

BODY SIZE AND SERUM LEVELS OF INSULIN AND LEPTIN IN RELATION TO THE RISK OF BENIGN PROSTATIC HYPERPLASIA

SARA E. DAHLE, ANAND P. CHOKKALINGAM, YU-TANG GAO, JIE DENG, FRANK Z. STANCZYK
AND ANN W. HSING*

From the Department of Epidemiology and Biostatistics, School of Public Health and Health Services, George Washington University, Washington, D. C., Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, Shanghai Cancer Institute, Shanghai, China, and Departments of Obstetrics and Gynecology and of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California

ABSTRACT

Purpose: Obesity has been implicated in the etiology of benign and malignant prostatic growth due to its influence on metabolic and endocrine changes. Because obesity is an important determinant of serum levels of insulin and leptin (the product of the obesity gene *Ob*), we investigated the role of obesity and serum levels of insulin and leptin in benign prostatic hyperplasia (BPH) etiology.

Materials and Methods: Fasting serum levels of insulin and leptin as well as the body mass index, a measure of overall obesity, and waist-to-hip ratio, an indicator of abdominal obesity, were determined in 200 men newly diagnosed with BPH who were hospitalized for surgery and in 302 randomly selected healthy male subjects from the population in Shanghai, China.

Results: A higher waist-to-hip ratio and higher serum insulin were significantly associated with an increased risk of BPH. Relative to men in the lowest waist-to-hip ratio quartile (less than 0.856) those in the highest quartile (greater than 0.923) were at 2.4-fold risk (odds ratio 2.42, 95% confidence interval [CI] 1.34 to 4.37, test for trend $p = 0.01$). Similarly relative to men in the lowest quartile of insulin (less than $5.87 \mu\text{U. per ml.}$) those in the highest quartile (greater than $9.76 \mu\text{U. per ml.}$) were at significantly increased risk (odds ratio 2.47, 95% CI 1.35 to 4.54, test for trend $p = 0.009$). The effect of insulin on BPH risk was more pronounced in men in low and middle tertiles of the waist-to-hip ratio (odds ratios comparing high to low insulin tertiles 2.8 and 2.7, respectively), while among men in the highest waist-to-hip ratio tertile insulin was not significantly associated with BPH risk. In contrast, we found no significant odds ratio comparing the highest to lowest quartiles of leptin (odds ratio 0.62, 95% CI 0.33 to 1.17) or body mass index (odds ratio 1.64, 95% CI 0.96 to 2.81).

Conclusions: Our results suggest that abdominal obesity and increasing serum insulin, and possibly overall obesity but not serum leptin are associated with a higher risk of BPH. Further prospective and laboratory studies are needed to confirm these results and elucidate the underlying mechanisms.

KEY WORDS: prostate, prostatic hyperplasia, insulin, leptin, obesity

Benign prostatic hyperplasia (BPH) is the most common prostate disease in older men.¹ Worldwide, approximately 55% of all men 60 to 70 years old have histological evidence of BPH and by age 85 years the prevalence is 90%.² Between 25% and 50% of those with histological BPH have clinical BPH, characterized by prostatic enlargement and/or urinary symptoms such as flow impedance and sensations of incomplete emptying.³ In the United States BPH accounts for 380,000 hospital stays,⁴ 1.7 million physician visits and 379,000 prostatectomies yearly.²

Despite the magnitude of the public health impact of BPH, little is known about its etiology. Because men who undergo castration when younger than 40 years do not have BPH,⁵ it has been suggested that androgens are involved in the development of BPH. However, the mechanism is poorly understood.

In addition to age and steroid hormones, putative risk factors for BPH include a family history of BPH, race/ethnicity, cigarette smoking, diet and obesity.² Obesity is impli-

cated because it is related to metabolic and endocrine changes and in men abdominal obesity is associated with higher serum estrogen, insulin and leptin, and lower free testosterone and sex hormone-binding globulin.⁶ A recent prospective study showed a positive association of abdominal obesity measured by waist circumference with BPH surgery.⁷ Abdominal obesity is an important determinant of insulin resistance and serum insulin since it correlates with depots of visceral (intra-abdominal) fat.⁸ Therefore, serum insulin and leptin (the product of the obesity gene *Ob*) may have a role in the development of BPH.

