromal smooth muscle tone.[44] According to a recent epidemiological study, BPH affects 70% of men aged 60–69 years old and 80% of those ≥70 years old.[42]

Many studies have shown that obese men have a higher risk for BPH, as shown in Table 1.[19,33,45–49,51] Even though there are many standards, according to patients' characteristics (e.g., race) in categorizing patients' BMI and WC to diagnose obesity, all studies have resulted in the same conclusion that obesity, central or general, is a risk factor for BPH and worsened urinary symptoms. Increased WC was significantly and positively associated with prostate volume, serum prostate-specific antigen, and International Prostate Symptom Score, and therefore worsened the patients lower urinary tract symptoms.[19]

There are many hypotheses that have been suggested for the effect of obesity on BPH. Central obesity exerts several systemic effects. Obesity will increase intra-abdominal pressure, which in turn increases bladder pressure and intravesical pressure, with the potential to exacerbate and cause worsened BPH symptoms.[52] Another mechanism is altered endocrine status. Increased estrogen to androgen ratio due to the enzyme P450 aromatase expressed by fat tissue.[53] Therefore, an adipose tissue mass will increase the aromatase activity and the conversion of the androgens to estrogens (testosterone to estradiol and androstenedione to estrone). Increased fat mass and aromatase activity reduces the testosterone concentrations and allows for the preferential deposition of abdominal adipose tissue/VAT as the positive caloric balance which results in a hypogonadal obesity cycle. Continued production of estradiol caused by fat mass accumulation may result in gonadotropin suppression, with a further reduction in the testosterone levels and the development of a progressive hypogonadal state thus favorable in the development of BPH.[54] Increased sympathetic nervous activity in central obesity has been known to influence the development of BPH and the severity of urinary obstructive symptoms.[38,45] However, difficulties in measuring sympathetic nervous activity and heterogeneity in characterizing obesity may cause lack of a conclusive relationship between sympathetic nervous activity and obesity.[45]

Another proposed hypothesis is the inflammation process and oxidative stress.[29,55–57] Central obesity promotes microvascular disease and inflammation, which in turn contributes to ischemia, oxidative stress, and an intraprostatic environment favorable to BPH.[52] Changes in regulation of programed cell death may lead to hyperplastic and precancerous transformation.[40] In patients with central obesity, there is evidence of increased chronic inflammation cause by the secretion of inflammation cytokines by the visceral fat.[50,58] Inflammation is a very intricate phenomenon involving humoral (cytokines) and cellular (leucocyte, monocyte, and macrophages) elements.[57] In normal mechanisms, there is a balance between proinflammatory (growth factor release and angiogenesis) and anti-inflammatory (decrease of those processes) processes, leading to inflammation resolution.[59] However, in chronic inflammation, mainly consisting of chronically activated T cells and mononuclear phagocytes, there is persistence of proinflammatory factors causing disturbances in the inflammation process. This will further promote the inflammation process by releasing more progrowth cytokines as well as various other growth factors.[59] T cells influence matrix formation and potential epithelial secretions. They then promote prostate stromal and epithelial proliferation/hyperplasia by inducing fibromuscular

Table 1
The Risk of Benign Prostate Hyperplasia Relating to Obesity in Various Studies Based on Obesity Status (Body Mass Index and Waist Circumference).

