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,2 A.A. Gde Oka,4 A.A.G. Budiartaha,1 Putra Manuaba,3 Sri Maliawan6

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 Immunoassay 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 ≤ 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.

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 mito-
genenic effect that in causes degenerative diseases.
Even though there is plenty of research and publica-
tions 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 follow-
ing 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 prolif-
eration of cellular elements with clinical manifesta-
tion 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.7 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)/22.5.8 Fasting insulin is
plasma insulin concentration which is measured in
fasting condition at least 8 hours (start on evening)
before measurement.9

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 immuno-
assay technique was used after 10 minutes of
centrifugation at 1500 g. The lowest level of detec-
tion 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 chemilumines-
cence 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)

<table>
<thead>
<tr>
<th>Case ($n=40$) Mean ± SD or Median (minimum–maximum)</th>
<th>Control ($n=40$) Mean ± SD or Median (minimum–maximum)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.55 ± 6.33</td>
<td>61.68 ± 6.35</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167.93 ± 3.37</td>
<td>167.50 ± 3.49</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>92 (65–104)</td>
<td>90 (59–101)</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>32.76 (21.22–36)</td>
<td>32.08 (20.66–37.5)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>104 (90–146)</td>
<td>102 (90–126)</td>
</tr>
<tr>
<td>SBP (mm/hg)</td>
<td>132.25 ± 12.70</td>
<td>123 ± 12.23</td>
</tr>
<tr>
<td>DBP (mm/hg)</td>
<td>81.6 ± 7.34</td>
<td>76.37 ± 7.42</td>
</tr>
<tr>
<td>WBC (10$^3$/µL)</td>
<td>11.36 ± 15.12</td>
<td>10.80 ± 13.38</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.35 ± 1.60</td>
<td>14.32 ± 1.76</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>22.80 ± 5.92</td>
<td>19.91 ± 5.78</td>
</tr>
<tr>
<td>SC (mg/dl)</td>
<td>0.94 ± 0.31</td>
<td>0.97 ± 0.25</td>
</tr>
<tr>
<td>SGOT (U/L)</td>
<td>24.5 (13–66)</td>
<td>24 (13–64)</td>
</tr>
<tr>
<td>SGPT (U/L)</td>
<td>30.82 ± 10.66</td>
<td>28.16 ± 12.89</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>226.43 ± 41.52</td>
<td>208.75 ± 42.20</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>150 (107–356)</td>
<td>148.5 (67–438)</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>133.53 ± 24.16</td>
<td>123.73 ± 33.05</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>40.27 ± 8.78</td>
<td>41.53 ± 8.53</td>
</tr>
<tr>
<td>FBG (mg/dl)</td>
<td>28 (81–289)</td>
<td>29 (79–253)</td>
</tr>
<tr>
<td>2hPP blood glucose (mg/dl)</td>
<td>186 (93–345)</td>
<td>115 (89–447)</td>
</tr>
<tr>
<td>Fasting insulin (µIU/ml)</td>
<td>6.45 (2–79.2)</td>
<td>4.45 (1.1–24.7)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.88 (0.48–56.12)</td>
<td>1.19 (0.27–10.37)</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>1.45 (0.3–13.5)</td>
<td>1.00 (0.2–9.2)</td>
</tr>
<tr>
<td>IL-6 (pg/L)</td>
<td>1.07 (0.25–5.68)</td>
<td>0.71 (0.15–3.62)</td>
</tr>
</tbody>
</table>

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

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

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 median (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).

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 3 Relationship between Two-Constructs Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Regression weight</th>
<th>Standardized regression weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>WC→hsCRP</td>
<td>0.17</td>
<td>0.57</td>
</tr>
<tr>
<td>WC→IL-6</td>
<td>0.07</td>
<td>0.55</td>
</tr>
<tr>
<td>WC→HOMA-IR</td>
<td>0.27</td>
<td>0.43</td>
</tr>
<tr>
<td>hsCRP→HOMA-IR</td>
<td>0.09</td>
<td>0.04</td>
</tr>
<tr>
<td>IL-6→HOMA-IR</td>
<td>1.69</td>
<td>0.34</td>
</tr>
<tr>
<td>LP→BPH</td>
<td>0.14</td>
<td>0.21</td>
</tr>
<tr>
<td>HOMA-IR→BPH</td>
<td>0.21</td>
<td>0.03</td>
</tr>
<tr>
<td>hsCRP→BPH</td>
<td>–0.12</td>
<td>–0.64</td>
</tr>
<tr>
<td>IL-6→BPH</td>
<td>1.00</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Table 4 Relationship between Construct Variables with BPH as Dependent Variable

<table>
<thead>
<tr>
<th>Effects</th>
<th>WC→BPH</th>
<th>IL-6→BPH</th>
<th>hsCRP→BPH</th>
<th>HOMA-IR→BPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total effect</td>
<td>0.38</td>
<td>1.35</td>
<td>–0.09</td>
<td>0.21</td>
</tr>
<tr>
<td>Direct effect</td>
<td>0.19</td>
<td>1.01</td>
<td>–0.12</td>
<td>0.21</td>
</tr>
<tr>
<td>Indirect effect</td>
<td>0.13</td>
<td>0.35</td>
<td>–0.02</td>
<td>0.00</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Effects</th>
<th>WC→IL-6</th>
<th>WC→hsCRP</th>
<th>WC→HOMA-IR</th>
<th>IL-6→HOMA-IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total effect</td>
<td>0.07</td>
<td>0.17</td>
<td>0.40</td>
<td>1.67</td>
</tr>
<tr>
<td>Direct effect</td>
<td>0.07</td>
<td>0.17</td>
<td>0.27</td>
<td>1.67</td>
</tr>
<tr>
<td>Indirect effect</td>
<td>0.00</td>
<td>0.00</td>
<td>0.13</td>
<td>0.00</td>
</tr>
</tbody>
</table>

The 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 BPH, 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 TNFa.\(^10\,11\)

![Figure 1 Results derived from path analysis structural model](image-url)
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-kB (nuclear factor-kB), 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-kB and inducible nitric oxide synthase (iNOS).13 NF-kB 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-kB 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.12,13,15

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.16,18 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


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