OBESITY MODIFIES PROSTATIC SPECIFIC ANTIGEN IN MEN OVER 45 YEARS

Constanza Lopez Fontana1, Maria Eugenia Maselli1, Rafael Perez Elizalde1,2, Nicolas Di Milta1, Pablo Corica Alberto3 and Jose Daniel Lopez Laur1,4.

2Laboratorio de Alta Complejidad Pérez Elizalde. Mendoza. Argentina. 

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-

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.

Keywords: Obesity. Body mass index. Prostate-specific antigen. Plasma hemodilution. Prostate cancer screening.

Constance López Fontana
Laboratorio de Enfermedades Metabólicas y Cáncer.
Universidad Juan Agustín Maza.
Acceso Este Lateral Sur 2256
Guaymallén, Mendoza. CP 5519
cotyman7@yahoo.com
Accepted for publication: October 21st, 2010
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 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/m²), overweight (BMI 25 to 29.9 kg/m²), obese (BMI 30 to 39.9 kg/m²), and morbidly obese groups (BMI ≥ 40 kg/m²). 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/m² (range, 24 to 46 kg/m²). 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/m²; n=68), 1.4 ± 0.06 ng/ml in overweight patients (BMI 25 to 29.9 kg/m²; n=222), 1.05 ± 0.07 ng/ml in obese patients (BMI 30 to 39.9 kg/m²; n=114), and 0.85 ± 0.22 ng/ml in morbidly obese patients (BMI ≥ 40 kg/m²; n=9). The age of four groups were similar (p=0.40)

### Table I. Participant Inclusion and Exclusion Criteria.

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

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>
<thead>
<tr>
<th>Parameter</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m2)</td>
<td>body weight (kg)/ height (m$^2$)</td>
</tr>
<tr>
<td>BSA (DuBois) (m2)</td>
<td>body weight (kg) $0.425 \times$ height (cm) $0.725 \times 0.007184$</td>
</tr>
<tr>
<td>Plasma volume (l)</td>
<td>body surface area $\times 1.67$</td>
</tr>
<tr>
<td>PSA mass (µg)</td>
<td>Serum PSA (ng/ml) $\times$ plasma volume (l)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI: body mass index; BSA: body surface area; PSA: prostate-specific antigen.
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.
## TABLE IV. PLASMA VOLUME, SERUM TESTOSTERONE, PSA MASS, AND PROSTATE VOLUME ACCORDING TO BMI GROUPS.

<table>
<thead>
<tr>
<th>BMI</th>
<th>Normal weight</th>
<th>Overweight</th>
<th>Obese</th>
<th>Morbidly obese</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SE</td>
<td>Mean</td>
<td>SE</td>
</tr>
<tr>
<td>Plasma Volume (l)</td>
<td>3.2</td>
<td>0.03</td>
<td>3.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Serum testosterone (ng/ml)</td>
<td>2.6</td>
<td>0.6</td>
<td>2.7</td>
<td>0.2</td>
</tr>
<tr>
<td>PSA mass (µg)</td>
<td>4.5</td>
<td>0.3</td>
<td>4.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Prostate volume (cc)</td>
<td>32.1</td>
<td>4.3</td>
<td>47.9</td>
<td>5.2</td>
</tr>
</tbody>
</table>

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

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


41