In earlier reports we showed that abdominal obesity, as measured by the waist-to-hip ratio, and higher serum insulin are associated with an increased risk of prostate cancer in China.^{9,10} Since prostate cancer and BPH share a similar hormonal milieu and may have common pathogenic mechanisms, in this study we examined the role of obesity, insulin and leptin in BPH.

MATERIALS AND METHODS

Study population. This study was part of a larger population based, case-control study of prostate disease in Shang-

Accepted for publication March 28, 2002.

* Requests for reprints: Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd., Room 7058 MSC 7234, Bethesda, Maryland 20892-7234.

hai, China, which has been described previously.⁹⁻¹¹ At the mandatory reporting of each incident primary prostate cancer case to 1 of the 28 collaborating hospitals in the catchment area of the Shanghai Cancer Registry between 1993 and 1995 the next patient with BPH (defined as symptomatic enlarged prostate requiring surgery) admitted to that hospital for transurethral prostate resection or prostatectomy was invited to participate in the study. Participants with BPH were permanent residents in the 10 districts of Shanghai who had no history of any cancer. Healthy men randomly selected from the 6.5 million household registration records of permanent residents of Shanghai, China were frequency matched by age to the men with prostate cancer and included in the study as population controls.

Data collection. Using a structured questionnaire trained interviewers obtained information on demographic characteristics such as age, marital status, educational attainment, personal medical history, usual adult dietary patterns, smoking history, alcohol use and body size. Men with BPH were interviewed at the hospital and controls were interviewed at home. Interviewers also gathered data on anthropometric measures, including height, weight, and the circumferences of the waist and hip. The interview response rate was greater than 95% for patients with BPH and population controls. The average time between subject identification and interview was less than 30 days. Written informed consent was obtained from all study participants. The institutional review boards at the United States National Cancer Institute, Bethesda, Maryland, and Shanghai Cancer Institute, Shanghai, China approved this study.

To minimize the influence of possible undiagnosed prostate cancer 6 patients with BPH and 4 population controls with serum prostate specific antigen (PSA) greater than 50 ng./ml. were not included in this analysis. Also, in addition to eliciting the medical history of BPH, to identify unrecognized or undetected BPH in the population controls, we performed a detailed physical examination including digital rectal examination and transrectal ultrasound, and measured serum PSA. Based on this information 23 controls (7.6%, median PSA 1.5 ng./ml.) reported a history of physician diagnosed BPH that presumably was symptomatic but did not warrant treatment, 60 (19.9%, median PSA 2.8 ng./ml.) were diagnosed with presumably asymptomatic BPH during physical examination, and an additional 27 (8.9%, median PSA 7.5 ng./ml.) had a PSA of greater than 4 ng./ml., presumably indicating slight or early BPH. These control subgroups were excluded from sequential statistical analysis to evaluate the impact of possible BPH in symptomatic and asymptomatic controls on the risk estimates.

Blood collection. A total of 206 patients with BPH (85% of those interviewed) and 330 controls (70%) provided 20 ml. overnight fasting blood for the study. Blood samples were processed within 3 hours of collection at a central laboratory in Shanghai. Serum fractions were stored at -70C before being shipped frozen to the United States on dry ice.

Laboratory methods. Frozen serum samples were received in good condition by the National Cancer Institute repository and later shipped on dry ice to a laboratory elsewhere, where laboratory personnel blinded to case-control status measured serum levels of insulin and leptin using commercially available radioimmunoassay kits. The sensitivity limits for the insulin and leptin assays were 2 μ U. per ml. and 0.5 ng./ml., respectively.¹⁰ A total of 45 split samples from a single individual were interspersed among the study samples to assess intraassay and interassay variation, of which the coefficients of variation were 4% and 6% for the insulin assay and 3.9% and 4.7%, respectively, for the leptin assay. Separately total serum PSA, plasma insulin-like growth factor-I (IGF-I), and its binding proteins IGFBP-1 and IGFBP-3 were assayed elsewhere.

