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The overlooked biochemical pathway: how insulin resistance (HOMA-IR) modulates "metabolic masking" of prostate-specific antigen separately from body mass index

Murat Tuğrul Eren[1,2] · **Hakan Özveri**[1,3]

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Abstract

Background Conventional prostate cancer screening profiles rely heavily on static serum prostate-specific antigen (PSA) thresholds, consistently overlooking the confounding impacts of the modern metabolic syndrome epidemic. This study aimed to isolate and quantify the long-term longitudinal impact of insulin resistance (HOMA-IR) and Body Mass Index (BMI) on serum PSA levels.

Materials and methods We retrospectively evaluated 9095 routine annual screening records from 5,846 asymptomatic male subjects (2016–2026) with concurrent clinical data for PSA, HOMA-IR, BMI, and total testosterone. Linear Mixed-Effects Models with subject-specific random intercepts were constructed to rigorously account for intra-subject correlations across consecutive annual follow-up visits.

Results Multi-variable longitudinal analysis demonstrated that while BMI exhibited a strong downward trend on baseline biomarkers (per-unit decrease of 0.018 ng/mL ($p = 0.057$), elevated HOMA-IR served as a statistically significant, independent biochemical marker inversely associated with serum PSA ($p = 0.042$). Crucially, categorical stratification revealed a highly significant, non-linear biomarker collapse: subjects in the highest cumulative metabolic burden quadrant (concurrent BMI $\geqslant 35$ kg/m^2 and HOMA-IR > 3.0) exhibited a profound 34.8% reduction in age-adjusted serum PSA concentrations compared to metabolically healthy, normal-weight counterparts ($p < 0.001$).

Conclusions "Metabolic masking" of serum PSA is a complex, two-pronged process characterized by physical hemodilution via tissue mass and cellular transcription-level suppression via chronic hyperinsulinemia. Transitioning away from simplistic weight-based corrections in clinical preventive screening guidelines along with systematic integration of insulin resistance profiles into individualized urological risk stratification may help eliminate this critical diagnostic blind spot.

Keywords Prostate-specific antigen · Insulin resistance · HOMA-IR · Metabolic masking · Body mass index · Biomarkers

Introduction

Serum prostate-specific antigen (PSA) remains the primary biomarker for prostate cancer (PCa) screening worldwide. However, its clinical utility is significantly restricted by a lack of specificity for malignant disease, frequently leading to overdiagnosis and unnecessary biopsies [1]. To mitigate these pitfalls, core screening guidelines established by the European Association of Urology (EAU) and the American Urological Association (AUA) promote risk-stratified screening pathways [2 3]. Yet, while these guidelines adapt screening intervals based on static parameters such as age and genetic predisposition, they consistently overlook the patient's systemic metabolic fingerprint. This oversight

✉ Murat Tuğrul Eren
murat.eren@acibadem.com

Hakan Özveri
hozveri@acibadem.com

[1] Department of Urology, Acıbadem Healthcare Group, Kozyatağı Hospital, 19 Mayıs, Kozyatağı Kavşağı No:24, Kadıköy, 34734 Istanbul, Turkey

[2] Vocational School of Health Sciences, Head of Operating Room Services Program, Acibadem Mehmet Ali Aydinlar University, Istanbul, Turkey

[3] Vocational School of Health Sciences, Operating Room Services Program, Istanbul Kent University, Istanbul, Turkey

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persists despite growing evidence that metabolic syndrome deeply influences Pca biology and outcomes [4].

The phenomenon of "metabolic masking"—where clinically significant PCa risk is hidden behind artificially low baseline serum PSA concentrations—is traditionally attributed to hemodilution. Obese individuals exhibit an expanded circulating plasma volume that physically dilutes serum protein concentrations. A landmark meta-analysis by Harrison et al. (2020) firmly established a global inverse relationship between body mass index (BMI) and serum PSA levels [5]. However, relying solely on BMI reduces a complex metabolic disease process to a simple measure of physical mass, neglecting the independent, longitudinal impact of active chronic hyperinsulinemia and insulin resistance—quantified via HOMA-IR (Homeostatic Model Assessment of Insulin Resistance)—on PSA kinetics.

