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ORIGINAL ARTICLE

The Role of Hepcidin Levels in Colorectal Cancer Patients

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Abstract

Background: Colorectal cancer is a worldwide health issue with high-cost treatment process. Several experimental studies have clarified the role of Hepcidin as a new reliable marker that helps to predict colorectal cancer development and prognosis.

Our study Aims to measure Hepcidin levels in patients diagnosed with colorectal cancer, study the importance of Hepcidin levels and its correlation with recurrence.

Purposes: Comparing Hepcidin levels between healthy controls and colorectal cancer patients, and its levels according to tumor stages. In addition to evaluating its role as a predictive marker of tumor development and prognosis.

Materials and methods: Our study included 51 participants classified as 39 patients who visited Tishreen University Hospital in Lattakia and were diagnosed with colorectal cancer, and 12 healthy subjects as control group. Blood samples were taken before undergoing any type of treatment, whether surgical, chemical or radiological. CEA, CA19-9 and Hepcidin levels were measured in all participants.

Results: We found a correlation between Hepcidin levels and tumor markers such as CEA and CA19-9. Hepcidin levels were elevated in colorectal cancer patients compared to healthy controls, with a significant difference between Hepcidin levels in colorectal cancer patients according to the stage of the tumor.

Keywords

Hepcidin, Colorectal cancer, CEA, CA19-9

Introduction

Colorectal cancer is classified as the third most common cancer worldwide in males after lung cancer and prostate cancer, and the second most common cancer in females after breast cancer, where about 1.9 million new cases were recorded in 2020, and it is considered the second cause of cancer-deaths, with estimated deaths of approximately 935,000 cases of total cancer deaths in 2020 [1]. It constitutes about 11% of all diagnosed cancers worldwide [2]. With a preponderance in developing countries an 3-4 times higher than developed ones, due to the nature of the low-fiber and high-fat diet in these countries. It is estimated that by 2035 the death rate of colorectal cancer will increase by (60-71.5)%. (The estimate of these figures varies from country to country depending on the degree of economic development and environmental changes) [3].

Hepcidin is mainly produced by the liver, and it plays an important role in iron metabolism [4], as it is the main regulator of iron levels in the solution, as it reduces its absorption in the duodenum and reduces the release of iron from phagocytes [5,6].

Iron absorption is regulated by Hepcidin, the expression of which is controlled by several factors, including iron stores, infections, anemia, and erythropoiesis [7].

Hepcidin levels rise in oncological patients with stimulation from inflammatory media, in particular Interleukin-6, BMP6 and CRP, and this increase is responsible for iron metabolism disorders, which is considered a cause of iron deficiency anemiadue to the role of Hepcidin in preventing the absorption of iron from small intestines and preventing its release from phagocytes, which leads to exacerbation of chronic

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anemia in patients and tumor progression. Elevated Hepcidin levels also lead to the accumulation of iron in the colon cells and this leads to an increase in essential Wnt signals in the incidence of colorectal cancer [7].

A recent study showed that about 6% of IDA iron deficiency anemia patients develop colorectal cancer, and IDA appears in colorectal cancer patients with the right side more often than the left side, the reason for this is most likely due to chronic occult bleeding associated with injury in the right colon compared to obvious bleeding in left colon cancer, which reveals the disease faster [4]. A few studies indicated that high levels of Hepcidin in intestinal mucosa of colorectal cancer patients compared to controls. Hepcidin levels are also associated with the stage of tumor as we found higher levels in advanced stage compared to stage T1-T2 [8,9].

Patients and Methods

Sample collection

Our study included 39 patients from Tishreen University Hospital in Lattakia who were diagnosed with colorectal cancer, blood samples were taken before undergoing any type of treatment, whether surgical, chemical or radiological. The Hepsidin levels in the patient group were measured and compared with the Hepcidin values in the healthy control group of 12 patients. The study extended for 12 months, during the follow-up all patients were checked out with Hepcidin levels were monitored several times.

Objectives

Comparing Hepcidin levels between healthy controls and colorectal cancer patients and its variation with tumor development. In addition to evaluating Hepcidin levels between relapsed and non-relapsed patients and its role as a predictive marker of the degree of tumor and its prognosis.

Statistical Analysis

- Statistical analyzes were conducted using the Statistical Package for the Social Sciences (SPSS), version 26. The Shapiro-Wilk test was performed to check the normal distribution.
- Graphic forms and tables were used in the characterization of values. Averages, Standard Deviations and Central Tendency Measures were used to characterize quantitative data.
- The t-test was performed if the distribution was normal, and the Mann-Whitney U test for the non-normal distribution. The receiver operation characteristic curve (ROC Curve) was used to analyze the optimal cut-off value of Hepcidin for predicting breast cancer. Results were considered statistically significant when p-value < 0.05.

Results

Sample characteristic

After considering the previously mentioned criteria, the study sample included 51 participants divided of two groups as following: The first group included of 39 patients diagnosed with colorectal cancer and consisted of 23 females (58.97%) and 16 males (41.03%), the age of patients ranged from (48-78) years with an average age (60.48 ± 7.67). Control group included 12 women whom age ranged from (31.33 ± 10.9). Colorectal cancer patients were chosen from all different stages (1, 2, 3) equally (n = 13) and all of them were followed for 16 months since the beginning of this study. We found that 4 patients died during the follow-up. 8 patients relapsed (20.5%), of which 3 patients died, meanwhile 31 patients were non-relapsed (79.5%).

Main variables in colorectal cancer patients according to tumor-stage

We found a statistically significant difference in tumor markers levels in colorectal cancer patients according to the stage of tumor (p-value < 0.05) (Table 1).

