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Research Article

The Role of Omentin-1 and Fibroblast Growth Factor-23 in Iraqi Patients with Prostate Cancer during Chemotherapy

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Abstract

Background: Omentin-1 is mainly expressed in stromal vascular cells of adipose tissue and can also be expressed in airway goblet cells, mesothelial cells, and vascular cells. Fibroblast growth factor 23 (FGF-23), generated by bone cells, regulates phosphate and vitamin D metabolism by regulating phosphate reabsorption in the kidneys and inhibiting vitamin D activation. Vitamin D is a fat-soluble vitamin that regulates calcium absorption, bone health, and immunological function. Prostate cancer is a significant health concern for men worldwide. Several studies demonstrated a link between these variables and cancer as they exert important anti-inflammatory, antioxidative, and anti-cancer functions.
Objectives: To assess the impact of Omentin and FGF-23 biochemical functions, as well as the anti-cancer properties of vitamin D.
Patients and methods: This is a case-control study on serum samples collected from Iraqi prostate cancer patients after receiving chemotherapy at Al Amal Center in Imam Hussein Medical City in Karbala between November 2022 to May 2023. The serum samples were collected from two groups: The control group consisted of 30 healthy males. The patient group consisted of 30 prostate cancer patients after receiving chemotherapy, both groups aged 45 – 80 years. The two groups were matched for body mass index. ELISA technology was used to estimate serum levels of the aforementioned biochemical parameters with vitamin D.
Results: The patient group had a significantly higher FGF-23 level than the control group (309.5±41.65) versus (163.1±22.4). On the other hand, Irisin, Omentin and Vitamin D mean serum concentrations were significantly lower in-patient group (15.2±4.24), (13.8±4.28) and (4.4±0.69), respectively, compared to control group (60.8±3.5), (38.8±6.59), and (18.9±2.36), respectively. (ROC) curve analysis identified the best AUC values of FGF-23, Omentin, and Vitamin D (0.995, 0.959, 0.937), respectively, which suggests a high level of accuracy.
Conclusions: These parameters may serve as critical indicators for prostate cancer patients and their disease progress. Vitamin D insufficiency is a risk factor for these individuals.
Keywords: Chemotherapy; Irisin; FGF-23; Omentin-1; Prostatic cancer.

Introduction

Prostate cancer (PCa) is the world's second most frequent malignant cancer and the fifth highest cause of cancer-related death among males (1,2). Prostate tumours develop and spread slowly, postmortem examinations revealed that, many cases over the age of 50 years (and a number of younger men), who died of other conditions, also had prostate cancer that had never manifested when they were alive. In many cases, neither they nor their healthcare providers were aware of their condition (3). Within an average age at onset of 68 years, PCa is the most frequent male illness. Men over the age of 75 account for two-thirds of all prostate cancer fatalities. (4). Despite advances in medical technology, identifying and curing prostate cancer remains a significant challenge. Men are frequently unaware of the possible hazards of prostate cancer until it is too late, although early diagnosis is essential for effective treatment. As a result, many men die from the illness needlessly (5). More than 3.3 million men in the United States have been diagnosed with prostate cancer and are still living. However, Prostate cancer kills around one out of every 44 men (6). Omentin or interlectin-1, is a novel adipocytokine of 313 amino acids. Circulating omentin-1 can be applied as an indicator for bone metabolism (7), inflammatory illnesses, malignancies, sleep apnea syndrome, preeclampsia, cancer, and polycystic ovary syndrome (8). It can also be regarded as an acute-phase response with a therapeutic potential (9). Fibroblast growth factor-23 (FGF-23) is a 251 amino acid, 32 kDa glycoprotein. It is a member of endocrine FGFs, FGF-19, and FGF-21(10, 11). FGF-23 induces the growth of prostate tumors. FGF-23 autocrine synthesis promotes the proliferation of certain types of cancers, such as breast cancer, prostate cancer, and renal cell carcinoma (12-14). Irisin is a 112 amino acid-glycoprotein (15, 16). It is produced by different tissues, including skeletal muscle and fat cells. Irisin transforms white adipose tissue, which stores energy, into beige or brown adipose tissue, that is more metabolically active (17). Recent investigations revealed a relationship between irisin and cancer (18). Serum irisin levels are considerably lower in breast cancer patients (19), obesity-related cancer, and

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hormone-related malignancies such as prostate cancer compared to healthy people (20). Thus, the current study is designed to assess the impact of Omentin and FGF-23 biochemical functions, as well as the anti-cancer properties of vitamin D.

