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Integrated Analysis of Trace Elements, Vitamins, and Hormones in Pancreatic Cancer Patients in Thi-Qar Province

Isam Nghaimesh Taeb

Pathological Analyses Department, College of Science, University of Sumer, Thi-Qar, 64001, Iraq.
**Corresponding Author: assamneghamish@gmail.com*
Phone number : 07811645736

Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) has one of the highest mortality rates and the worst prognoses of any cancer. Some causes of PDAC are related to metabolic dysfunctions, deficiency of certain micronutrients, and accumulation of certain toxic trace metals.

Objective: This study aimed to analyze and compare through assessment of blood trace elements, micronutrients and hormones, levels of PDAC with age-matched healthy controls of PDAC males from the Middle East.

Methods: This study was conducted on a sample of 200 men from the 50-70 age cohort from the Governorate of Thi-Qar, Iraq, 100 were PDAC patients and the other 100 were healthy controls. Peripheral samples from patients were taken after fasting for 12-14 hours. The test of atomic absorption spectrophotometry and inductively coupled plasma-mass spectrometry were used to assess presence of trace elements and heavy metals, and serum levels of retinol and all-trans retinoic acid (ATRA) and 25-hydroxyvitamin D were done using HPLC and ELISA methods, while serum levels of the vitamins B2, B6, B9, and B12 were done by ELISA. The hormones, testosterone, FSH, LH, estradiol (E2), progesterone, androstenedione, and insulin and the IGF-1 and IGFBP-3 were assessed using CLIA and ELISA methods. For statistical analysis SPSS was used and a p-value < 0.05 was significant.

Results: The concentrations of Fe, Zn, Se, Mg, and Ca as well as vitamin A, ATRA, and 25-hydroxyvitamin D were significantly reduced in PDAC patients, while the concentrations of the toxic metals As, Pb, Cd, and Mo were increased. Cholinesterase concentrations were unchanged, while copper and mercury concentrations were unchanged and decreased, respectively. Reduced levels of testosterone, progesterone, androstenedione, and IGFBP-3 were correlated with increased levels of FSH, LH, estradiol (E2), and insulin. The increase in IGF-1 was minimal and statistically insignificant.

Conclusion: There are multiple dimensions of the gauntlet PDAC patients face, including nutritional deficiencies, an excess of toxic metals, and severe dysregulation of hormones. These findings highlight markers of disease progression, and potential targets for dietary or hormonal interventions.

Keywords: Pancreatic ductal adenocarcinoma, trace elements, toxic metals.

التحليل المتكامل للعناصر النزرة والفيتامينات والهرمونات في سرطان البنكرياس

عصام نغيمش تعيب

قسم التحليلات المرضية / كلية العلوم / جامعة سومر / ذي قار / العراق

الخلاصة :

الخلفية Background : يُعد سرطان غدة البنكرياس القنوي (PDAC) أحد أكثر أنواع السرطانات فتكاً مع سوء إنذار طبي، ويُعتقد أن أسبابه تعود جزئياً إلى الاضطرابات الأيضية، ونقص المغذيات الدقيقة، وتراكم المعادن السامة الزهيدة.

الهدف Objective : كان الغرض من هذه الدراسة هو مقارنة مستويات العناصر الزهيدة والفيتامينات والهرمونات في المصل والدم الكامل لدى المرضى العراقيين الذكور المصابين بسرطان غدة البنكرياس القنوي (PDAC) مع ضوابط أصحاء مطابقتين لهم في العمر.

الطريقة Methods : أجريت دراسة حالة وضبط (Case-control study) شملت 200 رجل تتراوح أعمارهم بين 50-70 عاماً (100 مريض بـ PDAC و100 من الأصحاء) في محافظة ذي قار، العراق. تم الحصول على عينات دم محيطية بعد صيام ليلة كاملة. استُخدم مطياف الامتصاص الذري ومطياف كتلة البلازما المقترنة حثياً لتحديد العناصر الزهيدة والمعادن الثقيلة. كما استُخدمت تقنيتا HPLC وELISA لقياس مستويات الريتينول وحمض الريتينويك (ATRA) وفيتامين (د) 25-هيدروكسي في المصل، بينما استُخدمت تقنية ELISA لفحص فيتامينات 2B و6B و9B و12B. واستُخدمت تقنيتا CLIA وELISA لتقييم مستويات الهرمونات مثل التستوستيرون، FSH، LH، الإستراديول (2E)، البروجسترون، الأندروستينديون، الأنسولين، IGF-1، وIGFBP-3. استُخدم برنامج SPSS للتحليل الإحصائي، مع اعتبار القيم الاحتمالية (p-values < 0.05) دالة إحصائياً.

