The illusion of prostate-specific antigen decline in patients with metabolic syndrome and insulin resistance

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What’s known on the subject? and What does the study add?
Studies have shown that PSA is negatively associated with obesity as a result of hemodilution or metabolic effect. Hemodilution could be the main reason for low PSA levels in obese men. However, the intrinsic metabolic effects such as insulin resistance (IR) or metabolic syndrome (MS) on PSA level have not been clearly evaluated although obesity is closely tied to MS and IR.

We regarded MS and IR as the pathophysiological cornerstone of metabolic disorder in obesity and analyzed the relationships among MS, IR, and PSA levels, and plasma volume by using the concept of PSA mass, the total circulating PSA protein. PSA mass did not change depending on the severity of the obesity, MS or IR. Even the group with both MS and IR, which could be the most metabolically disturbed in this study, did not have different PSA mass, comparing with the group without any MS or IR. Thus, the decline in PSA level in men with MS or IR can be also explained by increased plasma volume other than any intrinsic metabolic effects.

OBJECTIVE
• To investigate the detailed mechanism of prostate-specific antigen (PSA) decline in metabolic syndrome (MS) and insulin resistance (IR), which lowers the predictive value of the PSA test, we examined the effect of haemodilution and the possibility of an intrinsic metabolic effect.

PATIENTS AND METHODS
• We analysed 28,315 men who underwent routine check-ups. We compared the age-adjusted mean PSA levels in subjects with and without MS before and after adjusting or stratifying the plasma volume. We analysed changes in PSA level, plasma volume and PSA mass according to obesity grade, number of MS components, IR severity and diagnosis of MS, IR or both using an analysis of covariance.

RESULTS
• The PSA levels were lower in the group with MS than in the group without MS (P = 0.001), but this difference disappeared after adjusting or stratifying the plasma volume (P > 0.05 for all). The PSA levels decreased, plasma volume increased, and PSA mass did not change as the number of MS components increased (P = 0.002, P < 0.001, P = 0.55, respectively) or the IR severity increased (P = 0.001, P < 0.001, P = 0.34, respectively).
• Similarly, PSA levels were lower, plasma volumes were higher and PSA masses were the same in subjects with MS (P = 0.002, P < 0.001, P = 0.10, respectively), IR (P = 0.018, P < 0.001, P = 0.94, respectively), or both (P = 0.003, P < 0.001, P = 0.86, respectively) than in subjects without those conditions.

CONCLUSION
• The PSA decline in MS and IR may result simply from a haemodilution effect and be unrelated to intrinsic metabolic disturbances. For this reason, PSA levels could be underestimated in patients with MS or IR because of haemodilution.

KEYWORDS
prostate-specific antigen, metabolic syndrome, insulin resistance

INTRODUCTION
Metabolic syndrome (MS) and insulin resistance (IR), which is the pathophysiological cornerstone of metabolic disorder, are related to the metabolic disturbance of several organs, [1,2] and studies have reported that the regulation of PSA level and prostate volume is associated with metabolic or hormonal disturbance [3–8]. Secondary hyperinsulinaemia, a result of IR, leads to hormonal changes such as a decrease of sex-hormone-binding globulin, testosterone, or free testosterone and an increase of aromatase [9,10]. These hormonal changes and other metabolic disturbances in MS and IR could affect PSA levels [7,8,11] but a detailed mechanism for this has not yet been elucidated.

Levels of PSA are negatively associated with body mass index (BMI), primarily as a result of a haemodilution effect caused by increased plasma volume [12,13]. Because an increase in
BMI is closely tied to MS and IR, the decline in PSA levels in men with MS or IR could also result from a haemodilution effect. However, the potential metabolic effects of MS and IR on PSA level should also be assessed in detail. Metabolic syndrome comprises many metabolic abnormalities and not all men with MS or IR are obese, although obesity is the most common cause of MS or IR [1,2,7].

Most studies have shown that PSA levels are low in patients with MS or IR [5–7], and so these conditions could affect the validity of PSA tests in prostate cancer screening [14]. If we could clarify the mechanism of PSA decline then the predictive value of the PSA test could be improved for people with MS or IR. We tried to examine the haemodilution effect, as well as the possibility of an intrinsic metabolic effect on PSA in MS or IR.