Statistical analysis. We used pairwise t tests from multiple linear regression models to compare aged adjusted mean insulin and leptin in BPH cases and controls. Selected characteristics were compared in cases and controls using p values from t and Mantel-Haenszel chi-square tests. Possible correlations of select factors with insulin and leptin in controls were explored using Spearman correlations.

We used multiple logistic regression to calculate odds ratios and 95% confidence intervals (CIs) for the relationship of serum insulin and/or leptin to measures of obesity, including the body mass index in kg./m.², a measure of overall obesity, and the waist-to-hip ratio, a measure of abdominal obesity, with BPH risk after adjusting for other potential risk factors, including age, education and plasma IGF-I.^{12,13} We also constructed a series of regression models to evaluate the effect of excluding from the control group subjects with possible undetected or asymptomatic BPH. The combined effects of obesity measures with insulin or leptin on BPH risk were also assessed. For regression analysis insulin, leptin, the body mass index and the waist-to-hip ratio were categorized into quantiles based on their distributions in controls. Tests for linear trend were performed using these quantile levels as ordinal variables. All p values are 2-sided.

RESULTS

Table 1 lists the demographic and anthropometric characteristics of the 200 patients with BPH and 302 population controls. Relative to controls, men with BPH were significantly younger, had a significantly higher waist-to-hip ratio, were significantly more likely to be married and were significantly less likely to be current smokers. There was no significant difference in education, mean caloric intake, height, weight or body mass index in cases and controls.

Table 2 shows the age adjusted risks of BPH associated with quartiles of the body mass index and waist-to-hip ratio. Although increasing quartiles of body mass index were not statistically significant they were associated with BPH risk after adjustment for age alone with a 64% excess risk among men in the highest quartile relative to men in the lowest

TABLE 1. Selected characteristics of patients with BPH and population controls in China

Selected Characteristics	BPH	Control	p Value
No. pts.	200	302	
Mean age (years) \pm SD	69 \pm 6	71.9 \pm 7.0	<0.001
Mean ht. \pm SD (cm.)	167.8 \pm 5.3	167.5 \pm 5.8	0.57
Mean wt. \pm SD (kg.)	62.9 \pm 10.2	61.4 \pm 10.1	0.13
Mean body mass index \pm SD (kg./m. ²)	22.3 \pm 3.3	21.9 \pm 3.3	0.17
Mean waist circumference \pm SD (cm.)	81.8 \pm 9.4	82.5 \pm 10.7	0.44
Mean hip circumference \pm SD (cm.)	90.4 \pm 8.3	92.6 \pm 8.5	0.01
Mean waist-to-hip ratio \pm SD	0.90 \pm 0.05	0.89 \pm 0.06	<0.001
Mean total calories \pm SD (Kcal./day)	2,444 \pm 599	2,342 \pm 728	0.09
Median PSA (ng./ml.)	6.75	1.55	
No. married (%)	195 (97.5)	277 (91.7)	<0.01
No. education greater than junior middle school	118 (59.0)	154 (51)	0.08
No. smokers (%)	103 (51.5)	199 (65.9)	<0.001
No. diabetes (%)	11 (5.5)	12 (4)	0.51

TABLE 2. Odds ratios of BPH in relation to the body mass index and waist-to-hip ratio

Anthropometric Factors	No. Pts./No. Controls	Odds Ratio Adjusted for Age (95% CI)	Odds Ratio Further Adjusted for Education Anthropometric Factors (95% CI)*
Body mass index quartile (kg/m. ²):			
1 (less than 19.487)	36/67	1 (referent)	1 (referent)
2 (19.487–21.385)	49/82	1.13 (0.65–1.97)	1.05 (0.60–1.85)
3 (21.386–23.437)	48/74	1.15 (0.66–2.02)	1.09 (0.61–1.93)
4 (greater than 23.437)	67/76	1.64 (0.96–2.81)	1.50 (0.86–2.63)
p Value (test for trend)		0.06	0.13
Waist-to-hip ratio quartile:			
1 (less than 0.856)	24/74	1 (referent)	1 (referent)
2 (0.856–0.891)	56/75	2.39 (1.32–4.34)	2.25 (1.23–4.09)
3 (0.892–0.923)	61/76	2.45 (1.36–4.41)	2.27 (1.25–4.12)
4 (greater than 0.923)	59/77	2.42 (1.34–4.37)	2.04 (1.10–3.78)
p Value (test for trend)		0.01	0.06