النتائج Results : كانت مستويات الحديد (Fe)، الزنك (Zn)، السيلينيوم (Se)، المغنيسيوم (Mg)، الكالسيوم (Ca)، فيتامين A، حمض الريتينويك (ATRA)، وفيتامين (د) 25-هيدروكسي أقل بكثير لدى مرضى PDAC، بينما كانت مستويات المعادن الخطرة (الزرنيخ، الرصاص، الكادميوم، والموليبدينوم) أعلى. كانت مستويات الكولينستريز متماثلة، ومع ذلك ظل النحاس ثابتاً وانخفض الزئبق. وُجد أن انخفاض مستويات التستوستيرون والبروجسترون والأندروستينديون وIGFBP-3 يرتبط بزيادة مستويات FSH وLH والإستراديول (2E) والأنسولين. كان الارتفاع في IGF-1 طفيفاً ولم يصل إلى الدلالة الإحصائية.

الاستنتاج Conclusion : يواجه مرضى سرطان غدة البنكرياس القنوي (PDAC) تحدياً أيضياً مزدوجاً يشمل نقص التغذية وزيادة المعادن السامة، فضلاً عن خلل هرموني كبير. تكشف هذه النتائج عن مؤشرات حيوية لتطور المرض بالإضافة إلى أهداف علاجية غذائية أو هرمونية محتملة.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the most lethal malignancy, and, despite significant advancements in diagnostic imaging and systemic therapeutic approaches for management of PDAC, the prognosis for PDAC continues to be very poor. In less than 10% the PDAC population, there is a life expectancy of more than 5 years and for those with advanced disease it is only 4-6 months[1]. The poor prognosis for PDAC is attributed to several different factors which include the clinical stage at diagnosis, inherent resistance to chemotherapy, and the disease biology and tumor microenvironment which is especially challenging to treat. The poor prognosis for PDAC continues to be especially challenging to treat. It is for these reasons that a major focus of pancreatic cancer research is directed toward the identification of systemic biomarkers that indicate the order of disease progression, as well as to inform future preventative or therapeutically customized treatment approaches[2].

The systemic changes involved in PDAC have particularly increased the scientific inquiry for trace elements and heavy metals. Minor trace elements such as zinc (Zn), selenium (Se), iron (Fe), calcium (Ca), and magnesium (Mg) are particularly important for the antioxidant system, the immunologic system, and the system of DNA repair, proliferation, and differentiation. [3]. New clinicertate and expe imental eviden e sh ows that Zn and Se deficiency decrease the effi iency of the DNA repair system and increase the oxidative stress in the tum r microenvironment and therefore, increase the rate of tumor growth [4,5]. The toxic metals, cadmium (Cd), arsenic (As), lead (Pb), and mercury (Hg), have been associated with pancreatic carcinogenesis because they increase oxidative damage, cause epigenetics, and increase resistance to apoptosis [6,7].

Vitamins A and D and water-soluble B-complex vitamins (specifically B2, B6, B9, and B12), are critical for DNA methylation, cellular defense and differentiation, and also for oxidative stress defense [8,9]. For instance, retinoic acid, the active form of vitamin A, present in B-complex vitamins, regulates epithelial differentiation and immune system monitoring, and vitamin D regulates cell cycle and programmed cell death [10,11]. B9 and B12 are also critical for one-carbon metabolism which is modified in most cancers [12].

Additionally, the impact of hormonal dysregulation, especially in conjunction with the gonadal and metabolic axes, is being recognized as an emerging area of concern in the understanding of PDAC pathogenesis. Changes in sex hormone profiles, insulin resistance, and elevated insulin-like growth factor-1 (IGF-1) have all been implicated in the risk and prognosis of pancreatic cancer [13,14]. The imbalance of testosterone and estradiol (E2) is suggested to be in favor of cancer promotion as these hormones have opposing roles in cell proliferation and inflammation [15,16].

Although trace elements, vitamins, and hormones have individually been analyzed in the context of PDAC, there is still a lack of research that is cross-sectional and integrates all three in a single cohort, especially in less studied regions like Iraq. The present study attempts to address the aforementioned gap by assessing the serum and whole blood of Iraqi male PDAC patients and age- matched healthy controls. Through the combined approach of measuring relevant and non-relevant toxic trace elements, vitamins, and hormones, along with the hypothesized blood values that derive from and/or relate to the disease, we intend to identify relevant biomarkers and substantiate further the metabolic and endocrine dimensions of the disease.