SUBJECTS AND METHODS

Our study group included 35 229 Korean men with available PSA data who underwent routine health check-ups at the Healthcare System Gangnam Centre of Seoul National University Hospital, Korea, from September 2003 to April 2010. Because some of these participants underwent health check-ups several times, we excluded data other than the initial screening data from men who underwent two or more check-ups. Then, we excluded 5967 men for whom data were missing regarding age, height, weight, waist circumference, blood pressure, fasting blood glucose, triglyceride, high-density lipoprotein cholesterol, or medication history. PSA, prostate-specific antigen; TRUS, transrectal ultrasound; MS, metabolic syndrome; IR, insulin resistance.

Before the study, written informed consent was obtained from all participants, and the institutional review board approved all procedures. Medications and clinical conditions such as diabetes mellitus, hypertension, dyslipidaemia and prostate-related medication problems were self-reported on a printed form, and a family physician performed an interview about current medications and disease status.

The clinical variables of height, weight, waist circumference and blood pressure were measured directly. Blood was drawn for measurement of serum glucose, triglyceride, high-density lipoprotein, insulin and PSA levels in the morning after participants had fasted for at least 12 h. The BMI was calculated as the weight in kilograms divided by the square of the height in metres (kg/m²) and was classified according to the Asian obesity criteria recommended by the World Health Organization’s Regional Office for the Western Pacific [15].

The definition of MS was based on the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria of the American Heart Association and the National Heart, Lung, and Blood Institute [16]. Metabolic syndrome was diagnosed if any three of the following five components were present: elevated waist circumference (≥90 cm), elevated triglyceride level (≥150 mg/dL or drug treatment for elevated triglyceride), reduced high-density lipoprotein level (<40 mg/dL or drug treatment for reduced high-density lipoprotein), elevated blood pressure (systolic pressure ≥130 mmHg, diastolic pressure ≥85 mmHg, or antihypertensive drug treatment in a patient with a history of hypertension), and elevated fasting blood glucose level (≥100 mg/dL or drug treatment for elevated glucose).

The homeostasis model assessment of insulin resistance (HOMA IR) index was calculated using the HOMA algorithm [17]: glucose (mg/dL) × insulin (μU/mL) / 405.
dL) × insulin (μU/mL)/405. The threshold value of IR was defined as 2.56 on the basis of a study on Korean men [18]. The PSA mass (in μg) was defined as the total amount of PSA protein in the circulation [13]. Body surface area, plasma volume, and PSA mass were estimated using the following formulae [19,20]:

\[
\text{Body surface area (m}^2) = \text{body weight (kg)}^{0.425} \times \text{height (m)}^{0.725} \times 0.007184
\]

\[
\text{Plasma volume (L)} = \text{body surface area (m}^2) \times 1.670
\]

\[
\text{PSA mass (μg)} = \text{PSA level (ng/mL)} \times \text{plasma volume (L)}.
\]

To examine the relationships among PSA, plasma volume and MS, we used an analysis of covariance to analyse the differences in PSA levels between two groups, with and without MS, after adjusting for age and plasma volume. We also stratified the plasma volume into quartiles and compared PSA differences between two groups within each quartile. For further evaluation of the haemodilution or metabolic effects on PSA levels, we analysed changes in PSA level, plasma volume and PSA mass according to obesity grade, number of MS components (representing MS severity), HOMA IR index quartile (representing IR severity), presence of MS and presence of IR by using an analysis of covariance for the adjusted mean. Finally, we examined changes in PSA level, plasma volume and PSA mass in subjects with both MS and IR compared with the subjects without any MS or IR, the subjects with only IR, and the subjects with only MS, using an analysis of covariance. We performed all statistical analysis with the stata software, version 10.1 (StataCorp, College Station, TX, USA), with two-sided \( P < 0.05 \) considered statistically significant.

