The Link between NAFLD and Colorectal Cancer: Insights from Liver Function Enzymes and Serum Biomarkers in a Case-Control Study

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ABSTRACT

Background: Colorectal cancer (CRC) is a major killer, and nonalcoholic fatty liver disease (NAFLD) affects almost one-quarter of the global population. **The aim of study:** is to Investigate the correlation between nonalcoholic fatty liver disease (NAFLD) and an increased risk of colorectal cancer (CRC), as well as the relationship between liver function enzymes and specific serum biomarkers in CRC patients with NAFLD. **Methodology:** A case-control study involving 60 participants was conducted from February to August 2022. The patients with colon cancer were examined at Baghdad Medical City's Al-Amal Hospital for Radiation and Nuclear Medicine and Oncology Teaching Hospital, and blood samples were taken. Thirty patients with NAFLD who had just been diagnosed with colorectal cancer (CRC) were recruited. The study included 30 healthy individuals who served as controls. Colorimetric method kits were used to determine liver function enzymes. Also, the serum biomarkers cathepsin B, Obestatin, and kininogen-1 were calculated by ELISA. The serum levels of liver function enzymes, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) were evaluated in newly diagnosed CRC patients who suffered NAFLD and compared with healthy controls. **Results:** It was indicated that all tested enzymes were significantly elevated in newly diagnosed CRC patients with NAFLD. The correlation was conducted between liver function enzymes and biological markers. In the patient group, positive correlations were detected between ALT and cathepsin-B, obestatin, and kininogen-1 (r = 0.43, 0.66, and 0.52, respectively), with a significance in correlation recorded with obestatin and kininogen-1 (p = 0.007 and 0.047, respectively). AST inversely (negatively) correlated with cathepsin-B, obestatin, and kininogen-1, with no significance in control. However, in the patient group, the correlation was shifted to be positive with no significance. In the control group, ALP positively correlated with cathepsin-B, obestatin, and kininogen-1 (r = 0.1, 0.33, and 0.57, respectively). No significant differences were recorded between ALP, cathepsin-B, and obestatin. Meanwhile, the positive correlation between ALP and kininogen-1 was significant (p = 0.026). **Conclusion:** This study found significant liver function enzyme increases in newly diagnosed colorectal cancer (CRC) individuals with NAFLD. Selected blood biomarkers and liver function enzymes were positively correlated in CRC patients with NAFLD. These data suggest that NAFLD may raise the risk of colorectal cancer, which could inform future studies and clinical practice.

Keywords: NAFLD, CRC, LFT, Biomarkers, Cathepsin-B, Obestatin.

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INTRODUCTION

Epithelial carcinoma, also known as colorectal cancer (CRC), originates in the mucosal lining of the colon or rectum due to the uncontrolled growth of epithelial cells. This genetically diverse cancer often involves KRAS and BRAF oncogenic mutations. Globally, CRC ranks third in frequency and fourth in cancer-related mortality. In Iraq, it is the fourth most common cancer (1-4). Cancer and metabolic disorders have significant global health and

economic impacts, often co-occurring and influencing disease severity. Non-alcoholic fatty liver disease (NAFLD), a prevalent gastrointestinal metabolic disorder, affects approximately 25% of the world's population. Factors like obesity, poor nutrition, a sedentary lifestyle, and hyperlipidemia contribute to NAFLD, which can lead to metabolic disorders such as hyperlipidemia and type 2 diabetes if left undiagnosed and untreated (5-7). Additionally, untreated NAFLD can progress to NASH/fibrosis, cirrhosis, and HCC and is associated with gastrointestinal malignancies, including CRC (5,8). The liver enzymes involved are alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). Due to their extensive distribution in human tissues, ALT and AST are used for diagnosis and treatment. ALT is primarily found in the liver and very little elsewhere (9). Chronic hepatitis, acute viral hepatitis, alcoholic hepatitis, cirrhosis, and toxic ischemic injury increase both enzymes (10,11). The enzyme alkaline phosphatase (ALP) has no specific function. It is mainly produced by the liver and bone osteoblasts, with some help from leukocytes, intestines, kidneys, and the placenta. Located in cell membranes, ALP is implicated in liver, intestinal mucosa, and kidney transport. High ALP levels are connected to infiltrative liver disease, hepatitis, intrahepatic cholestasis, and extrahepatic bile obstruction (12). ALP levels are usually elevated in metastatic colorectal cancer patients. Lysosomal proteases, cathepsins, regulate tumour growth, invasion, migration, metastases, and angiogenesis (9). In normal cells, endopeptidase cathepsin B (CTSB) works in endolysosomes (13). Obestatin, generated from the ghrelin precursor protein, has 23 amino acids. It has many physiological activities and is linked to multiple illnesses, including stomach neuroendocrine tumors (14). Cysteine-containing proteinase inhibitor Kninogen-1 (KNG-1) has six subchains (15). To determine whether or not there is a connection between biomarkers like CTSB, obesatin, and KNG-1 and liver enzymes like ALT, AST, and ALP, the purpose of this inquiry is to investigate the association between these biomarkers.

