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Research Paper

Aberrantly glycosylated PSMA in urine as a potential marker for prostate cancer

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ABSTRACT

Early detection of prostate cancer (PCa) requires the development of reliable non-invasive biomarkers. In this study, we describe a simple, non-invasive assay to detect a prostate-specific membrane antigen (PSMA) glycoisoform directly from unprocessed urine. PSMA was analyzed in urine samples from PCa patients ($n = 40$) and benign controls ($n = 37$) using lectin MGL-coated europium-doped nanoparticles. MGL showed enhanced binding to PCa-derived PSMA, indicating aberrant glycosylation. Evaluation of individual samples demonstrated that the PSMA-MGL glycovariant assay significantly discriminated PCa from benign conditions ($p = 0.01$ pilot, $p = 0.02$ validation). Moreover, this assay exhibited a three-fold improvement in sensitivity over conventional antibody-based PSMA detection. ROC analysis showed an AUC of 0.648 for PSMA-MGL, which increased to 0.734 when combined with free-PSA and urinary creatinine, highlighting the enhanced diagnostic potential of this multi-marker, non-invasive approach.

1. Introduction

Urine is a biofluid that can be collected easily and non-invasively in large volumes. It is a relatively less complex medium compared to plasma or serum and thus has lower matrix interference in bioaffinity assays [1]. In addition to metabolic waste products, urine contains a wide variety of small proteins, nucleic acids, and complex biomarkers that collectively reflect physiological and pathological states of the body. Importantly, the urinary tract system is in direct anatomical and functional continuity with the prostate, and therefore urine naturally harbors secreted proteins, nucleic acids, and exfoliated cells derived from the prostate gland [2]. This direct exposure to prostatic secretions enables urine to serve as a reservoir of disease-specific molecular signatures, making it an ideal medium for identifying diagnostic and prognostic biomarkers for prostate cancer (PCa) [3].

As PCa is one of the most common cancers in men, the need for the development of non-invasive diagnostic methods is crucial [4]. Urine-based cancer detection offers a promising approach for the early diagnosis and monitoring of urogenital diseases and has been well studied in finding biomarkers, especially for PCa [5,6]. Several urine-based biomarker assays such as PCA3 [7], SelectMDx [8], Mi-Prostate Score [9], and ExoDx [10] have been developed to improve PCa detection, however, they have not yet been fully integrated into clinical guidelines or healthcare practices [4]. There still remains a need to find alternatives to traditional blood-based tests like prostate-specific antigen (PSA), which often lack specificity and lead to unnecessary biopsies [11].

Among candidate biomarkers, prostate-specific membrane antigen (PSMA) has attracted considerable attention. PSMA is a transmembrane glycoprotein highly expressed on PCa cells and certain other solid tumors [12]. It is extensively glycosylated, with glycans accounting for approximately 30 % of its molecular mass, and contains 10 predicted N-linked glycosylation sites [13]. Its elevated expression is associated with higher tumor grade and disease aggressiveness, while limited expression in normal tissues allows for high specificity in imaging and therapeutic applications [14]. Clinically, PSMA is primarily used in positron

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emission tomography (PET)-based targeted imaging, which has markedly improved the detection of PCa lesions, including small or metastatic tumors [15]. Beyond imaging applications, recent studies have explored non-invasive detection of PSMA in urine to develop accessible biomarkers for early PCa diagnosis. Wang et al. reported the presence of PSMA on urine-derived exosomes, highlighting its potential as a diagnostic biomarker at the time of initial biopsy [16]. Furthermore, Allelein et al. characterized PCa-derived extracellular vesicles from urine to improve diagnostic accuracy [17]. These findings demonstrate the feasibility of urine-based assays for PSMA detection as a non-invasive alternative to traditional biopsy.

Beyond protein expression, alterations in glycosylation provide an additional layer of specificity for PCa biomarkers. Glycoprofiling of urinary proteins has gained increasing attention, as aberrant glycosylation is a hallmark of cancer and can provide biomarker candidates with greater specificity than protein abundance alone. Alterations in both N- and O-glycans including increased N-glycan branching, enhanced core fucosylation, and elevated O-GlcNAcylation have been identified as potential diagnostic and prognostic markers [18,19]. Even PSA, the FDA-approved biomarker, shows altered N-glycosylation at asparagine 69 during cancer progression [20].

