OBESITY MODIFIES PROSTATIC SPECIFIC ANTIGEN IN MEN OVER 45 YEARS

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Summary.- OBJECTIVES: To determine whether lower serum prostate-specific antigen (PSA) concentration in obese men is caused by plasma hemodilution and/or decreased serum testosterone levels.

METHODS: A sample of 413 men, from 45 to 75 years old, were randomly selected for the study among those who participated in prostate cancer screening at 2 urban urology practices in Argentina and Puerto Rico. Weight, height, serum testosterone and total PSA concentration were determined. Body mass index (BMI), body surface, plasma volume, and PSA mass were calculated. Prostate volume was estimated by transrectal ultrasound using the prolate ellipsoid formula.

RESULTS: Mean age was 59 years old (range, 45 to 75) and mean BMI was 28.8 kg/m2 (range, 24 to 46). Mean serum PSA concentration was 1.43 ng/ml in normal weight patients (n=68), 1.4 ng/ml in overweight patients (n=222), 1.05 ng/ml in obese patients (n=114), and 0.85 ng/ml in morbidly obese patients (n=9). BMI was directly correlated with plasma volume (r= 0.687; p= 0.001) and inversely correlated with serum PSA concentration (r= -0.235; P= 0.001). PSA mass tended to be lower in obese and morbidly obese patients (P= 0.0063) compared to normal weight and overweight subjects. Serum testosterone concentration (P= 0.91) and prostate volume (P= 0.068) were similar among all BMI groups.

CONCLUSIONS: Obese men had lower serum PSA concentrations than normal weight men mainly due to plasma hemodilution. PSA mass tended to be lower in obese patients, but it is unlikely a consequence of lower serum testosterone concentrations.

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Resumen.- OBJETIVO: Determinar si las menores concentraciones séricas de antígeno prostático específico (PSA) encontradas en los sujetos obesos son consecuencia de bajos niveles de testosterona circulante y/o del mayor volumen plasmático (-VP- hemodilución). MA

MÉTODOS: Fueron seleccionados 413 individuos de sexo masculino entre 45 y 75 años. El trabajo consistió en una evaluación de la composición corporal median-

te antropometría (medición de peso y talla y cálculo del índice de masa corporal –IMC-, superficie corporal-SC- y VP), estimación de peso prostático por ecografía transrectal (ETR) y un análisis de laboratorio incluyendo dosaje de la PSA total y, en un subgrupo de pacientes (n= 108), determinación de la concentración sérica de testosterona. Se calculó la masa de PSA circulante (PSA masa). El análisis estadístico se realizó mediante Anova I y el coeficiente de correlación de Pearson (p<0.05).

RESULTADOS: La edad promedio fue de 59,08 años y la media de IMC de 28,80 kg/m2. Los sujetos con IMC entre 20-24,9 kg/m2 (n= 68) presentaron una media de PSA de 1,43 ng/ml; en los voluntarios con sobrepeso (n=222), IMC entre 25-29,9 kg/m2, la media encontrada de fue de 1,40 ng/ml; en los obesos tipo I (n=114), IMC entre 30-39,9 kg/m2, se halló una PSA media de 1,05 ng/ml y finalmente en los obesos tipo II (n= 9), IMC > 40 kg/m2 , el PSA tuvo un valor medio de 0,85 ng/ml. Un mayor IMC se asoció significativamente con un mayor VP (r= 0,687; p =0,001) y con una menor concentración sérica de PSA (r= -0,235; p= 0,001). Por su parte, el PSA masa fue menor en los pacientes obesos tipo I y II que en los voluntarios con sobrepeso y normopeso aunque estadísticamente no significativo (p<0.063). El peso prostático y los niveles de testosterona fueron similares en todos los voluntarios independientemente del estado nutricional que presentaran.