METHODOLOGY

1. Study design

The research was conducted on a sample of 60 individuals in a case-control study from February 2022 to August 2022. Patients diagnosed with colon cancer from Al-Amal Hospital for Radiation and Nuclear Medicine and the Oncology Teaching Hospital at Baghdad Medical City were subjected to blood sample collection. Blood samples were collected from individuals who were receiving treatment at various facilities. The patients' medical files collected various clinicopathological characteristics, such as age, gender, tumor site, grade, and stage. Participants were provided information regarding the study's objective, and consent letters were obtained. The research was conducted after obtaining ethical approval from the hospital and the Ethical Committee of the Chemistry Department at Al-Nahrain University. The study participants were divided into two groups. Group I includes 30 patients who were recently diagnosed with colorectal cancer (CRC) and also have nonalcoholic fatty liver disease (NAFLD). This group is composed of 18 males and 12 females. A total of thirty individuals who were in good health were included in this study as control subjects. The group comprised fifteen males and fifteen females, aged 30 to 40. Each participant, including patients and healthy control subjects, provided a 5-milliliter blood sample. The blood sample was allowed to clot for an hour at room temperature before being centrifuged at 5,000 RPM for 10 minutes. After separation into smaller portions, all sera were frozen at -80℃ until ready for use. Liver function enzymes of Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), and Alkaline Phosphatase (ALP) were measured by colorimetric methods kits from Randox (UK). The concentrations of CTSB, OBS, and KNG-1 in the sera were determined using the Human Cathepsin B SimpleStep ELISA® Kit (Abcam (UK)), Human Obestatin SimpleStep ELISA® Kit (Abcam (UK)), and Human Kininogen 1 ELISA Kit (LSBio (USA)), respectively.

2. Statistical analysis

The statistical analysis used GraphPad Prism version 9.2 (GraphPad Software Inc., La Jolla, CA). Student's *t*-test and two-way ANOVA were used to determine whether group variance was significant or not. Pearson's coefficient r was employed to assess correlation. Quantitative parametric data were subjected to the Shapiro-Wilk test to confirm the normal distribution and were expressed as mean ± SD, and statistical differences were defined as * $p \leq 0.05$.

RESULTS

1. Evaluation of Serum Liver Enzymes (ALT, AST, and ALP)

The serum levels of liver function enzymes, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) were evaluated in newly diagnosed CRC patients who suffered NAFLD and compared with healthy controls. All tested enzymes were significantly elevated in newly diagnosed CRC patients with NAFLD (Table.1) and Figure (1). The mean level of ALT in the patients' group was 64.39±2.3 U/L, significantly (p <0.0001) higher than the control group's 24.78±1.85 U/L. The same significant (p <0.0001) ALP elevation was observed in the patient group, 230.3±9.94 compared with the control, 94.2±3.11 U/L. AST level was higher in CRC patients (52.9±3.58U/L) and was statistically significant (p = 0.0003) compared to healthy controls (18.40±3.31 U/L).

TABLE (1): MEAN SERUM LEVEL (±SD) ANALYSIS OF LIVER FUNCTION ENZYMES ALT, ALP, AND AST IN NEWLY DIAGNOSED CRC PATIENTS WITH NAFLD COMPARED WITH CONTROLS. ** P < 0.01.

Parameters	Mean ± SD		p-value
	Control	CRC Patient + NAFLD	
ALT (U/L)	24.78±1.85	64.39±2.3	<0.0001 **
ALP(U/mL)	94.2±3.11	230.3±9.94	<0.0001 **
AST (U/L)	18.40±3.31	52.9±3.58	0.0003 **