* Multivariate model adjusted for age (continuous) and education (none, primary school, junior middle school, senior middle school, college and above college), body mass index further adjusted for waist-to-hip ratio (quartiles) and waist-to-hip ratio further adjusted for body mass index (continuous).

quartile (odds ratio 1.64, 95% CI 0.96 to 2.81). These excesses were dampened after adjusting for other anthropometric factors, such as the waist-to-hip ratio. Compared with men in the lowest waist-to-hip ratio quartile (less than 0.856), those in the upper 3 quartiles were at significant 2.4-fold risk after adjusting for age with an odds ratio of 2.42 (95% CI 1.34 to 4.37) for the highest quartile. Further adjustment for education and the body mass index did not appreciably alter the risk estimates for the waist-to-hip ratio.

Table 3 shows the Spearman coefficients of the correlations of insulin and leptin with each other and with other selected factors in the 302 population controls. There was a significant positive correlation of insulin with leptin ($r = 0.52$, $p < 0.001$). Insulin and leptin positively and significantly correlated with weight, body mass index, waist circumference, hip circumference, waist-to-hip ratio, IGF-I, IGF-II and IGFBP-3 ($p < 0.001$). Insulin and leptin negatively correlated with IGFBP-1.

Mean age adjusted serum insulin was significantly higher ($p < 0.001$) in BPH cases relative to controls (9.9 $\mu\text{U. per ml.}$, 95% CI 8.7 to 11.2 versus 7.6, 95% CI 6.7 to 8.5). Mean age adjusted serum leptin was nonsignificantly higher in cases compared with controls (3.3 ng./ml., 95% CI 2.8 to 3.7 versus 3, 95% CI 2.6 to 3.6, $p = 0.15$). Table 4 lists odds ratios and the 95% CI for the BPH risk associated with insulin and leptin levels. In the age adjusted model men in the highest quartile of insulin were at 2.5-fold increased risk for BPH (odds ratio 2.54, 95% CI 1.46 to 4.39) compared with men in the lowest quartile with a significant trend (test for trend $p =$

TABLE 3. Spearman correlation coefficients of insulin, leptin and selected other factors in 302 population controls in China

Selected Factors	Insulin	Leptin
Insulin	1	
Leptin	0.52*	1
Age	-0.12	-0.06
Ht.	0.1	-0.02
Wt.	0.3	0.33*
Body mass index (kg/m. ²)	0.28	0.37*
Waist circumference	0.42	0.58*
Hip circumference	0.37	0.55*
Waist-to-hip ratio	0.3	0.38*
Total calories	0.05	0.1
IGF-I	0.32	0.31*
IGFBP-1	-0.39	-0.49*
IGFBP-3	0.18	0.27*

All statistical tests were 2-sided.

* $p < 0.001$.

0.001). Men in the highest leptin quartile were at slightly increased risk but it was not statistically significant (odds ratio 1.29, 95% CI 0.76 to 2.17). When further adjusted for education and anthropometric factors, the odds ratio for insulin changed little. However, adjusting for these factors resulted in nonsignificant reductions in risk associated with the leptin level (odds ratio comparing highest to lowest quartile 0.62, 95% CI 0.33 to 1.17). Further adjustment for IGF-I, which is associated with BPH risk in this study population,¹³ did not materially alter the risk estimates for insulin or leptin.

To examine the effect of possible undiagnosed BPH in controls on the risk estimates for insulin and leptin we performed multiple logistic regression analysis using 3 exclusion criteria in sequence. We excluded only self-reported BPH history, self-reported BPH history and BPH detected on medical/physical examination, and self-reported BPH history, BPH detected on medical/physical examination and PSA greater than 4 ng./ml. Table 5 shows the odds ratios and CIs for insulin and leptin adjusted for age, education, body mass index and waist-to-hip ratio after excluding BPH or possible BPH diagnoses sequentially from the control group. Sequential exclusion of these groups of controls yielded risk estimates for insulin and leptin similar to those using all controls.

