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The Prospect of Using Serum Taurine Level as a Potential Biomarker for Early Detection of Colorectal Carcinoma and Its Correlation with Other Prognostic Markers

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Abstract

Background: Colorectal carcinoma is the third leading cause of cancer-related deaths in the USA, resulting in an estimated of more than 49,000 deaths in 2016 and estimated 1.4 million cases and 693,900 deaths occurring in 2012 worldwide. In Egypt, it remains a heavy problem as about 40% of cases occur in individuals under 40 years of age. Current studies have proposed that changes in systemic taurine levels can be used to predict the formation and malignant transformation of certain tumors. Also, recent studies shown that it can be used as early biomarker in breast cancer, uterus cancer, diabetic retinopathy, liver fibrosis and hepatocellular carcinoma.

Aim: Investigate the probability of using serum taurine level as a pre- early biomarker for Colorectal carcinoma especially in pre-cancerous condition in Egyptian patients and comparing between serum taurine level and specific biomarkers before and after surgical treatment.

Patients and methods: From a lot of Egyptian patients attended to National Cancer Institute, Cairo University, presented with abdominal troubles and gastrointestinal problems after full examination and diagnosis, 106 patients -after their approval- were classified into three groups: The first group consists of ninety-one patients were diagnosed with colorectal carcinoma with various stages, The second group is involving eight patients were diagnosed as benign tumors and The third group including only seven patients were diagnosed with inflammatory diseases. Ten health volunteers were enrolled as a frank control. For first group and second group serum taurine measured preoperatively (day before operation) and postoperatively (after 45 days from operation).

Results: While, CEA and CA19.9 showed highly significant differences in all groups comparing with control group but still clinically- for inflammatory group and benign tumor group- within normal ranges. Serum taurine level showed highly significant changes between CRC group, benign group, inflammatory group and control group, as in CRC group taurine level dropped by approximately 77.5% (13.6 ± 1.9 µmol/L) below normal in control group (60.6 ± 6.7 µmol/L) moreover, lowered by ≈ 61% (23.4 ± 2.6 µmol/L) in benign group compared by control group and for inflammatory group; its level decreased by 50% (34.8 ± 2.7 µmol/L) compared to control.

Conclusion: Serum taurine results in our study showed that, besides CRC biomarkers; it is most attractive, more precious and more accurate early biomarker for early detecting of any malignant change which may led to CRC by other mean it is the most sensitive and more specific tumor marker for CRC. As a result, we can recommend measuring its level regularly with other prognostic tumor biomarkers and screening examination for all people with abdominal and

gastrointestinal problems and for precancerous patients as a pre-early biomarker for colorectal carcinoma. So, it needs further studies to confirm that observations on large scale of population as it obvious the small sample size in early stage and lack data due to limited financial resources and it needs more efforts to collect first and precancerous stages patients.

Keywords: Colorectal carcinoma; Egyptian patients; Serum taurine; CEA; CA 19.9

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Abbreviation

CRC: Colorectal Carcinoma; Tau: Taurine; CEA: Carcinoembryonic Antigen; CA 19.9: Carbohydrate Antigen 19.9

Introduction

With increasing social mobility and economic growth, as a result, transitions in human development are associated with increases in cancer rates overall and for certain types [1]. Especially colorectal carcinoma has been considered one of the clearest markers of transition [2]. CRC is the third leading cause of cancer-related deaths in the USA, resulting in an estimated of more than 49,000 deaths in 2016 [3]. It is the third most common cancer in men (746,000 cases, 10.0% of the total) and the second in women (614,000 cases, 9.2% of the total) worldwide. Almost 55% of the cases occur in more developed regions. Also, it is most often found in those aged 50 years or older worldwide [4,5]. The declines in CRC incidence have not occurred equally in all populations. In sharp contrast to the decline in CRC incidence and mortality among older individuals, incidence is rising in adults younger than age 50 [6,7]. In the United States in 2017, there are projected to be 135,430 individuals newly diagnosed with CRC and 50,260 deaths from the disease [8]. In Egypt, A population-based study in Garbiah, Egypt has shown high rates of CRC in patients aged 40 years and younger [9].