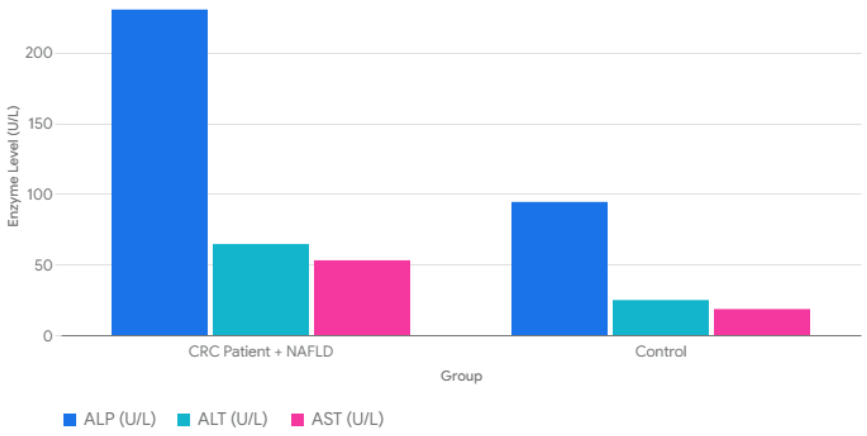

Figure (1): Mean serum level of ALT, ALP, and AST in newly diagnosed CRC patients with NAFLD compared with controls. ** p ≤0.05 considered as significant.

2. Correlation between Liver Function Enzymes and Serum Biomarkers

Correlation analysis by Pearson (r) and the probability (p) of data from CRC patients with NAFLD was determined and compared with the control group. The correlation was conducted between liver function enzymes and biological markers (cathepsin-B, obestatin, and kininogen-1). In the CRC patients with NAFLD group, results revealed that positive correlations were detected between ALT and cathepsin-B, obestatin, and kininogen-1 (r^2 = 0.43, 0.66, and 0.52, respectively), with a significance in correlation recorded with obestatin and kininogen-1 (p = 0.007 and 0.047, respectively). The same pattern of positivity between ALT and cathepsin-B, obestatin, and kininogen-1 in the control group was detected with no significant differences (Table 2). AST inversely (negatively) correlated with cathepsin-B, obestatin, and kininogen-1, with no significance in control. However, in the patients' group, the correlation was shifted to be positive with no significance. ALP positively correlated with cathepsin-B, obestatin, and kininogen-1 (r^2 = 0.1, 0.33, and 0.57, respectively) in the control group. No significant differences were recorded in ALP with cathepsin-B and obestatin. Meanwhile, the positive correlation between ALP and kininogen-1 was significant (p = 0.026).

Table (2): The r^2 value (p value) correlation of the control group and newly diagnosed CRC with NAFLD

Parameters	**r^2 Value (p) in Control Group**		
	Cathepsin-B	**Obestatin**	**Kininogen-1**
ALT	0.11 (0.690) NS	0.33 (0.232) NS	0.21 (0.455) NS
AST	-0.27 (0.398) NS	-0.01 (0.967) NS	-0.26 (0.418) NS
ALP	0.1 (0.822) NS	0.33 (0.229) NS	0.57 (0.026) *
Parameters	r Value (p) in CRC with NAFLD Group		
	Cathepsin-B	Obestatin	Kininogen-1
ALT	0.43 (0.114) NS	0.66 (0.007) **	0.52 (0.047) *
AST	0.01 (0.982) NS	0.12 (0.673) NS	0.24 (0.383) NS
ALP	0.1 (0.777) NS	0.22 (0.419) NS	0.31 (0.261) NS

NS: Non-significant, * $p \leq 0.05$, ** $p < 0.01$.

DISSCUSION

Non-alcoholic fatty liver disease (NAFLD) is characterized by excess fat accumulation in the liver of individuals who drink little to no alcohol. It encompasses a spectrum of conditions - from simple steatosis to non-alcoholic steatohepatitis (NASH), which can progress to cirrhosis and hepatocellular carcinoma. The pathophysiology behind NAFLD is not entirely understood but likely involves insulin resistance, genetic and epigenetic factors, gut microbiota, and nutritional factors (16). Aminotransferases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) , are sensitive indicators of hepatocellular injury and are commonly used to assess liver dysfunction (17). Alkaline phosphatase (ALP) has the highest concentration in the liver and bones. In liver disease, cholestasis leads to impaired bile flow and retention of ALP in serum (18). Numerous studies have demonstrated that patients with NAFLD have higher ALT, AST, and ALP levels compared to healthy controls. The degree of aminotransferase elevation generally correlates with the histological severity of the disease (19, 20). In a study by (21) ALT levels were nearly 2-fold higher and significantly associated with NAFLD patients detected type 2 diabetes versus controls, while AST was 66% higher (21). Another study by (22) also showed that increased levels of ALT, ALP, and AST are the surrogate markers for associated nonalcoholic fatty liver disease patients with other diseases (22). In addition, ALT, AST, and ALP, along with different parameters, are considered significant predictors for NAFLD. Elevated ALP has also been associated with NAFLD, especially advanced fibrosis (23). A few hypothesized mechanisms relate ALP to liver fibrosis - ALP modulates collagen secretion by hepatic stellate cells and bone morphogenetic protein and Wnt signaling, key pathways implicated in fibrogenesis. Patients with