Table 6 shows the combined effects of the waist-to-hip ratio with insulin and leptin in regard to BPH risk for each combination of waist-to-hip ratio tertiles with insulin/leptin tertiles relative to the low waist-to-hip ratio, low insulin/leptin group. For example, men with a medium waist-to-hip ratio (0.874 to 0.909) and medium insulin (6.44 to 8.79 $\mu\text{U. per ml.}$) were at 2.7-fold risk (odds ratio 2.71, 95% CI 1.13 to 6.53) relative to men with a low waist-to-hip ratio (less than 0.874) and low insulin (less than 6.44 $\mu\text{U. per ml.}$). The increasing risk of BPH associated with higher insulin was most evident in men in the low and medium waist-to-hip ratio tertiles (odds ratio for increasing insulin tertiles 1, 1.27 and 2.77, and 0.96, 2.71 and 2.72, respectively). However, among those in the highest tertile of waist-to-hip ratio increasing insulin was not associated with increased risk (odds ratio for increasing insulin tertiles 3.08, 2.29 and 2.05). Notably no insulin associated risk was indicated since these point estimates were relative to the low tertiles of the waist-to-hip ratio and insulin. In contrast to insulin, no clear risk patterns emerged for serum leptin, although increasing levels appeared to be associated with an increased risk of BPH in men in the lowest waist-to-hip ratio tertile.

DISCUSSION

The results of this case-control study in China show that abdominal obesity (waist-to-hip ratio) and higher serum insulin were significantly associated with an increased risk of BPH, while the effect of overall obesity (body mass index) on BPH risk was borderline. There was no clear association of serum leptin with BPH risk. Our observation that the waist-to-hip ratio is associated with an increased risk of BPH in this relatively lean population (average body mass index 21 kg/m.²) is of special interest and consistent with that of a previous epidemiological study in American health professionals.⁷ In our population only 4% of study subjects were overweight (body mass index greater than 27.8 kg/m.²) versus 24% of American men.⁹ Despite the low prevalence of overall obesity about 26% of the men in our study were abdominally obese (waist-to-hip ratio greater than 0.92), compared with 60% of men in the United States.⁹ The lack of a significant body mass index association in the study may have been partly due to the limited variation in body mass index in study subjects, while the much lower insulin levels in men in this study relative to western men¹⁰ may in part reflect the lower prevalence of obesity in China. Although the

TABLE 4. Odds ratios of BPH in relation to serum insulin and leptin

	No. Pts./No. Controls	Odds Ratio Adjusted for Age (95% CI)*	Odds Ratio Further Adjusted for Education, Anthropometric Factors (95% CI)*,†	Odds Ratio Further Adjusted for IGF-I (95% CI)*,†,‡
Insulin quartile (μ U./ml.):				
1 (less than 5.87)	28/74	1 (referent)	1 (referent)	1 (referent)
2 (5.87–7.51)	44/74	1.57 (0.87–2.81)	1.67 (0.91–3.06)	1.60 (0.87–2.94)
3 (7.52–9.76)	46/76	1.40 (0.78–2.51)	1.37 (0.75–2.49)	1.23 (0.67–2.25)
4 (greater than 9.76)	80/75	2.54 (1.46–4.39)	2.47 (1.35–4.54)	2.19 (1.18–4.05)
p Value (test for trend)		0.001	0.009	0.034
Leptin quartile (ng./ml.):				
1 (less than 1.99)	42/75	1 (referent)	1 (referent)	1 (referent)
2 (1.99–2.95)	42/74	0.87 (0.50–1.51)	0.70 (0.39–1.26)	0.67 (0.37–1.21)
3 (2.96–4.99)	57/76	1.25 (0.74–2.11)	0.82 (0.46–1.46)	0.71 (0.39–1.28)
4 (greater than 4.99)	58/75	1.29 (0.76–2.17)	0.62 (0.33–1.17)	0.53 (0.28–1.01)
p Value (test for trend)		0.18	0.23	0.08

* Insulin model adjusted for leptin (continuous) and leptin model adjusted for insulin (continuous).

† Adjusted for age (continuous) and education (none, primary school, junior middle school, senior middle school, college and above college), body mass index (continuous) and waist-to-hip ratio (quartiles).

‡ Adjusted for IGF-I (continuous).