Indeed, it has been said that the 21st century is the era of the large intestine. As the number of cases of colorectal polyps that are diagnosed and treated via colonoscopy has now increased [10]. Approximately 15-25% of all CRC patients have distant metastases (TNM* Stage IV) at the time of the primary diagnosis [11]. Rise in the proportion of stage metastasized CRC patients was observed over the last two decades [12]. Metastasis is the leading cause of CRC-related mortality and is responsible for about 90% of CRC patient deaths [13]. The global CRC burden is expected to increase by 60% to more than 2.2 million new cases and 1.1 million deaths by 2030, correlating with human development levels and with the adoption of western lifestyles [14].

Modifiable risk factors such as excess body weight and unhealthy behaviors (sedentary lifestyles, unhealthy dietary patterns and smoking) increase the risk of CRC [15,16]. Till lately, colonoscopy has been considered the “Gold Standard” for detection CRC and high-risk adenomas [17-19], but its invasiveness, associated discomfort and potential risks of complications needed for the screening itself represent marked disadvantages [20]. So, tumor biomarkers such as CEA, CA19.9 and fecal occult blood testing (FOBT) have been clinically utilized. However, their sensitivity and specificity are unsatisfying [21,22]. CA19.9 has been used as a marker for CRC, but it is less sensitive than CEA [23]. It is not recommended in routine follow-up after surgery [24]. Also, the FOBT has low sensitivity, especially for early stage colorectal cancer. Thus, examinations involving a combination of conventional screening methods have been used for the diagnosis of colorectal cancer; however, such examinations only detect about 40% of colorectal cancers [25]. However, about 20% of CRC tumors have been reported not to produce elevated serum levels of CEA despite metastatic disease. The role of CEA in early diagnosis of CRC is controversial due to its insufficient sensitivity and organ specificity [26,27]. Increased concentrations of CEA are rarely observed in early stages of the disease.

For CRC staging, the stage is based on how far the cancer has grown into the intestine wall, cancer staging is one of the most crucial factors in determining prognosis and treatment options. If it is based on physical exam, biopsy, and any imaging tests it is called clinical stage. And if the results of staging are after surgery combined with stage, called pathological stage. The most common staging system used for CRC is TNM system by American Joint Committee on Cancer (AJCC) [28].

Taurine (Taurine; 2-aminoethanesulfonic acid) an essential non-protein containing sulfur amino acid, involved in a wide range of physiological processes, among the most abundant organic molecules in human body [29]. Present in high concentrations in the liver, also in enormous amounts in the brain, retina, heart and platelets [30]. The best food sources are meat and fish [31,32]. Taurine involved in cell volume regulation, enhances stability of membranes and directly stabilizes membrane proteins and modulates inflammation [33-35]. Moreover, studies showed that taurine involved in apoptosis regulation [36,37]. Lately, it has been used as an antipyretic and anti-inflammatory agent, to treat liver and Gallbladder disease, Cardiovascular disease, Diabetes and Cataract [38-42].

Recently, Taurine can be used as an early biomarker as in Breast cancer, Uterus cancer, Diabetic retinopathy, Liver fibrosis, Hepatocellular Carcinoma (HCC) [43-47]. Newly taurine was used to ameliorate hepatotoxic effect of dinitrotoluene in rats [48].

Current studies have proposed that changes in systemic taurine levels can be used to predict the formation and malignant transformation of certain tumors. Taurine as an effective antioxidant may hinder the increase of Reactive Oxygen Species (ROS) in tumors, leading to a delay of the development of cancer [49]. In addition, Taurine could play a role in the process of anti-tumors by down-regulating matrixmetalloproteinase-2 (MMP-2), up-regulating N-acetylgalactosaminyltransferase and meanwhile inhibiting potential invasion and metastasis induced by ionizing radiation [50]. It is said that taurine may induce apoptosis in cancer cells through two pathways:

(I) Stimulation of the increased PUMA (p53-upregulated modulator of apoptosis) expression.

(II) Up-regulation of the pro-apoptotic *Bax* gene expression and down-regulation of the anti-apoptotic Bcl-2 gene expression, finally leading to the increased activity of caspase-3/9.