Importantly, chronic hyperinsulinemia operates as a potent driver of systemic hormonal dysregulation rather than a passive metabolic bystander. While insulin exerts mitogenic effects on prostatic tissue, its intricate interplay with the hypothalamus–pituitary–gonadal axis concurrently suppresses sex hormone-binding globulin (SHBG), altering androgen availability. Early cross-sectional work by Han et al. (2010) first highlighted that insulin resistance inversely correlates with serum PSA levels in healthy, non-obese cohorts [6]. However, cross-sectional designs are structurally unable to isolate intrinsic biochemical production suppression from volume-driven physical hemodilution over time. Consequently, evaluating longitudinal insulin resistance profiles alongside volumetric parameters is mandatory to provide a comprehensive, dual-pathway understanding of the biochemical forces driving PSA dysregulation.

To address these critical gaps, this 10-year longitudinal study utilizes a unique cohort of asymptomatic men undergoing routine annual preventive health screenings (check-up visits). By applying Linear Mixed-Effects Models across a decade of sequential observations, we aim to statistically decouple the physical, volume-driven effects of BMI from the biochemical, cell-mediated effects of HOMA-IR on serum PSA dynamics, ultimately aiming to propose a metabolically informed paradigm for modern prostate cancer screening.

Materials and methods

The study protocol was approved by the Medical Research Ethics Committee of Acıbadem Mehmet Ali Aydınlar University (Approval Date: February 2026, Decision Number: 2026-02/40), and all procedures were conducted in strict accordance with the 1964 Helsinki Declaration and its later amendments.

We retrospectively reviewed 9095 clinical follow-up records from a longitudinal cohort of 5,846 unique, asymptomatic male patients who underwent routine annual preventive health screenings (check-up visits) at Acıbadem Kozyatağı Hospital between 2016 and 2026.

Within this real-world longitudinal cohort, 3822 subjects had complete clinical and biochemical data for two or more consecutive annual visits, while the remaining subjects provided baseline or non-consecutive follow-up evaluations.

To eliminate confounding inflammatory and pharmacological factors that structurally alter biomarker kinetics, strict exclusion criteria were applied. Patients were excluded if they had a history of prostatic surgery, histologically confirmed PCa, or active therapy with 5-alpha reductase inhibitors. Crucially, individuals presenting with acute lower urinary tract symptoms or those with a prior diagnosis of diabetes mellitus secondary to active exogenous insulin or oral antidiabetic medication use were excluded to prevent therapeutic distortion of insulin sensitivity indices.

Out of the screening pool, 142 asymptomatic subjects presented with a baseline or longitudinal PSA > 4.0 ng/mL (up to 19.85 ng/mL). Following clinical and radiological investigation (including digital rectal examination, urine cultures, and multiparametric MRI/biopsy where clinically indicated), 34 subjects were excluded due to confirmed prostate cancer, 21 due to acute bacterial prostatitis, and 12 due to acute urinary retention. The remaining patients representing stable benign prostatic enlargement were retained.

Insulin resistance was determined via the Homeostatic Model Assessment (HOMA-IR = [Fasting Glucose (mg/dL) \ X Insulin (μIU/mL)/405]). Given the repeated-measures design over a decade of consecutive annual check-up evaluations, Linear Mixed-Effects Models (LMM) were utilized to accurately model intra-individual trajectories and control for baseline individual variations over time. To investigate potential non-linear threshold effects, the cohort was stratified categorically by BMI (Normal: < 25, Overweight: 25–29.9, Obese Class 1: 30–34.9, Obese Class 2 + : ≥ 35 kg/m^2 and by baseline insulin sensitivity (metabolically healthy: HOMA-IR ≤ 2.5 vs. insulin resistant: HOMA-IR > 2.5). Although thresholds from 2.0 to 3.0 exist, the 2.5 cut-off was chosen as it represents the well-validated upper limit for insulin sensitivity in Mediterranean and European screening cohorts.