CONCLUSIÓN: La principal causa de menor concentración de PSA en sujetos obesos sería la hemodilución por mayor volumen plasmático; sin embargo, también hay una discreta reducción en la secreción de proteína PSA en estos sujetos aunque no estaría relacionada bajos niveles de testosterona.

INTRODUCTION

Cancer is one of the most important causes of morbidity and mortality in the world, and specifically, prostate cancer is the second leading cause of cancer death in men over 50 years old (1). The dramatic increase in the incidence of prostate cancer in the last two decades constitutes one of the main challenges to public health (1). Early prostate cancer detection allows a wider spectrum of treatment options to decrease morbidity and improve survival rates.

Serum PSA concentration is currently the most reliable tumor marker for prostate cancer available to urologists. Despite its low predictive value, it is still, along with digital rectal examination, the mainstay of prostate cancer screening worldwide. Its sensitivity and specificity are enhanced by determination of PSA variants and molecular tests (hypermethylated genes, PCA 3, etc.).

Serum PSA concentration may vary in response to multiple factors. Prostatic manipulation (prostatic massage and biopsy), urethral instrumentation, exercise, immediately post-ejaculation, antiandrogen medications and 5-alpha reductase inhibitors, prostatic inflammation, benign prostatic hyperplasia with or without urinary retention, and prostate cancer, all induce significant variations in serum PSA concentration. However, the effect of male obesity on early prostate cancer detection by serum PSA concentration is currently one of the greatest challenges to urologists.

The incidence of obesity, defined as the excess of energy accumulated in the form of fat, has reached epidemic levels, negatively impacting public health and increasing health care costs. Early prostate cancer detection may be hindered in obese men due to technically difficult physical examination and imaging of the prostate (2) as well as a lower serum PSA concentration due to plasma hemodilution compared to normal weight men. Therefore, the most common indication for prostate biopsy, namely serum PSA concentration >4ng/ml in men over 50 years of age (3), may lead to delayed prostate cancer detection in obese (BMI > 30kg/m2) men (4). Excess adipose tissue stores are associated with overexpression of P450 aromatase, which peripherally converts androgens into estrogen, thus decreasing serum concentrations of androgens. Since the expression of PSA is mainly induced by androgens and regulated by the androgen receptor at the transcriptional level (5), this may be another reason for delaying the diagnosis of prostate cancer (6,7) in obese men.

The purpose of this study was to determine whether lower serum PSA concentrations in obese men participating in prostate cancer screening are due to plasma hemodilution and/or decreased serum testosterone.

EXPERIMENTAL METHODS

Population

We randomly invited to participate in the study 413 men, ages 45 to 75 years old, selected among those who participated in prostate cancer screening at several urban urology practices in Argentina and Puerto Rico, including the Área Urología, Facultad

de Ciencias Médicas at the Universidad Nacional de Cuyo in Mendoza, Argentina, the Departamento de Urología at the Hospital San Lucas in Guayama, Puerto Rico, the Laboratorio de Enfermedades Metabólicas y Cáncer, Facultad de Farmacia y Bioquímica at the Universidad Juan Agustín Maza in Mendoza, Argentina, and the Laboratorio de Alta Complejidad Pérez Elizalde in Mendoza, Argentina. Following approval of the study design by the Ethics Committee of the Argentinian Medical Federation and the Hospital San Lucas de Guayama IRB, participants gave informed consent for inclusion in the study. Inclusion and exclusion criteria for enrolling men in the study are listed in Table I.

Laboratory tests calculated clinical variables, and anthropometric parameters.

Patient weight, height, and serum total PSA concentration were determined in all men. Serum total PSA concentration was determined in ng/ml by microparticle enzyme immunoassay method using the Abbott IMX™ system (Abbott Laboratories, Abbott Park, IL). Serum testosterone concentration was determined in ng/ml by the electrochemoluminescence immunoassay method using the Siemens Advia Centaur™ system (Siemens Healthcare Diagnostics, Deerfiled, IL) in a group of 108 men at the Hospital San Lucas in Guayama. BMI, body surface, plasma volume, and PSA mass (a measure of total PSA independent of plasma volume) were calculated using the formulae depicted in Table II.

