ORIGINAL ARTICLE

Bali Medical Journal (*Bali Med J*) 2017, Volume 6, Number 1: 204-210
P-ISSN.2089-1180, E-ISSN.2302-2914



Published by DiscoverSys

# Waist circumference increased risk of benign prostatic hyperplasia through an increase in the level of interleukin-6 and insulin resistance in abdominal obesity patients


Wira Gotera,[1*] Wira Mahadita,[2] I. Made Bakta,[3] A.A. Gde Oka,[4] A.A.G. Budiartha,[1] Putra Manuaba,[5] Sri Maliawan[6]

## ABSTRACT

Inflammation in abdominal obesity (Ab-Ob) is associated with insulin resistance condition and hyperinsulinemia. Numerous studies have found that prevalence of prostatic hyperplasia was higher in individuals with central obesity. This study is aimed at testing and verifying whether and to what extent waist circumference (WC), interleukin-6 (IL-6), and insulin resistance (HOMA-IR) increase the risk of benign prostatic hyperplasia (BPH) in Ab-Ob.

The study design was *match-paired case-control.* Eighty patients were recruited for this study. Data analysis was done with student *t*-test, multivariate logistic regression analysis, and path analysis. IL-6 was measured with *sandwich enzyme immunoassay* with *Quantikine Immunoassay Kit* (R&D System, Inc. USA), hsCRP was measured with *the immunometric assay*, and fasting insulin level was measured with *Chemiluminescence Immunometric* method (Immulite ®2000).

From multivariate logistic regression analysis, we found that WC, IL-6, and HOMA-IR increase the risk of BPH significantly with an odds ratio (OR) value of 1.09 (IK = 1.03–1.15), $p = 0.005$; 1.69 (IK = 1.10–2.58), $p = 0.015$; and 1.37 (IK = 1.05–1.79), $p = 0.021$, respectively. *Path analysis* showed the existence of a significant relationship between WC and BPH (critical ratio [CR] = 2.87, $p = 0.004$), between WC and IL-6 (CR = 5.9, $p < 0.001$), and between WC and HOMA-IR (CR = 3.87, $p \leq 0.001$). There was a significant correlation between HOMA-IR and BPH (CR = 2.07, $p = 0.039$), between IL-6 and BPH (CR = 2.19, $p = 0.029$), and also an indirect relationship between WC and BPH through the increase of IL-6 and HOMA-IR.

We concluded that WC increased the risk of BPH through the increase of IL-6 and HOMA-IR in abdominal obesity patient.

**Keywords:** Waist Circumference, IL-6, HOMA-IR, *Benign Prostatic Hyperplasia*
**Cite This Article:** Gotera, W., Mahadita, W., Bakta, I.M., Oka, A.A.G., Budiartha, A.A.G., Manuaba, P., Maliawan, S. 2017. Waist circumference increased risk of benign prostatic hyperplasia through an increase in the level of interleukin-6 and insulin resistance in abdominal obesity patients. *Bali Medical Journal* 6(1): 204-210. DOI:10.15562/bmj.v6i1.464

[1]Endocrinology Division
[2]Department of Internal Medicine, Udayana School of Medicine, Sanglah General Hospital, Denpasar, Indonesia
[3]Hematology and Oncology Division, Department of Internal Medicine, Udayana School of Medicine, Sanglah General Hospital, Denpasar, Indonesia
[4]Urology Department, Udayana School of Medicine, Sanglah General Hospital, Denpasar, Indonesia
[5]Faculty of Mathematic and Natural Science, Udayana University, Denpasar, Indonesia
[6]Neurosurgery Department, Udayana School of Medicine, Sanglah General Hospital, Denpasar, Indonesia

[*]Correspondence to: Wira Gotera, Endocrinology Division
wiragotera@yahoo.co.id

Received: 2016-02-7
Accepted: 2017-03-07
Published: 2017-03-10

## INTRODUCTION

Obesity pandemic, particularly abdominal obesity (Ab-Ob), has become a global threat. Ab-Ob is often found simultaneously with another symptom, known as metabolic syndrome (MS), which is another risk factor for cardiovascular disease (CVD). Ab-Ob acts as a fundamental principle in the clinical course of MS as a risk factor for CVD.