Lectins, which are carbohydrate-binding proteins with defined glycan specificities, offer a valuable approach to investigate such glycosylation changes. Lectins enable the detection of subtle alterations by selectively recognizing distinct glycan epitopes that may not be captured by protein quantification alone [21]. Among these, macrophage galactose-type lectin (MGL) is of particular interest due to its high specificity for terminal *N*-acetylgalactosamine (GalNAc) residues [22]. These glycans are frequently overexpressed in malignant transformation, and MGL's selective recognition provides a means to capture and profile cancer-associated glycoproteins. A recent study from our group demonstrated the diagnostic potential of MGL, where an MGL-nanoparticle assay targeting free-PSA glycovariants in plasma provided better specificity for clinically significant PCa compared to conventional kallikrein tests [23].

In this pilot feasibility study, we assessed the diagnostic performance of glycoprofiling and protein profiling in urine samples using MGL-conjugated nanoparticles. The resulting PSMA-MGL assay effectively distinguished PCa from benign conditions directly in unprocessed urine.

2. Materials and methods

2.1. Clinical samples

Clinical urine samples were collected at the University of Turku Hospital laboratory over two-year period, without prior digital rectal examination (DRE), and stored at −80 °C until further analysis. The study included a total of 77 male participants, comprising 40 patients with PCa and 37 individuals with benign conditions, all diagnosed with benign prostatic hyperplasia (BPH). Among the PCa patients, Gleason grades were distributed as follows: Grade Group 2 (GG2, $n = 11$), Grade Group 3 (GG3, $n = 7$), Grade Group 4 ($n = 12$) and Grade Group 5 (GG5, $n = 10$). Detailed patient characteristics are presented in Table S1. The study was conducted with the approval of the University of Turku Ethics Committee and the Hospital District of Southwest Finland (Dnro: 112/180/2012), and all participants provided written informed consent.

Prior to analysis, the samples were thawed at room temperature (RT) and centrifuged at 1000 ×*g* for 5 min to remove cells and cellular debris. The resulting supernatant was collected and used in our immunoassays.

2.2. Biotinylation of capture antibodies

Monoclonal antibodies were biotinylated as described previously [24]. Briefly, the antibodies (2 mg/mL) were adjusted to pH 9.8 with carbonate buffer and incubated with a 40-fold molar excess of biotin isothiocyanate (10 mM in ethanol) for 4 h at RT. Excess biotin was removed by gel filtration using NAP-5 or NAP-10 columns (GE-Illustra) with TSA buffer (50 mM Tris-HCl, 150 mM NaCl, 0.5 g/L NaN_3, pH 7.5). The biotinylated antibodies were stabilized with 1 g/L BSA and stored at +4 °C. The antibodies used in this study are listed in Table S2.

2.3. Coating of detection antibodies and lectins on nanoparticles

Detection antibodies and lectins were conjugated to europium nanoparticles (Eu^{3+}-NPs; 1×10^{12} particles) by covalently linking antibody amino groups to activated carboxyl groups on the particles, as previously described with minor modifications [24]. Eu^{3+}-NPs were activated with NHS (8 mM) and EDC (2.6 mM) in MES buffer (50 mM, pH 6.1), then coupled with antibodies and blocked with 1 % BSA. After incubation (30 min, RT) and overnight mixing at +4 °C, conjugates were concentrated, washed in storage buffer (25 mM Tris, 150 mM NaCl, 0.1 % NaN_3, pH 8), stabilized with 0.2 % BSA, and stored at +4 °C. The lectins used in this study, along with their carbohydrate specificities, are detailed in Table S3.

2.4. Assay design

2.4.1. Two types of assays were utilized in this study

Protein and glycan profiling was performed using direct immunoassays, in which detection was achieved either with a panel of antibodies or lectins conjugated to Eu^{3+}-NPs. For protein and glycan profiling, we analyzed proteins such as integrins, tetraspanins, and selected tumor-associated markers, along with a diverse panel of lectins with different binding specificities to comprehensively assess glycosylation patterns, as described in our previous studies [25,26].