TABLE 5. Sequential odds ratios of BPH in relation to serum insulin and leptin after excluding possible patients with BPH from control group

	All Controls*,†		Excluding Only Self-Reported*,‡		Excluding Self-Reported or Medical/Physical Examination*,§		Excluding Self-Reported Medical/Physical Examination or PSA Greater Than 4 Ng./Ml.*,¶	
	No. Pts./No. Controls	Odds Ratio (95% CI)	No. Pts./No. Controls	Odds Ratio (95% CI)	No. Pts./No. Controls	Odds Ratio (95% CI)	No. Pts./No. Controls	Odds Ratio (95% CI)
Insulin quartile (μ U./ml.):								
1	28/74	1 (referent)	28/69	1 (referent)	32/54	1 (referent)	34/47	1 (referent)
2	44/74	1.67 (0.91–3.06)	44/69	1.72 (0.93–3.18)	40/54	1.39 (0.74–2.63)	39/48	1.24 (0.64–2.39)
3	46/76	1.37 (0.75–2.49)	46/69	1.43 (0.78–2.62)	47/54	1.37 (0.74–2.54)	47/47	1.29 (0.69–2.44)
4	80/75	2.47 (1.35–4.54)	80/69	2.49 (1.35–4.59)	79/55	2.24 (1.20–4.19)	78/48	2.08 (1.09–3.98)
p Value (test for trend)		0.009		0.009		0.014		0.028
Leptin quartile (ng./ml.):								
1	42/75	1 (referent)	44/69	1 (referent)	44/54	1 (referent)	44/46	1 (referent)
2	42/74	0.70 (0.39–1.26)	40/68	0.60 (0.33–1.09)	40/54	0.62 (0.33–1.16)	40/49	0.56 (0.29–1.09)
3	57/76	0.82 (0.46–1.46)	56/70	0.72 (0.40–1.30)	58/54	0.78 (0.42–1.44)	60/47	0.74 (0.39–1.42)
4	58/75	0.62 (0.33–1.17)	59/70	0.55 (0.29–1.05)	57/55	0.52 (0.27–1.03)	55/48	0.44 (0.22–0.91)
p Value (test for trend)		0.23		0.13		0.12		0.064

* Adjusted for age (continuous) and education (none, primary school, junior middle school, senior middle school, college and above college), body mass index (continuous) and waist-to-hip ratio (quartiles). Insulin model adjusted for leptin (continuous) and leptin model adjusted for insulin (continuous).

† Quartile range 1—less than 5.87, 2—5.87 to 7.51, 3—7.52 to 9.76 and 4—greater than 9.76 for insulin and 1—less than 1.99, 2—1.99 to 2.95, 3—2.96 to 4.99 and 4—greater than 4.99 for leptin.

‡ Quartile range 1—less than 5.86, 2—5.86 to 7.51, 3—7.52 to 9.76 and 4—greater than 9.76 for insulin and 1—less than 2.02, 2—2.02 to 2.95, 3—2.96 to 4.95 and 4—greater than 4.95 for leptin.

§ Quartile range 1—less than 5.96, 2—5.96 to 7.51, 3—7.52 to 9.90 and 4—greater than 9.90 for insulin and 1—less than 2.03, 2—2.03 to 2.95, 3—2.96 to 5.10 and 4—greater than 5.10 for leptin.

¶ Quartile range 1—less than 6.08, 2—6.08 to 7.52, 3—7.53 to 9.98 and 4—greater than 9.98 for insulin and 1—less than 2.02, 2—2.02 to 2.95, 3—2.96 to 5.33 and 4—greater than 5.33 for leptin.

exact mechanism linking abdominal obesity and BPH is unclear, in men abdominal obesity, which represents visceral and subcutaneous fat, is related to metabolic and endocrine effects that may influence BPH, including higher levels of free fatty acids, insulin and leptin but lower levels of free testosterone and sex hormone-binding globulin.⁶

