JOBS
مجلة العلوم الأساسية
Journal of Basic Science
Print -ISSN 2306-5249
Online-ISSN 2791-3279
العدد السابع والعشرون
٢٠٢٥م /١٤٤٦هـ
العدد السابع والعشرون
(693) (681)

دراسة بعض المعايير المناعية والكيميائية الحيوية لدى مرضى سرطان البنكرياس

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المستخلص

الخلفية: يُعد سرطان البنكرياس أكبر سبب للوفاة من السرطان في جميع أنحاء العالم، وقد تضاعف عبء هذا المرض بأكثر من الضعف على مدار ربع القرن الماضي. اهداف الدراسة: هدفت الدراسة الحالية إلى تقييم مستوى البيرين، والبروتين ١ المرتبط بـ (Kelch-like Ech KEAP1)، والسينتينين لدى مرضى البنكرياس ومجموعة الاصحاء. المواد وطرق العمل: أجريت هذه الدراسة في محافظات شمال العراق بين يناير ويونيو ٢٠٢٤. وقد تم تضمين ما مجموعه ٦٠ مريضًا، من الرجال والنساء الذين تتراوح أعمارهم بين ٤٠ و٨٠ عامًا، في الدراسة بعد تشخيص إصابتهم بسرطان البنكرياس من قبل أطباء متخصصين. تم تصنيف المشاركين بناءً على عوامل مثل الجنس والعمر ومؤشر كتلة الجسم ونوع العلاج الذي تلقوه. النتائج: فيما يتعلق بمستويات البيرينpyrin والكياب1KEAP ، والتي انخفضت في مجموعة المرضى، كانت ٣١٦.٩٦ ± ٥٧.٩١، ٢٤٧.١١ ± ٤٢.١٣ نانوغرام/لتر، مقارنةً بـ ٦٢٥.٢٥ ± ٤٩.٥٠، ٤٥٤.٨٩ ± ٣٠.٠١ نانوغرام/لتر في مجموعة الاصحاء (قيمة الاحتمال <٠.٠٠١). أما فيما يتعلق بمستويات السينتينين، فقد أظهرت زيادة طفيفة ولكنها ذات دلالة إحصائية في مجموعة المرضى (١.٩٩٧ ± ٠.١٧٨، ١٦٠.٠٦ ± ١٠.٠٨ نانوغرام/لتر) مقارنةً بمجموعة الاصحاء (١.١١٩ ± ٠.١٠٠، ٩٧.٩٨ ± ١١.٦٧ نانوغرام/لتر، قيمة الاحتمال <٠.٠٠١). الاستنتاج: خلصت الدراسة الحالية إلى انخفاض مستويات البيرلين، Keap1 في مجموعة المرضى، في حين ارتفعت مستويات السينتينين في مرضى البنكرياس.

الكلمات المفتاحية: مرضى البنكرياس، البيرين، والكياب 1 (Keap1)، والسينتينين.

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Investigating some immunological and biochemical parameters in pancreatic cancer patients

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Abstract

Background: Pancreatic cancer is the largest cause of mortality from cancer across the globe, and the burden of this disease has more than doubled over the course of the last quarter century. Aim of the study: The present study aimed to evaluate the level of Pyrin, Kelch-like Ech-associated Protein 1(KEAP1), and syntenin, in pancreatic patients and control. Materials and methods: This study took place in the northern Iraqi governorates between January and June 2024. A total of 60 patients, both men and women aged 40 to 80 years, were included in the study after being diagnosed with pancreatic cancer by specialized physicians. The participants were categorized based on factors such as gender, age, BMI, and the type of treatment they received. For comparison, control groups were carefully matched to these patient groups. Result: Regarding, pyrin, and Keap1 levels which is decreased in the patient group were 316.96 ± 57.91, 247.11 ± 42.13 ng/L, compared to 625.25 ± 49.50, 454.89 ± 30.01 ng/L in controls ($p<0.001$). Regarding, Syntenin showed a slight but statistically significant increase in the patient group (1.997±0.178, 160.06±10.08 ng/L) compared to controls (1.119±0.100, 97.98±11.67ng/L, $p<0.001$), at $p<0.001$. Conclusion: The present study concluded decrease pyrin, Keap1 levels in the patient group, while an increase Syntenin in pancreatic patients.