For the direct assay, 10 μL of each sample diluted in PBS (30 μL/well) was applied to a 96-well Maxisorp plate (Uniogen, Turku, Finland) and incubated for 2 h at +35 °C. Wells were washed twice with wash buffer (product: 42-01TY, Uniogen, Turku, Finland) using a DELFIA plate washer. Next, 2 % BSA in TSA buffer (30 μL/well) together with red assay buffer (20 μL/well; product: 42-02TY, Uniogen, Turku, Finland) was added, and plates were sealed and incubated for 2 h at +4 °C. After two additional washes, nanoparticles (1×10^7/well, 30 μL) were added and incubated for 1 h at RT on a plate shaker with gentle agitation.

Based on the direct assay results, we proceeded to set up a glycovariant assay to detect the combination of the most highly expressed protein, PSMA, and the most prominent lectin, MGL. In this sandwich assay (PSMA-MGL) biotinylated anti-PSMA antibodies were used to capture the protein on streptavidin-coated microtiter wells, followed by the detection using Eu^{3+}-NP conjugated with MGL. For comparison, we established a conventional, mere protein epitope targeting, immunoassay (PSMA-PSMA), utilizing a PSMA specific antibody both as a biotinylated capture and Eu^{3+}-NP conjugated detection reagent. The assays were applied for the analysis on a small pilot sample cohort ($n = 20$).

For the sandwich assay, streptavidin-coated plates (KaiSA96) were first coated with biotinylated anti-PSMA antibody (100 ng/well, 30 μL) for 1 h at RT, followed by two washes. Urine samples (50 μL) diluted with assay buffer were then added and incubated for 1 h at RT with slow shaking at 600 rpm. After washing, Eu^{3+}-NP tracers (1×10^7/well, 30 μL) were added and incubated 1.5 h at RT with slow shaking. Plates were washed four times, and fluorescence was measured (λ_ex 340 nm / λ_em 615 nm) with a Victor™ 1420 counter (PerkinElmer). All assays were run in triplicate, and signal-to-background ratios were analyzed.

2.5. Data analysis

Comparisons between the cancer and benign groups were performed using the nonparametric Mann–Whitney *U* test, where *p* value of <0.05 was considered significant. Diagnostic performance was evaluated using Receiver Operating Characteristic (ROC) curve analysis in IBM SPSS Statistics (version 29). The PSMA-MGL assay was also assessed in combination with serum free-PSA and urinary creatinine using the

logistic regression model. The study cohort was initially designed as a pilot ($n = 20$), and based on the encouraging results, an independent validation cohort ($n = 77$) was subsequently included.

3. Results

3.1. Protein and glycan profiling

Urine pooled samples from PCa patients with (GG 2–5) and benign controls were analyzed to identify protein and glycan alterations associated with disease status. The analysis of protein marker revealed differential expression patterns across the PCa subgroups and benign samples (Fig. 1A). Herein, CD81 showed mild expression across all PCa subgroups, with a slight increase observed in GG5. ITGA1 expression was elevated in GG3 and GG5 samples, while PSMA displayed notably higher expression specifically in GG4. In contrast, CD63 levels were more prominent in the benign group (Fig. 1A).

Our lectin assays showed distinct glycan profiles in the different groups of PCa clinical samples. Among the glycan binders, MGL showed the highest signal-to-background ratio across all PCa subgroups, followed by Gal-3 (Fig. 1B).

3.2. Development of protein-glycan sandwich assay

In the pilot cohort ($n = 20$), the glycovariant assay showed a three-fold increase in sensitivity compared to the conventional immunoassay and was able to clearly distinguish between benign and PCa samples (p value = 0.01) (Fig. 1C). Encouraged by these findings, we extended the analysis to a validation cohort ($n = 77$). It was found that the PSMA-MGL assay distinguished between the benign and PCa samples (p value = 0.02) (Fig. 1D). The diagnostic performance of the PSMA-MGL assay was evaluated using ROC curve analysis, both individually and in combination with serum free-PSA and urinary creatinine as independent markers. The assay alone yielded an Area Under the Curve (AUC) of 0.648. When combined with serum free-PSA and urinary creatinine, the AUC improved from 0.347 (serum free-PSA alone) and 0.513 (urinary creatinine) to 0.734, demonstrating the added value of the combined marker approach (Fig. 1E). For comparison, the performance of total-PSA is provided in Supplementary Fig. S1, highlighting how integration with PSMA-MGL enhances diagnostic accuracy over conventional PSA measurement. Normalization of samples using free-PSA, total-PSA and u-creatinine levels was also tested to account for inter-sample variability, but normalizations did not have any improved impact on the results (Supplementary Fig. S2).

