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Original Research

Inverse Association of Omentin-1 and Vitamin D with FGF-23 Levels in Prostate Cancer: A Predictive Biomarker Panel

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Introduction: Omentin-1 is typically expressed in vascular endothelial cells, mesothelial cells, airway goblet cells, and adipose tissue stromal cells. Fibroblast growth factor-23 (FGF-23) is primarily secreted by osteocytes, modulates renal phosphate reabsorption and suppresses vitamin D activation. Vitamin D , a fat-soluble vitamin, modulates immune responses, bone metabolism and calcium homeostasis. Prostate cancer remains a major worldwide health concern among males with emerging evidence linking these biomarkers to cancer progression due to their anti-inflammatory, antioxidant and potential anti tumorigenic properties. Objectives: This study aimes to determine whether serum levels of omentin-1, vitamin D, and FGF-23, taken together can predict prostate cancer status.

Materials and Methods: A case-control approach was conducted at a single center Al-Amal Centre/ Medical City of Imam Hussain in Karbala/ Iraq, during December 2022 until June 2023. Serum samples were collected from 30 prostate cancer patients' post-treatment and 30 age-matched (45–70 years) healthy male controls. Serum concentrations of FGF-23, omentin-1, irisin and vitamin D were measured using ELISA.

Results: The patient group exhibited significantly elevated FGF-23 levels (240.8 ± 55.2 ng/ml) compared to controls (163.1 ± 22.4 ng/ml $p < 0.001$). Conversely, the level of irisin; omentin-1; vitamin D was markedly reduced in patients (21.9 ± 3.2, 10.3 ± 2.9, and 6.4 ± 0.7 ng/ml respectively; $p < 0.001$) relative to controls (60.8 ± 3.5, 38.8 ± 6.6, and 19.1 ± 2.4 ng/ml respectively). The ROC curve analysis identified serum FGF-23 and omentin-1 and vitamin D as highly accurate molecular indicator for detecting PCa progression (with AUC value; 0.956, 0.958 and 0.938 respectively).

Conclusions: These circulating factors may be considered as promising diagnostic tools and vitamin D deficiency emerging as a particularly significant risk factor within this study cohort.

Introduction

Prostate Cancer (PCa) is the second most frequently tumor diagnosed in male and a top cause of male cancer mortality, representing a critical area of research focus in oncology [1, 2]. The progression of prostate cancer is usually characterized by slow gradual advancement. A silent tumor in aging males, usually remains asymptomatic and undiagnosed during their lifetime [3]. The epidemiology of PCa demonstrates by its association with age. Typically presenting around the seventh decade of life. With nearly two-thirds of deaths occurring in men over 75 [4].

A critical challenge in in PCa management is the asymptomatic tumor progression in early and curable stages, which could delay diagnosis until the tumor progressed, despite diagnosis and therapeutic techniques advancements [5]. In the United States PCa represents a health condition with a population about 3.3 million men with a diagnosis of this tumor, and the mortality rate is approximately 1 in 44 among affected individuals. Conventional PCa diagnosis may lack specificity

or lead to overdiagnosis of indolent disease, overtreatment and un-necessary invasive biopsy. Novel biomarkers are essential for more accurate prognosis and the precise identification of aggressive tumors [6].

Omentin Gene

Two isoforms; omentin-1 and omentin-2 are encoded by this gene with 83% amino acids sequence identity. These two isoforms are co-localized on chromosome 1q22-q23. Previous studies have established omentin-1's roles in metabolic regulation and immune responses. Its mature circulating form is a ~120 kDa glycosylated trimer and the bioactive surface is represented by a fibrinogen-like domain (38-82 residues) and a lectin-like domain (37-313 residues) [7].

Omentin-1 (Intelectin-1)

A Multifunctional Adipocytokine with Diagnostic and Therapeutic Potential; Omentin-1, also designated intelectin-1 (ITLN-1), is a 313-amino acid adipocytokine that has emerged as a potential biomarker for various pathological conditions including preeclampsia, inflammatory disorders, polycystic ovarian syndrome, obstructive sleep apnea, and malignancies [8]. This protein is recognized as a diagnostic marker and also as a key acute-phase reactant and represent a promising therapeutic agent [9, 10]. Local ITLN1 expression within the tumor microenvironment may represent a more reliable biomarker of malignant activity than circulating levels. [11]. The positive correlation between omentin-1 and the estradiol-to-testosterone ratio suggests that the reduction in omentin-1 is mechanistically linked to the specific hormonal environment created by ADT [12]. The therapeutic benefit of hormonal ablation in controlling cancers is usually accompanied by clinical issues includes changes in body composition, density of bone mineral, metabolic homeostasis and also sexual functions [13].