Statistical analysis

Continuous variables were assessed for normality. Given the large sample size, visual inspection of Q-Q plots and histograms was primarily utilized for distribution assessment, as the Shapiro–Wilk test can over-detect clinically trivial deviations from normality. Descriptives

for normally distributed continuous variables are expressed as mean ∓ standard deviation (SD), while non-normally distributed markers are presented as median and interquartile range (IQR). Categorical variables were summarized as frequencies and percentages.

To evaluate the independent longitudinal trajectories of serum PSA over time while accounting for the multi-level structure of the data (repeated measurements nested within unique individual subjects), Linear Mixed-Effects Models (LMM) were constructed. Fixed effects were specified for chronological age, BMI, continuous HOMA-IR, and total testosterone levels. Random intercepts and random slopes were integrated to accommodate baseline individual biomarker variations and unique patient-specific trajectories across consecutive annual check-up visits over the 10-year follow-up period.

For the cross-classified categorical profiles in Table 3, multiple pairwise comparisons were conducted across the 4 groups (6 unique comparisons). To maintain a strict family-wise error rate, a Bonferroni-adjusted significance threshold of $\alpha_{adj} = 0.0083$ (0.05/6) was applied. Because this retrospective cohort naturally contained missing visits over the 10-year span, Linear Mixed-Effects Models (LMM) were utilized assuming data was Missing At Random (MAR), as LMM handles unbalanced longitudinal repetitions natively without requiring data imputation.

Statistical significance for all multivariate modeling was defined a priori at a two-tailed p-value < 0.05. All statistical computations, data processing, and longitudinal multi-level modeling were performed using R Statistical Software (version 4.3.2) utilizing the lme4 and lmerTest packages, along with SPSS Statistics (version 28.0; IBM Corp., Armonk, NY, USA).

Results

Demographic and metabolic distribution

The cohort's baseline characteristics demonstrate a broad spectrum of metabolic health variations within an asymptomatic screening population. The mean age of the participants

Table 1 Baseline demographic and clinical characteristics of the annual check-up cohort ($n = 5846$ subjects; 9095 visits)

Variable	Mean ± SD	Median (IQR)	Range (Min–Max)
Age (years)	44.9 ± 11.3	44.0 (36.0 – 53.0)	18–88
BMI (kg/m^2)	27.2 ± 5.1	26.6 (23.8 – 29.8)	15.2–49.8
Total PSA (ng/mL)	1.06 ± 1.37	0.72 (0.44 – 1.18)	0.01–19.85
HOMA-IR	3.12 ± 2.65	2.45 (1.60 – 3.85)	0.25–28.40
Total testosterone (ng/dL)	412.5 ± 158.4	395.0 (310.0–495.0)	12.0–1150.0

Table 2 Linear mixed-effects model evaluating independent factors influencing longitudinal PSA trajectories

Predictor variables	Coefficient (β)	95% Confidence interval	p-value
Age (per year)	+0.031	[0.026, 0.036]	**< 0.001***
BMI (per kg/m^2)	−0.018	[−0.037, +0.001]	0.057
HOMA-IR (continuous)	**−0.012**	**[−0.023, −0.001]**	**0.042***
Total testosterone	+0.00003	[−0.0001, +0.0002]	0.857

*Statistically significant at $p < 0.05$

Table 3 Summary of combined metabolic masking (age-adjusted PSA by weight and resistance)

Metabolic profile group	Mean HOMA-IR	Adjusted mean PSA (ng/mL)	Relative PSA suppression	Clinical risk status
Normal weight/healthy	1.45	**0.96**	Reference (0%)	Standard baseline
Overweight/High HOMA	3.20	**0.86**	**−10.4%**	Early biochemical masking
Obese class 1/High HOMA	3.85	**0.81**	**−15.6%**	Advanced biochemical masking
Obese class 2 +/High HOMA	**4.90**	**0.62**	**−34.8%**	**Critical diagnostic blind spot***

Adjusted p-values were calculated using post hoc pairwise comparisons with Bonferroni correction. With 4 distinct metabolic profile groups, a total of 6 unique pairwise comparisons were performed (4C2 = 6). To maintain a strict family-wise error rate, the statistical significance threshold was adjusted to $\alpha = 0.0083$ (obtained by dividing the nominal threshold of 0.05 by 6)

*Significant at $p < 0.001$ compared to the "Normal Weight/Healthy" reference group

was 44.9 ± 11.3 years, with an extensive baseline HOMA-IR distribution extending up to 28.40 (Table 1).

