Asian Journal of Andrology (2010) 12: 400–404

www.nature.com/aja

Original Article

Relationship between insulin resistance, obesity and serum prostate-specific antigen levels in healthy men

June Hyun Han[1], Yong Taec Lee[1], Kyung Won Kwak[1], Seung Hyun Ahn[1], In Ho Chang[2], Soon Chul Myung[2], Seung Young Oh[3], Yong-Seong Lee[4], Wonyong Kim[5], Young-Woo Jin[6], Tae-In Choi[6], Sook Hee Sung[6]

[1]*Department of Urology, KEPCO Medical Foundation Hanil General Hospital, Seoul 132-703, Korea*
[2]*Department of Urology, Chung-Ang University Hospital, Seoul 140-757, Korea*
[3]*Department of Urology, Hyundae General Hospital, Namyangju 472-865, Korea*
[4]*Department of Urology, Hallym University Hangang Sacred Heart Hospital, Seoul 150-719, Korea*
[5]*Department of Microbiology, College of Medicine, Chung-Ang University, Seoul 156-756, Korea*
[6]*Radiation Health Research Institute, Korea Hydro & Nuclear Power Co., LTD, Seoul 132-703, Korea*

Abstract

The purpose of this study was to determine the relationship between insulin resistance, obesity and serum prostate-specific antigen (PSA) levels in healthy men with serum PSA level below 4 ng mL^{-1}. The men included in the study cohort were 11 827 healthy male employees of the Korea Hydro and Nuclear Power Co., LTD who had undergone medical checkups including fasting glucose, fasting insulin and serum PSA between January 2003 and December 2008. Insulin resistance was calculated by homeostasis model assessment (HOMA [fasting glucose × fasting insulin]/22.5) and quantitative insulin sensitivity check index (QUICKI; 1/[log (fasting insulin) + log (fasting glucose)]). Age-adjusted body mass index (BMI) was significantly increased according to increasing quartile of insulin resistance as determined by HOMA and QUICKI, respectively, in analysis of variance (ANOVA) test and Duncan's multiple comparison test ($P < 0.001$), but age-adjusted serum PSA concentration was significantly decreased according to increasing quartile of insulin resistance as determined by HOMA and QUICKI ($P < 0.001$). Age, BMI, insulin resistance by HOMA or QUICKI were significantly independent variables to serum PSA level in a multivariate linear regression analysis ($P < 0.001$). Insulin resistance was a significant independent variable to serum PSA level along with BMI. Insulin resistance and BMI were negatively correlated with serum PSA level in healthy men. Insulin resistance was positively correlated with BMI.

Asian Journal of Andrology (2010) 12: 400–404. doi: 10.1038/aja.2009.90; published online 22 March 2010.

Keywords: body mass index, insulin resistance, metabolic syndrome X, obesity, prostate-specific antigen

1 Introduction

Metabolic syndrome is a constellation of risk factors that is associated with cardiovascular disease and subsequent progression to type II diabetes mellitus [1, 2]. The prevalence of metabolic syndrome and type II diabetes is increasing dramatically not only in the Western but also in the Eastern world. The underlying pathological condition of metabolic syndrome is insulin resistance [3]. Early compensatory hyperinsulinemia allows maintenance of normal glucose tolerance, but as the degree of insulin resistance deteriorates, impaired glucose tolerance occurs and eventually causes diabetes [4].

Some components of metabolic syndrome or

Correspondence to: Dr Soon Chul Myung, Department of Urology, Chung-Ang University Hospital, 224-1, Heukseok Dong Dong-jak Ku, Seoul 140-757, Korea.
Fax: +82-2-6294-1406 E-mail: uromyung@cau.ac.kr
Received: 3 August 2009 Revised: 9 October 2009
Accepted: 15 December 2009 Published online: 22 March 2010

some clusters of these components were known to have an effect on serum prostate-specific antigen (PSA) concentration in healthy men [5]. Body mass index (BMI) among these components was known to influence serum PSA level the most and to be negatively correlated with serum PSA concentration [6, 7], even though there was a controversy regarding which one would affect serum PSA concentration between hemodilution according to increasing plasma volume in obese men and androgen metabolism based on aromatase and sex hormone-binding globulin [8–11]. In general, fasting blood glucose or diabetes is also known to be inversely correlated with serum PSA concentration.