Data from WHO in 2014 showed that more than 1.9 billion people were overweight. Out of this, 200 million men and 300 million women suffered from obesity.[1] Overall, more than 10% of world population is obese. MS is mostly found in India due to high prevalence of Ab-Ob, with 1.091 people out of 100 and affected men and women constituting 8% and 18% in this group.[2]

Aside from the constellation of risk factors giving rise to DM and CVD, MS or its component, particularly Ab-Ob, insulin resistance was associated with a degenerative disease called benign prostate hyperplasia (BPH).[1,3] BPH is one out of three degenerative diseases that is most commonly found in men (aside from hypogonadism and erectile dysfunction). As much as 15% of men age above 40 years were found with prostate disorders and prostatitis and as much as 20–40% among those also suffered BPH.

Ab-Ob is associated with a low-grade chronic systemic inflammatory condition, mobilization of macrophage infiltration to fat tissue, and an increase of pro-inflammatory cytokines such as TNF-α, IL-6, and CRP which are involved in insulin resistance and BPH pathogenesis. Secondary hyperinsulinemia due to insulin resistance has been thought to have association with clinical manifestation of lower urinary tract symptoms (LUTS). Hyperinsulinemia is associated with an increase in sympathetic nerve activity, increasing prostate's sympathetic nerve tone and aggravating LUTS.

The focus of studies nowadays is limited to analyzing the metabolic effect of insulin, even

though it is known that insulin also causes a mitogenic effect that in causes degenerative diseases. Even though there is plenty of research and publications about intra-abdominal fat and inflammation, there is a clear lack of research about the association between insulin resistance and increased risk of BPH. No studies have focused on the connection of inflammation and insulin resistance with BPH for Ab-Ob patients, both directly and indirectly.

This research aims to determine the extent to which waist circumference, IL-6, and HOMA-IR (insulin resistance) increase risk of BPH and to further prove that waist circumference increases risk of BPH through the increase of IL-6 and HOMA-IR (insulin resistance) in patients with Ab-Ob.

We expect this research, since it is proven that a larger waist circumference increases the risk of BPH through IL-6 and HOMA-IR enhancement, to confirm the pathophysiological hypothesis that chronic inflammation on Ab-Ob promotes insulin resistance and waist circumference increases risk of BPH through chronic inflammation and insulin resistance. In clinical practice, early decrease of WC in Ab-Ob patients could prevent BPH.

## RESEARCH DESIGN AND METHODS

### Research Design and Study Subject

This research was conducted with matched-pair case–control study design. Case group comprised Ab-Ob patients with BPH and control group comprised Ab-Ob patients without BPH. The target population was all Ab-Ob patients with or without BPH. Accessible population was patients with Ab-Ob and BPH that undergo treatment at Sanglah General Hospital, Wangaya Hospital, Denpasar.

Inclusion criteria were males with Ab-Ob and BPH, age > 40 years (case group), and males with Ab-Ob without BPH, age > 40 years (control group). Exclusion criteria included: smoking, malignancy (carcinoma), liver cirrhosis, receiving corticosteroids, alcohol consumption, and suffering from an acute infection.

Eligible patients have been chosen consecutively until the required number of patients were met. Case group was Ab-Ob patients with BPH (BPH confirmed with urology department). Each case was paired with a control group participant, which is an Ab-Ob patient without BPH in similar age. Required sample was calculated with the following assumptions: odds ratio (OR) = 3, considered as significant; type 1 error (α) = 0.05 (Zα = 1.96); type 2 error (β) = 0.1 (Zβ = 1.28); or power of 90%. Number of minimum participants required based on the above calculation was 38 pairs. This research involved 40 pairs of case and control group participants.

### Instruments and Material Collection Procedure

BPH is a prostate enlargement caused by the proliferation of cellular elements with clinical manifestation of LUTS. Prostate hyperplasia is viewed as a clinical manifestation if obstructive and irritative symptoms are acquired and the IPSS (International Prostatic Symptom Score) score ≥ 8. The digital rectal examination found a chewy consistency of prostate, like touching the nose tip, symmetrical right and left lobe, and nodules are not found. Further diagnosis of prostate hyperplasia confirmed with urology department after it used USG.[6] Abdominal obesity is obesity that is determined by waist circumference (WC) measurements. WC ≥ 90 cm in adult male is defined as Ab-Ob.[1] HOMA-IR (homeostatic model assessment of insulin resistance) is a measurement to assess insulin resistance, and the formula used for calculation is as follows: fasting insulin (μU/ml) x fasting glucose (mmol/L)/22.5.[7] Fasting insulin is plasma insulin concentration which is measured in fasting condition at least 8 hours (start on evening) before measurement.[7]

IL-6 concentration was ascertained from the serum samples' stored at a stable temperature of –20°C. Serums were collected until the required amount were fulfilled. Sandwich enzyme immunoassay technique was used after 10 minutes of centrifugation at 1500 g. The lowest level of detection was 0.5 pg/ml. IL-6 level was standardized with plasma albumin level and 1000 monocytes count. Quantikine HS Immunoassay Kit (R&D System, Inc., 614 McKinley N.E. Minneapolis, MN 55413, USA) was used for this analysis. Insulin level was analyzed using Immulite ®2000 with chemiluminescence Immunometric method. Normal value was 6–27 μIU/mL. Lowest concentration detected was 2 μIU/mL with a variation coefficient of 0.2–5.8%. Specificity of antibodies used has high specificity for insulin and the antibodies did not react with other serum components.