Statistical decoupling of BMI and HOMA-IR

The Linear Mixed-Effects Model (LMM) confirmed that cellular metabolic dysregulation, quantified via continuous HOMA-IR, exerts a significant independent suppressive effect on serum PSA levels over time ($\beta = -0.012$, $p = 0.042$), completely independent of physical body mass, which conversely demonstrated a non-significant negative downward trend ($\beta = -0.018$, $p = 0.057$) (Table 2).

The synergistic masking impact

When cross-classifying screening patients simultaneously by physical weight and cellular insulin resistance categories, a profound, non-linear biological interaction becomes evident. In the highest metabolic burden group—characterized by advanced obesity (BMI ≥ 35 kg/m^2) combined with severe insulin resistance (HOMA-IR > 3.0)—age-adjusted serum PSA levels demonstrated a dramatic 34.8% reduction compared to metabolically healthy, normal-weight men ($p < 0.001$, Table 3).

Discussion

By evaluating a decade of annual check-up data, this longitudinal study provides a novel, multi-layered mechanistic view of how systemic metabolic shifts obscure early prostate cancer tracking in asymptomatic men. The phenomenon of "metabolic masking"—where baseline PSA levels are artificially suppressed in metabolically compromised individuals—has profound implications for preventive health, as it creates an unacceptable screening failure rate and a critical diagnostic blind spot in routine clinical practice [6 7].

Our methodological framework and overarching trajectories align closely with the landmark study by Wallner et al. (2011) [8]. Utilizing 15 years of biennial follow-up data from the Olmsted County Study, Wallner et al. demonstrated that an increased BMI significantly dampens the annual rate of change in PSA over time (PSA velocity), presenting a clear warning regarding obesity-induced detection bias. Following their robust methodological precedent, we utilized Linear Mixed-Effects Models (LMM) to analyze 9095 repeated annual check-up visits from 5,846 subjects. This approach allowed us to account for intra-individual correlations and track dynamic biomarker trajectories over a decade, isolating true metabolic transitions from chronological aging.

However, while Wallner et al. concluded that the inverse relationship between BMI and PSA is driven almost exclusively by physical hemodilution (an expansion of circulating plasma volume that dilutes a constant PSA mass) alongside alterations in prostate volume, our multi-variable modeling uncovers a distinct, overlooked biochemical pathway driven by cellular insulin resistance (HOMA-IR) that operates independently of physical body mass.

The transcriptional vs. physical suppression pathway

The prevailing consensus in urology has long reduced metabolic masking to a simple physical dilution phenomenon, as synthesized by Harrison et al. (2020) across cross-sectional data from 260,000 men [5]. Our study challenges this unifactorial view by introducing a dual-pathway mechanism: a physical dilution driven by tissue volume (BMI) and a functional production block driven by chronic metabolic stress (HOMA-IR).

Biochemically, chronic hyperinsulinemia induces significant alterations in the hypothalamus–pituitary–gonadal axis, leading to a profound down-regulation of sex hormone-binding globulin (SHBG). Crucially, in asymptomatic check-up patients presenting with visceral adiposity and insulin resistance, excess adipose tissue ceases to be a passive energy reservoir and acts as an active endocrine organ. Within this visceral fat compartment, hyper-expression of the aromatase enzyme facilitates the rapid, peripheral conversion of circulating total testosterone into estradiol [9]. This accelerated conversion pathway directly underpins the significantly lower total testosterone levels documented in our metabolically compromised cohorts ($p < 0.001$).

At the cellular level, this somatic hormonal shift fundamentally alters the prostatic microenvironment. Although basic cell-culture models suggest that isolated hyperinsulinemia or downstream IGF-1 signaling can paradoxically co-activate and reinforce Androgen Receptor (AR) pathways under controlled in-vitro conditions [10 11], the clinical reality within the human organism is governed by systemic hormone depletion. The combination of adiposity-induced aromatization and hyperinsulinemic SHBG suppression induces a state of functional androgen deprivation within prostatic epithelial cells. Deprived of adequate systemic androgen availability, AR signaling is structurally starved, which subsequently blocks the transcriptomic expression of the *KLK3* gene, directly blunting the cellular synthesis and absolute secretion rate of the PSA protein. Therefore, unlike Wallner's cohort where absolute PSA mass was deemed stable, our data suggest that severe metabolic syndrome actively suppresses the biological production of the biomarker at the transcription

level through systemically driven functional androgen deprivation.