The insulin finding is consistent with an earlier clinical study showing that the median yearly BPH growth rate increased with increasing fasting plasma insulin.¹⁴ Insulin may affect the risk of BPH through 1 of at least 3 possible pathways, namely obesity and sex hormones, sympathetic nerve activity and the IGF axis.^{1,14} Abdominal obesity alters levels of insulin and sex hormones.¹⁵ Sex hormones are involved with androgenic actions within the prostate,^{15,16} where androgens bind to the androgen receptor and activate DNA synthesis and cellular proliferation, which may then increase the risk of BPH. Insulin may influence BPH risk directly by increasing the transcription of genes involved in sex hormone metabolism and, thus, influencing androgens and estrogens, or indirectly through altered hormone metabolism as a result of obesity.¹⁷ Higher insulin is associated with lower sex hormone-binding globulin, which may in-

crease the amount of androgen/estrogen entering prostatic cells,¹⁸ thereby increasing the risk of BPH.

In our study the insulin effect was most pronounced in men in the low waist-to-hip ratio tertiles (0.909 or less), suggesting that insulin may also affect the development of BPH through a nonobesity pathway. One such pathway may involve the sympathetic nervous system. Insulin has a stimulating effect on the hypothalamic nucleus that regulates the sympathetic nervous system.¹⁹ It has been suggested that pathogenesis of BPH is related to increased sympathetic nerve activity.¹⁴ Furthermore, hyperinsulinemia increases levels of catecholamine in plasma and tissue,¹⁹ which may have a trophic effect on the growth of prostatic cells.¹⁴

The IGF axis may also be a pathway for insulin involvement in BPH. IGF-I has been shown to regulate prostate epithelial growth.²⁰ In 2 previous epidemiological studies, including this study population and a prospective study of western men, IGF-I was associated with an increasing risk of BPH, while IGF-BP-3 was associated with decreasing BPH risk.^{13,21} Because the insulin receptor shares homology with the IGF receptor, insulin can bind to and activate it, thus, activating the IGF signaling pathway and any effects the IGF

TABLE 6. Odds ratios of BPH in relation to combined tertiles of insulin/leptin and waist-to-hip ratio

	Waist-to-Hip Ratio Tertile 1 (less than 0.874)		Waist-to-Hip Ratio Tertile 2 (0.874–0.909)		Waist-to-Hip Ratio Tertile 3 (greater than 0.909)	
	No. Pts./No. Controls	Odds Ratio (95% CI)	No. Pts./No. Controls	Odds Ratio (95% CI)	No. Pts./No. Controls	Odds Ratio (95% CI)
Insulin tertile (μ U./ml.):						
1 (less than 6.44)	11/41	1 (referent)	13/37	0.96 (0.37–2.48)	19/21	3.08 (1.21–7.84)
2 (6.44–8.79)	18/41	1.27 (0.52–3.11)	24/29	2.71 (1.13–6.53)	22/30	2.29 (0.94–5.61)
3 (greater than 8.79)	20/18	2.77 (1.04–7.39)	30/30	2.72 (1.13–6.54)	41/52	2.05 (0.87–4.80)
Leptin tertile (ng./ml.):						
1 (less than 2.29)	22/54	1 (referent)	22/25	2.06 (0.93–4.59)	15/20	1.89 (0.78–4.54)
2 (2.29–4.04)	12/25	1.00 (0.41–2.45)	21/44	0.98 (0.46–2.12)	26/31	1.80 (0.84–3.87)
3 (greater than 4.04)	16/21	1.51 (0.63–3.62)	24/28	1.54 (0.69–3.42)	41/52	1.28 (0.63–2.61)

Adjusted for age (continuous), insulin model adjusted for leptin (continuous), leptin model adjusted for insulin (continuous).

axis may have on prostatic growth.²⁰ In addition, since IGF-BPs regulate IGF-I bioavailability, the inverse correlation of insulin with IGF-BP-1 and the positive correlation of insulin with IGF-I suggest that insulin may be associated with increased IGF-I bioavailability, thus, increasing BPH risk. Despite these correlations in the current investigation adjusting for IGF-I levels did not change the observed effect of insulin on BPH risk, suggesting that insulin has effects on BPH risk that are independent of the IGF axis.