According to their BMI, patients were divided into normal weight (BMI 20 to 24.9 kg/m^2), overweight (BMI 25 to 29.9 kg/m^2), obese (BMI 30 to 39.9 kg/m^2), and morbidly obese groups (BMI ≥ 40 kg/m^2). Prostate gland volume was calculated with the prolate ellipsoid formula using a 6.5 MHz. biplanar endorectal transducer in all patients.

Statistical analysis

The association of BMI with serum PSA concentration, plasma volume, and serum testosterone concentration was assessed using the Pearson and Spearman correlation coefficients based on the normality of the variables as established by the Kolmogorov-Smirnov test. Comparisons between groups were made using the ANOVA I test and the level of significance was determined at $P < 0.05$.

RESULTS

Participants age, weight, height, BMI and body surface area in the four groups are listed in Table III. Mean age was 59 years old (range, 45 to 75 years old) and mean BMI was 28.8 kg/m^2 (range, 24 to 46 kg/m^2). Mean serum PSA concentration significantly varied among BMI groups, from the highest in normal weight men to the lowest in morbidly obese men (P=0.002). Mean serum PSA concentration was 1.43 ± 0.12 ng/ml in normal weight patients (BMI 20 to 24.9 kg/m^2; n=68), 1.4 ± 0.06 ng/ml in overweight patients (BMI 25 to 29.9 kg/m^2; n=222), 1.05 ± 0.07 ng/ml in obese patients (BMI 30 to 39.9 kg/m^2; n=114), and 0.85 ± 0.22 ng/ml in morbidly obese patients (BMI ≥ 40 kg/m^2; n=9). The age of four groups were similar (p=0.40)

TABLE I. PARTICIPANT INCLUSION AND EXCLUSION CRITERIA.

Inclusion Criteria	Exclusion Criteria
- -Age 45 to 75 years	- History of HGPIN, ASAP, or Cancer on prostate biopsy
- No prostate, endocrine, or metabolic disease	- Persistent serum PSA 4-10ng/ml and more than 1 negative prostate biopsy
- Not on medication/s known to alter serum PSA	- Family history of prostate cancer
- Less than ± 3kg variation in body weight within the last 3 months	- Participation in another research study or nutritional intervention within the last 3 months

Abbreviations: HGPIN: high grade prostatic intraepithelial neoplasia; ASAP: atypical small acinar proliferation.

Plasma volume was also significantly different among BMI groups, from the smallest in normal weight men to the largest in morbidly obese men (P=0.001) (Figure 1). PSA mass tended to be lower in obese and morbidly obese patients (P= 0.0063) compared to normal weight and overweight patients. Serum testosterone concentration (P= 0.91) and prostate volume (P= 0.068) were similar among BMI groups (Table IV).

BMI was directly correlated with plasma volume (r= 0.687; P= 0.001) and inversely correlated with serum PSA concentration (r= -0.235; p= 0.001) (Figure 2). Serum testosterone concentration did not correlate with serum PSA concentration (r= -0.106; P=0.276) or PSA mass (r= -0.095; P= 0.328).

DISCUSSION

Even though some epidemiologic (8,11) studies have indicated a direct relationship between obesity and prostate cancer, a direct cause-effect relationship between the two could not be conclusively demonstrated by others (12). However, obese men do suffer from higher cancer recurrence rates (13) and mortality (7,14,15) following treatment of prostate cancer compared to normal weight men. The difficulty associating obesity to prostate cancer may arise from the fact that obesity may promote development or hasten progression of prostate cancer at multiple levels (7,16-18). Lower sex hormone-binding globulin in obese patients may increase the fraction of biologically active testosterone (11,19). Elevated serum insulin and IGF-1 concentrations in obese may facilitate progression of prostate cancer (11,19). Leptin, a hormone with mutagenic activity, is also elevated in obese men (20).

