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Study of Age, Body Mass Index, Stages of Colon Cancer Development, and Type of Treatment on Meprin Alpha Levels Among Colon Cancer Patients

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Abstract

Colon cancer is a disease that is characterized by the development of malignant cells in the epithelium or lining of the distal part of the colon. This study includes study of age, body mass index, stages of colon cancer development, and quality of treatment on meprin α (MEPA) levels among colon cancer patients as compared with the control group. This study has been conducted on (134) sample with ages ranging from (25-76) years: (74) of them are colon cancer patients from the patients treated in Mosul oncology and nuclear medicine hospital and Ibn-Sina teaching hospital/ Mosul and (60) samples as control group in Mosul city for the period from January to July 2020. The results showed that the normal mean of MEPA is (82.12± 3.65 ng / mL) in control group for both gender. While the activity of MEPA for colon cancer patients were (106.72±4.52 ng / mL), the level of enzyme was also affected by age and gender, whereas it increases with age in both the control group and colon cancer patients, its activity in males is higher than in females in control group only, and the effect of body mass index is observed in both the control group and the patients. The results also showed a significant increase in the activity of MEPA in colon cancer patients as compared with the control group, while there was a significant increase in colon cancer patients in stages II, III and IV compared with patients in the first stage. The effect of the type of treatment, as it has been found that the activity of enzyme was significantly lower for MEPA in the group of patients undergoing surgical removal of colon tumors and patients treated with chemotherapy as compared without treatment patients (Newly diagnosed). It was noted that MEPA is affected by various factors such as gender, age, BMI, as well as the development of colon cancer and the type of treatment used.

Introduction:

Meprins are membrane-bound and secreted zinc metalloproteases, most of these enzymes (Metalloproteases) are secreted from cells or plasma membrane bound, and they act intracellularly and extracellularly. They are involved in tissue differentiation and remodeling during embryogenesis and in processing biologically active peptides and cytokines in adult

tissues. Metalloproteinases are involved in many diseases for example cancer and inflammatory diseases [1].

Meprins were discovered in 1980 as a consequence of a search for proteolytic enzymes in diabetic mice [2]. Meprins are membrane-bound and secreted zinc metalloproteases extensively glycosylated and highly expressed in kidney and small intestinal epithelial cells, leukocytes, and certain cancer cells [1].

The inhibitors for metalloproteinases are of great medical interest and have provided optimism in clinical trials. The metzincin superfamily contains most of the known metalloendoproteinases (Zinc containing enzymes that cleave peptide bonds internally on protein substrates) [1].

There are two types of meprin subunits, α and β, which form disulphide-bonded homo- and hetero-oligomers. Meprin has also been detected in certain epithelial carcinomas, such as colorectal cancer [1], where soluble hMEPA (Human meprin α) is secreted not only apically but also baso- laterally, thereby increasing the proteolytic potential of tumor cells for the destruction of the basement membrane [3]. The abnormal meprin secretion also observed in experimentally induced acute renal failure in rats [1]. All these findings suggest a contribution to epithelial differentiation, cell migration, matrix remodelling and also to inflammatory processes, tumor growth and metastasis [4]. In the intestine, pro- human MEPA is activated by trypsin [5].

Meprins are capable of hydrolyzing a wide variety of substrates, from peptides to proteins. MEPA cleaves the tight junction protein occludin, which impairs epithelial barrier function and enhances monocyte migration [2].

Meprins are expressed in various cancer cells (for example colon and breast cancer) and are thought to play a role in tumor cell invasion and migration [6]. Studies of MEPA have shown that decreased expression of this subunit is associated with increased intestinal inflammation in an experimental model of intestinal bowel. Furthermore, the human MEP1A gene is a susceptibility gene for inflammatory bowel disease [7]. Meprins also influence the course of urinary tract infections and in the pathogenesis of kidney diseases and are associated with diabetic nephropathy [8]. Meprins also cleave amyloid precursor protein (APP) in vivo, implying a role in neurodegenerative diseases, such as Alzheimer‘s disease [1].