It is biologically plausible that leptin may increase the risk of BPH due to its vital role in regulating body weight. We noted a nonsignificant decrease in BPH risk with leptin. The nonsignificant decreased risk associated with leptin was present in men in the lowest waist-to-hip ratio tertile but not at higher waist-to-hip ratios. The reasons for this finding are unclear. To date only 1 other study has investigated the role of leptin in relation to BPH and consistent with the findings of the current investigation no association of the leptin level and the risk of BPH in elderly men was indicated.²² The null finding for leptin may have been due in part to the high variability of leptin among individuals with a similar body mass index²³ and to the fact that the difference in observed mean leptin levels in cases and controls in this study was relatively small at 13.2%. Therefore, larger studies may be needed to observe a leptin effect.

This study has several unique strengths. Selection bias, if any, should have been minimal since controls were a random sample of the population and the procedures used to select clinically significant BPH cases for the study involved minimal exclusion and selection criteria. Furthermore, the response rate was high with most participants completing the interview and physical examination, and with blood collection in more than 70% of interviewed patients and controls. Misclassification of BPH status in controls and its effect on the risk estimates should also have been minimal since several steps, including digital rectal examination, transrectal ultrasound and PSA testing, were taken in the study to identify undiagnosed BPH in controls and on sequential analysis excluding controls with asymptomatic BPH did not alter the insulin results. Also, laboratory measurement errors were likely to be minimal because strict precautions were taken to minimize laboratory variation. The small coefficients of variation for the insulin and leptin assays (less than 6%) provide strong evidence that the assay results are reproducible. Since laboratory personnel were blinded to case-control status, any possible measurement error was likely to be nondifferential. Fasting blood samples were used in the study to measure insulin since insulin varies with food intake. Although insulin levels are highly pulsatile, since single fasting serum insulin measurements have been shown to compare well with measurements made using the hyperinsulinemic euglycemic glucose clamp (the gold standard for assessing insulin resistance), fasting insulin levels may be a useful marker for insulin resistance.²⁴

The limitations of the study should be mentioned. Because of the retrospective nature of this study, it is possible that

disease status may have caused insulin to be elevated in men with BPH if BPH influenced dietary intake or energy metabolism, which would likely have affected patient insulin. However, few patients reported dietary changes and to our knowledge there is no evidence that hyperplastic cells in the prostate gland increase insulin levels. Furthermore, since patients with BPH lost only a mean of 0.38 pounds relative to their usual adult weight, only 10 or fewer (5%) lost more than 10 pounds and another 5% gained more than 10 pounds, it is unlikely that weight loss due to BPH in these men had any material impact on the results of this study. It is also possible that, although we excluded subjects with an extremely high PSA of greater than 50 ng./ml., undiagnosed prostate cancer in patients or controls may have influenced the results. However, when 60 cases and 20 controls with even modestly elevated PSA greater than 10 ng./ml. were excluded from analysis, the risk estimates were essentially unchanged, thus, ensuring that the observed risks were in fact due to BPH and not to undiagnosed prostate cancer. In addition, although the interviewers were unaware of but not blinded to case-control status, it is unlikely that this influenced waist-to-hip ratio and body mass index results because interviewers were trained to record measurements in duplicate to specified tolerances (1 kg. for weight, and 2 cm. for height, waist and hip measurements) and body size was not a suspected risk factor for BPH at the time of the interview. Nevertheless, prospective studies are needed to confirm these results.

Few BPH risk factors have been established. Thus, it is possible that our findings may have been confounded by unidentified risk factors also related to studied exposures. In this study we controlled for age, an established BPH risk factor, as well as for several other potential confounders, such as education, anthropometric measurements and IGF-I. Adjusting for these covariates did not materially alter the risk estimates for the body mass index, the waist-to-hip ratio, insulin or leptin.

CONCLUSIONS

The results of this case-control study suggest that abdominal obesity and elevated insulin are associated with a higher risk of BPH. We did not detect an association of leptin with BPH, although leptin is closely related to insulin and obesity. With the aging of the population worldwide BPH is an increasingly important public health concern. Future studies, especially prospective epidemiological investigations, are necessary to confirm our results and elucidate further the underlying mechanisms involved.

Serum insulin and leptin were measured at the laboratory of F. Z. Stanczyk, total serum PSA was measured at Dianon Systems, Stratford, Connecticut, and IGF-I, IGF-BP-1 and IGF-BP-3 were measured at Diagnostic System Laboratory, Webster, Texas.

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