Additionally, technically difficult physical examination and prostate imaging along with hemodiluted serum PSA concentration in obese men may hinder early diagnosis of prostate cancer (11). The American Urological Association (21) and European Urological Association (22) guidelines as well as Consenso Nacional Interdisciplinario de Argentina 3 recommend prostate biopsy in men with serum PSA concentration > 4ng/ml and/or abnormal digital rectal examination.

PSA is a serine protease of the kallikrein family that cleaves seminogelin in the seminal fluid leading to liquefaction of the semen. It is produced by epithelial cells lining prostatic tubules and acini. PSA half-life is 3 days and its serum concentration varies 7 to 12% daily (1). Prostatic manipulation (prostatic massage and biopsy), urethral instrumentation, exercise, immediate post-ejaculation period, antiandrogen medications and 5-alpha reductase inhibitors, and prostatic inflammation, all induce significant variations in serum PSA concentration. Currently, several reports suggest that excess in body fat influences serum PSA concentration (12,16).

In our study, serum PSA concentration in obese men was significantly lower than that of normal weight men and was inversely correlated with increasing BMI and plasma volume. These results are in agreement with that of other reports showing a 10 to 32% lower serum PSA level in men with BMI > 30kg/m^2 (17,18). Importantly, serum testosterone concentration was similar in all BMI groups and did not correlate with serum PSA concentration or PSA mass, suggesting that the lower serum PSA in obese patients was mainly due to plasma hemodilution, reproducing conclusions from other reports (2,23). In contraposition to other reports (2,17,18), we observed a trend of lowering PSA mass

TABLE II. FORMULAE USED TO DETERMINE BMI, BODY SURFACE, PLASMA VOLUME, AND PSA.

Parameter	Formula
BMI (kg/m2)	body weight (kg)/ height (m)2
BSA (DuBois) (m2)	body weight (kg) 0.425 x height (cm) 0.725 x 0.007184
Plasma volume (l)	body surface area x 1,67
PSA mass (µg)	Serum PSA (ng/ml) x plasma volume (l)

Abbreviations: BMI: body mass index; BSA: body surface area; PSA: prostate-specific antigen.

TABLE III. PARTICIPANTS AGE AND ANTHROPOMETRIC DATA (N=413).

	Normal weight		Overweight		Obese		Morbidly obese	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Age (years)	60.1	1.2	59.3	0.6	58.2	0.8	55.3	1.1
Weight (kg)	75.2	0.8	84	0.4	100.8	0.9	137.2	5.3
Height (cm)	177	0.8	174.5	0.4	175.1	0.6	175.3	3.0
BMI (kg/m²)	23.9	0.1	27.5	0.1	32.8	0.2	44.7	1.7
BSA(m²)	1.92	0.02	1.99	0.01	2.16	0.01	2.46	0.06

Abbreviations: BMI: body mass index; BSA: body surface area

with increasing BMI may indicate a downregulation of PSA secretion, not explained by serum testosterone level. Determinations of serum androgens other than testosterone, intraprostatic androgen concentration, and serum adipokines in future investigations may help elucidate the reason/s for lower serum PSA concentration in obese men.