Patients and methods

A case-control study was carried out. Patients' and controls' serum samples were collected and tested at Al Amal Oncology Center in Karbala between November 2022 to May 2023. Irisin, Omentin-1, FGF-23 and Vitamin D levels were examined by using the following Kits: (SEN576Hu, SEA933Hu, SEA746Hu, CEA920Ge), respectively, Cloud-Clone Corp, USA. The ELISA technology was used to estimate serum levels of the aforementioned biochemical parameters with vitamin D. Inclusion criteria for cases and controls: The study included 60 samples, of which 30 samples were taken from (prostate cancer patients receiving either Cabazitaxel© or Taxotere© chemotherapy), and 30 healthy controls. The cases and controls were selected between the ages of 45-80 years. Exclusion criteria for cases and controls: Prostate cancer patients and controls with other diseases such as cardiovascular disease, thyroid disorder, and diabetes **were excluded.** Ethical approval was obtained from the research committee in the Kerbala Directorate of Health/ Ministry of Health (Ref: 206 in 27/November 2022). Statistical methods: The results were expressed as mean± SD. The student t-test was used to compare mean values between cases and controls. P-values of <0.05 were considered to be significant. Pearson correlations between variables were determined using a simple linear regression model. The SPSS package - version 28 was used for data storage and analysis (21).

Results

Table 1 shows a lower mean concentration of Irisin in the patients' group (15.2±4.25), compared to the healthy group (60.8±3.5), (p <0.001). The mean level of serum FGF-23 in PCa patients treated with chemotherapy was (309.5±41.65) compared to that of healthy controls (163.1±22.4), (p <0.001), The mean level of serum omentin concentration was significantly lower in patients (13.8±4.28) compared to the healthy control group (38.8±6.59), (p <0.001) with. The mean Vitamin D concentrations of the patients were (4.4±0.69) compared to that of the control group (18.9±2.36), *(p <0.001).*

Table 1: Mean concentrations of Irisin, Omentin, FGF-23, and Vitamin D in prostatic cancer patients and controls

Parameters	Mean ± SD		*P value*
	Controls (No. 30)	Patients (No.30)	
Irisin pg/ml	60.8±3.5	15.2±4.25	0.0001
Omentin ng/ml	38.8±6.59	13.8±4.28	0.0001
FGF-23 pg/ml	163.1±22.4	309.5±41.65	0.0001
Vitamin D ng/ml	18.9±2.36	4.4±0.69	0.0001

The correlations between FGF-32 and Omentin with other parameters among prostate cancer patients on chemotherapy were shown in Tables (2 and 3). Table 2 shows a non-significant correlation between FGF-23 with all parameters, negatively with Omentin and Irisin. However, positively with Vitamin D.

Table 2: Correlation between FGF-23 with Irisin, Omentin & Vitamin D

	Factors	Irisin	Omentin	Vitamin D
FGF-23	R (Pearson)	-0.028	-0.351	0.042
	P	0.883	0.058	0.824

Table 3 shows a non-significant correlation between Omentin with other parameters, positive with Irisin, but negative with Vitamin D.

Table 3: Correlation between Omentin with Irisin & Vitamin D

	Factor	Irisin	Vitamin D
Omentin	R (person)	0.13	-0.173
	P	0.493	0.360

The Receiver Operating Characteristic (ROC) curve assessment for Irisin, FGF-23, Omentin and Vitamin D across every group is demonstrated in Table 4. It depicts the relationship between sensitivity and specificity in the ROC curve. The findings recorded an exceptional Area Under the Curve (AUC) value of the aforementioned parameters with the following details: 0.734, 0.955,0.959 and 0.937, respectively. This indicates a good level of discrimination between the groups for Irisin, and high level for other parameters.

Table 4: The Receiver Operating Characteristic (ROC), sensitivity, and specificity of Irisin, FGF-23, Omentin and Vitamin D

Variables	Area under the curve	Sensitivity	Specificity	95% C.I.		Cut off value
				L.B.	U.B.	
Irisin	0.734	0.852	0.718	0.644	0.824	21.793
FGF-23	0.955	0.953	0.998	0.993	0.988	252.66
Omentin	0.959	0.935	0.962	0.929	0.990	25.788
Vit D	0.937	0.927	0.952	0.902	0.963	15.5