## Results

Table 1 shows the general characteristics of the study population. In the total population, the prevalence of obesity and MS were 41.5% (11 758/28 315) and 31.7% (8985/28 315), respectively. In the sample used for analysis of both MS and IR, the prevalence of obesity, MS and IR was 43.0% (4681/10 874), 33.7% (3666/10 874) and 31.0% (3367/10 874), respectively. Ninety-eight percent of the study population had ≤9 ng/mL PSA, which is the general threshold in PSA screening.

The age-adjusted mean PSA level was lower in the group with MS than in the group without MS (\( P = 0.001 \)), but there were no significant differences between the two groups after adjustment for plasma volume (\( P = 0.10 \)). Similarly, there were no significant differences in the age-adjusted mean PSA levels between the two groups within each quartile of plasma volume (Table 2).

The PSA level decreased significantly, plasma volume increased significantly, but PSA mass did not change as the number of MS components present increased (\( P = 0.002, P < 0.001, P = 0.55 \), respectively) or the HOMA IR index increased (\( P = 0.001, P < 0.001, P = 0.34 \), respectively). Similarly, PSA levels were lower, plasma volumes were higher and PSA masses were the same for subjects with MS compared with subjects without MS (\( P = 0.002, P < 0.001, P = 0.10 \)) and for subjects with IR compared with subjects without IR (\( P = 0.018, P < 0.001, P = 0.94 \), respectively; Table 3). Results were the same when the PSA level, plasma volume, and PSA mass values were compared with respect to obesity grade (\( P < 0.001, P < 0.001, P = 0.10 \), respectively; data not shown). When we examined changes in PSA level, plasma volume and PSA mass in subjects with and without a combination of MS and IR, the results remained the same (\( P = 0.003, P < 0.001, P = 0.86 \), respectively; Fig. 2).

| TABLE 1 Baseline characteristics (n = 28 315) |
|-----------------------------------------------|
| Mean ± SD or Number (%)                        |
| Total (n = 28 315)                             |
| Group without MS (n = 19 330)                  |
| Group with MS (n = 8985)                       |
| Age (year) (%)                                  |
| 50.6 ± 10.1                                   |
| 50.6 ± 10.1                                   |
| 52.2 ± 10.2                                   |
| PSA (ng/mL) (%)                                |
| 1.107 ± 0.928                                 |
| 1.104 ± 0.903                                 |
| 1.112 ± 0.978                                 |
| PSA mass (μg) (%)                              |
| 3.350 ± 2.771                                 |
| 3.296 ± 2.660                                 |
| 3.469 ± 2.991                                 |
| Height (cm) (%)                                |
| 170.1 ± 5.8                                  |
| 170.0 ± 5.8                                  |
| 170.4 ± 5.7                                  |
| Weight (kg) (%)                                |
| 71.2 ± 9.4                                   |
| 68.9 ± 8.4                                   |
| 76.4 ± 9.4                                   |
| BMI (kg/m²) (%)                                |
| 24.6 ± 2.7                                   |
| 23.8 ± 2.4                                   |
| 26.3 ± 2.6                                   |
| Normal (<23.0) (%)                            |
| 7 763 (27.4)                                  |
| 7003 (36.2)                                  |
| 760 (8.5)                                    |
| Overweight (23.0–24.9) (%)                   |
| 8 794 (31.1)                                  |
| 6719 (34.8)                                  |
| 2 075 (23.1)                                 |
| Obesity (25.0–29.9) (%)                      |
| 10 902 (38.5)                                 |
| 5419 (28.0)                                  |
| 5 483 (61.0)                                 |
| Severe obesity (≥30.0) (%)                   |
| 856 (3.0)                                    |
| 189 (1.0)                                    |
| 667 (7.4)                                    |
| Plasma volume (mL)                            |
| 3042.3 ± 218.9                               |
| 2997.6 ± 205.1                               |
| 3138.6 ± 216.6                               |
| Waist circumference (cm) (%)                 |
| 87.7 ± 7.3                                   |
| 85.4 ± 6.4                                   |
| 92.8 ± 6.4                                   |
| Triglyceride (mg/dL) (%)                     |
| 136.1 ± 89.8                                 |
| 111.6 ± 62.2                                 |
| 188.9 ± 114.0                                |
| HDL (mg/dL) (%)                               |
| 50.1 ± 11.6                                  |
| 52.1 ± 11.4                                  |
| 45.9 ± 10.8                                  |
| Systolic BP (mmHg) (%)                       |
| 119.9 ± 14.2                                 |
| 117.0 ± 13.4                                 |
| 126.3 ± 13.8                                 |
| Diastolic BP (mmHg) (%)                      |
| 79.3 ± 10.9                                  |
| 77.1 ± 10.3                                  |
| 84.1 ± 10.7                                  |
| FBG (mg/dL) (%)                               |
| 101.8 ± 21.7                                 |
| 97.1 ± 17.0                                  |
| 112.1 ± 26.6                                 |
| Number of MS components (%)                   |
| 0                                             |
| 5 350 (18.9)                                 |
| 5350 (27.7)                                  |
| 0 (0)                                        |
| 1                                             |
| 7 108 (25.1)                                 |
| 7108 (36.8)                                  |
| 0 (0)                                        |
| 2                                             |
| 6 872 (24.3)                                 |
| 6872 (35.6)                                  |
| 0 (0)                                        |
| 3                                             |
| 5 179 (18.3)                                 |
| 0 (0)                                        |
| 5 179 (57.6)                                 |
| 4                                             |
| 2 834 (10.0)                                 |
| 0 (0)                                        |
| 2 834 (31.5)                                 |
| 5                                             |
| 972 (3.4)                                    |
| 0 (0)                                        |
| 972 (10.8)                                   |
| Insulin (μU/mL) (%)                           |
| 9.056 ± 4.491†                               |
| 7.981 ± 3.612†                               |
| 11.171 ± 5.239†                              |
| HOMA IR (%)                                   |
| 2.328 ± 1.442*†                              |
| 1.926 ± 1.076†                               |
| 3.119 ± 1.717†                               |