CONCLUSION

Plasma hemodilution appears to be the main reason for the observed lower serum PSA concentration in obese men compared to their normal weight counterparts. Serum testosterone concentration did not explain lower serum PSA in obese men.
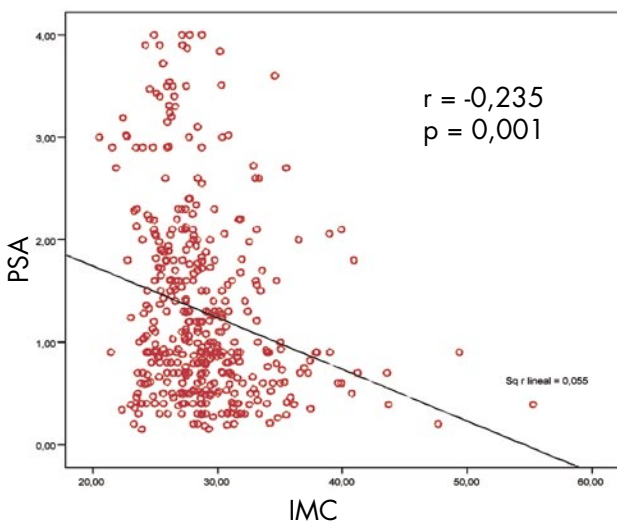

r = -0,235
p = 0,001

Sq r lineal = 0,055

FIGURE 1. Correlation between serum PSA
concentration and BMI.

r= 0,687
p= 0,001
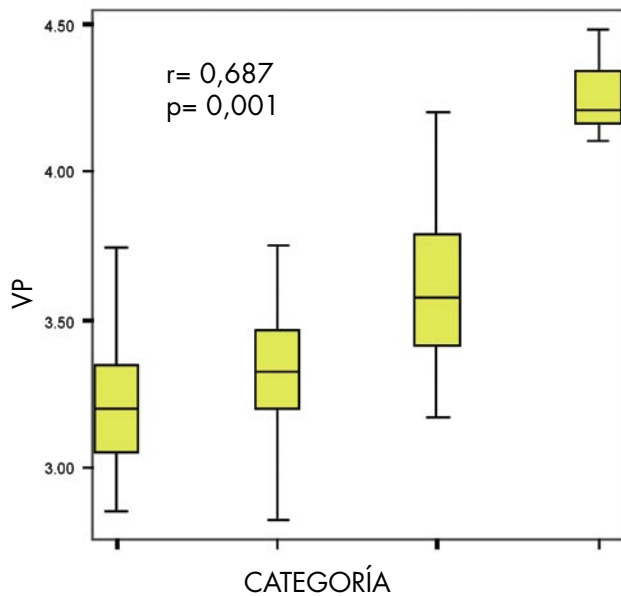
FIGURE 2. Plasma volume according to BMI.

TABLE IV. PLASMA VOLUME, SERUM TESTOSTERONE, PSA MASS, AND PROSTATE VOLUME ACCORDING TO BMI GROUPS.

	BMI								P value
	Normal weight		Overweight		Obese		Morbidly obese		
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	
Plasma Volume (l)	3.2	0.03	3.3	0.01	3.6	0.02	4.1	0.1	0.0001
Serum testosterone (ng/ml)	2.6	0.6	2.7	0.2	2.5	0.2	2.9	0.8	0.913
PSA mass (µg)	4.5	0.3	4.6	0.2	3.7	0.2	3.4	0.8	0.063
Prostate volume (cc)	32.1	4.3	47.9	5.2	32.3	4.0	46.2	2.1	0.068

Abbreviations: BMI: body mass index; BSA: body surface area

REFERENCES AND RECOMMENDED READINGS (*of special interest, **of outstanding interest)

1. López Laur JD. Manual de Urología Moderna. Editorial Atlante, 2005.
**2. Bañez LL, Hamilton RJ, Partin AW, Sun L, Rodriguez C, Wang Y et al. Obesity-related plasma hemodilution and PSA concentration among men with prostate cancer. JAMA 2007, 298:2275-2280.
3. Consenso Nacional Inter-Sociedades sobre pautas para el Diagnóstico y Tratamiento de Cáncer de Próstata. Ministerio de Salud y Ambiente de la Nación. 2008.
4. World Health Organization. 1998. Obesity. Preventing and Managing the global epidemia. Report no 794. WHO, Geneva.
5. López Laur JD, Pérez Elizalde RF, Di Milta N, Maselli ME, Vanrel MC, Recalde GM et al. Effect of hemodilution on prostatic specific antigen in obese men. J Urol 2009, 181: S652. #1806.
6. Physical status: the use and interpretation of anthropometry: report of a WHO Expert Committee. World Health Organ Teach Rep Ser. 1995, 854:1-452.
7. Das UN. Is obesity an inflammatory condition? Nutrition 2001, 17:953-966.