Study reference	Population studied (n)	Control (n)	Findings
Lee et al[19]	• WC ≥ 100 cm (119) • WC 90–99 cm (137)	• WC < 90 cm (153)	Higher WC related to worse BPH symptoms (OR = 1.68, P = 0.002)
Giovannucci et al[45]	• WC ≥ 109 cm (258)	• WC ≤ 89 cm (415)	Abdominal obesity associated with BPH (OR = 2.38, 95% CI 1.42–3.99
Wang et al[48]	• WC ≥ 90 cm (270)	• WC < 90 cm (216)	The only independent risk factor of BPH is abdominal overweight/ obesity (OR 2.112, 95% CI 1.284–3.47, P = 0.003)
Rohrmann et al[51]	• WC > 102 cm (2,797)	• WC < 94 cm (not clearly mentioned)	Higher WC was more likely to have LUTS (OR = 1.48, 95% CI 0.87–2.54).
Parsons et al[33]	• BPH (91)	• Control (331)	Odds ratio for BPH • Overweight men (BMI, 25–29.9 kg/m^2): 1.41 (95% CI, 0.84–2.37) • Obese men (BMI, 30–34 kg/m^2): 1.27 (95% CI, 0.68–2.39) • Severely obese men (BMI > 35 kg/m^2); 3.52 (95% CI, 1.45–8.56; P < 0.01)
Xie et al[49]	• BPH (317)	• Control (332)	• Overweight men increased risk of BPH (OR: 1.61, 95% CI 1.15–2.26) • Obese men (OR 2.07, 95% CI 1.04–4.14) • The OR increased 1.12-fold per increase in 1 unit of BMI (95% CI 1.06 –1.18)
Lee et al[46]	• Obese (58) • Overweight (38)	• Normal weight (50)	Higher BMI (≥ 25 kg/m^2) and central obesity were at significantly increased risk of BPH (OR = 4.88, P = 0.008)
Penson et al[47]	• Severely obese (942) • Obese (1,512) • Overweight (2,691)	• Normal weight (2,046)	Worsened BPH symptoms were significantly associated with a BMI of ≥ 35 kg/m^2 (OR 1.38, 95% CI 1.17–1.63).

BMI, body mass index; BPH, benign prostate hyperplasia; CI, confidence interval; LUTS, lower urinary tract symptoms; OR, odds ratio; WC, waist circumference.

growth and by an autocrine or paracrine loop.[40,50] The amount of prostate enlargement corresponds to the extent and severity of the inflammation.[39]

There are several inflammation processes associated with BPH development in obese patients, such as toll-like receptor (TLR), cyclooxygenase-2 (COX-2), and macrophage inhibitory cytokine-1 (MIC-1). TLR is a transmembrane receptor responsible for the initiation of a range of host-defense mechanisms in response to microbial products[28] and can be found in prostate tissue and acts as a proinflammatory cytokine. Poulain-Godefroy et al[28] observed an increased expression of TLRs in VAT of approximately 1.35 to 1.4 fold compared with SAT. This expression in fat cells induces cytokine secretion, which triggers further inflammation.[28]

Chronic inflammation continuously produces COX-2, which modulates the production of angiogenic factors to induce angiogenesis, increases the carcinogenic potential of cells through the oxidation of procarcinogens to carcinogens, increases cell growth, and decreases apoptosis.[40] Nitric oxide is one of the free radicals associated with prostatic inflammation. It also enhances COX activity, which has been detected in all inflammatory cells in the epithelium and interstitial spaces of human prostate tissue.[56] Di Silverio et al[39] and Hamid et al[40] showed that, in human BPH tissue, COX-2 could produce a significant increase in prostate cell apoptotic inhibitory activity causing cell proliferation in the prostate. The relationship between COX-2 and central obesity in humans is still debatable; however, a study by Ghoshal et al[27] have found that in mice, genetic deficiency of COX-2 resulted in a significant reduction in total body weight and percent body fat.

Induction of anti-inflammatory factors such as MIC-1 is an early response due to inflammation in the prostate.[60] MIC-1 was down regulated in BPH tissues compared with normal prostate tissue.[40] This may be caused by gland destruction by inflammatory infiltrates, followed by replacement of the stromal component in symptomatic BPH.[41] However, Dostalova et al[61] revealed that central obesity is associated with significantly higher serum MIC-1 levels, although the exact mechanism is still poorly understood. It is possible that expression of circulating MICs might be in a different concentration than prostatic MICs, especially in the transition zone (site of BPH).[40]

5. Obesity and PCa

PCa is the second most commonly diagnosed cancer and the sixth most common cause of cancer-related mortality among men worldwide.[62] According to GLOBOCAN 2012,[63] it was shown that PCa is the third most common cancer in men (after lung and colorectal cancer) and has around a 9.8% incidence and 8.9% mortality amongst all cancers in Indonesia.

Studies have reported the association between obesity and many cancers including PCa.[64–67] A detailed explanation from many studies is shown in Table 2.[22,68–72] Throughout many studies it is shown that obesity is a risk factor for the development of prostate cancer (odds ratio 1.097–2.47) and even the progression towards high grade disease (odds ratio 1.49–2.56).