*The sample size is 10 874 men because insulin has been measured routinely only since 2007. †7208 participants with metabolic syndrome and ‡3666 participants without metabolic syndrome. MS, metabolic syndrome; PSA, prostate specific antigen; PSA mass, total circulating PSA protein; BMI, body mass index; HDL, high density lipoprotein cholesterol; BP, blood pressure; FBG, fasting blood glucose; HOMA IR, homeostasis model assessment of insulin resistance.
DISCUSSION

Our cross-sectional study attempts to examine the reason for the observed decline in PSA levels in connection with MS and IR. Previous studies have reported that increased BMI could be responsible for the PSA decline in MS [6]. This appears to be a reasonable proposal. However, BMI is a factor composed of many other factors that could affect PSA levels, and so it is too inclusive and nonspecific to use BMI to explain the PSA decline in MS or IR. For this reason, we tried to analyse the relationship between PSA level and MS or IR in more detail, focusing on haemodilution from increased plasma volume, as well as intrinsic metabolic effects.

The sample size for our study was 28,315 men; for those who underwent repeated screening, we used only the data from the initial examination. The initial data are likely to be more similar to the data of the general population because they are not distorted by possible medical interventions.

TABLE 2 Relationships among PSA, Plasma volume, and Metabolic syndrome

|                      | Mean PSA (ng/mL) | 95% CI     | Number | P value |
|----------------------|------------------|------------|--------|---------|
| Before stratification for plasma volume |                   |            |        |         |
| Total subjects       | 1.119 (1.106–1.132), n = 19,330 | 1.081 (1.063–1.100), n = 8,985 | 0.001  |
| Total subjects*      | 1.113 (1.100–1.127), n = 19,330 | 1.093 (1.073–1.113), n = 8,985 | 0.10   |
| After stratification for plasma volume(ml) |                   |            |        |         |
| 1st quartile (<2896.0) subjects | 1.197 (1.171–1.224), n = 5,989 | 1.217 (1.154–1.279), n = 1,090 | 0.58   |
| 2nd quartile (2896.0–3035.4] subjects | 1.139 (1.114–1.164), n = 5,315 | 1.105 (1.061–1.149), n = 1,766 | 0.20   |
| 3rd quartile (3035.4–3180.2] subjects | 1.104 (1.078–1.129), n = 4,602 | 1.068 (1.033–1.103), n = 2,475 | 0.11   |
| 4th quartile (≥3180.2] subjects | 1.016 (0.990–1.042), n = 3,424 | 0.996 (0.970–1.021), n = 3,654 | 0.29   |

*Adjustment for age and plasma volume. P value was calculated using an ANCOVA before and after stratification for plasma volume quartiles. Adjustment for age in all analyses. PSA, prostate-specific antigen; MS, metabolic syndrome.