NASH have been found to exhibit significantly higher ALP than those with simple steatosis. In a large study of biopsy-proven NAFLD, ALP increased with advancing fibrosis stage. It was an independent predictor of advanced fibrosis, performing better than AST and ALT in receiver operating characteristic analysis (24). The elevations in ALT, AST, and ALP correlate with the extent of liver injury and inflammation, explaining why levels are considerably higher in patients with advanced NAFLD. These enzymes exhibit moderate sensitivity and specificity for diagnosing steatohepatitis and advanced fibrosis according to specific cut-off values, but lack high accuracy to replace liver biopsy. Nonetheless, these biomarkers provide simple, inexpensive, non-invasive means for clinicians to identify patients requiring more targeted investigation. Serial monitoring also facilitates the assessment of disease progression and response to therapeutic interventions. Further research should establish appropriate reference ranges specific to NAFLD and optimize predictive models incorporating aminotransferases, ALP, and other biomarkers to improve diagnostic precision (25). NAFLD is highly prevalent in cancer populations, with rates as high as 50% in some studies. This stems from shared risk factors between NAFLD and cancer: obesity, diabetes, dyslipidemia, and insulin resistance. Additionally, some chemotherapeutic agents used in cancer treatment, like irinotecan and methotrexate, are associated with steatohepatitis development. Hence, assessing NAFLD in cancer patients has important prognostic and therapeutic implications (26). In a prospective study of CRC patients undergoing surgery, those with NAFLD had significantly higher mean ALT and AST preoperatively. ALT, AST, and ALP also individually correlated with the degree of steatosis and lobular inflammation on histology. This aligns with findings from a separate study where higher ALT and AST were predictive of NAFLD versus simple steatosis among CRC patients. Looking beyond CRC, a cross-sectional analysis of various gastrointestinal malignancies found that patients with radiological evidence of hepatic steatosis exhibited considerably higher ALT and AST versus non-steatotic counterparts (27). NAFLD has been linked to colorectal neoplasia in a number of studies, including two meta-analyses. On the other hand, a broad range of liver conditions, from straightforward steatosis to steatohepatitis with severe fibrosis, are included in NAFLD. Research on the correlation between colorectal neoplasia and the severity of non-alcoholic fasting lipomatosis is scarce and unreliable (28, 29).

Obestatin is a peptide hormone released from the gastrointestinal tract that has been shown to play a role in appetite regulation and weight homeostasis. The association between liver injury markers and obestatin was investigated in patients with NAFLD. It was demonstrated that serum obestatin levels were significantly higher in NAFLD patients than in healthy controls. Obestatin levels positively and significantly correlated with ALT. Increased obestatin in NAFLD patients may represent a compensatory mechanism to improve insulin sensitivity and protect against further liver injury from accumulated fat. This observed positive correlation between obestatin and ALT levels can potentially serve as a prognostic marker reflecting the severity of metabolic and inflammatory derangements in NAFLD patients (30). Further longitudinal studies are warranted to elucidate the causal links between altered obestatin signaling and the pathogenesis of NAFLD (31). On the other hand, Kininogen-1, as a protein that participates in blood coagulation pathways and inflammation, was reported to be associated with serum kininogen-1 levels and liver fibrosis in NAFLD patients based on proteomic studies. Kininogen-1 levels were significantly higher in NAFLD patients compared to healthy controls, with a positive correlation between kininogen-1 and serum ALT levels. As ALT is released from damaged hepatocytes, this suggests kininogen-1 rises in tandem with the extent of hepatic necroinflammation. The authors propose that peripheral blood kininogen-1 may reflect alterations in hepatic production and clearance in the setting of worsening NAFLD. With further validation, serum kininogen-1 levels could serve as a clinically useful biomarker signifying NAFLD disease activity and severity of liver injury (32).

CONCLUSION

The study revealed significant elevations in liver function enzymes in newly diagnosed colorectal cancer (CRC) patients with nonalcoholic fatty liver disease (NAFLD). The study also highlighted positive correlations between specific serum biomarkers and liver function enzymes in CRC patients with NAFLD. These findings underscore the potential link between NAFLD and an increased risk of colorectal cancer, providing valuable insights for further research and potential clinical implications in the management of these conditions.