There are several mechanisms most commonly proposed to explain the association between obesity and PCa, which are the insulin/insulin-like growth factor (IGF)-1 axis, altered sex hormones (decreased serum testosterone and peripheral aromatization of androgen), and adipokine signaling caused by inflammation.[62,64] Insulin alone does not induce somatic cell mutations; however, it has anabolic, antiapoptotic, and, in supraphysiological concentrations, mitotic effects. Activation of insulin on the intracellular transduction pathway may affect the growth of cancer cells, especially when high concentrations of insulin are present, as occurs in obesity.[64] Central obesity and hyperinsulinemia are associated with increased circulating amounts of bioactive IGF-1, a growth factor with a recognized pathogenic role in many cancers, which in turn elevate circulating growth factors. Gallagher and LeRoith[73] confirmed that growth hormone receptor is upregulated by an increase of insulin concentration in portal circulation thus increasing growth hormone receptor signaling and hepatic IGF-1 synthesis, in hyperinsulinemia state, which induces neovascularization and prevents apoptosis.[64]

The androgens testosterone and dihydrotestosterone have been known to have an important role in the development of the prostate gland, PCa progression, and involvement in earlier stages of PCa development. Increased serum insulin levels inhibit hepatic sex hormone-binding globulin (SHBG) synthesis. SHBG, a carrier protein that specifically binds circulating testosterone and dihydrotestosterone and reduces their availability to tissues, correlates

Table 2
The Risk of Prostate Cancer Relating to Obesity in Various Studies Based on Obesity Status (Body Mass Index and Waist Circumference).

Study reference	Population studied (n)	Control (n)	Findings
De Nunzio et al[22]	• PCa (246)	• Control (422)	Central adiposity was significantly associated with PCa (OR 1.66, CI 95% 1.05—2.63, $P = 0.03$) and high-grade disease (OR 2.56, CI 95% 1.38—4.76, $P = 0.003$)
Nemesure et al[70]	• PCa (963)	• Control (941)	WC of $\geq$ 102 cm had an OR of 1.84 (95% CI 1.19—2.85) compared with those with WC of < 90 cm
Irani et al[69]	• PCa (194)	• Control (194)	Obesity was significantly associated with PCa (OR 2.47, 95% CI 1.41—4.34)
De Nunzio et al[68]	• PCa (363)	• Control (522)	Obesity was significantly associated with PCa (OR 1.097, 95% CI 1.029—1.171)
Rundle et al[72]	• PCa (494)	• Control (494)	Obesity at the time of biopsy was associated with PCa incidence during follow-up (OR 1.57; 95% CI 1.07—2.30)
Park et al[71]	• Obese (408)	• Normal weight (805)	Obesity was significantly associated with a higher risk of detection on PCa in biopsy patients (OR = 1.446, $P = 0.024$)
			Obesity was significantly associated with a higher rate of high-grade PCa detected from the biopsy (OR = 1.498, $P = 0.039$)

BMI, body mass index; CI, confidence interval; OR, odds ratio; PCa, prostate cancer; WC, waist circumference.

inversely to BMI. Total testosterone bioavailability, plus chemically bound/unavailable testosterone, also correlates inversely with BMI and insulin. This relationship can be explained by long-loop feedback inhibition of pituitary luteinizing hormone secretion by bioavailable (non-SHBG bound) testosterone, which leads to reduced testicular androgen synthesis. In obese men, total testosterone, SHBG, luteinizing hormone pulse amplitude, diurnal luteinizing hormone, and bioavailable testosterone are all reduced.[74] Men with PCa who have low testosterone tend towards a more aggressive phenotype. However, the low T environment in obese men may be one plausible link between obesity and aggressive PCa, although the exact mechanisms remain unknown.[62]

Prabhat et al[31] concluded that central obesity had a higher correlation with hormonal and metabolic alterations compared with BMI, which may contribute to various mechanisms, such as chronic inflammation.[31] Central adiposity, which was evaluated in European patients at risk of PCa, is a state of chronic subclinical inflammation associated with adipokine signaling such as higher levels of leptin, lower levels of adiponectin, which have, though controversially, been associated with PCa.[22] Leptin, the adipocyte-derived hormone, is elevated in central obesity and exerts a predominantly protumor effect in human PCa cell lines, by promoting angiogenesis and increased sympathetic nervous system activity.[75] In contrast to leptin, adiponectin has largely antitumor effects by inhibiting cancer cell growth, metastasis, inhibiting dehydrotestosterone, and it inhibits inflammation by inhibiting the activity of mature phagocytic macrophages; however, serum levels of adiponectin are reduced in central obesity.[76] All of these mechanisms result in increased proliferation, decreased apoptosis, and transition from androgen dependence to androgen independence. The mechanism of how obesity might affect PCa is shown in Fig. 1.