Discussion

The lower Irisin level among PCa patients in the current study is in line with the results of Tekin et al, which showed that Irisin regulates cell division and proliferation in prostate cancer cells (22). The significantly lower Irisin levels are in prostatic cancer patients in the current study may indicate that it can be used as a biomarker with PSA, as also suggested by other studies (23). Irisin levels can be at their lowest in prostate cancer patients who have just

received chemotherapy, due to the marked weight loss and muscle mass loss (24). FGF-23, which is largely generated by osteocytes in the bone, is essential for controlling the metabolism of phosphate and vitamin D (25). To assist in keeping the body's mineral balance, it works on the kidneys and parathyroid gland. Phosphate excretion in the urine is enhanced as a result of FGF-23's reduction of phosphate reabsorption in the kidneys (18). Additionally, it prevents the kidneys from producing calcitriol, an active form of vitamin D that contributes to even lower phosphate levels (26). It is well known that FGF-23 levels rise when active vitamin D (calcitriol) signaling is insufficient. This happens to lessen intestinal phosphate absorption and increase urine phosphate excretion (27). Analysis of human tumour samples, in vitro experiments, and animal models have provided strong evidence that fibroblast growth receptors (FGFRs) are crucial for PCa development. The higher FGF-23 concentration in of prostate cancer patients in the current study is consistent with the results of the study of Teishima *et. al*. (28). Androgen-inhibiting therapy for PCa patients contributes to osteoporosis and thus increases FGF-23 values, as indicated by Hussein *et. al*. (29). All the aforementioned facts support the findings of the current study of higher serum FGF-23 levels in prostate cancer patients compared to controls.

Intelectin-1) ITLN1)might help with the growth and spread of tumors. Since the blood levels of ITLN1 are very changeable and vary depending on the kind of cancer, the expression of ITLN1 in the local tumor might be more indicative of malignant behavior (15). Generally, testosterone and estradiol levels tend to fall with hormonal prostate cancer treatment associated with chemotherapy, such as androgen deprivation therapy (ADT). Since testosterone and other androgens are frequently required for the formation of prostate cancer cells, ADT seeks to reduce the quantities of these substances in the body. Estradiol is produced in part from testosterone through the process of aromatization; thus, a drop in testosterone synthesis or its effects also results in a fall in estradiol levels (30). Omentin and the ratio of estradiol to testosterone were also shown to be positively correlated. Perhaps because of the drop in this proportion following hormonal or chemotherapeutic treatments, the concentration of Omentin-1 may also be reduced (31). A major side effect of hormone therapy for prostate cancer is a drop in both testosterone and estradiol levels, which is frequently accompanied by other diverse effects such as changes in energy levels, bone health, muscle mass, and sexual function. Based on variables namely the kind of hormonal therapy, the length of the treatment, and individual variations in hormone metabolism, the precise magnitude of the drop and its impact might vary across people (32). Vitamin D insufficiency and racial inequities are linked to a slew of ailments, including cancer, putting a strain on the healthcare system (33-35). There are two types of Vitamin D: D2 [ergocalciferol] and D3 [cholecalciferol]. Human skin produces Vitamin D3 in reaction to UVB light, but Vitamin D2 is acquired from plant sources such as edible (UV-exposed) mushrooms in our diets, albeit at varied amounts and with lower efficacy (36). The two types of Vitamin D are physiologically inactive and must be changed to 2(OH)D in liver by Vitamin D-25-hydroxylase (37). The predominant form of Vitamin D in circulation is 25 (OH)D, and its measurement in the clinical environment offers information about one's Vitamin D status (38). FGF-23 inhibits the production of 1,25(OH)2D in the kidney by suppressing the transcription of the Vitamin D-activating enzyme 1-hydroxylase (CYP27B1). A rise in FGF-23 results in a reduction in the levels of serum Vitamin D in prostate cancer patients (39). Although Vitamin D is commonly recognized due to its function in the equilibrium of minerals management, its deficiency is additionally connected to the emergence and progression of some cancer forms. New Vitamin D-mediated molecular processes that govern cancer cell self-regeneration, and demise have been discovered in recent epigenomic, transcriptomic, and proteomic investigations. Tumor microenvironmental research has further introduced dynamic links between the immune system and the anti-neoplastic capabilities of Vitamin D. The preponderance of research demonstrates that low circulation Vitamin D ratios are linked to an elevated risk of tumors; whereas supplemental intake alone or in conjunction with additional chemo-immunotherapeutic medications may enhance clinical results even more (40).

Limitations

The study was and only two tumor centers (Al-Amal) at Imam Hussein Medical City in Karbala, and Oncology Hospital Teaching in Baghdad.

Conclusion

FGF-23, Omentin and Vitamin D may be useful biomarkers and indicators for prostate cancer patients and their disease progress. Vitamin D insufficiency is a risk factor for these individuals. They might serve as biomarkers to accurately predict the progression of the stage of prostate cancer.

Authors' declaration

Conflicts of Interest: The authors declare no conflict of interest. We confirm that all the Figures and Tables in the manuscript belong to the current study. Besides, the Figures and images, which do not belong to the current research, have been given permission for re-publication attached to the manuscript.

Authors sign on ethical consideration's approval- Ethical Clearance: The local ethical committee approved the project in (Karbala Directorate of Health/ Ministry of Health (Ref: 206 in 27/November 2022).