If serum PSA level is adjusted by metabolic factor such as BMI, we believe that serum PSA level should be adjusted by insulin resistance rather than BMI. Insulin resistance can be easily obtained using formulas such as homeostasis model assessment (HOMA) and quantitative insulin sensitivity check index (QUICKI). First of all, insulin resistance is a more essential pathological condition to metabolic syndrome than BMI. Therefore, we hypothesized that higher insulin resistance contributes to a lower serum PSA concentration, which may lead to delayed prostate cancer diagnosis among individuals with metabolic syndrome. We investigated the relationship between insulin resistance, BMI and serum PSA level in healthy men with serum PSA level below 4 ng mL^{-1}.

2 Patients and methods

2.1 Patient selection

From January 2003 to December 2008, 34 860 healthy male employees of the Korea Hydro and Nuclear Power Co., LTD aged 22–60 years underwent a routine medical checkup. Among these men, we enrolled 11 827 healthy male employees with a serum PSA level < 4 ng mL^{-1} who underwent a fasting glucose test and a fasting insulin test.

Those with a previous diagnosis of prostate cancer, prostate cancer detected by biopsy, a history of prostate surgery, clinical symptoms of prostatitis with evidence of urinary tract infection (pyuria or bacteriuria) on urinalysis and insulin or oral hypoglycemic medication were excluded from this study. Radiation Health Research Institute of Korea Hydro & Nuclear Power Co., LTD has the database of employees' periodic medical checkup for evaluation of the effects of radiation and dosimetry. All men underwent detailed clinical examinations. Anthropometric measurements, including height, weight and BMI, were determined. Before a physician examined an individual participant, a blood sample was obtained for laboratory examination of serum PSA (Tandem-R; Hybritech, San Diego, CA, USA), fasting insulin (Immunoradiometric assay, Biosource, Nivelles, Belgium) and fasting blood sugar.

2.2 Calculation of insulin resistance

Insulin resistance was calculated by HOMA and QUICKI. The formulas for calculating the HOMA index and QUICKI are as follows: HOMA = [fasting glucose (mmol L^{-1}) × fasting insulin (μU mL^{-1})]/22.5) and QUICKI = 1/[log (fasting insulin [μU mL^{-1}]) + log (fasting glucose [mg dL^{-1}])].

2.3 Statistical analysis

SPSS version 12.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Analysis of variance (ANOVA) test and Duncan's multiple comparison test were used to assess the means of PSA and BMI stratified by increasing quartile of insulin resistance as determined by HOMA and QUICKI, respectively. Multivariate linear regression analysis was used to determine the independent contributors to serum PSA level.

3 Results

Table 1 presents the characteristics of the 11 827 individuals included in the analysis. The study cohort age was 41.58 ± 8.29 years. Serum PSA level was 0.97 ± 0.60 ng mL^{-1}, and the average of serum PSA concentration was decreased with increasing BMI category (P = 0.009). Mean ± SD of BMI was 24.03 ± 2.66 kg m^{-2}. Insulin resistance by HOMA and QUICKI was 27.29 ± 33.70 and 2.65 ± 0.32, respectively, which was increased with increasing BMI category (P < 0.001).

Age was significantly increased with increasing quartile of insulin resistance as determined by HOMA and QUICKI (P < 0.001) (Tables 2 and 3). Age-adjusted BMI was significantly increased with increasing quartile of insulin resistance as determined by HOMA and QUICKI, respectively, in ANOVA test and Duncan's multiple comparison test (P < 0.001), and age-adjusted serum PSA concentration was significantly decreased with increasing quartile of insulin resistance as determined by HOMA and QUICKI (P < 0.001) (Tables 2 and 3). Age, BMI, insulin

Table 1. Characteristics of the 11 827 individuals included in the analysis (mean ± SD).