WC measurement was performed in the middle of the lower edge of the last costae and superior iliac crest in a horizontal plane. The examiner sat beside the subject and used a measuring tape without applying pressure. Measurement was performed at the end of normal expiration. Waist circumference was measured with accuracy approaching 0.1 cm.

### Statistical Analysis

Characteristic data of patients in this research were analyzed descriptively. Mean ± standard deviation (normally distributed data) and median (inter-quartile; not normally distributed data) were used for numerical data and frequency was used for nominal data. Kolmogorov–Smirnov test was used as the normality test needed to analyze numerical

data. Mean test between the characteristic data of groups was performed with a parametric test if data were numerical and normally distributed with student's *t*-test. Non-parametric analysis (Man–Whitney *U* test) was used for non-normal distribution of data despite the transformation of logarithms. Logistic regression analysis was performed to control confounding variables so that the effect of independent variable over the dependent variable can be observed exclusively. Estimated odds ratio (OR) was presented with confidence interval (CI) at 95%.

Path analysis was carried out to observe the direct relationship between WC and BPH/LUTS and an indirect relationship between WC and BPH through an increase of IL-6 and HOMA-IR. The level of significance (α) in this research was set at probability value of $p < 0.05$. Statistical test was performed with SPSS software for MAC version 21 and AMOS version 23.

**Table 1** **Baseline Characteristics of Subjects from Case Group (Ab-Ob with BPH) and Control Group (Ab-Ob without BPH)**

| | Case ($n = 40$) Mean ± SD or Median (minimum-maximum) | Control ($n = 40$) Mean ± SD or Median (minimum-maximum) | *p* value |
|---|---|---|---|
| Age (years) | 61.55 ± 6.33 | 61.68 ± 6.35 | 0.994 |
| Height (cm) | 167.93 ± 3.37 | 167.50 ± 3.49 | 0.330 |
| Weight (kg) | 92 (65–104) | 90 (59–101) | 0.075 |
| BMI (kg/m$^2$) | 32.76 (21.22–36) | 32.08 (20.66–37.5) | 0.163 |
| Waist circumference (cm) | 104 (90–146) | 102 (90–126) | 0.002 |
| SBP (mm/hg) | 132.25 ± 12.70 | 123 ± 12.23 | 0.001 |
| DBP (mm/hg) | 81.6 ± 7.34 | 76.37 ± 7.42 | 0.003 |
| WBC ($10^3$/μL) | 11.36 ± 15.12 | 10.80 ± 13.38 | 0.651 |
| Hemoglobin (g/dl) | 13.35 ± 1.60 | 14.32 ± 1.76 | 0.013 |
| BUN (mg/dl) | 22.80 ± 5.92 | 19.91 ± 5.78 | 0.357 |
| SC (mg/dl) | 0.94 ± 0.31 | 0.97 ± 0.25 | 0.126 |
| SGOT (U/L) | 24.5 (13–66) | 24 (13–64) | 0.444 |
| SGPT (U/L) | 30.82 ± 10.66 | 28.16 ± 12.89 | 0.315 |
| Total cholesterol (mg/dl) | 226.43 ± 41.52 | 208.75 ± 42.20 | 0.063 |
| triglycerides (mg/dl) | 150 (107–356) | 148.5 (67–438) | 0.341 |
| LDL (mg/dl) | 133.53 ± 24.16 | 123.73 ± 33.05 | 0.556 |
| HDL (mg/dl) | 40.27 ± 8.78 | 41.53 ± 8.53 | 0.599 |
| FBG (mg/dl) | 137 (81–289) | 98 (79–253) | 0.001 |
| 2hPP blood glucose (mg/dl) | 186 (93–345) | 115 (89–447) | 0.053 |
| Fasting insulin (μIU/ml) | 6.45 (2–79.2) | 4.45 (1.1–24.7) | 0.034 |
| HOMA-IR | 1.88 (0.48–56.12) | 1.19 (0.27–10.37) | 0.004 |
| hsCRP (mg/L) | 1.45 (0.3–13.5) | 1.00 (0.2–9.2) | 0.500 |
| IL-6 (pg/dL) | 1.07 (0.25–5.68) | 0.71 (0.15–3.62) | 0.006 |

Note: SBP = systolic blood pressure; DBP = diastolic blood pressure; BMI = body mass index.