Keywords: pancreatic patients, pyrin, Keap1, and Syntenin.

1.Introduction

Cancer is an abnormal proliferation of cells in a tissue or organ that causes the cells to change their nature, eventually producing a lump or mass and spreading to other body regions in most cases (Abdullah, Y. J et al .,2021). Pancreatic cancer is currently the third leading cause of cancer-related death in the United States, with around 62,200 new cases diagnosed each year, resulting in 48,800 deaths. Approximately 90% of pancreatic neoplasms are categorized as pancreatic ductal adenocarcinomas (PDAC).

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In contrast to many other cancers, where early detection and breakthroughs in cancer treatments have significantly improved survival rates, pancreatic ductal adenocarcinoma (PDAC) typically presents at an advanced stage in over 80% of patients, resulting in a dismal 5-year survival rate of 11% (Stoffel et al., 2023). Pyrin is a significant protein (86 kDa) encoded by the MEFV gene in humans. Pyrin is mostly found in neutrophils, eosinophils, monocytes, dendritic cells, and synovial fibroblasts, but is not significantly prevalent in lymphocytes. The expression can be elevated by many cytokines, including IFN-γ, LPS, TNF-α, IL-4, and IL-10 (Gavrilin et al., 2009; Heilig & Broz, 2018). Pyrin is categorized as a cytosolic pattern recognition receptor (PRR) that modulates innate immune responses upon detecting pathogen or host-derived danger signals, referred to as pathogen/danger-associated molecular patterns (PAMPs/DAMPs (Broz & Dixit, 2016 & Al-Badri et al .,2022).

Keap1 is widely expressed in a variety of cell types and tissues, with a predominant location in the perinuclear region of the cytoplasm, as well as in the nucleus, endoplasmic reticulum, and inclusion bodies (Al-Karawi, et al., 2024). Keap1's level and activity are influenced by various mechanisms, including transcriptional regulation, epigenetic alterations, miRNAs, somatic mutations, post-translational modifications, and degradation (Kopacz et al., 2020). Keap1 has a crucial function in cancer prevention and progression. It is an adapter for the ubiquitin ligase complex that modulates Nrf2 activity (Best et al., 2019). The Keap1/Nrf2 pathway serves as the principal sensor of the intracellular redox state.

In the typical redox state, Keap1 is associated with Nrf2 (nuclear factor erythroid-derived 2-like 2), which results in the repression of Nrf2 activity through degradation via the ubiquitin-proteasome pathway (Yamamoto et al., 2018). KEAP1 and NRF2 are known to influence oncogenesis, cellular proliferation, apoptosis, and tumor formation, which is why the KEAP1/NRF2 axis is notoriously deregulated in cancer cells (de la Vega et al., 2018). In humans, the SDCBP gene encodes a protein known as syntenin-1 (Grootjans et al., 1997). Syntenin was initially identified as a binding companion of the C-terminal cytoplasmic domain of syndecan;

consequently, it is also known as the syndecan binding protein (SDCBP). In addition, it is known as melanoma differentiation-associated gene-9 (MDA-9) as a result of the established modulation of syntenin expression in human melanoma cells by mezerein and interferon-gamma therapy(Lin et al., 1998 & Kadhim *et al* .,2023). The overexpression of syntenin-1 has been documented in breast cancer (Liu et al., 2018) and liver cancer (Liu et al., 2014).

The objective of this study is to evaluate the levels of pyrin and KEAP1 in the serum of pancreatic patients compared to a control group, and to investigate the association between these parameters and the disease.

2.Methods

2.1. Study population

This study took place in the northern Iraqi governorates between January and June 2024. A total of 60 patients, both men and women aged 40 to 80 years, were included in the study after being diagnosed with pancreatic cancer by specialized physicians. The participants were categorized based on factors such as gender, age, BMI, and the type of treatment they received. For comparison, control groups were carefully matched to these patient groups.and measure the marker Keap1 , Pyrin and Synterin vy ELIZA .

2.2. Study design

Venous blood specimens were obtained from both healthy subjects and patients. Five millilitres of blood were extracted from each participant and placed into gel tubes. The samples were subsequently centrifuged at 6000 rpm for 10 minutes to isolate the serum. The collected serum was meticulously placed into miniature Eppendorf tubes, with each sample designated by the patient's name, age, and sampling date. The samples were subsequently preserved in a deep freezer at -20°C for future biochemical investigation.