So, taurine significantly inhibited the cell proliferation of colon cancer cells and promotes the occurrence of apoptosis [51]. Also, there are cellular and molecular changes induced by taurine, leading to the induction of apoptosis in human breast cancer cell lines MCF-7 and MDA-MB-231. MCF-7 is p53 proficient (p53+/+) and MDA-MB-231 is a p53 null mutant (p53-/-). Taurine is a potent candidate for the chemotherapy of breast cancer through increasing the PUMA expression independent of p53 status [52]. So, our aim to investigate the probability of using serum taurine level as a pre-early biomarker for colorectal carcinoma especially in precancerous condition in Egyptian patients and comparing between serum taurine level and specific biomarkers before and after surgical treatment.

Patients and Methods

Two-hundred and fifty Egyptian patients (males and females) who attended National Cancer Institute, Cairo university; most of them were referred from private clinics and non-specialized hospitals, complain with abdominal troubles and gastrointestinal problems and bleeding per rectum, after full investigation, clinical examination, biochemical analysis, screening examination according to their cases (Ultra sound, CT or endoscopy either rectal or colonoscopy) and histopathological examination, we choose 'after their approval' one-hundred patients and six which diagnosed as CRC patients aged (19-69 years old) and excluded the others from participated in these studies because they diagnosed as non-colonic diseases like; Irritable colon, Gastroenteritis, Pancreatitis, Liver flexure or Chronic cholecystitis.

According to Histopathological architecture, we divided patients to:

1. Inflammatory group number=7.
2. Benign tumor group number=8 which was assessed preoperatively and postoperatively.
3. Malignant tumor group number=91 which was assessed preoperatively and postoperatively and divided into
   - Grade 1=6.
   - Grade 2=68.
   - Grade 3 with metastasis=17.

This work approved by ethical committee of National Cancer Institute - Cairo University

Lastly, ten health volunteers were enrolled as a frank control. For all included subjects we measured biochemical analysis; CBC, ALT, AST, Albumin, Total Bilirubin, Creatinine, Blood urea, Sodium, Potassium, CEA, CA19.9 and Taurine.

Blood sample collection: Venous blood samples were extracted from all patients for estimation of serum taurine levels after fasting for at least 12 hours. Otherwise, measuring of serum AST (Aspartate Transaminase), ALT (Alanine Transaminase), Blood urea, Creatinine, Albumin, Bilirubin, Sodium, Potassium, CEA and CA19.9 were not needed fasting period.

Serum taurine was determined by High Performance Liquid Chromatography (HPLC) according to the pre-column extraction and derivatization methodology of McMahon et al. In the present work, we use Shimadzu HPLC model LC-10AT. Serum ALT, AST, Albumin, Bilirubin, Creatinine, Urea, Sodium, Potassium were performed using Cobas C111 (Roch), CEA and CA 19.9 determination kits were purchased Cobas e411 (Roch).

No relation between gender or age and either severity or progression of colorectal carcinoma when adjustments were made according to the disease duration.

Statistical analysis

The data will be analyzed using Microsoft Excel 2010 and statistical package for social science (SPSS version 24.0) for windows (SPSS IBM, Chicago, IL). Continuous normally distributed variables were represented as mean ± SD with 95% confidence interval, while non-normal variables were summarized as median with 25 and 75 percentile and using the frequencies and percentage for categorical variables; a p value<0.05 will be considered statistically significant. To compare the means of normally distributed variables between groups, the student's t test was performed, and Mann-Whitney test will be used in non-normal variables and χ^2 test or Fisher's exact test will be used to determine the distribution of categorical variables between groups. The diagnostic performance of taurine, CEA and CA 19.9 will be assessed by Receiver Operating Characteristic (ROC) curves. The area under the ROC (AUROC) will be used as an index to compare the accuracy of tests. The cut-off for diagnosis of group of the study will be taken from the point of maximum combined sensitivity and specificity. The sensitivity and specificity for relevant cut-offs were also displayed. Spearman's rank correlation coefficient (r) will be done to show the correlation between different parameters in this study.

Results

This investigation included one hundred and six CRC patients presented with abdominal pain, gastrointestinal troubles and or melena. Ten healthy volunteers enrolled as frank control.

Regarding to the data of liver and kidney functions in **Table 1** result revolves that the values of serum ALT, AST, T Bil, Uric acid, Na and K for all involved groups showed non-significant changes ($p>0.05$) between different groups of patients and each other or with control group. For serum ALP, CREAT and Urea data, no significant changes ($p>0.05$) between the difference CRC groups, but significant ($p<0.05$) increase in malignant group with frank control group. The ALB showed increase significant different ($p<0.05$) between benign group and inflammatory group, while showed high-significant change decreased ($p<0.01$) between malignant and benign groups.