**Table 2** **Effect of Association between WC, IL-6, and HOMA-IR over BPH in Ab-Ob Subjects**

| Independent variables | Unadjusted OR | 95% CI | *p* value | Adjusted OR | 95% CI | *p* value |
|---|---|---|---|---|---|---|
| WC (cm) | 1.09 | 1.03–1.15 | 0.005 | 1.11 | 1.04–1.18 | 0.001 |
| hsCRP (mg/dl) | 1.13 | 0.97–1.31 | 0.117 | 1.22 | 1.02–1.47 | 0.032 |
| IL-6 (pg/dl) | 1.69 | 1.10–2.58 | 0.015 | 1.88 | 1.19–2.98 | 0.007 |
| HOMA-IR | 1.37 | 1.05–1.79 | 0.021 | 1.45 | 1.07–1.98 | 0.018 |

Note: WC = waist circumference; adjusted OR after controlling for Hb, SBP, and DBP.

## RESULTS

### Baseline Characteristic of Subjects

This study involved 80 males, 40 for case group (Ab-Ob with BPH) and 40 for control group. After Kolmogorov–Smirnov test was performed for normality, logarithmic transformation of some variables was conducted; it was found that for several parameters data were not normally distributed, including hs-CRP, IL-6, fasting insulin, fasting blood glucose and 2-hour postprandial, HOMA-IR, TG, SC, and weight and BMI ($p < 0.05$). Characteristic data of the subjects are presented in Table 1.

Normally distributed data were presented in mean ± SD, while non-normally distributed data were presented in medial (interquartile). Mean difference test (*t*-test for normally distributed data, Man–Whitney *U* test for non-normal distribution of data) showed that several variables have significantly differed between the case and the control groups. Fasting glucose (Z = –3.325, $p = 0.001$), fasting insulin (Z = –2.15, $p = 0.034$), and HOMA-IR (Z = –2.843, $p = 0.004$) were significantly higher in the case group than in the control group. Only IL-6 (Z = –2.732, $p = 0.006$) was considerably higher in the case group compared to the control group for inflammatory parameters, but this is not the case with hsCRP ($p = 0.5$). From the characteristics of subjects, other variables which significantly differed between case and control groups were Hb (13.35 ± 1.60 vs. 14.32 ± 1.76 g/dL, $p = 0.013$) and blood pressure, both SBP (132.25 ± 12.70 vs. 123 ± 12.23 mmHg, $p = 0.001$) and DBP (81.6 ± 7.34 vs. 76.37 ± 7.42 mmHg, $p = 0.003$).

**Table 3** Relationship between Two-Constructs Variables

| Variables | Regression weight | | | Standardized regression weight |
|---|---|---|---|---|
| | Estimate | CR | P | |
| WC→hsCRP | 0.17 | 6.11 | *** | 0.57 |
| WC→IL-6 | 0.07 | 5.90 | *** | 0.55 |
| WC→HOMA-IR | 0.27 | 3.87 | *** | 0.43 |
| hsCRP→HOMA-IR | 0.09 | 0.46 | 0.65 | 0.04 |
| IL-6→HOMA-IR | 1.69 | 3.54 | *** | 0.34 |
| LP→BPH | 0.19 | 2.87 | 0.004 | 0.36 |
| HOMA-IR→BPH | 0.21 | 2.07 | 0.039 | 0.24 |
| hsCRP→BPH | –0.12 | –0.64 | 0.52 | –0.06 |
| IL-6→BPH | 1.00 | 2.19 | 0.029 | 0.23 |

**Table 4** Relationship between Construct Variables with BPH as Dependent Variable

| Effects | WC→BPH | IL-6→BPH | hsCRP→BPH | HOMA-IR→BPH |
|---|---|---|---|---|
| Total effect | 0.38 | 1.35 | –0.09 | 0.21 |
| Direct effect | 0.19 | 1.01 | –0.12 | 0.21 |
| Indirect effect | 0.13 | 0.35 | –0.02 | 0.00 |

**Table 5** Relationship between Construct Variables and Relationship between Construct Variables and Independent Variables of WC

| Effects | WC→IL-6 | WC→hsCRP | WC→HOMA-IR | IL-6→HOMA-IR |
|---|---|---|---|---|
| Total effect | 0.07 | 0.17 | 0.40 | 1.67 |
| Direct effect | 0.07 | 0.17 | 0.27 | 1.67 |
| Indirect effect | 0.00 | 0.00 | 0.13 | 0.00 |

### Relationship of WC, IL-6, and HOMA-IR with BPH on Ob-Ab

Hb, SBP, and DBP were controlled with logistic regression multivariate analysis to find adjusted OR from WC, IL-6, and HOMA-IR. The results are presented in Table 3.