It is thought that androgens might promote the initiation and progression of well-differentiated PCa, while protecting against poorly differentiated cancers.[74] However, an increased risk for
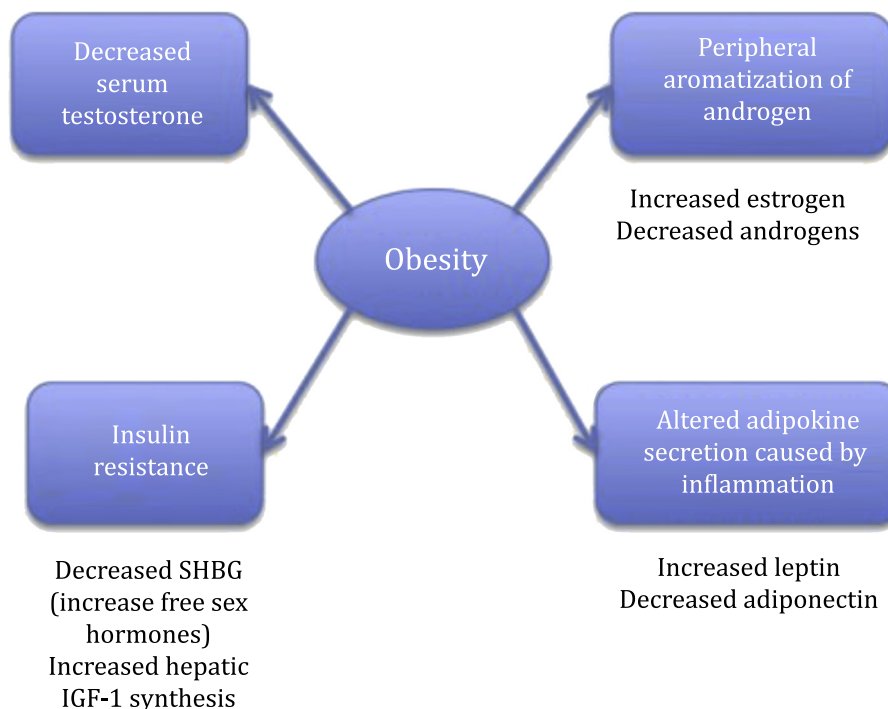

Fig. 1. Possible mechanisms for obesity-related prostate cancer progression. IGF-1, insulin-like growth factor-1, SHBG, sex hormone-binding globulin. *Note.* From "Obesity and prostate cancer: a role for adipokines" by T. Mistry, J.E. Digby, K.M. Desai, H.S. Randeva, 2007, *European Urology, 52*, p. 46—53. Copyright 2007, Elsevier B.V. European Association of Urology. Adapted with permission.

poorly differentiated PCa has been associated with hyper-insulinemia and leptin.[22,31,58,73,75,76] A recent study indicates that obese people have low testosterone levels, raised insulin and leptin, characteristics of adiposity, which increases the risk for poorly differentiated, androgen dependent PCa.[77]

6. Conclusion

Central obesity is one of the modifiable risk factors in relation to prostate diseases. Adipose tissue, favoring VAT, is an important risk factor for the development of BPH and PCa. Many mechanisms have been hypothesized to explain the correlation between obesity and risk of BPH and PCa, such as increased estrogen-to-androgen ratio and increased sympathetic nervous activity, promotion of inflammation process, which in turn contributes to ischemia, oxidative stress, and an intraprostatic environment favorable to BPH and PCa. A greater understanding of the pathogenesis of prostate disease and adiposity could allow the development of new therapeutic markers, prognostic indicators, and drug targets. It may also provide scientific evidence to promote weight loss and other lifestyle modifications as beneficial adjuvant therapies for prostate diseases.

Conflicts of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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