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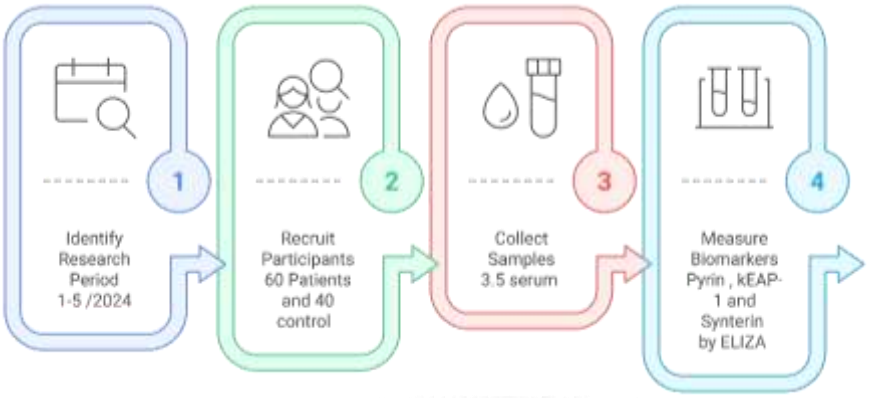

Figure1: Overview the steps of study design

2.3. Assessment of immunological and biochemistry markers levels:

The levels of pyrin, Keap1, and Syntenin were quantified using the Enzyme-Linked Immunosorbent Assay (ELISA). This method is based on the sandwich principle, which detects target proteins through a color change reaction catalyzed by an enzyme. The ELISA kits were obtained from Mysource Company (USA) with catalogue numbers 1110, 1159, 1458, and 11589.

2.4. Statistical analysis

Statistical analysis was conducted using SPSS 29 (version 4.3.2, 2023). The visualization of combined plots was achieved with the GridExtra package. Descriptive statistics were computed for all variables to summarize the data effectively.

3.Result

The bar chart compares the serum concentrations (ng/l) of Keap1 and Pyrin in control and patient groups. In both markers, the control group showed significantly higher concentrations than the patient group. Specifically, the mean Keap1 level in controls was 454.8 ± 30.0 ng/l, while in patients it was markedly lower at 247.1 ± 42.1 ng/l. Similarly, Pyrin levels were elevated in the control group (625.2 ± 49.5 ng/l) compared to the patient group (316.9 ± 57.9 ng/l). These differences were statistically significant<0. 001.As shown in the figure1.

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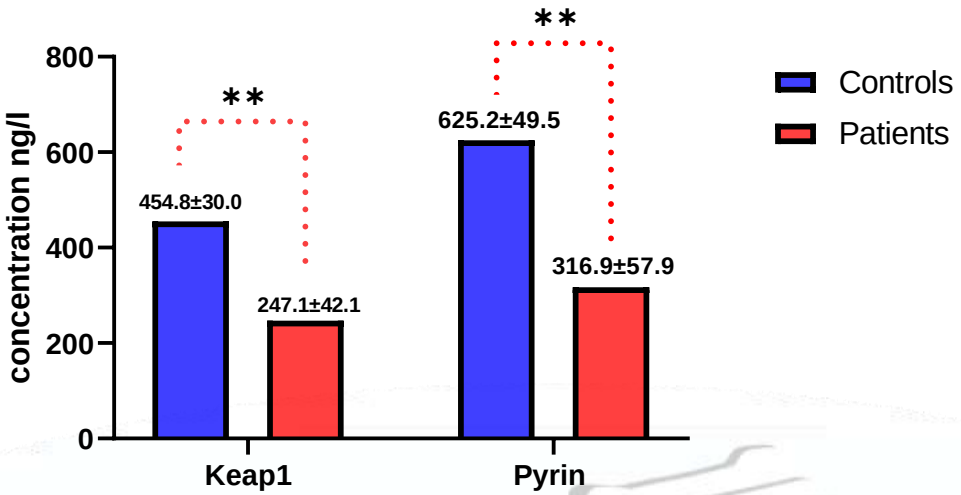

Figure1: Pyrin and Keap1levels were compared between the control and patient groups. The symbol * indicates a highly significant difference (p<0.001).**

Figure2 presents the analysis of Synterin levels were significantly elevated in the patient group compared to controls. The mean concentration of Synterin in the control group was 1.11 ± 0.10, whereas in the patient group it increased to 1.99 ± 0.17. This marked elevation suggests a potential association between elevated Synterin levels and the pathological condition observed in the patient cohort. Further statistical analysis is warranted to determine the significance and potential clinical implications of this difference.