Fibroblast Growth

FGF-23 is a 251-amino acid endocrine hormone (molecular weight: 32 kDa) encoded by the FGF-23 gene and belongs to the FGF-19/21/23 subfamily. It exhibits mitogenic and anti-apoptotic effects and regulates phosphate homeostasis through modulation of renal phosphate transport [14, 15].

FGF-23 in Prostate Cancer

Pathogenicity and oncogenesis; FGF-23 serves as a potent mitogen in prostate oncogenesis. An autocrine mechanism is observed includes tumor proliferation in prostate, breast and renal carcinoma [16-18]. Its primary site of synthesis is the osteocyte and play a principal physiological role in modulating vitamin D and phosphate levels [19]. The effect of this protein includes two complementary pathways; first, the direct effect on proximal renal tubules by suppressing of phosphate reabsorption [20]. Second, through indirect inhibition of renal 1 α-hydroxylate activity which diminishes the production of calcitriol [21]. The dual effect creates a hypo-phosphatemic condition. This was supported by preclinical studies, including human tumor specimen, in vitro models and animal systems demonstrate that vitamin D deficiency with FGF-23 overexpression induce prostate carcinogenesis [22].

The role of Irisin

Irisin is a glycoprotein composed of 112 amino acids secreted from skeletal muscle and fat tissue

[23]. It functions in browning of white adipose tissues. enhancing their metabolic activity [24]. Clinical oncology evidences represent an important irisin expression pattern, dysregulation of irisin expression across several major cancers including breast cancer, obesity related malignancies, hormone dependent cancers and prostate carcinoma [25,26].

Vitamin D; Metabolism and clinical importance

Vitamin D is found in 2 primary forms. The first form is ergocalciferol (D2). The second form is cholecalciferol (D3) [27]. The activation of both forms requires 25-hydroxylation in the liver [28], but cholecalciferol (D3) demonstrate some advantages in bioavailability and efficacy. So, the serum concentration of cholecalciferol (D3) considered as the main biomarker for vitamin D deficiency indication [29]. Vitamin D deficiency is epidemiologically associated with increased cancer risk and adverse oncological outcomes, with marked racial disparities compounding its role as a significant public health challenge [30-32].

“The hypothesis of this study is that a combined panel of omentin-1, FGF-23, and vitamin D can more accurately predict prostate cancer status than individual biomarkers.”

Study Design and Population

This study employed a case-control study, in which serum samples from both PCa patients and healthy controls were obtained and analyzed at Al Amal Oncology Centre in Karbala/ Iraq, within December 2022 and June 2023. Serum concentrations of irisin, omentin-1; FGF-23 and vitamin D have been quantified by the use of ELISA. Analyses were employed by the use of commercial ELISA kits from Cloud-Clone Corp. (USA) were employed: SEN576Hu (for irisin), SEA933Hu (for omentin-1), SEA746Hu (for FGF-23), and CEA920Ge (for vitamin D) according to the manufacturer’s instructions.

Inclusion criteria: The study comprised a total of 60 participants, including 30 prostate cancer patients receiving hormonal therapy with Zoladex and thirty apparently healthy controls. Both cases and controls were selected within the age range of 45 to 70 years.

Irisin was investigated as an exploratory, mechanistic biomarker within the panel.

Exclusion criteria: for prostate cancer patients and controls included a history of diabetes, thyroid disorders, or cardiovascular diseases to minimize potential confounding effects.

The Ministry of Health’s Kerbala Directorate of Health’s study committee granted ethical permission (Ref: 206 in 27/November 2022).