Variable	Total	BMI (kg m^{-2})			*P*-value
		≤ 23	> 23 and < 25	≥ 25	
N (%)	11 827 (100)	4 184 (35.4)	35 96 (30.4)	4 047 (34.2)	
Age (years)	41.58 ± 8.29	40.60 ± 8.25	42.20 ± 8.25	42.05 ± 8.27	< 0.001*
PSA (ng mL^{-1})	0.97 ± 0.60	0.99 ± 0.60	0.97 ± 0.61	0.95 ± 0.60	0.009*
HOMA	27.29 ± 33.70	19.93 ± 24.53	26.24 ± 32.95	35.83 ± 40.04	< 0.001*
QUICKI	2.65 ± 0.32	2.54 ± 0.28	2.64 ± 0.30	2.77 ± 0.32	< 0.001*

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; HOMA, homeostasis model assessment; PSA, prostate-specific antigen; QUICKI, quantitative insulin sensitivity check index.
*ANOVA test.

Table 2. Comparison of age, BMI and serum PSA level according to increasing quartile of insulin resistance determined by HOMA index (mean ± SD).

Variable	Quartiles of HOMA				*P*-value
	0–25	25–50	50–75	75–100	
N	3 029	2 984	2 952	2 954	
Age (years)	40.91 ± 7.93$^{\triangleq}$	41.57 ± 8.47$^{\triangleq}$	41.64 ± 8.42$^{\triangleq}$	42.22 ± 8.29$^{\triangleq}$	< 0.001*
BMI (kg m^{-2})	22.94 ± 2.35$^{\triangleq}$	23.48 ± 2.41$^{\triangleq}$	24.34 ± 2.42$^{\triangleq}$	25.40 ± 2.77$^{\triangleq}$	< 0.001*
PSA concentration (ng mL^{-1})	0.999 ± 0.596$^{\triangleq}$	0.977 ± 0.586$^{\triangleq}$	0.969 ± 0.619$^{\triangleq}$	0.927 ± 0.608$^{\triangleq}$	< 0.001*
Age-adjusted BMI (kg m^{-2})	22.93 ± 0.21$^{\triangleq}$	23.49 ± 0.14$^{\triangleq}$	24.33 ± 0.02$^{\triangleq}$	25.38 ± 0.17$^{\triangleq}$	< 0.001*
Age-adjusted PSA (ng mL^{-1})	1.016 ± 0.048$^{\triangleq}$	0.977 ± 0.042$^{\triangleq}$	0.968 ± 0.051$^{\triangleq}$	0.937 ± 0.041$^{\triangleq}$	< 0.001*

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; HOMA, homeostasis model assessment; PSA, prostate-specific antigen.
$^{\triangleq}$Duncan's post-comparison test. *ANOVA test.

Table 3. Comparison of age, BMI and serum PSA level according to increasing quartile of insulin resistance determined by QUICKI (mean ± SD).

Variable	Quartiles of QUICKI				*P*-value
	0–25	25–50	50–75	75–100	
N	3 222	2 701	2 961	2 945	
Age (years)	40.95 ± 7.95$^{\triangleq}$	41.57 ± 8.48$^{\triangleq}$	41.64 ± 8.43$^{\triangleq}$	42.22 ± 8.28$^{\triangleq}$	< 0.001*
BMI (kg m^{-2})	22.97 ± 2.35$^{\triangleq}$	23.48 ± 2.42$^{\triangleq}$	24.35 ± 2.42$^{\triangleq}$	25.40 ± 2.77$^{\triangleq}$	< 0.001*
PSA concentration (ng mL^{-1})	0.998 ± 0.593$^{\triangleq}$	0.977 ± 0.589$^{\triangleq}$	0.968 ± 0.619$^{\triangleq}$	0.927 ± 0.609$^{\triangleq}$	< 0.001*
Age-adjusted BMI (kg m^{-2})	22.53 ± 0.06$^{\triangleq}$	23.46 ± 0.14$^{\triangleq}$	24.33 ± 0.02$^{\triangleq}$	25.42 ± 0.17$^{\triangleq}$	< 0.001*
Age-adjusted PSA (ng mL^{-1})	1.016 ± 0.048$^{\triangleq}$	0.978 ± 0.042$^{\triangleq}$	0.971 ± 0.051$^{\triangleq}$	0.934 ± 0.041$^{\triangleq}$	< 0.001*

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; PSA, prostate-specific antigen; QUICKI, quantitative insulin sensitivity check index.
$^{\triangleq}$Duncan's post-comparison test. *ANOVA test.