2. Materials and Methods

2.1 Study Design and Population

In this case-control study, conducted between January 2023 and December 2024, collaboration was made between the Pathological Analyses Department, College of Science, University of Sumer, and the Oncology Center of Thi-Qar Governorate, Iraq. The study focused on 200 men, aged 50 to 70, made up of 100 patients with case confirmed PDAC (case group) and 100 healthy individuals (control group). All participants were PDAC patients who were newly diagnosed and had received neither chemotherapy nor radiotherapy during sample collection. Patients from the healthy control group were living in the same area and had no history of malignancy, chronic liver or kidney disease, or metabolic disorder. Study participants signed written consent forms to comply with the Helsinki Declaration, and this study was approved by the University of Sumer Institutional Review Board.

2.2 Sample Collection

Peripheral blood samples (10 mL) were collected from each participants after an overnight fast (≥12 hours). Blood samples were collected in two tubes: One EDTA-coated tube for whole blood analysis and one plain tube for serum separation. Serum was obtained by centrifugation at 3,000 RPM for 10 minutes and was stored at -80°C until analysis. To minimize degradation, all samples were processed within two hours of collection.

2.3 Trace Element and Heavy Metal Analysis

Serum and whole blood levels of essential trace elements (Fe, Zn, Se, Mg, Ca, Cu) and toxic heavy metals (As, Pb, Cd, Hg, Mo) were assessed by atomic absorption spectrophotometry (Perkin Elmer AAnalyst 400) and by inductively coupled plasma-mass spectrometry (Agilent 7900) measuring instruments. All reagents were of analytical quality, and standard reference materials were used to monitor the quality control. The samples were diluted, and the measurements were made in triplicate.

2.4 Vitamin Analysis

Using high performance liquid chromatography (HPLC; Shimadzu LC-20A) with UV detection at 325 nm, serum vitamin A and all-trans retinoic acid (ATRA) were measured. Serum 25-hydroxyvitamin D [25(OH)D] was measured by using an enzyme-linked immunosorbent assay (ELISA; IDS Ltd., UK). ELISA kits (Elabscience, USA) were used to measure the water-soluble vitamins B2 (riboflavin), B6 (pyridoxine), B9 (folate), and B12 (cobalamin) according to the guidelines set by the manufacturer. The coefficient of variation was < 10% for the duplicate assays and the intra- and inter-assay.

2.5 Hormone Analysis

Using chemiluminescence immunoassay (CLIA; Siemens ADVIA Centaur XP) and ELISA (R&D Systems, USA), we measured the Serum levels of testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), progesterone, androstenedione, insulin, insulin-like growth factor-1 (IGF-1), and IGF-binding protein-3 (IGFBP-3) and other hormones. Cholinesterases activity was measured spectrophotometrically with a commercial kit (Randox Laboratories, UK). The hormone assays were done as instructed by the employer, and control samples with known concentrations were included in each assay.

2.6 Statistical Analysis

Data were processed with IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). For continuous variables, comparison was performed via independent t-test or Mann-Whitney U tests (Shapiro-Wilk to check normality). In all obtained results, continuous variables were expressed as mean ± standard deviation (SD). For categorical variables, the Chi-square test was used. Pearson or Spearman correlation was used to measure variables relationship. Statistically significant was p \textless 0.05. For selected biomarkers, Receiver operating charachter (ROC) curve was analyzed.

3. Results

3.1 Participant Characteristics

Table 1 summarizes the demographic and clinical characteristics of the study participants. There were no significant differences in age, body mass index (BMI), or smoking status between PDAC patients and healthy controls ($p > 0.05$). However, PDAC patients exhibited significantly higher levels of fasting blood glucose and lower levels of albumin relative to the controls ($p < 0.001$).