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العلاقة بين مرض الكبد الدهني غير الكحولي وسرطان القولون والمستقيم: رؤى من إنزيمات وظائف الكبد والمؤشرات الحيوية في المصل في دراسة الحالات والشواهد

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[2,1] قسم الكيمياء ، كلية العلوم ، جامعة النهرين ، العراق

الخلاصة

خلفية عن الموضوع : سرطان القولون والمستقيم (CRC) هو سبب رئيسي للموت, ومرض الكبد الدهني غير الكحولي (NAFLD) يؤثر على ما يقرب من ربع سكان العالم. توجد علاقة بين NAFLD الموجود مسبقًا وزيادة خطر الإصابة بسرطان القولون والمستقيم وسرطان الكبد الانتقالي. **الهدف من الدراسة:** دراسة العلاقة بين مرض الكبد الدهني غير الكحولي (NAFLD) وزيادة خطر الإصابة بسرطان القولون والمستقيم (CRC)، وكذلك العلاقة بين إنزيمات وظائف الكبد والمؤشرات الحيوية المحددة في مصل الدم لدى مرضى CRC الذين يعانون من NAFLD. من بين ستين مشاركًا، **المواد وطرق العمل:** أجريت دراسة الحالات والشواهد في الفترة من فبراير إلى أغسطس 2022. تم فحص المرضى المصابين بسرطان القولون في مستشفى الأمل للأشعة والطب النووي ومستشفى الأورام التعليمي بمدينة بغداد الطبية، حيث تم اخذ عينات من الدم من 30 مريضا يعانون من NAFLD الذين تم تشخيص إصابتهم بسرطان القولون والمستقيم (CRC). شملت الدراسة 30 فرداً سليماً كانوا بمثابة الضوابط. تم تحديد إنزيمات وظائف الكبد باستخدام الطرق اللونية، كما تم حساب المؤشرات الحيوية في الدم: كاثيبسين ب، أوبيستاتين، وكينينوجين-1 بواسطة تقنية ELISA. تم تقييم مستويات مصل إنزيمات وظائف الكبد، ألانين أمينوترانسفيراز (ALT)، أسبارتات أمينوترانسفيراز (AST) والفوسفاتيز القلوي (ALP) في مرضى CRC الذين تم تشخيصهم حديثًا والذين عانوا من NAFLD ومقارنتهم مع الاشخاص الاصحاء. **النتائج:** أشارت النتائج بوضوح إلى أن جميع الإنزيمات التي تم اختبارها كانت مرتفعة بشكل ملحوظ في مرضى CRC الذين تم تشخيصهم حديثًا والذين يعانون من NAFLD. تم إجراء دراسة لعلاقة الارتباط بين إنزيمات وظائف الكبد والعلامات البيولوجية، وكشفت نتائج مجموعة المرضى أنه تم اكتشاف ارتباط إيجابي بين ALT وcathepsin-B، obestatin وkininogen-1 (معامل الارتباط 0.43 =، 0.66 و 0.52، على التوالي) مع أهمية في الارتباط المسجلة مع obestatin وkininogen-1 (ع = 0.007 و 0.047، على التوالي). يرتبط AST عكسيا (سلبيا) مع كاثيبسين-B، أوبيستاتين وكينينوجين-1 مع عدم وجود أهمية في الاشخاص الاصحاء. ومع ذلك، في مجموعة المرضى، تحول الارتباط ليكون إيجابيا مع عدم وجود أهمية. ALP يرتبط بشكل إيجابي مع كاثيبين-B، أوبيستاتين وكينينوجين-1 (معامل الارتباط = 0.1، 0.33 و 0.57، على التوالي) في المجموعة الضابطة. لم يتم تسجيل أي فروق ذات دلالة إحصائية لـ ALP مع الكاثيبين-B والأوبستاتين. في حين أن الارتباط الإيجابي بين ALP وkininogen-1 كان كبيرا (0.026). **الاستنتاجات:** وجدت دراستنا زيادات كبيرة في إنزيمات وظائف الكبد لدى الأفراد الذين تم تشخيصهم حديثًا بسرطان القولون والمستقيم (CRC) والذين يعانون من NAFLD. ارتبطت المؤشرات الحيوية المختارة للدم وأنزيمات وظائف الكبد بشكل إيجابي لدى مرضى CRC المصابين بـ NAFLD. تشير هذه البيانات إلى أن NAFLD قد يزيد من خطر الإصابة بسرطان القولون والمستقيم، مما قد يفيد الدراسة المستقبلية والممارسة السريرية.

الكلمات المفتاحية: مرض الكبد الدهني غير الكحولي ، سرطان القولون ، المؤشرات الحيوية ، كاثبسين بي ، اوبستاتين ، كنيونجين-1.