Table 4. Multivariate linear regression analysis to examine significant determinants to serum PSA level.

	Parameter estimate	Standard error	*P*-value		Parameter estimate	Standard error	*P*-value
Age (years)	0.005	0.001	< 0.001	Age (years)	0.005	0.001	< 0.001
BMI (kg m^{-2})	–0.007	0.002	0.002	BMI (kg m^{-2})	–0.006	0.002	0.007
HOMA	–0.0005	< 0.001	0.006	QUICKI	–0.053	0.019	0.006

Abbreviations: BMI, body mass index; HOMA, homeostasis model assessment; PSA, prostate specific antigen; QUICKI, quantitative insulin sensitivity check index.

resistance by HOMA or QUICKI were significantly independent variables to serum PSA level in multivariate linear regression analysis ($P < 0.001$) (Table 4).

4 Discussion

The underlying pathological condition of metabolic syndrome is insulin resistance. Insulin resistance can be defined as a state in which normal amounts of insulin produce a suboptimal biological response [4]. There are a number of tests used to assess the degree of insulin resistance. The hyperinsulinemic euglycemic glucose clamp technique is the 'gold standard' for quantifying insulin sensitivity *in vivo* because it directly measures the effects of insulin to promote glucose use under steady-state conditions [12]. It is based on the principle that if glucose production by the liver is suppressed by an intravenous infusion of insulin, then the amount of exogenous glucose required to maintain euglycemia provides an estimate of the insulin sensitivity of target tissues. However, it is impractical in clinical practice and is difficult to perform in epidemiological research.

HOMA was developed in 1985 and widely used to predict insulin sensitivity [13, 14]. It is a simpler test and is more appropriate for large epidemiological studies. It is a mathematical model by which values of insulin sensitivity can be calculated when simultaneous fasting plasma glucose and fasting insulin concentrations are known. It gives an estimate of basal insulin resistance, unlike other techniques that measure stimulated insulin resistance. Katz *et al*. [15] reported a new QUICKI for assessment of insulin sensitivity, which correlated better than HOMA and minimal model and clamp methods.

In our study, age was significantly increased with increasing quartile of insulin resistance as determined by HOMA and QUICKI ($P < 0.001$). Age-adjusted serum PSA concentration was significantly decreased with increasing quartile of insulin resistance by HOMA and QUICKI ($P < 0.001$). Serum PSA level was inversely correlated with insulin resistance, similar to BMI. Age-adjusted BMI was significantly increased with increasing quartile of insulin resistance by HOMA and QUICKI ($P < 0.001$). Therefore, BMI was directly proportional to insulin resistance. Insulin resistances determined by HOMA or QUICKI, and BMI were significantly independent variables to serum PSA level in multivariate analysis ($P < 0.01$).

Obesity is the most influencing factor to serum PSA concentration among the components of metabolic syndrome and it is also the most common cause of insulin resistance. Insulin resistance as determined by HOMA or QUICKI was reported to be significantly correlated with BMI [16, 17]. Insulin resistance and obesity are inversely related with sex hormone-binding globulin and total testosterone [18]. Kaplan *et al*. [19] showed that aging men with obesity and metabolic syndrome have a significant decrease in total serum testosterone levels compared with aging metabolically healthy men.

Recently, the phenomenon that total testosterone level decreases in these metabolic circumstances of men was explained by the hypogonadal–obesity–adipocytokine cycle [4]. Increasing abdominal obesity leads to increased activity of the enzyme aromatase, present in adipose tissue, which converts testosterone to estrogen, the resulting low testosterone level increases lipoprotein lipase enzyme activity and triglyceride uptake leading to increased obesity and insulin resistance. This in turn causes further androgen deficiency and visceral fat deposition. Estradiol inhibits gonadotrophin release from the pituitary. Furthermore, testosterone levels are also lowered as a result of leptin resistance at the hypothalamic–pituitary level and because of the inhibitory effect of leptin on the testicular axis. We thought that insulin resistance and BMI might influence serum PSA level through the hypogonadal–obesity–adipocytokine cycle.