TABLE 3 Changes in PSA, Plasma volume, and PSA mass according to Metabolic syndrome and insulin resistance

|                      | Number | Mean PSA (ng/mL) | 95% CI | Mean plasma volume (ml) | 95% CI | Mean PSA mass (μg) | 95% CI | P value |
|----------------------|--------|------------------|--------|-------------------------|--------|-------------------|--------|---------|
| Metabolic syndrome   |        |                  |        |                         |        |                   |        |         |
| Number of components |        |                  |        |                         |        |                   |        |         |
| 0                    | 5,350  | 1.139 (1.114–1.163) | 2,910.8 (2,905.7–2,916.0) | 3.308 (3.235–3.382) |
| 1                    | 7,108  | 1.121 (1.100–1.142) | 2,985.5 (2,985.1–2,993.9) | 3.334 (3.271–3.398) |
| 2                    | 6,872  | 1.102 (1.080–1.123) | 3,056.2 (3,051.8–3,060.7) | 3.349 (3.284–3.413) |
| 3                    | 5,179  | 1.096 (1.071–1.121) | 3,124.7 (3,119.5–3,129.8) | 3.409 (3.334–3.483) |
| 4                    | 2,834  | 1.068 (1.034–1.107) | 3,174.0 (3,167.1–3,181.0) | 3.372 (3.272–3.473) |
| 5                    | 972    | 1.040 (0.983–1.109) | 3,230.9 (3,218.9–3,242.8) | 3.340 (3.168–3.512) |
| P value              | 0.002  |                  | <0.001 |                         |        |                   | 0.55   |         |
| State                |        |                  |        |                         |        |                   |        |         |
| No                   | 19,330 | 1.119 (1.106–1.132) | 2,991.9 (2,989.2–2,994.7) | 3.332 (3.294–3.371) |
| Yes                  | 8,985  | 1.081 (1.063–1.100) | 3,150.7 (3,146.6–3,154.8) | 3.390 (3.333–3.446) |
| P value              | 0.002  |                  | <0.001 |                         |        |                   | 0.10   |         |
| Insulin resistance   |        |                  |        |                         |        |                   |        |         |
| HOMA IR index        |        |                  |        |                         |        |                   |        |         |
| 1st quartile (0.057–1.432) | 2,724  | 1.101 (1.070–1.132) | 2,960.9 (2,953.4–2,968.4) | 3.251 (3.157–3.346) |
| 2nd quartile (1.433–1.990) | 2,713  | 1.085 (1.053–1.116) | 3,024.2 (3,016.7–3,031.7) | 3.264 (3.169–3.359) |
| 3rd quartile (1.991–2.800) | 2,719  | 1.031 (1.000–1.062) | 3,068.0 (3,060.5–3,075.5) | 3.150 (3.055–3.245) |
| 4th quartile (2.801–3.794) | 2,718  | 1.031 (0.999–1.062) | 3,142.3 (3,134.8–3,149.8) | 3.229 (3.134–3.324) |
| P value              | 0.001  |                  | <0.001 |                         |        |                   | 0.34   |         |
| State                |        |                  |        |                         |        |                   |        |         |
| No                   | 7,552  | 1.074 (1.056–1.093) | 3,011.5 (3,006.9–3,016.0) | 3.222 (3.165–3.279) |
| Yes                  | 3,402  | 1.034 (1.005–1.062) | 3,132.0 (3,125.2–3,138.8) | 3.226 (3.141–3.311) |
| P value              | 0.018  |                  | <0.001 |                         |        |                   | 0.94   |         |