Hence, MEPA is a potential therapeutic targets for the treatment of fibrosis and/or associated conditions. The best inhibitor of meprins described so far is the hydroxamate derivate actinonin [7]. Hydroxamate inhibitors chelate the zinc ion in the active site of MEPA. These compounds can regulate metalloprotease activity, but they are mostly nonspecific targeting many zinc-endo peptidases due to their inhibitory mechanism. This is the reason for early abortion of several clinical trials where hydroxamate inhibitors are tested in cancer treatment to decrease MEPA activity during metastasis [9]. To further elucidate MEPA function in health and disease it will be essential to delineate how and under which physiological and pathophysiological conditions MEPA activity is regulated.

Due to the limited information available on MEPA separation from serum. The lack of biochemical studies on the relationship of the MEPA with colon cancer disease, especially after the increase in the number of colon cancer patients in the Iraqi society, the study objectives focuses on: To estimate the activity of MEPA enzyme in the serum of colon cancer patients and healthy groups, beside of, Study the effect of age, gender, body mass index, different stages of colon cancer and type of treatment on levels on the activity for the MEPA.

Materials and Methods

Patients and control

This study includes (74) colon cancer patients whom diagnosed and proved by colonoscopy and biopsy (38 males and 36 females). Samples have been collected over the period from January 2020 to July 2020 from the patients treated in Mosul oncology and nuclear medicine hospital and Ibn-Sina teaching hospital/ Mosul. Clinical diagnosis in each case is established according to the oncologist. All patients are (25 -76) years age. The patients in the study are clinically and histologically diagnosed as early stages (A and B), advanced stage (C) and metastasis stage (D) colon cancer patient, and free from other chronic diseases such as diabetes, hypertension, or other cardiac, renal and liver diseases. Female cases are not pregnant or lactating.

The Control group consists of (60) normal healthy individuals (33 males and 27 females) with negative finding to any benign or malignant colonic disease of any type, who are free from signs and symptoms of cancer or chronic diseases, matched in age with patients, and had no history for any gastrointestinal disorder. Questionnaire for complete clinical and personal history of the patient and control are recorded from each person containing information. Both patients and controls gave informed, written consent for participation. The number of patients, age, gender, family history, stage of tumor diagnosis, smoking, obesity and drug.

Blood Sample Collection:

Ten millilitres of venous blood have been taken from patients and control individuals and left for (15) minutes at room temperature for coagulation, then serum was separated by centrifugation at (3000 xg) for 15 minutes, and divided in (4) aliquots and kept frozen at (-20°C) until analysis.

Determination of Human MEPA

Serum MEPA activity has been determined by using kit assayed according to the manufactured procedure (Bioassay technology Laboratory, Cat. No. E0387Hu, Shanghai, China).

Statistical analysis

The data analysis is performed using the ready-made statistical package SPSS 20 (SPSS Software, SPSS Inc., Chicago, Illinois, USA). All results are expressed as the mean ± standard diviation (SD). For the comparison of significance between groups, the results have been analyzed statistically using t-test to find the significant differences between the study groups and the probability level $P \leq 0.05$ is considered significant for multiple variable comparisons are analyzed by one-way analysis of variance (ANOVA).

Results and Discussion

The Activity and Normal Range of MEPA in the Serum of the Control Group

It has been found that the mean range of MEPA activity (82.12 ± 3.65 ng / mL) in the serum of the control group in Mosul city, for both gender, and for the two age groups, (Table 1), and this rate is consistent with what Hou *et al*. [10] found, as well as, found by Mohammad *et al*. [7] in healthy people, is close to our findings.

It has been found that the activity of MEPA in serum of the patients with colon cancer, of both gender and for ages (25-76 years), was (106.72 ± 4.52 ng / mL) (Table 1). The effect of some factors on the MEPA activity in the serum of the control group has been studied, namely:

Effect of gender according to age

The effect of gender on the MEPA activity in serum of the control group according to age was studied, as the control group was divided into two age groups and for both gender, the MEPA activity increased with age increasing of males in the serum of the control group for the first age group ((25-50) years) compared with the second age group ((51-76) years) at ($P \leq 0.05$). It was also observed that there was no significant difference between the first age group compared with the second (Older) age group for females.