This study has several limitations. First, prostate cancer was not excluded by prostate biopsy and there was no evidence that the enrolled individuals were perfectly healthy. Second, prostate volumes and serum testosterone levels were not evaluated and were not considered in the statistical analysis. Third, we did not find out which variable was superior to affect serum PSA concentration between insulin resistance and BMI, but we confirmed an inverse relationship between insulin resistance, BMI and serum PSA level in men with a low risk of prostate cancer. To our knowledge, no other studies have evaluated the direct relationship between insulin resistance and serum PSA level. Further investigation is necessary to show which metabolic factor between insulin resistance and BMI is more influential to serum PSA level and which mechanism between androgen metabolism and hemodilution is more associated with serum PSA concentration.

In conclusion, insulin resistance was a significant

independent variable to serum PSA, together with BMI. Both insulin resistance and BMI were negatively correlated with serum PSA level in healthy men. Insulin resistance was positively correlated with BMI.

Acknowledgment

This study was supported by a grant from the Korea Healthcare Technology R&D Project, Ministry for Health, Welfare & Family Affairs, Republic of Korea (A085138), which provided only financial support and has no specific scientific role in this study.

References

1 Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, *et al*. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001; 24: 683–9.
2 Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation 2005; 112: 3066–72.
3 Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988; 37: 1595–607.
4 Kapoor D, Malkin CJ, Channer KS, Jones TH. Androgens, insulin resistance and vascular disease in men. Clin Endocrinol 2005; 63: 239–50.
5 Han JH, Choi NY, Bang SH, Kwon OJ, Jin YW, *et al*. Relationship between serum prostate-specific antigen levels and components of metabolic syndrome in healthy men. Urology 2008; 72: 749–54; discussion 754–5.
6 Chang IH, Han JH, Ahn SH. Association of obesity with prostate specific antigen and prostate specific antigen velocity in healthy young men. J Urol 2008; 179: 886–90; discussion 890–1.
7 Han JH, Chang IH, Ahn SH, Kwon OJ, Bang SH, *et al*. Association between serum prostate-specific antigen level, liver function tests and lipid profile in healthy men. BJU Int 2008; 102: 1097–101.
8 Banez LL, Hamilton RJ, Partin AW, Vollmer RT, Sun L, *et al*. Obesity-related plasma hemodilution and PSA concentration among men with prostate cancer. JAMA 2007; 298: 2275–80.
9 Amatruda JM, Hochstein M, Hsu TH, Lockwood DH. Hypothalamic and pituitary dysfunction in obese males. Int J Obes 1982; 6: 183–9.
10 Pasquali R, Casimirri F, Cantobelli S, Melchionda N, Morselli Labate AM, *et al*. Effect of obesity and body fat distribution on sex hormones and insulin in men. Metabolism 1991; 40: 101–4.
11 Chang IH, Ahn SH, Han JH, Kim TH, Kim YS, *et al*. The clinical significance in healthy men of the association between obesity related plasma hemodilution and tumor marker concentration. J Urol 2009; 181: 567–72; discussion 572–3.
12 DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 1979; 237: E214–23.
13 Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, *et al*. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412–9.
14 Haffner SM, Kennedy E, Gonzalez C, Stern MP, Miettinen H. A prospective analysis of the HOMA model. The Mexico City Diabetes Study. Diabetes Care 1996; 19: 1138–41.
15 Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, *et al*. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 2000; 85: 2402–10.
16 Esteghamati A, Khalilzadeh O, Anvari M, Ahadi MS, Abbasi M, *et al*. Metabolic syndrome and insulin resistance significantly correlate with body mass index. Arch Med Res 2008; 39: 803–8.
17 Kim SH, Abbasi F, Reaven GM. Impact of degree of obesity on surrogate estimates of insulin resistance. Diabetes Care 2004; 27: 1998–2002.
18 Haffner SM, Karhapaa P, Mykkanen L, Laakso M. Insulin resistance, body fat distribution, and sex hormones in men. Diabetes 1994; 43: 212–9.
19 Kaplan SA, Meehan AG, Shah A. The age related decrease in testosterone is significantly exacerbated in obese men with the metabolic syndrome. What are the implications for the relatively high incidence of erectile dysfunction observed in these men? J Urol 2006; 176: 1524–7; discussion 1527–8.