Table 2 shows that WC associated with BPH increases the risk of the prostate (OR = 1.96, $p = 0.005$). This showed that if other variables are constant and did not change, a 1-cm increase in WC leads to BPH risk elevation by 1.09. This value remains significant after controlling confounding variables Hb, DBP, and SBP (adjusted OR = 1.11, $p = 0.001$). A similar result was obtained for the inflammation variable. IL-6 had OR = 1.69 with $p = 0.015$. The increase of IL-6 by 1 pg/dl resulted in a 1.69 times increase in BPH risk. The OR value of IL-6 remained significant after controlling confounding variables Hb, SBP, and DBP (adjusted OR = 1.88, $p = 0.007$). hsCRP was not significantly increasing the risk of BPH but after controlling for confounding variables Hb, SBP, and DBP it was to be exerting significant influence over BPH in Ab-Ob (adjusted OR = 1.22, $p = 0.032$). This result also showed the role of HOMA-IR (insulin resistance) in increasing the risk of BPH. HOMA-IR OR value was 1.37 with $p = 0.021$. The increase of HOMA-IR by 1 will increase the risk of BPH by 1.37 times, which remained significant even after controlling for confounding variables with adjusted OR = 1.45, $p = 0.018$.

### Path Analysis

Path analysis was used to analyze the cause–effect relationship between WC, IL-6, HOMA-IR and BPH. Exogenous variables in this analysis were: WC, IL-6, hsCRP, and HOMA-IR. The endogenous variable was BPH. The model was made based on pathophysiological theory and hypothesis, and the results are presented in Figure 1.

The results of direct analysis of BPH were: WC to BPH/LUTS was 0.19 (19%), HOMA-IR to BPH/LUTS was 0.21 (21%), IL-6 to BPH/LUTS was 1.00 (100%), hsCRP to BPH was 0.12 (12%). The direct

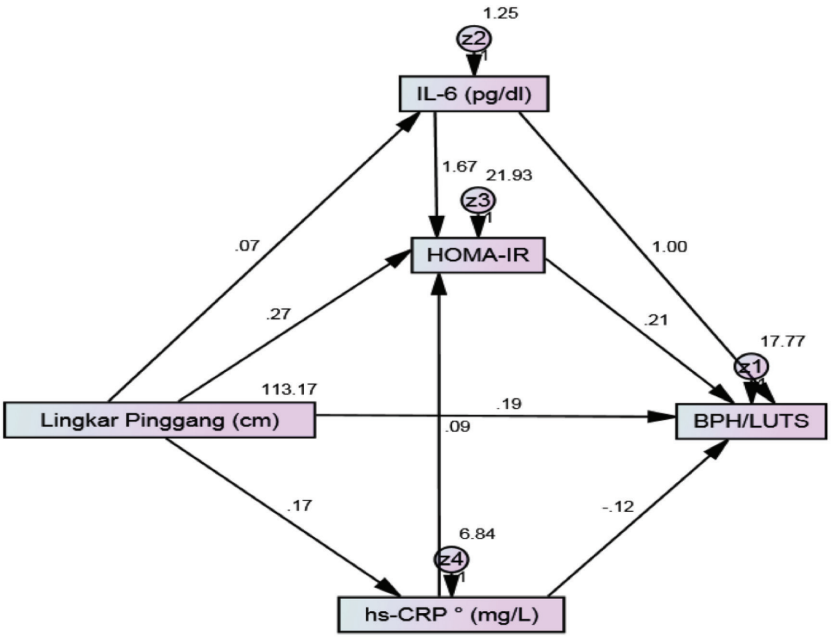


**Figure 1** Results derived from path analysis structural model

effects of WC on other variables were as follows: WC to IL-6, hsCRP, and HOMA-IR are 7%, 17%, and 27%, respectively. The relationships between the constructs are presented in Table 3, which are derived from AMOS analysis. Critical ratio (CR) was used to determine the effect of independent variables on a dependent variable. The higher the CR value, the more significant is its effect.