P value was calculated using an ANCOVA. Adjustment for age in all analyses. PSA, prostate-specific antigen; PSA mass, total circulating PSA protein; HOMA IR, homeostasis model assessment of insulin resistance.
Several studies have already shown that PSA is negatively associated with BMI as a result of a haemodilution or metabolic effect [7,8,12,13]. Haemodilution by increased plasma volume could be the main reason for low PSA levels in patients with high BMIs, according to the latest studies [12,13]. Because MS is closely related to BMI, we also considered the haemodilution effect on PSA levels in patients with MS. This study showed no difference in PSA levels between subjects with and without MS after adjusting for the plasma volume. The effect of plasma volume became more obvious when we examined the relationship between PSA level and MS after stratifying the plasma volume into quartiles (Table 2).

The relationships among MS, IR and PSA levels and the plasma volume were analysed using the concept of PSA mass, the total amount of PSA protein in circulation as calculated from the PSA level and plasma volume [13]. The PSA mass did not change in a manner dependent on obesity grade, the number of MS components (representing MS severity), HOMA IR index quartile (representing IR severity), presence of MS, or presence of IR, even when PSA levels decreased (Table 3). Even when the group with both MS and IR, which could be the most metabolically disturbed in this study, was compared with the group without any MS or IR, the group with only IR, and the group with only MS, there was no difference in PSA mass (Fig. 2). Hence, the decline in PSA level in MS or IR can be explained by increased plasma volume.

These results are in agreement with those found in previous studies that showed a stable PSA mass regardless of obesity [12,13]. An interesting finding was that plasma volume increased more in the group with only MS than in the group with only IR. In other words, MS could have a greater haemodilution effect than IR, and so it is likely that PSA levels are lower in patients with only MS than in those with only IR (Fig. 2).

Because MS is the clustering of cardiovascular risk factors and IR is the pathophysiological cornerstone of metabolic disorder, they are related to several hormonal changes [1,2,9,10]. Previous studies revealed that individual metabolic markers observed in obesity could be related to PSA levels, indicating that metabolic disturbance might influence PSA levels [6–8]. In addition, other studies reported that secondary hyperinsulinaemia, a result of IR, is linked to several hormones that can affect PSA, including sex-hormone-binding globulin, testosterone, free testosterone and aromatase [9–11]. However, in our study, MS and IR showed no relationship to PSA after adjusting for plasma volume. Nevertheless, if there is a metabolic effect through an indirect mechanism of the PSA increase in prostate volume and the plasma volume were analysed using an analysis of covariance. Adjustment for age in all analyses.

![Mean PSA, ng/mL](chart1)

![Mean Plasma Volume, mL](chart2)

![Mean PSA mass, μg](chart3)

FIG. 2. Prostate-specific antigen (PSA), plasma volume and PSA mass according to a combination of metabolic syndrome and insulin resistance. PSA mass, total circulating PSA protein; MS, metabolic syndrome; IR, insulin resistance according to the homeostasis model assessment of insulin resistance. P value was calculated using an analysis of covariance. Adjustments for age in all analyses.
In addition, we may not have excluded all subjects with prostate cancer, because biopsies were not taken for all participants. However, the prevalence of prostate cancer in eastern Asia is not high [24]. We excluded subjects with PSA levels > 15 ng/mL, and 98% of the study population had a PSA level < 4 ng/mL. We also excluded people with abnormal ultrasound findings, although not all participants underwent ultrasonographic imaging. The probability that men with cancer were included is very low. A direct comparison between the total study population and the sample used for analysis of both MS and IR is debatable because the two groups may not be identical. However, there seem to be few biological differences between the two groups. Regular insulin testing began in 2007, and no indications were given for insulin measurement. Finally, plasma volume calculations may not be as accurate as direct measurement of plasma volume using an isotope [25], and the use of such calculations for PSA evaluation must also be validated.

In conclusion, the decrease in PSA levels that is observed in patients with MS or IR could simply be the result of a haemodilution effect and not related to intrinsic metabolic disturbances. When interpreting PSA levels in men with MS or IR, we should consider that the PSA level could be underestimated because of haemodilution.

CONFLICT OF INTEREST

None declared.

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Abbreviations: MS, metabolic syndrome; IR, insulin resistance; BMI, body mass index.