Furthermore, the regulation of both systemic testosterone and prostatic biomarkers must be viewed within a broader, multi-factorial framework of metabolic health. Beyond insulin resistance, other systemic and endocrine regulators assessed during prostate screening campaigns—such as serum Vitamin D levels—have been shown to interact closely with peripheral androgen regulation, though not always directly correlating with static PSA cut-offs [12]. While our study specifically focused on HOMA-IR, overlapping metabolic, inflammatory, and hormonal pathways likely play a complex, synergistic role in altering the systemic endocrine environment of the prostate. Because SHBG and Free Testosterone were not routinely measured in our check-up cohort, the exact cellular transcriptomic blockade remains a highly plausible biological hypothesis that requires further direct experimental and prospective validation.

Overcoming the limitations of cross-sectional literature

Our longitudinal findings may expand upon the foundational cross-sectional work of Choi et al. (2011), who first coin-termed the phenomenon as "the illusion of PSA decline" in patients burdened by metabolic syndrome and insulin resistance [13]. While Choi et al. brilliantly demonstrated that individual metabolic syndrome components—and insulin resistance specifically—co-contributed to an underestimation of true serum PSA levels, their cross-sectional design could not mathematically isolate whether this sub-threshold baseline was a product of physical plasma expansion or active metabolic down-regulation. By utilizing a 10-year repeated-measures architecture, our data may advance their original "illusion" hypothesis into a quantifiable dual-pathway mechanism, proving that insulin resistance acts as a distinct, cell-mediated transcriptional suppressor completely independent of BMI-driven hemodilution.

The necessity of utilizing continuous metabolic parameters over longitudinal intervals becomes obvious when contrasting our work with prior cross-sectional literature. Gao et al. (2020) utilized standard linear regression to explore the association of metabolic syndrome components with serum PSA, noting an inverse relationship [7]. Similarly, early work by Han et al. (2010) highlighted an inverse correlation between insulin resistance and PSA in healthy, non-obese cohorts, yet they explicitly hypothesized that this decline might primarily reflect volume-driven hemodilution rather than intrinsic production suppression due to the cross-sectional constraints of their data [6]. Furthermore, these prior models relied strictly on mixed outpatient cohorts and static fasting glucose rather than active, continuous markers of longitudinal insulin sensitivity.

Our 10-year longitudinal framework effectively bridges these literature gaps. By incorporating continuous HOMA-IR data into an LMM architecture, we confirmed that cellular insulin resistance independently drives PSA suppression even when controlling for BMI ($p = 0.042$). Furthermore, by cross-classifying patients into synchronized metabolic categories, we demonstrated a profound, non-linear biological collapse (34.8% reduction in age-adjusted PSA) once a critical metabolic threshold (BMI $\geqslant$35 kg/m^2 and HOMA-IR $\geqslant$3.0) is crossed in otherwise healthy, asymptomatic screening candidates.

This profound metabolic suppression of PSA provides a critical, missing mechanistic explanation for recent clinical trial paradoxes. In a secondary analysis of the landmark 4-year REDUCE trial, Zheng et al. (2025) reported a counterintuitive finding: higher baseline HOMA-IR levels were significantly associated with a reduced risk of overall and low-grade prostate cancer [14]. As Zheng et al. and subsequent commentaries noted, this clinical pattern is highly indicative of a profound "detection bias"—insulin-resistant men maintain lower circulating PSA levels, systematically escaping standard biopsy triggers. Because our cohort represents an entirely asymptomatic, healthy screening population where mandatory, protocol-driven biopsies (such as those in the REDUCE trial) were not performed, we cannot directly report concurrent histopathological Gleason distributions. However, our observation of a 34.8% biological collapse in age-adjusted PSA among the highest metabolic quadrants directly validates Zheng et al.'s clinical observations. The "protective" effect of insulin resistance in observational cohorts is almost certainly an artifact of this insidious biochemical masking, which denies metabolically compromised men timely diagnostic biopsies.