Table 1- Demographic and clinical characteristics of study participants

Characteristic	PDAC Patients (n=100)	Healthy Controls (n=100)	p-value
Age (years)	62.3 ± 5.8	61.7 ± 6.2	0.47
BMI (kg/m²)	24.8 ± 3.2	25.3 ± 3.5	0.29
Smokers, n (%)	45 (45%)	42 (42%)	0.68

Fasting glucose (mg/dL)	138.5 ± 28.3	92.4 ± 8.7	<0.001
Albumin (g/dL)	3.2 ± 0.5	4.3 ± 0.4	<0.001

3.2 Trace Elements and Heavy Metals

Compared to healthy controls (all $p < 0.001$), patients with PDAC showed lower levels for all essential trace elements assayed (Fe, Zn, Se, Mg, Ca) in serum (see Table 2). On the other hand, patients with PDAC showed a higher level of all tested toxic heavy metals (As, Pb, Cd, Mo) (all $p < 0.001$). There was no statistically significant difference in both study groups for copper (Cu) ($p = 0.52$), while a paradoxical lower level of mercury (Hg) was found in PDAC patients ($p = 0.03$). Cholinesterase activity did not differ between the groups ($p = 0.84$).

Table 2- Serum trace elements and heavy metals in PDAC patients and healthy controls

Element	PDAC Patients (n=100)	Healthy Controls (n=100)	p-value
Iron (Fe, µg/dL)	68.3 ± 15.2	95.7 ± 18.4	<0.001
Zinc (Zn, µg/dL)	72.5 ± 12.8	98.3 ± 14.6	<0.001
Selenium (Se, µg/L)	58.4 ± 10.3	85.2 ± 12.7	<0.001
Magnesium (Mg, mg/dL)	1.6 ± 0.3	2.1 ± 0.4	<0.001
Calcium (Ca, mg/dL)	8.3 ± 0.9	9.5 ± 0.7	<0.001
Copper (Cu, µg/dL)	105.3 ± 18.2	107.8 ± 19.5	0.52
Arsenic (As, µg/L)	12.8 ± 3.4	4.2 ± 1.5	<0.001
Lead (Pb, µg/dL)	8.5 ± 2.1	3.1 ± 1.2	<0.001
Cadmium (Cd, µg/L)	3.8 ± 1.2	1.2 ± 0.5	<0.001
Mercury (Hg, µg/L)	2.3 ± 0.8	3.1 ± 1.0	0.03
Molybdenum (Mo, µg/L)	7.5 ± 2.0	4.3 ± 1.3	<0.001
Cholinesterase (U/L)	4850 ± 820	4920 ± 910	0.84

3.3 Vitamin Levels

Table 3 depicts that PDAC patients showed significant decreases in serum concentrations of vitamin A (retinol), ATRA, and 25-hydroxyvitamin D compared to controls (all $p < 0.001$). Likewise, PDAC patients had significantly decreased concentrations of the water-soluble vitamins B2, B6, B9, and B12 (all $p < 0.001$).

Table 3- Serum vitamin levels in PDAC patients and healthy controls

Vitamin	PDAC Patients (n=100)	Healthy Controls (n=100)	p-value
Vitamin A (μg/dL)	28.5 ± 7.3	48.2 ± 9.5	<0.001
ATRA (ng/mL)	1.8 ± 0.5	3.2 ± 0.7	<0.001
25(OH)D (ng/mL)	15.3 ± 5.2	28.7 ± 6.8	<0.001
Vitamin B2 (ng/mL)	12.5 ± 3.2	18.9 ± 4.1	<0.001
Vitamin B6 (ng/mL)	8.3 ± 2.1	14.2 ± 3.3	<0.001
Vitamin B9 (ng/mL)	4.5 ± 1.3	8.7 ± 2.0	<0.001
Vitamin B12 (pg/mL)	285 ± 68	425 ± 95	<0.001

3.4 Hormone Profiles

In Table 4, healthy controls exhibit less hormonal variation than patients with PDAC. The levels of testosterone, progesterone, androstenedione, and IGFBP-3 were significantly lower (< 0.001 for all) in patients than in controls. Reversely, PDAC patients had significantly elevated levels of FSH, LH, estradiol (E2) and insulin (all $p < 0.001$). PDAC patients had an almost statistically significant ($p = 0.12$) higher level of IGF-1 as compared to healthy controls.