Statistics and data analysis

Using T-test to compare between studied groups. With p-value of < 0.05; significant statistical association. Pearson ’s correlation values were obtained by use of a simple linear regression model to assess associations between variables. All statistical analyses and data management were conducted using ROC curve and SPSS software, version 28.0 (Released 2021; IBM Corp. USA).

For all inferential tests a two-tailed approach was used [33,34].

A priori power analysis indicated that a sample size of N=30 per group provides 80% power ($\alpha=0.05$) to detect a medium-to-large effect size (Cohen’s $d \geq 0.7$). To account for multiple

comparisons, a Bonferroni correction was considered; however, all reported p-values (< 0.001) remained statistically significant after adjustment.

Results

As shown in Table 1, the mean serum irisin level was significantly lower within patient group (21.9 ± 3.2) ng/ml in comparison to the healthy control category (60.8 ± 3.5) ng/ml, p < 0.001).

Parameters	Mean ± SD		P-value
(ng/ml)	Controls (NO.30)	Patients (No.30)	
Irisin	60.8 ± 3.5	21.9 ± 3.2	0.0001
Omentin-1	38.8 ± 6.6	10.3 ± 2.9	0.0001
FGF-23	163.1 ± 22.4	240.8 ± 55.2	0.0001
Vit. D	19.1 ± 2.4	6.4 ±0.7	0.0001

Table 1. Circulating Levels of Irisin, Omentin-1, FGF-23 and Vit. D (ng/ml) in Control and PCa Groups.

Similarly, the average level in serum of FGF-23 (ng/ml) in prostate cancer group undergoing hormonotherapy was significantly elevated (240.8 ± 55.2) compared to apparently healthy controls (163.1 ± 22.4) with (p < 0.001). The mean serum concentration for omentin-1 (ng/ml) were also markedly reduced in PCa patients (10.3 ± 2.9) relative to the apparently healthy control group (38.8 ± 6.6) with (p < 0.001). Furthermore, the average level for vitamin D level (ng/ml) was significantly lower in patients (6.4 ± 0.7) than in controls (19.1 ± 2.4), (p < 0.001). Body mass index in patients is ranging from overweight to mild obesity (BMI: 26.0 – 29.0 kg/m^2; Overweight - Obese class I) and for healthy control group is ranging from normal to overweight (BMI: 24.5 – 27.0 kg/m^2; Normal - Overweight). Tables 2 and 3 illustrate the relationship between FGF-23 and omentin-1 with other measured parameters in PCa patients receiving hormonal therapy.

	Factors	Irisin	Omentin-1	Vit. D
FGF-23	R (Pearson)	-0.011	0.473	0.162
	P	0.954	0.008	0.393

Table 2. Statistical Relationship between FGF-23 with other 3 Parameters.

	Factor	Irisin	Vit. D
Omentin-1	R (person)	0.055	0.615
	P	0.774	0.0001

Table 3. Statistical Relationship between Omentin-1 with (Irisin and Vit. D).

Table 2 represents a non-significant negative relationship between FGF-23 and irisin, and a non-significant positive association with vitamin D. However, a statistically significant positive correlation was observed between FGF-23 and omentin-1. The data in Table 3 indicate a statistically significant positive correlation between omentin-1 and vitamin D values. The correlation between omentin-1 and irisin was positive but not significant.

ROC Curve Analysis: This curve was employed to find out the discriminatory effect of irisin; omentin-1; FGF-23 and vitamin D as important biomarkers (Table 4).

Variables	Area under the curve	Sensitivity	Specificity	95% C.I		Cut off value
				L.B.	U.B.	

Irisin	0.733	0.852	0.718	0.644	0.824	21.794
FGF-23	0.956	0.953	0.998	0.993	0.988	252.65
Omentin-1	0.958	0.935	0.962	0.929	0.99	25.787
Vit. D	0.938	0.927	0.952	0.902	0.963	15.51

Table 4. ROC Curve and AUC Analysis for Irisin, Omentin-1, FGF-23 and Vit. D.

This curve graphically explained the inverse relationship between sensitivity and specificity for these biomarkers. The Area Under the Curve (AUC) values for ROC analysis was:

Irisin: moderate discriminative ability (AUC = 0.733; 95% CI: 0.644–0.824). FGF-23: excellent diagnostic accuracy (AUC = 0.956; 95% CI: 0.993–0.988), omentin-1: (AUC = 0.958; 95% CI: 0.929–0.990) and vitamin D: (AUC = 0.938; 95% CI: 0.902–0.963).