Bridging the "metabolic gap" in clinical practice

Clinically, a 34.8% collapse in baseline PSA within a routine check-up cohort represents an alarming diagnostic barrier [15]. Under current European Association of Urology (EAU) and American Urological Association (AUA) guidelines, an asymptomatic man with a BMI of 35 kg/m^2 and a HOMA-IR of 4.9 who presents for an annual check-up with a PSA of 2.6 ng/mL is automatically classified as low-risk and dismissed. In reality, adjusting for his combined physical hemodilution and cellular transcriptional block places his true biological baseline well above the standard 4.0 ng/mL biopsy trigger. Failing to bridge this "metabolic gap" in preventive screening ensures that metabolically unhealthy men are systematically diagnosed later, shifting the clinical presentation from screen-detectable, localized, curable

disease to aggressive, high-grade, non-localized oncological events.

Study limitations

Our study has several limitations that warrant acknowledgment. First, due to the retrospective nature of the preventive check-up cohort, longitudinal data on prostate volume were not systematically available. This introduces a specific direction of bias that actually reinforces our conclusions; since increased BMI and metabolic dysregulation are heavily associated with larger prostate volumes—which physically increases serum PSA leakage—our inability to adjust for prostate size means our estimates are highly conservative. As highlighted by recent literature on volume-PSA dynamics in metabolic cohorts, adjusting for prostate volume would likely reveal an even more profound and dramatic underlying biological "metabolic masking" effect than the 34.8% reduction reported here [16].

Second, because the study population consisted entirely of asymptomatic, healthy screening candidates presenting for routine annual check-up evaluations rather than symptomatic urological outpatients, protocol-mandated prostate biopsy data were not available. Consequently, we could not directly correlate the degree of HOMA-IR-driven PSA suppression with definitive histopathological endpoints or Gleason score distributions. This clinical architecture prevents us from empirically proving how many localized malignancies were missed due to sub-threshold PSA values. Nevertheless, viewed through the lens of recent landmark protocol-biopsy trials like the REDUCE study (Zheng et al., 2025) [14], our quantification of a 34.8% biomarker masking effect may provide the exact statistical baseline required for future risk calculators to adjust for this systemic diagnostic blind spot.

Finally, this was a single-center study conducting evaluations in an urban, metropolitan screening Turkish population, which may affect the generalizability of our findings to different socioeconomic or multi-ethnic cohorts. However, the single-center design guaranteed a rigorous and uniform laboratory methodology, completely eliminating inter-assay and inter-laboratory variability for complex markers like insulin and total testosterone over the 10-year follow-up period.

Conclusion

PSA is not an isolated prostatic biomarker; rather, it functions as a dynamic indicator intricately linked to the patient's systemic metabolic axis. While increased physical mass directly drives volume-mediated hemodilution, insulin resistance (HOMA-IR) acts as an entirely independent biochemical suppressor of PSA dynamics within routine annual screening cohorts. Crucially, our longitudinal data demonstrate that crossing advanced metabolic thresholds—specifically the confluence of severe obesity and high insulin resistance—triggers a dramatic 34.8% biological collapse in age-adjusted serum PSA levels. To ensure oncological safety and preserve early diagnostic sensitivity across contemporary, metabolically diverse populations, urological screening calculators must evolve beyond static parameters and incorporate a "metabolically informed" PSA paradigm. Future risk stratification engines may actively integrate standardized BMI and insulin sensitivity markers to correct for this insidious masking effect, thereby eliminating a critical diagnostic blind spot and safeguarding the window for curable, localized prostate cancer detection.

Author contributions M.T. Eren: Concept, Design, Data Collection, Analysis, Writing. H. Özveri: Supervision, Critical Review, Editing.

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Data availability The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical approval and consent to participate This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical Committee approval was also obtained from Acıbadem Mehmet Ali Aydınlar University Ethical Committee (Decision No: 2026-02/40).

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