There was a significant relationship between WC and hsCRP (CR = 6.11, $p < 0.001$), WC and IL-6 (CR = 5.90, $p < 0.001$), WC and HOMA-IR (CR = 3.87, $p \leq 0.001$), WC and BPH (CR = 2.87, $p = 0.004$), HOMA-IR and BPH (CR = 2.07, $p = 0.039$), and between IL-6 and BPH (CR = 2.19, $p = 0.029$). The pattern of relationships between variables, both direct or indirect relationships, is presented in Tables 4 and 5.

## DISCUSSION

### LP and BPH in Ob-Ab

This study confirmed that WC is associated with BPH, increasing the risk of BPH (OR = 1.09, $p = 0.005$). It showed that if the other independent variables are constant or did not change then a 1-cm increase of WC will increase the risk of BPH by 1.09 times. This value, after controlling for confounding variables Hb, SBP, and DBP, remained significant (adjusted OR = 1.11, $p = 0.001$). Path analysis also found that WC was strongly and significantly associated with BPH (CR = 2.87, $p = 0.004$), and with a strong load factor, standardized regression weight reached 23%. Further analysis found that WC is both directly and indirectly related to BPH, with total effects, directly and indirectly, at 38%, 19%, and 13%, respectively.

These results are consistent with the research conducted by Lee et al.[8] They examined the influence of obesity over BHP using BMI as a measurement parameter. This research involved 146 males aged > 40 years who did not suffer from DM. The size of the prostate was examined by transrectal ultrasound. Subjects were divided into three groups: normal (BMI = 22.9 kg/m$^2$), overweight (BMI = 23–24.9 kg/m$^2$), and obesity (BMI ≥ 25 kg/m$^2$), and two groups based on waist circumference (WC > 90 cm, WC ≤ 90 cm). The highest prostate volume was found in the obese group ($p = 0.03$) and the Ab-Ob group ($p = 0.002$). After adjusting for several confounding variables, Ab-Ob was found to be a major risk factor for BPH (prostate volume > 20ml; OR = 3.37, $p = 0.037$).

Based on our research we can prove that WC increases the risk of BPH on Ab-Ob in the early stage. The pattern of relationships between WC and BPH could be directly and indirectly measured using different parameters, which is discussed further in the following section.

### Inflammation and BPH in Ob-Ab

This study found that IL-6 significantly increases the risk of BPH (OR = 1.69, $p = 0.015$). If the levels of IL-6 increased by 1 mg/dl, then it will increase the risk of BPH by 1.69 times. The OR value of IL-6 remained significant even after controlling for confounding variables such as Hb, SBP, and DBP (adjusted OR = 1.88, $p = 0.007$). On the other hand, hsCRP has not significantly increased the risk of BPH, but after controlling for confounding variables Hb, SBP, and DBP it was found that it did induce an increase in the incidence of BPH in Ab-Ob patients (adjusted OR = 1.22, $p = 0.032$). From the path analysis, it was found that only IL-6 was closely associated with BPH (CR = 2.19, $p = 0.029$), with the loading factor reaching 23%. hsCRP was not significantly related to BPH. In the analysis of patterns of relationships, both direct or indirect relationships, it was found that IL-6 has total effect over BHP, both directly and indirectly.

Several epidemiological studies showed that more than 25% of malignancy cases were associated with chronic inflammation.[4,9] Chronic and excessive release of inflammatory mediators theoretically lead to an increase in initiation, promotion, and progression of tumors, including hyperplasia prostate. In Ab-Ob subjects, adipose tissue is in a state of chronic inflammation, which has a major role in the occurrence of insulin resistance, dyslipidemia, and type 2 diabetes, as well as other comorbid diseases such as cardiovascular disease and cancer. This inflammation is characterized by elevated levels of CRP, IL-6, IL-8, and TNFα.[10,11]


Published by DiscoverSys | *Bali Med J* 2017; 6 (1): 204-210 | doi: 10.15562/bmj.v6i1.464

The mechanisms which explain how chronic inflammation induced by Ab-Ob increase the risk of BPH include: (a) increased production of pro-inflammatory mediators such as cytokines, chemokines, and reactive oxygen intermediates (ROI); (b) increased expression of oncogenes, COX-2 (cyclooxygenase-2), 5-LOX (5-lipoxygenase), and MMPs (matrix metalloproteinases); and (c) increase in pro-inflammatory transcription factors such as NF-κB (nuclear factor-κB), STAT3 (signal transducer and activator of transcription 3), and AP-1 (activator protein 1).[12,13]