*8. Hsing AW, Sakoda LC, Chua S Jr. Obesity, metabolic syndrome, and prostate cancer. Am J Clin Nutr 2007, 86:s843-57.
9. Freedland SJ, Platz EA. Obesity and prostate cancer: making sense out of apparently conflicting data. Epidemiol Rev 2007, 29: 88-97.
**10. Mistry T, Digby J, Desai K, Randeva H. Obesity and Prostate Cancer: A role for Adipokines. European Association of Urology 2007, 52: 46-53.
*11. López Fontana C, Di Milta N, Maselli ME, Recalde GM, Vanrell MC, Pérez Elizalde R et al. The rol of leptin and adiponectin on prostate cancer. Arch Esp Urol 2009, 62 (2):103-8.
12. Han JH, Choi NY, Bang SH, Kwon OJ, Jin YW, Myung SC et al. Relationship Between Serum Protate-Specific Antigen Levels and Components of Metabolic Syndrome and Healthy Men. Urology 2008, 72(4):749-54.
*13. Freedland SJ, Sun L, Kane CJ, Presti JC, Terris MK, Amling CL et al. Obesity and Oncological outcome after radical prostatectomy: impact of prostate-specific antigen-based prostate cancer screening: results from the Shared Equal Access Regional Cancer Hospital and Duke Prostate Cen-

ter Databases. BJU Int 2008, 102:969-74.

*14. Price MM, Hamilton RJ, Robertson CN, Butts MC, Freedland SJ. Body mass index, prostate-specific antigen and digital rectal examination findings among participants in a prostate cancer screening clinic. Urology 2008, 71:787-91.

15. Freedland SJ, Terris MK, Presti JC Jr, Amling CL, Kane CJ, Trock B et al. Search Database Study Group. Obesity and biochemical outcome following radical prostatectomy for organ confined disease with negative surgical margins. J Urol 2004, 172:520-4.

16. Larré S, Azzouzi AR, Cancel-Tassin G, Cormier L, Villette JM, Hoffman P et al. Impact of obesity on PSA in prostate cancer screening. Prog Urol. 2007, 17:815-8.

**17. Baillargeon J, Polloxk BH, Kristal AR, Bradshaw P, Hernandez J, Basler J et al. The association of body mass index and prostate-specific antigen in a population-based study. Cancer 2005, 103:1092-5.

18. Werny DM, Thompson T, Saraiya M, Freedman D, Kottiri BJ, German RR et al. Obesity is negatively associated with prostate-specific antigen in U.S. men, 2001-2004. Cancer Epidemiol Biomarkers Prev. 2007, 16:70-6.

19. Goldstraw MA, Besrani D, Amoroso P, Kirby RS. Is obesity a risk factor for prostate cancer?. BJU int 2007; 726-728.

20. Frankenberry KA, Somasundar P, Mc Fadden DW, Vona-Davis LC. Leptin induces cell migration and the expression of growth factors in human prostate cancer cells. Am J Surg 2004;188:560-5.

21. Carroll P, Albertsen P, Greene K, Barbaian R. PSA best practice statment 2009: Update. AUA Guidelines.

22. Heidenreich A, Bolla M, Jovian S. Guidelines on prostate cancer. EAU editions: 1-138. 2009.

**23. Ohwaki K, Endo F, Muraishi O, Hiramatsu S, Yano E. Relationship between Prostate-specific antigen and Hematocrit: Does hemodilution lead to lower PSA concentrations in men with a higher body mass index? Urology 2010, 75:648-52.