When comparing the gender of males and females for each age group, a significant increase has been found in the MEPA activity in males as compared to females in the two age groups (Table 1), and this was consistent with what Broder and Becker-Pauly [11] found, the MEPA activity was higher in males than in females, as administration of 17 beta-estradiol to adult mice decreased the activity of meprin-A in kidney slices and the electrophoretic mobility of meprin-A. These results indicated that estrogens affect posttranslational modifications of meprin-A.

There has been increasing interest in studying gender differences to learn more about disease pathogenesis and to discover more effective treatments.

Previous advances have been made of these differences in histology, physiology, and immunology, and they have implications for diseases [11]. Among the potential mechanisms regulated by gender hormones are: altered vasoactive factors release, transcription factors, pro-fibrotic and pro-inflammatory cytokines. Moreover, female hormones may influence the defense in response to pathophysiological events by its antioxidant property [12]. The antioxidant effect of estrogen is mediated by the hydroxyl group at the C3 position of the A ring of the steroid molecule. Specifically, it has been reported that cancer disease in males was associated with faster progression than females independently of differences in blood pressure [13]. Since the immune system weakens with age [12, 14], this is likely to be the reason behind the increase in enzyme levels with age and for both gender.

The group of colon cancer patients has been divided into two age groups and for both gender, as shown in Table (1). When studying the effect of gender on the enzyme activity in the serum of the colon cancer patients group according to age, it has been found that there is significant increase at the level of probability ($P \leq 0.05$) in the enzyme activity with increasing age for both females and males (of the enzyme between the first age group and the older age group) (Table 1), indicating that the enzyme is affected by age factor. Our results are with agreement with the finding of Herzog *et al*. [13] who found that MEPA levels increase with ageing and are associated this elevation to increase the secretion of MEPA by ageing.

When comparing the enzyme activity between the males and females of the same age group, it is noticed that there was no significant difference at the level of probability ($P \leq 0.05$) this means that the enzyme activity is not affected by gender in colon cancer patients.

Table 1: The effect of gender according to age on serum MEPA activity of control and patients group.

Ages group	Control group MEPA activity (ng/mL) (mean ± SD)		Patients group MEPA activity (ng/mL) (mean ± SD)	
	Males (n=33)	Females (n=27)	Males (n=38)	Females (n=36)
(25-50) years	79.94 ± 3.57 b	81.37 ± 3.35 c	78.51 ± 3.79 a	79.94 ± 3.57 b
(51-76) years	84.29 ± 3.74 b	87.81 ± 4.14 c	80.78 ± 3.34 a	84.29 ± 3.74 b
Total mean	82.12 ± 3.65 b	84.59± 3.75 c	79.64 ± 3.56 a	82.12 ± 3.65 b

- Different letters (a, b, c) in horizontal indicate that the means are different significantly at $P \leq 0.05$, among the studied groups.

Effect of body mass index (BMI)

Body mass index (BMI) is calculated as weight (kg) divided by the square of height (m^2) [15]. BMI is classified as follows: underweight is a BMI<18.50; normal weight is 18.5 ≤ BMI<25.0; overweight is 25.0 ≤ BMI<30.0; obese was BMI ≥ 30.0[15]. The control group has been divided into three groups according to body mass index (BMI) as shown in Table (2), as a significant increase is observed at the probability level (P≤0.05) in the activity of MEPA with an increase in body mass index (BMI). This is consistent with what was mentioned by Arnold *et al*. [16] of increasing the activity of the enzyme by increasing the body mass index (BMI), and the reason for this was due to the enzyme's role in increasing fat mass, reducing fat burning, producing heat and reducing energy consumption, as well as a result of generating insulin resistance and releasing leptin from fat tissues. Increasing its activity in the blood of obese individuals leads to activation of the release of the active hormonal form of premature [17].