Comparison of Hepcidin levels between patients and the healthy controls

When performing t test, we noticed that the p-value ≤ 0.05, which indicates a statistically significant difference in Hepcidin levels between healthy and colorectal cancer patients (Table 2).

Comparison of Hepcidin levels between patients according to the stage of cancer

There was a statistically significant difference between Hepcidin levels among colorectal cancer patients according to the stage of tumor. We compared each two stages separately (Table 3), and noticed a strong coloration between Hepcidin and the development of the tumor.

Comparison of Hepcidin levels between relapsed and non-relapsed colorectal cancer patients

Hepcidin levels were significantly higher in the colorectal cancer group than in healthy controls. No significant statistically differences were found between relapsed and non-relapsed patients according to CEA and CA19-9 levels as shown in Table 4.

Comparison of Hepcidin levels and other tumor marker (CEA, CA19-9)

When studying the correlation between Hepcidin and other variables, a positive and statistically significant correlation was found with both CEA and CA19-9 (Table 5).

Results and Discussion

Our study included 51 participants, 12 healthy

Table 1: Tumor markers levels in study sample according to tumor-stage.

	Stage	N	Mean	Median	SD	p-value
CEA	1	13	11.2	13.7	6.4	0.004
	2	13	23.05	26.6	11.1	
	3	13	31.38	39.5	17	
CA19-9	1	13	7.04	8.5	3.4	0.004
	2	13	14.05	15.4	8	
	3	13	28.9	33.6	16.4	

Table 2: Hepcidin levels in colorectal cancer patients and healthy controls.

t-Test: Two-Sample Assuming Unequal Variances		
	Colorectal cancer Hepcidin ng/ml	Non-cancer Hepcidin ng/ml
Mean	44.7359	5.566667
Variance	1147.649	23.79697
Observations	39	12
Hypothesized Mean Difference	0	
Df	43	
t Stat	6.988938	
P(T<= t) one-tail	6.68E-09	
t Critical one-tail	1.681071	
P(T<= t) two-tail	1.34E-08	
t Critical two-tail	2.016692	

Table 3: Hepcidin and colorectal cancer stages.

Anova: Single Factor						
SUMMARY						
Groups	Count	Sum	Average	Variance		
stage 1	13	144.7	11.13077	11.92731		
stage 2	13	463.8	35.67692	88.15359		
stage 3	13	1136.2	87.4	249.9133		
ANOVA						
Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	39410.74	2	19705.37	168.906	5.08E-19	3.259446
Within Groups	4199.931	36	116.6647			
Total	43610.67	38				

Table 4: Hepcidin, CEA and CA19-9 levels in relapsed and non-relapsed patients.

	Hepcidin (ng/ml)	
	Relapsed	Non-Relapsed
Mean	76	36.6
Median	89.45	27.5
Std. Deviation	35.3	28.8
Minimum	15.4	5.6
Maximum	109.3	101.4
P-value*	0.001	

*Shapiro-Wilk test

		Mean	Median	SD	Min	Max	p-value
CEA	Non-relapsed	20.8	17	14	0.9	47.7	0.465
	Relapsed	26.1	31	17.2	1.4	47.8	
CA19-9	Non-relapsed	15.1	9.9	12.4	1.2	44.9	0.251
	Relapsed	22.9	17	18.4	2.2	47.8	

Table 5: Hepcidin levels and other tumor marker.

Spearman Correlation test			
		CA19-9	CEA
Hepcidin Levels	Correlation Coefficient	0.435**	0.445**
	Sig. (2-tailed)	0.006	0.005
**Correlation is significant at the 0.01 level (2-tailed)			
*Correlation is significant at the 0.05 level (2-tailed)			

controls and 39 patients diagnosed with colorectal cancer with an average age of 60.48 years, which is close to the values of the average age of patients in similar global studies [8,10], while the small sample size in our study compared to the rest of the global studies was one of the limitations and obstacles that we faced during the research [11].

Our study showed an increase in Hepcidin levels in colorectal cancer patients compared to healthy people with a statistically significant difference of $p \leq 0.05$, which corresponds to International Studies [12,13]. A statistically significant difference was found between the Hepcidin levels in patients based on the tumor stage, which is consistent with the study conducted by PAN XIANG-TAO in 2017 [8]. Therefore, monitoring Hepcidin levels in colorectal cancer patients can be a predictive factor for controlling the patient's condition progression.

We studied the main variables and its relationship with recurrence. There was no statistically significant difference in the levels of CEA and CA19-9 among relapsed and non-relapsed. Even though these values changed due to in tumor progression, we could not ensure that to the stage of tumor. These changes might be according to drugs, bleeding, nutrition deficiency and undiagnosed pathologies [14-16].

When studying the relationship of Hepcidin with relapses, a significant increase in Hepcidin levels was found in patients who relapsed compared to non-relapsed patients, with a statistically significant difference, which indicates the importance of the role of Hepcidin as a prognostic marker for the condition of patients, in line with other International experimental studies [10,13].

Conclusion and Recommendations

Hepcidin is as a predictive marker in colorectal cancer and its importance as a prognostic indicator during the development of the tumor.

Future studies are recommended to evaluate the role of Hepcidin among large number of patients in order to follow up the treatment process and determine Hepcidin importanceas a predictive marker of tumor.

Statement & Declarations

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis. All authors read and approved the final manuscript.

Ethical approval

This research received approval from the scientific research ethics committee at Tishreen University and Tishreen University Hospital.

Consent to participate

Written informed consent was obtained from all individual participants included in the study.

Consent to publish

The authors affirm that human research participants provided informed consent for publication of this manuscript.

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