Infiltration of chronic inflammation often occurs in the peripheral area of the prostate. These inflammatory mediators further activate other pro-inflammatory transcription factors such as NF-κB and inducible nitric oxide synthase (iNOS).[13] NF-κB is a strong inducer of genes associated with the anti-apoptosis activity (BCL-XL) and genes that regulate the cell's lifecycle (cyclin D1). NF-κB and iNOS are critical for immune cell activation and can induce mitogenic and anti-apoptosis effects.[15]

Pro-inflammatory cytokines also induce leukocytes to produce reactive oxygen (ROS) and nitrogen species (RNS), which in turn induce DNA mutations that trigger the formation of tumors.[9] Infections and release of pro-inflammatory cytokines as a result of chronic inflammation in prostate lead to formation of lesions in the form of proliferative inflammatory atrophy (PIA), focal atrophy of the prostate tissue accompanied by epithelial tissue proliferation, and inflammatory cells infiltration.[9,15,16]

This study confirmed that IL-6 as a parameter of inflammation increases the risk of BPH and is directly or indirectly related to BPH.

### Insulin resistance and BPH in Ab-Ob

This study also showed the role of HOMA-IR (insulin resistance) in increasing the risk of BPH. OR value of HOMA-IR was 1.37, with $p = 0.021$. If HOMA-IR rose by 1 point, it increased the possibility of BPH incidence by 1.37 times. After controlling for confounding variables, this value remained significant with adjusted OR = 1.45, $p = 0.018$. From the path analysis, it was found that insulin resistance has a dynamic and meaningful relationship with BPH (CR = 2.07, $p = 0.039$) and the load factor reached 24%. Further analysis found that HOMA-IR also had a direct 21% influence in incidences of BPH, but it did not have an indirect effect.

Hyperinsulinemia is associated with an increased prostate size by 45% in the experimental mice. The role of Ab-Ob in causing insulin resistance significantly increased insulin levels, in relation to mitogenic and growth-promoting effects. Insulin itself is known to act as a growth factor that increases the risk of prostate enlargement, broadly through the activation of IGF system, thus increasing the production and bioavailability of IGF-1.[17] This suggests that obesity with hyperinsulinemia has a strong relationship with BPH.[18,19] Hyperinsulinemia and insulin resistance on the other hand also increase sympathetic nervous system activity by increasing the cytosolic-free calcium in smooth muscle cells and neural tissue, causing enhancement of prostate smooth muscles tone and thus increasing symptoms of LUTS and BPH.[20] In this research, we could prove that insulin resistance (HOMA-IR) enhances the risk of BPH in Ab-Ob subjects and has a direct and significant relationship with incidences of BPH.

### LP Increases Risk of BPH through Increased IL-6 and HOMA-IR in Ob-AB Subjects

It has been proven that WC, IL-6, and HOMA-IR increase the risk of BPH significantly in Ab-Ob subjects. The pattern of relationships, both direct or indirect relationships, between variables are presented in Tables 5 and 6. WC has a direct effect (19%) and indirect effect (13%) on the incidence of BPH, and its total effect was 38%. Likewise, IL-6 has a direct 101% effect on the incidence of BPH and an indirect effect of 35% over BHP incidences. However, HOMA-IR had only a direct effect of 21% in BPH incidences and did not have an indirect effect. Table 5 presents the pattern of relationships between the construct and its relationship with independent variables of WC. There was a direct correlation between WC and inflammatory parameters, with IL-6 by 7% and hsCRP by 17%. WC also has a direct effect (27%) and indirect effect (13%) on insulin resistance (HOMA-IR). The pattern of this relationship has also illustrated the direction, a direct effect of IL-6 at 16.7% over HOMA-IR.

A population study by Wang et al.[21] found that only WC was a significant predictor of BPH risk. This study is a fairly large epidemiological study involving 539 subjects. From multivariate analysis it was found that only WC ≥ 90 cm increased the risk of BPH, which is not however applicable to PSA and BMI. CoLaus Study reports a positive correlation of IL-6 and hsCRP as inflammatory parameters with HOMA-IR (insulin resistance) and fasting blood glucose.[22] The study involved 2800 subjects. Sub-analytical study of the research found that BMI influenced inflammatory conditions through IL-6 and hsCRP elevation.

Path analysis in this study clearly demonstrated that WC was associated with the incidence of BPH directly or indirectly through elevations in IL-6 and HOMA-IR. This analysis also found that IL-6

was directly associated with HOMA-IR (insulin resistance). Thus, it was obviously proven that WC increased the risk of BPH through elevations in IL-6 and HOMA-IR (insulin resistance) in Ab-Ob subjects.