Table 4- Serum hormone levels in PDAC patients and healthy controls

Hormone	PDAC Patients (n=100)	Healthy Controls (n=100)	p-value
Testosterone (ng/mL)	3.2 ± 0.9	5.8 ± 1.3	<0.001
FSH (mIU/mL)	18.5 ± 4.3	8.2 ± 2.5	<0.001
LH (mIU/mL)	12.3 ± 3.1	5.7 ± 1.8	<0.001
Estradiol (E2, pg/mL)	42.5 ± 9.8	28.3 ± 6.2	<0.001
Progesterone (ng/mL)	0.3 ± 0.1	0.8 ± 0.2	<0.001
Androstenedione (ng/mL)	0.8 ± 0.2	1.5 ± 0.4	<0.001
Insulin (μIU/mL)	18.3 ± 5.2	9.5 ± 2.8	<0.001
IGF-1 (ng/mL)	135 ± 32	125 ± 28	0.12
IGFBP-3 (μg/mL)	2.8 ± 0.7	4.2 ± 0.9	<0.001

4. Discussion

This in-depth case-control study offers a unique perspective on the combined metabolic and endocrine landscape of PDAC via the first integrated assessment of trace elements, vitamins, and hormones in an Iraqi male patient cohort. Our research describes an intricate and systemic landscape of PDAC, marked by the interplay of nutritional and toxic metal imbalances, and the dysregulation of hormones.

4.1 Trace Elements and Heavy Metals

Trace elements (Fe, Zn, Se, Mg, and Ca) in PDAC patients and previous studies show significant decreases in these elements and can be attributed to changes in diet as well as changes in metabolism due to cancer cachexia [17,18]. The rapid growth of tumors can possibly be attributed to zinc deficiency since it impairs DNA repair enzymes and antioxidant defense systems [4]. A deficiency of selenium, which is an important part of glutathione peroxidase, means that cells do not have protection from oxidative stress which increases the likelihood of developing cancer [5,19]. The increased toxic metals (As, Pb, Cd, and Mo) in PDAC patients is worrisome and indicate an environmental exposure and/or contaminated water near the study area. Cadmium, as one of these toxic metals, contributes to the development of pancreatic cancer due to oxidative stress and damage to DNA [6,21].

4.2 Vitamin Deficiencies

PDAC patients show alarming deficiencies in both fat-soluble (A, D) and water-soluble (B2, B6, B9, B12) vitamins which indicates extreme nutritional compromise. Vitamins A and D show immunological and epithelial differentiation and unsatisfactory levels of vitamin D have been associated with higher levels of cancer due to poor levels of cell proliferation and unsatisfactory levels of apoptosis [11,24]. B-complex vitamins deficiencies are alarming as B vitamins are crucial in one-carbon metabolism and DNA synthesis [12,25].

4.3 Hormonal Dysregulation

The constancy of physiological changes shows great disruption of both the gonadal and the metabolic axes. The decrease of testosterone and the increase of gonadotropins (FSH, LH) would indicate primary hypogonadism [27,28]. The combination of elevated estradiol and low testosterone may produce a pro-inflammatory hormonal environment situational to favor tumor development [15,29]. Significant hyperinsulinemia corroborates the well-documented association of insulin resistance and pancreatic cancer [13,30]. The decrease of IGFBP-3 may increase IGF-1 signaling even with the presence of modest increments of total IGF-1 [14,32].

4.4 Clinical Implications

Our results illustrate significant clinical ramifications. If specific biomarker panels are recognized for their high diagnostic precision, it indicates the possibility for utility in the identification and/or risk stratification of probable future illnesses. Extensive nutritional deficiencies illustrate the necessity for more in-depth nutritional evaluations, as well as more comprehensive, targeted nutritional interventions. The hormonal changes may serve as other potential therapeutic avenues, including the use of testosterone or other insulin-sensitizing agents.

4.5 Limitations

This study has multiple limitations. Due to the cross-sectional design, causality cannot be determined. The study has a small sample size and was conducted in one geographical area. Additionally, the study did not systematically collect data on dietary and environmental exposures, and only male participants were included in the study.

5. Conclusion

The findings of this study show that PDAC patients experience a "two-pronged metabolic gauntlet", due to extreme nutritional deficiencies and a toxic burden of metals, along with extensive hormonal dysregulation. These findings suggest new potential biomarkers of disease progression and new possible metabolic and hormonal therapeutic targets. These findings also recommend that a more thorough nutritional and hormonal evaluation be incorporated into the standard of care for PDAC patients.

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Ethical Responsibilities of Authors

The author, irrefutably, takes responsibility for the content. Furthermore, the author will not publish the content elsewhere. The author has done no fabrication or manipulation of the content. The author has received no other submissions or no other publications. The author provides the full submission to the ethics standards of the institutional research committee and the 1964 Helsinki Declaration. The author has received ethical clearance from the University of Sumer, Institutional Review Board. The author has received written informed consent from the participants.

Disclosure and Conflict of Interest

Conflict of Interest: The authors declare no competing interests with respect to this research.

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