4. Discussion

While PSA glycoforms have been extensively studied in both body fluids and prostate tissues [23,27,28] with their altered glycosylations linked to PCa aggressiveness [29,30], PSMA glycoforms have been far less explored as potential biomarkers [31]. Consistent with prior reports, PSMA's restricted expression in normal tissues and high expression in PCa cells reinforces its value as a biomarker for imaging and emerging non-invasive diagnostic assays [32,33]. Beyond its over-expression in PCa, PSMA is also heavily glycosylated and recent studies have focused on different types of glycosylations, including sialylation [34], fucosylation [35] and increased branching [36]. Nevertheless, there is still scope for studying PSMA glycosylation alterations in PCa.

In this study, we demonstrated that glycoprofiling combined with protein profiling of urine can identify molecular signatures to distinguish PCa patients from benign controls. We identified distinct protein and glycan markers being expressed in different stages of PCa. The highly expressed markers were then selected to construct the glycovariant assays. The combination of PSMA with the lectin MGL provided a 3-fold increase in the sensitivity. The PSMA-MGL glycovariant assay improved the diagnostic performance compared to the conventional PSMA-PSMA assay, which detects only the protein. These results highlight the potential of integrating glycan markers into diagnostic platforms for non-invasive PCa detection. Our study extends previous findings by demonstrating that protein glycovariants can enhance detection accuracy over conventional immunoassays [37]. Importantly, the combination of protein and glycan signatures could reduce dependence on PSA testing alone, thereby minimizing unnecessary biopsies and enabling earlier detection of clinically significant PCa.

Lectin MGL has been studied in various cancers [38,39] and has emerged as a tool for detecting cancer-associated glycosylations. It has a high specificity for terminal GalNAc residues, which are often found in known cancer antigens like Tn and sTn [40]. In our study, we observe its diagnostic potential when combined with PSMA. The strong performance of MGL in our assay is partially explained by its multivalent

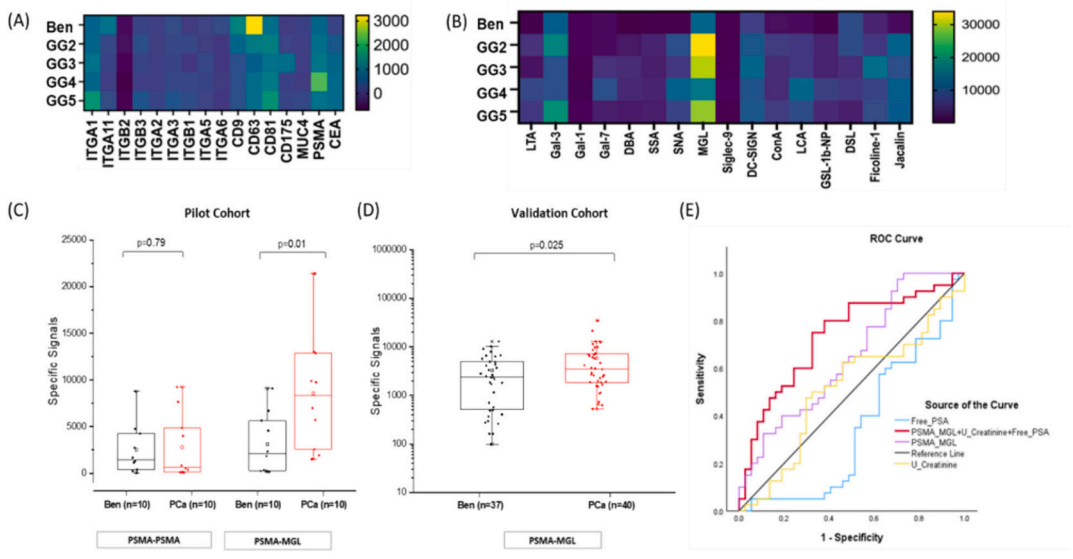

Fig. 1. (A) Heat Map showing the expression profiles of selected protein markers and (B) glycan markers across different stages of PCa and Benign conditions. (C) Box plot comparing the performance of conventional (PSMA-PSMA) assay with the glycovariant (PSMA-MGL) assay in the pilot cohort, and (D) evaluating PSMA-MGL assay performance in the validation cohort. (E) ROC illustrating the diagnostic performance of serum free-PSA, PSMA-MGL, urinary creatinine, and their combined effect.