The group of patients has been divided into three groups according to the body mass index (BMI) Table (2), a significant increase (P≤0.05) is observed in the enzyme activity with an increase in the body mass index (BMI) in the serum of patients. Some previous researches showed that high BMI (Overweight or obese) was an important risk factor for a variety of diseases [18, 19], and that may result heavy health and economic burden, such as increased mortality and morbidity and higher annual medical care cost [19]. Colon cancer incidence and mortality among individuals younger than 50 years (Early-onset colon cancer) are increasing. The reasons for such increases are largely unknown, although the increasing prevalence of obesity may be partially responsible [20]. In colon cancer, due to the enzyme's function in reducing fat catabolism, and this indicates the association of colon cancer with obesity [21]. Recently, many epidemiological studies have found that obesity, which is defined as an abnormal increase of adipose tissue mass with increasing size and number of adipocytes, is associated with an increased risk of colorectal cancer. However, the potential mechanism of this relationship is largely unknown [12].

Table 2: The effect of body mass index (BMI) on MEPA activity in the serum of patients and control group.

BMI (kg/m^2)	Control group MEPA activity (ng/mL) (mean ± SD)	Patients group MEPA activity (ng/mL) (mean ± SD)
Normal (≤ 25) (n=36)	52.12 ± 1.69 a	89.82 ± 2.29 a
Over weight (26-30) (n=18)	89.16 ± 1.58 b	109.21 ± 3.58 b
Obese (≥ 31) (n=6)	105.08 ±7.68 c	121.14 ±7.68 c

- Different letters (a, b, c) in vertical indicate that the means are different significantly at P≤0.05, among the studied groups.

Effect of Colon Cancer in Different Stages on MEPA

Depending on the period of stages in colon cancer in patients group was divided into four subgroups (Stages I, II, III and IV), which were listed in Table (3).

MEPA activity of colon cancer patients in different stages shows in Table (3). Among 74 cases, 6 (8.1%) were at stage I, 6 (8.1%) at stage II, 29 (39.2 %) at stage III, and 33(44.6 %) at stage IV. Significant differences were found in stage distribution. The proportion of stages III (125.44±4.42 ng/mL) and IV (128.54±5.79 ng/mL) tumours increased, while the proportion of stages tumors I (82.3±5.75 ng/mL) and II (89.16±4.81 ng/mL) decreased. These agree with a study reported that the proportion of early stage colon cancer decreased with time, and that of later stage cancer gradually increased [21, 22].

The results showed that MEPA significant increase in stage III and IV groups compared to stage I and II groups.

Namely, despite great progress made in colon cancer screening it is usually diagnosed too late, at least 20% of colon cancer cases are diagnosed on surgical operation due to large bowel obstruction. The result of current study suggests that serum MEPA activity might be a factor that contributes to increase colon cancer risk. To clarify the biology of this relation, serum MEPA activity was determined in different clinical stages of the disease. We found out that serum MEPA activity differ in patients depending on the clinical stage of the disease. In comparing the clinical stages, the result showed a significant higher MEPA activity in III and IV stages as compared with both I and II stages (Table 3). Existing data showed that MEPA regulate the matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF), which is considered of importance for promoting tumor invasion and angiogenesis in colon cancer [23]. To explore the molecular mechanism underlying MEPA role in colon cancer, genetic factors might help in the explanation. It has been reported that genetic polymorphisms in the promoter region of the MEPA gene may be independent predictors of circulating MEPA activity in humans [11].

Table 3: Serum MEPA in different stages of colon cancer patients.

	Stages (mean±SD)			
	Stage I (n=6)	**Stage II (n=6)**	**Stage III (n=29)**	**Stage IV (n=33)**
MEPA (ng/mL)	82.3±5.75 a	89.16±4.81 a	125.44±4.42 b	128.54±5.79 b

- Different letters (a, b, c, d) in horizontal indicate that the means are different significantly at P≤0.05, among the studied groups.

Effect of Treatment Types on MEPA in Serum of Colon Cancer Patients

MEPA activity of colon cancer patients in different types of treatment shows in Table (4). Among 74 cases, 30 (40.5%) were newly diagnostic cases with colon cancer without any treatment, 23 (31%) were given chemotherapy and 21(28.5%) were underwent surgery to eradicate colon tumors. Significant differences were found in MEPA activity among the three subgroups in which the activity decreased in both chemotherapical and surgical treatmentsas compared with newly diagnosed colon cancer cases.