These values indicate that irisin has a moderate discriminative power. Omentin-1, FGF-23 and vitamin D possess excellent discriminative power between control and patients and predicting disease progression and treatment response. For FGF-23, a cutoff of 252.65 ng/ ml, sensitivity (95.3%), specificity (99.8%), suggesting it as a suitable biomarker for diagnostic conformation, although a small part of prostate cancer cases (≈4.7%) may be missed.

Optimal cutoff values were determined using the Youden index to maximize the combined sensitivity and specificity.

Discussion

The decreased level of irisin in studied PCa patients is consistent with Tekin et al. [35], they identified irisin as an important key regulator for PCa cell proliferation. Another study reported a significant low level of irisin in PCa patients, suggesting irisin as a promising biomarker which could enhance the diagnosis and prognosis alongside prostate- specific antigen (PSA) [36]. In treated patients,

the decline in irisin circulatory levels reflects a catabolic consequence induced by therapy, characterized by weight loss and decline in primary tissue source (muscle mass loss) [37]. Consistent with current data, Teishima et al. confirmed that FGF-23 levela are increased in PCa patients [38]. The elevated FGF-23 serum levels in PCa patients in this study is consistent with Hussein et al. which noted that androgen-deprivation therapy in PCa patients can elevate FGF-23, through the induction of osteoporosis [39]. The suppression of vitamin D synthesis by FGF2-3 regulated by downregulation of renal enzyme 1α-hydroxylase (CYP27B1), create a physiological environment for inverse relationship between increased FGF-23 and decreased 1,25-dihydroxyvitamin D [1,25 $(OH)_2D$] observed in PCa patients serum levels [40]. Beyond the classical function of vitamin D and its role in mineral homeostasis, it also recognized as a key regulator in carcinogenesis. Recent evidences from epigenomic, transcriptomic and proteomic studies have proved its involvement in cancer cell regulation, self renewal and apoptosis. Beside direct role and cellular effects, vitamin D display important immunomodulatory capacities in tumor microenvironment and anti-neoplastic effects. Low circulating levels of this vitamin are correlated with increased cancer risk. Therefore, vitamin D supplementation, as monotherapy or conjugated with immunotherapy represent a promising strategy for oncological outcome improvement [41,42]. Our findings demonstrate that a combined panel of vitamin D, omentin-1, and FGF-23 offers promising diagnostic potential. Vitamin D deficiency, supported by evidence of impaired activation by elevated FGF-23, is a central feature of our patient cohort. This mechanism is consistent with Layne., et al and suggests that vitamin D supplementation warrants investigation as a therapeutic adjunct [43].

In conclusion, this study suggests that a combined panel of vitamin D, omentin-1, and FGF-23 may serve as a diagnostic tool to complement PSA in prostate cancer detection. However, prospective validation in independent cohorts and assessment of clinical utility in risk stratification are required before clinical implementation.

Declarations

The authors declare no conflicts of interest.

Funding

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Clinical trial registration

Not applicable.

Conflicts of interest/Competing interests

Authors declare that they have no conflicts of interest.

Availability of data and material

The data sets used and/or analyzed during the current study are available from the corresponding authors per reasonable request.

Code availability

No custom code was used in this study.

Authors' contributions

The author contributed to the conception and design of the study, data collection, data analysis, and drafting and final revision of the manuscript. The author approved the final version for submission.

Ethics approval

This study was approved by the Ethic Committee of the Ministry of Health / Karbala Health Directorate; No. 206 Date: 27/11/2022.

Consent to participate

Written informed consent was obtained from all participants prior to their inclusion in the study, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication

Written informed consent was obtained from all participants, and the trial was conducted in accordance with the Declaration of Helsinki.

Originality Declaration for Figures and Tables

All tables included in this manuscript are original and have been created by the authors specifically for the purposes of this study. No previously published or copyrighted images have been used. The authors confirm that all graphical elements, illustrations, and visual materials were generated from the data obtained in the course of this research or designed uniquely for this manuscript.

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Declaration on

AI paraphrasing tools were used.

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