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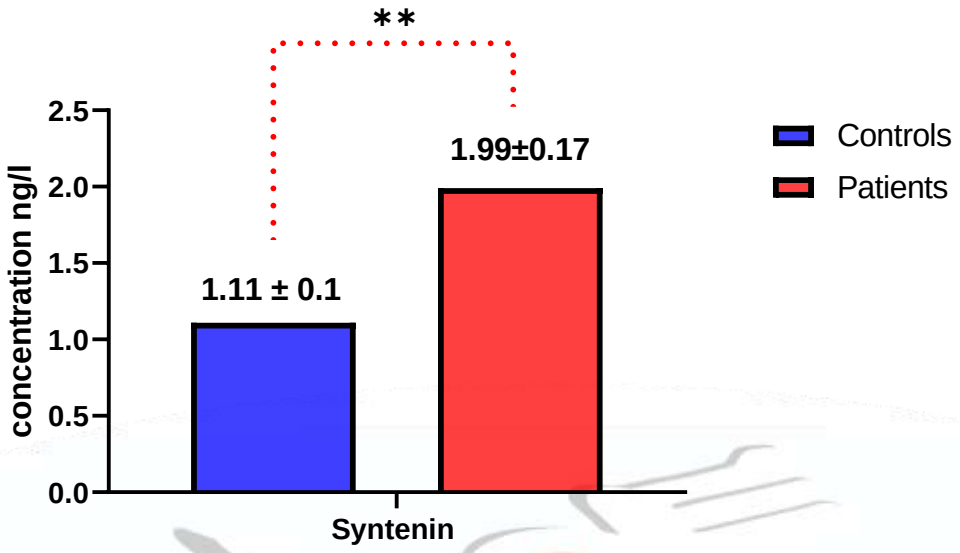

Figure2: Syntenin levels in the control and patient groups were compared. The symbol *** indicates a highly significant difference ($p<0.001$).

Discussion

The current study revealed that reduced serum pyrin levels in pancreatic patients are consistent with several studies highlighting the complex interplay between Pyrin, inflammation, and cancer progression. Pyrin, encoded by the MEFV gene, is predominantly expressed in innate immune cells such as neutrophils, monocytes, and dendritic cells, with its expression regulated by cytokines like IFN-γ, TNF-α, and IL-10 (Isohookana et al., 2015; Lister et al., 2011). The role of Pyrin in the innate immune system, mainly through its involvement in inflammasome assembly and activation of caspase-1, links it to the regulation of inflammatory responses (Hayes et al., 2015). Studies have demonstrated that inflammasomes, including those regulated by Pyrin, play dual roles in cancer. On the one hand, inflammasomes exert tumor-suppressive effects by modulating cytokine production, immune cell activity, and cellular responses (Kadhim *et al* ., 2024). On the other hand, chronic inflammasome activation can contribute to pro-tumorigenic inflammation, as seen in pancreatic cancer (Chow *et al.*, 2012; Feig *et al.*, 2012). The reduction in Pyrin levels observed in our study aligns with evidence that dysregulated inflammasome activity is associated

with impaired immune responses in the tumor microenvironment(Bartsch *et al.*, 2012).

Kelch-like ECH-associated protein 1 (Keap1) showed significantly lower levels in pancreatic cancer patients than healthy controls. Our findings are consistent with a previous study by (sohookana, J *etal* ., 2024), which reported the absence of Keap1 expression in approximately 70% of pancreatic cancer cases, with only about 30% of cases showing detectable Keap1 expression. This finding suggests that Keap1 transcription remains relatively low in pancreatic cancer tissues, contrasting with the much higher levels of Nrf2 observed in these tumors, and emphasizes the imbalance between Keap1 and Nrf2, which may play a critical role in promoting tumor progression by allowing Nrf2 to evade its usual regulation. Multiple prior investigations have shown that the expression of Keap1 in tumor tissues significantly differs from that in surrounding tissues. The Keap1 gene was inactivated or altered at various structural loci in cancerous tissues of individuals with lung, ovarian, and liver malignancies (Wang, R *et al* .,2024).