Conflict of Interest/ None

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Authors' contributions

Study conception & design: (Ammar H. Alqazzaz & Anwar F. Al-Taie). Literature search: (Ammar H. Alqazzaz & Anwar F. Al-Taie).
Data acquisition: (Ammar H. Alqazzaz & Anwar F. Al-Taie). Data analysis & interpretation: (Ammar H. Alqazzaz & Anwar F. Al-Taie). Manuscript preparation: Ammar H. Alqazzaz). Manuscript editing & review: (Ammar H. Alqazzaz & Anwar F. Al-Taie).

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دور الأومينتين-1 وعامل نمو الخلايا الليفية-23 (FGF-23) في المرضى العراقيين المصابين بسرطان البروستاتا أثناء العلاج الكيميائي

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الخلاصة:
الخلفية: يتم التعبير عن Omentin-1 بشكل رئيسي في الخلايا الوعائية اللحمية للأنسجة الدهنية ويمكن التعبير عنه أيضًا في الخلايا الكأسية للمجرى الهوائي والخلايا الظهارية المتوسطة والخلايا الوعائية. تم العثور على Omentin-1 كمضاد للإلتهابات ومضاد للأكسدة ومضاد للسرطان. ينظم عامل نمو الخلايا الليفية 23، الناتج عن الخلايا العظمية، إستقلاب الفوسفات وفيتامين (د) عن طريق تنظيم إعادة إمتصاص الفوسفات في الكلى وتثبيط تنشيط فيتامين (د). فيتامين (د) قابل للذوبان في الدهون وينظم إمتصاص الكالسيوم وصحة العظام والوظيفة المناعية. يتم الحصول عليه في الغالب عن طريق التعرض لأشعة الشمس والتغذية. يعد سرطان البروستاتا مصدر قلق صحي كبير للرجال في جميع أنحاء العالم. وهو ثاني أكثر أنواع السرطان شيوعًا لدى الرجال. وأظهرت العديد من الدراسات وجود صلة بين هذه المتغيرات والسرطان لأنها تمارس وظائف مهمة مضادة للإلتهابات ومضادات الأكسدة ومضادة للسرطان.
الأهداف: تم تصميم دراسة حالات وعينة ضابطة لدراسة تقييم تأثير الأومينتين والوظائف البيوكيميائية لـ FGF-23، بالإضافة إلى الخصائص المضادة للسرطان لفيتامين (د).
المنهجية: تم جمع عينات البحث من الذكور العراقيين المصابين بسرطان البروستاتا. المرضى الذين تم تشخيصهم بعد تلقي العلاج الكيميائي في مركز الأمل في مدينة الإمام الحسين الطبية في كربلاء للفترة بين تشرين الثاني ٢٠٢٢ الى آيار ٢٠٢٣. وكانت العينات عبارة عن مصل من الذكور الذين تتراوح أعمارهم بين 45 و 80 سنة، و 30 عينة لمجموعة الأصحاء الذين كانوا مرافقين لمرضى سرطان البروستاتا و 30 عينة للمرضى بعد العلاج الكيميائي، وتمت مطابقة الحالات والعينة الضابطة أيضًا حسب مؤشر كتلة الجسم. تم استخدام تقنية ELISA لحساب مستويات مصل العوامل الكيميائية الحيوية المذكورة أعلاه مع فيتامين (د).
النتائج: وجد ارتفاع كبير للغاية في مستويات FGF-23 (41.65±309.5) (p <0.001)عند المرضى، مقارنة بالمجموعة الضابطة (163.1 ± 22.4). كما وجد انخفاض معنوي في تركيز الإيريسين والأومنتين وفيتامين (د) في الأمصال لدى المرضى (4.24±15.2)(p <0.001) ، (4.28±13.8) (p <0.001)و (0.69 ±4.4) (p <0.001)على التوالي، مقارنة بمجموعة الاصحاء الضابطة (3.5 ± 60.8)، (6.59 ± 38.8)، و (2.36 ± 18.9)، على التوالي. حدد تحليل منحنى (ROC) أفضل قيم AUC لـ FGF-23، وOmentin، وفيتامين (د) (0.995)، (0.959)، 0.937)، على التوالي، مما يشير إلى مستوى عالٍ من الدقة.
الإستنتاجات: قد يكون الأومينتين-1 وعامل نمو الخلايا الليفية-23 وفيتامين (د) علامات حيوية ومؤشرات مفيدة لمرضى سرطان البروستاتا ولتطور مرضهم. يعد نقص فيتامين د أحد عوامل الخطر بالنسبة لهؤلاء الأفراد.
مفتاح الكلمات: سرطان البروستات، العلاج الكيمائي، الاومنتين-1، عامل نمو الخلايا الليفية-23، الايريسين