Colon cancer is the third most common cancer worldwide with an estimated one million new cases and a half million deaths each year [24]. Many surgeons feel that operative exploration is sufficient to guide subsequent treatment in colon cancer [25]. The patients with colon cancer (Surgical and after chemotherapy) and without treatment patients were showed significant value by statistically (p≤0.05). Improved surgical techniques coupled with adjuvant chemotherapies and novel biotherapies are making positive impacts on the 5-year survival rates for patients with colorectal cancer.

Table 4: The effect of treatment type on MEPA in serum of colon cancer patients.

	Colon cancer patients groups (mean±SD)		
	Without Treatment (Newly diagnostic) (n=30)	**Chemotherapy Treatment (n=23)**	**Surgical Treatment (n=21)**
MEPA (ng/mL)	118.38±4.26	101.11 ± 3.31a	90.21±3.78 b,c

Different letters (a, b, c) indicate that the means are different significantly at P≤0.05, among the three studied groups:

a: Obtained by comparing chemotherapy group vs. without therapy group.

b: Obtained by comparing surgery group vs. without therapy group.

c: Obtained by comparing surgery group vs. chemotherapy group.

However, this benefit is optimal mostly for patients with localized early stage disease (Stage I patients have a 95 %, while stage II is 82 %) [26]. This survival rate drops to 61% in patients with regional lymph node spread (Stage III) and very dismal (8%) for stage IV-disease patients with distant metastasis. Yet less than 40% of all patients are diagnosed with early stage disease. The need for improved early detection and effective therapies is urgent and is actively being pursued [27].

Conclusion:

The mean value of MEPA activity in colon cancer patients was significantly higher compared to control group. It was noted that MEPA is affected by various factors such as gender, age, BMI, as well as the development of colon cancer and the type of treatment used.

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الخلاصة:

سرطان القولون هو مرض يتميز بتطور الخلايا الخبيثة في الظهارة أو بطانة الجزء البعيد من القولون. تتضمن هذه الدراسة دراسة العمر ومؤشر كتلة الجسم ومراحل تطور سرطان القولون وجودة العلاج المستخدم على مستويات ميبرين ألفا (MEPA) بين مرضى سرطان القولون مقارنة بمجموعة السيطرة. أجريت هذه الدراسة على (202) عينة تتراوح أعمارهم بين (25-78) سنة: (74) منهم مرضى سرطان القولون من المرضى الذين عولجوا في مستشفى الأورام والطب النووي بالموصل ومستشفى ابن سينا التعليمي / الموصل و(60) عينة كمجموعة ضابطة في مدينة الموصل للفترة من كانون الثاني إلى تموز 2020. أظهرت النتائج أن المعدل الطبيعي لـMEPA هو (82.12 ± 3.65 نانوغرام / مل) في المجموعة الضابطة لكلا الجنسين. بينما بلغ فعالية MEPA لمرضى سرطان القولون (106.72 ± 52.4 نانوغرام / مل). لوحظ ان المستوى من الإنزيم يتأثر أيضًا بالعمر والجنس، حيث يزداد مع تقدم العمر في كل من المجموعة الضابطة ومرضى سرطان القولون، ويكون نشاطه عند الذكور أعلى منه في الإناث في المجموعة الضابطة فقط، ويلاحظ تأثير مؤشر كتلة الجسم في كلا المجموعتين المجموعة السيطرة والمرضى. وأشارت النتائج الى ان هناك زيادة معنوية في فعالية MEPA في مرضى سرطان القولون مقارنة بالمجموعة السيطرة، بينما كانت هناك زيادة معنوية في مرضى سرطان القولون في المراحل الثانية والثالثة والرابعة مقارنة بالمرضى في المرحلة الأولى. لملاحظة تأثير نوع العلاج وجد أن نشاط الإنزيم كان أقل بشكل ملحوظ بالنسبة لـ MEPA في مجموعة المرضى الذين خضعوا للإزالة الجراحية لأورام القولون والمرضى الذين عولجوا بالعلاج الكيميائي مقارنة بالمرضى بدون علاج (مشخصين حديثا). لوحظ أن MEPA يتأثر بعوامل مختلفة مثل الجنس والعمر ومؤشر كتلة الجسم وكذلك تطور سرطان القولون ونوع العلاج المستخدم.