## CONCLUSIONS

From the results and discussion of this study, we have arrived at the following conclusions: Waist circumference increased the risk of BPH in abdominal obesity, IL-6 increased the risk of BPH in abdominal obesity, HOMA-IR increased the risk of BPH in abdominal obesity, and waist circumference increased the risk of BPH through IL-6 and HOMA-IR elevations in abdominal obesity.

## REFERENCES


1. WHO. Obesity and overweight fact sheet. Geneva: WHO Media Centre; 2014, pp. 1–5.
2. Johnson. The metabolic syndrome epidemiology and clinical aspect (3th ed.). Back-Nielsen: Springer; 2013, p. 33.
3. Gorbachinsky I, Akpinar H, Assimos DG. Metabolic syndrome and urologic diseases. Rev Urol. 2010;12:157–80.
4. Hsing AW, Sakoda LC. Obesity, metabolic syndrome, and prostate cancer. Am J Clin Nutr. 2007;86:843–45.
5. Madiyono B. In: Sastroasmoro S, editor. Dasar-Dasar Metode Penelitian Klinis (3rd ed.). Jakarta: Sagung Seto; 2010, pp. 302–01.
6. Nickel JC, Probst CEM, Whelan TF, Paterson RF, Razvi H. 2010 Update: Guidelines for the management of benign prostatic hyperplasia. Can Urol Assoc J. 2010;4(5):310–16.
7. Mathews DR, Hosker JP, Rudenski AS, Naylor BA, Tracer DF, Turner RC. Homeostatic model assessment: Insulin resistance and beta cell function from plasma glucose and insulin concentrations in man. Diabetologia. 1985;28:412–19.
8. Lee S, Min HG, Choi SH, Kim YJ, Oh SW, Kim YJ, Park Y, Kim SS. Central obesity as a risk factor for prostatic hyperplasia. Obesity. 2006;14(1):172–8.
9. Bruton AJ, Tilling M, Holly JM. Metabolic imbalance and prostate cancer progression. Int J Mol Epidemiol Gen. 2010;1(4):248–371.
10. Pandona P, Aljada A, Chanduri A. Metabolic syndrome: A comprehensive perspective based on interaction between obesity, diabetes, and inflammation. Circulation. 2005;3:1448–54.
11. De Nunzio, Kramer G, Marberger M. The controversial relationship between benign prostatic hyperplasia and prostate cancer: The role of inflammation. Eur Urol. 2011;60:106–17.
12. Braun S, Bitton-worms K, Leroith D. The link between the metabolic syndrome and cancer. Int J Biol Sci. 2011;7(7):1003–15.
13. Ramos-nino, ME. The role of chronic inflammation in obesity-associated cancers. ISRN Oncology. 2012;1–26.
14. Dasgupta S, Srinidhi S, Vishwanatha JK. Oncogenic activation in prostate cancer progression and metastasis: Molecular insights and future challenges. J Carcinog. 2012;11(4):39–49.
15. Chungta B, Lee R, Te A, Kaplan S. Role of inflammation in benign prostatic hyperplasia. Rev Urol. 2011;13(3):147–50.
16. Patel JC, Maughan BL, Agarwal AM, Batten JA, Zhang TY, Agarwal N. Emerging molecularly targeted therapies in castration refractory prostate cancer. Prostate Cancer. 2013;12:1–12.
17. Giovannuci E. Nutrition, insulin, insulin-like growth factors, and cancer. Horm Metab Res. 2003;35:694–704.
18. Renehan AG, Frystyk J, Flyvbjerg A. Obesity and cancer risk: The role of the insulin–IGF axis. Trends Endocrinol Metab. 2006;17(8):328–36.
19. Allott EH, Masko EM, Freedland SJ. Obesity and prostate cancer: Weighing the evidence. Eur Urol. 2013;63:800–9.
20. Sarma AV, Parsons, JK, McVary K, Wei JK. Diabetes and benign prostatic hyperplasia/lower urinary tract symptoms—What we do know? J Urol. 2009;182:32–7.
21. Wang HH, Hsieh CJ, Lin KJ, Chu SH, Chuang CK, Chen HW, Hsieh ML, et al. Waist circumference is a dependent risk factor for prostatic hyperplasia in Taiwanese males. Asian J Surg. 2011;34(4):163–7.
22. Vidal P, Bastardot F, Kanel R, Paccaud F, Preisig M, Waeber G, Vollenweider P. Association between circulating cytokine levels, diabetes, and insulin resistance in population-based sample (CoLaus Study). Clin Endocrinol (Oxf). 2013;78(2):232–41.