Recent clinical studies suggest that Keap1 expression levels are linked to outcomes in pancreatic cancer patients. For example, high levels of Keap1 on the cell membrane have been connected with longer relapse-free periods and better overall survival, indicating its potential role as a prognostic marker (Zhang, J. *et al* .,2025). In contrast, loss of Keap1 function, whether through genetic changes or promoter methylation, can lead to increased activity of Nrf2, which may promote resistance to chemotherapy. From a treatment perspective, targeting the Keap1–Nrf2 pathway presents both benefits and risks (He, X *et al* ,. 2024). While Nrf2 activators might protect healthy cells from oxidative stress, their use in cancer could worsen tumor growth. On the other hand, Nrf2 inhibitors have shown promise in making pancreatic cancer cells more sensitive to chemotherapy, emphasizing the need for careful selection of treatment timing and context (Zuo, J *etal* ., 2024). In comparison, the role of pyrin in pancreatic cancer is still not fully understood. Pyrin is mainly involved in inflammatory processes through inflammasome formation. Since chronic inflammation is a known risk factor

for pancreatic cancer, pyrin and related proteins may influence tumor progression. However, there is limited direct evidence, and further studies are needed to clarify pyrin's involvement in pancreatic cancer.

Our findings of elevated serum syntenin-1 levels in pancreatic cancer patients compared to the control group highlight the role of syntenin-1 in cancer progression and metastasis. Syntenin-1, encoded by the SDCBP gene, is a multifunctional protein initially identified as a binding partner of the syndecan cytoplasmic domain. Its expression has been linked to various physiological processes, including intracellular trafficking, cellular signaling, exosome biogenesis, and transcriptional regulation, collectively contributing to cancer cell proliferation, invasion, and metastasis (Das et al., 2018). Elevated levels of syntenin-1 have been consistently observed in various cancer types, including breast, prostate, lung, colorectal, liver, and pancreatic cancers, as well as glioblastoma. These studies highlight its role as an oncogene that promotes tumorigenesis, angiogenesis, and metastatic progression (Das et al., 2019; Iwamoto et al., 2020).

However, Syntenin-1, also known as syndecan-binding protein (SDCBP), is a scaffold protein involved in various cellular functions, such as adhesion, migration, and signal transduction. Recent studies have shown that its expression is significantly higher in pancreatic cancer tissues compared to normal pancreatic tissues. This elevated expression is associated with increased tumor cell growth, movement, and invasiveness (Fraile-Martinez *et al*.,2024).

One of the ways in which syntenin-1 contributes to cancer progression is by promoting epithelial–mesenchymal transition (EMT) through the PI3K/AKT signaling pathway, a mechanism closely linked to metastasis (Daley, *et al*.,2024). Additionally, it has been observed that microRNA miR-216b, which normally suppresses syntenin-1 expression, is often reduced in pancreatic cancer, leading to further elevation of syntenin-1 levels and enhanced tumor development (Wang, R *etal*.,2024). Syntenin-1 also plays a crucial role in the formation and function of exosomes, small vesicles that help cancer cells communicate and spread. Through its involvement in exosome production and content regulation, syntenin-1 helps transport

oncogenic molecules that support tumor growth, blood vessel formation, and metastasis. Because of its central role in pancreatic cancer progression, syntenin-1 is being investigated as a potential biomarker for prognosis and as a target for therapeutic intervention. Developing treatments that reduce syntenin-1 activity or expression may offer new strategies to manage this aggressive cancer (Soini, Y., et al 2024 & Hartikainen, J *et al* .,2022).

Conclusion:

The pancreatic cancer is global problem and the current study interesting to the some immunological and biomarker for pancreatic cancer patients. Furthermore, the results of current study revealed the significant decrease in the level of pyrin, Keap and of patient compared to control. while increase Syntenin in pancreatic patients.

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