avidity effect when conjugated in Eu^{3+}-NP, which enhances binding to clustered tumor-associated glycans. A similar performance was previously reported in ovarian cancer, where MGL-based Eu^{3+}-NP assay improved discrimination of serum CA125 between malignant and benign controls [41]. Likewise, recent studies have demonstrated the potential of MGL in detecting aberrant glycosylation patterns in colorectal cancers [39,42]. These findings highlight the potential of MGL-based assays for early detection of cancers.

We also assessed our assay performance in the context of PSA testing, a major consideration in PCa screening. While total PSA remains widely used, its limited specificity often leads to over diagnosis and overtreatment [43]. Serum free-PSA remains clinically valuable for improving specificity of PCa screening, particularly in men with borderline or intermediate total-PSA levels [23]. Our results align with this correlation, as integration of serum free-PSA with PSMA-MGL, with the addition of urinary creatinine value, significantly improved AUC values (Fig. 1E). Sample normalization using free-PSA, total-PSA and u-creatinine levels was also evaluated to address inter-sample variability, however, these normalizations did not improve the results (Supplementary Fig. S2).

Although some glycosylations of PSMA have been previously reported, our study began with a broader approach by exploring altered glycosylations in whole urine, without targeting any particular protein. All aspects of glycosylations were studied including sialylation, fucosylation (Supplementary Fig. S3), branching, etc. We identified PSMA to be overexpressed in PCa and its glycan alteration was detected by MGL lectin in a pilot cohort and extended the study to a larger validation cohort. It is important to note that the individual glycosylations of PSMA were not studied in this study. Furthermore, low performance of certain lectins could be due to the variations in sample type, differences in glycan accessibility or abundance, and the inherent binding specificity and sensitivity of the lectins used.

Despite the promising potential of these biomarkers, this study has limitations. The relatively small sample size within each PCa subgroup may affect the robustness and generalizability of the findings. High inter-individual variability in protein and glycan expression, influenced by age, diet, comorbidities, or medication, can also introduce inconsistencies in biomarker measurement. Additionally, variability in sample collection, storage and processing further introduces uncertainty. Post hoc power calculations based on the pilot effect size indicated that approximately 70–80 subjects would be needed to achieve 80 % statistical power ($\alpha = 0.05$) for detecting differences between benign and cancer groups using the Mann–Whitney U test. While the total validation cohort ($n = 77$) reached this target for the main comparison, the individual PCa subgroups contained substantially fewer cases, resulting in lower statistical power for detecting subgroup-specific differences. Additionally, it is important to note that while PSMA is more commonly applied in disease monitoring and therapeutic guidance, its utility as a primary diagnostic marker requires further validation.

To address these limitations, future studies will involve a more systematic analysis of the same patient cohort, incorporating multiple biomarkers and multivariate analyses to evaluate their combined clinical performance. This approach will also include carefully planned cohort sizes to ensure sufficient statistical power for subgroup comparisons.

5. Conclusion

Our study demonstrates that urine-based protein-glycan assay, particularly PSMA-MGL, exhibits promise in distinguishing PCa patients from benign controls. Moreover, combining PSMA-MGL with free-PSA and creatinine adjustment further improves diagnostic performance. However, further validation in larger, independent cohorts using standardized protocols is essential to confirm the clinical utility of these markers.

CRediT authorship contribution statement

Misba Khan: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Md. Khirul Islam:** Writing – review & editing, Visualization, Supervision, Methodology, Conceptualization. **Pekka Taimen:** Writing – review & editing, Resources. **Peter J. Boström:** Writing – review & editing, Resources. **Urpo Lamminmäki:** Writing – review & editing, Supervision. **Janne Leivo:** Writing – review & editing, Supervision, Software, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2025.120790.

Data availability

Data will be made available on request.

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Corrigendum

Corrigendum to "Aberrantly glycosylated PSMA in urine as a potential marker for prostate cancer" [Clin. Chim. Acta 582 (2026) 120790]

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