Tables 2 and 3 illustrated that for CEA there is a highly significant change ($p<0.01$) between all groups and control groups but no significant different ($p>0.05$) between inflammatory group and benign group preoperatively while postoperatively no significant changes ($p>0.05$). CA19.9 data showed highly significant different increased ($p<0.01$) between inflammatory group {4.2 (2.0- 21.5)} and benign group {19.9 (15.9-29.0)} with frank control group but, still clinically within border line (up to 22.3 µ/mL), while there is a high-significant change ($p<0.01$) between malignant group with all patient groups and control group. The data presented the decreased high-significant changes ($p<0.01$) in Tau results between all groups themselves and with control group while dropped by approximal 77.5% (13.6 ± 1.9 µmol/L) below normal in control group (60.6 ± 6.7 µmol/L) moreover, lowered by ≈ 61% (23.4 ± 2.6 µmol/L) in benign group compared by control group. And for inflammatory group; its level decreased by 50% (34.8 ± 2.7 µmol/L) compared to control. Measuring serum taurine level besides CRC biomarkers show that it is most attractive, more precious and most accurate early biomarker for early detecting of any malignant change which may led to CRC by other mean it is the most sensitive and more specific tumor marker for CRC (**Table 4**).

Table 1 The liver and kidney functions in diverse groups of patients.

Laboratory data	Control N=10	Inflammation N=7	Benign tumor N=8	Malignant tumor N=91
Age	20-49 yrs	25-68 yrs	22-59 yrs	19-69 yrs
Chronicity	0	3-7 mth	2-4 mth	2 mth-3 yrs
T. BIL. (0-1.2 mg/dL)	0.5 (0.3-0.5)	0.5 (0.4-0.5)	0.5 (0.4-0.5)	0.5 (0.4-0.7)
AST (0-40 IU/L)	19.5 (15.5-21.3)	19.0 (17.0-22.0)	19.5 (16.3-27.8)	24.0 (17.0-34.0)
ALT (0-33 U/l)	16.0 (10.0-19.0)	9.0 (8.0-26.0)	11.5 (7.5-35.8)	17.0 (10.0-25.0)
ALP (30-120 U/l)	80.0 (65.0-89.3)	99.0 (47.0-128.0)	102.0 (76.8-118.8)	110.0 (84.0-154.0)[a]
ALB (3.5-5.2 g/dL)	3.9 ± 0.5	3.6 ± 0.6	4.1 ± 0.2[b]	3.7 ± 0.6cc
CREAT (0.3-1 mg/dL)	0.7 (0.5-0.8)	0.7 (0.7-1.0)	0.8 (0.6-1.2)	0.8 (0.7-1.0)[a]
UREA (10-50 mg/dL)	20.8 ± 6.2	27.7 ± 14.2	24.0 ± 5.6	27.4 ± 11.0[a]
Uric Acid (2.7-5.7 mg/dL)	4.6 ± 1.2	4.7± 0.8	5.3 ± 2.0	4.9 ± 1.8
Sodium (135-150 mmol/L)	138.7 ± 5.2	136.3±3.6	137.8 ± 4.7	136.5 ± 14.9
Potassium (3.5-5.5 mmol/L)	4.1 ± 0.4	4.4 ± 0.4	3.9 ± 0.8	4.1 ± 0.6

T. BIL (Total Bilirubin), AST (Aspartate Transaminase), ALT (Alanine Transaminase), CREAT (Creatinine) and ALP (Alkaline Phosphatase) are represented as Median and interquartile range (25%-75%), while ALB (Albumin). UREA., URIC ACID, SODIUM (Na) and POTASSUM (K) represented as mean ± SD. Groups bearing (a) initial are significantly different from control group. Groups bearing (b) initial are significantly different from Inflammation group. Groups bearing (c) initial are significantly different from benign tumor group. *p value ≤ 0.05 significant while **p value ≤ 0.01 highly significant.

Table 2 Hb is represented as mean ± SD, while RBCs, HCT, MCV, MCH, MCHC, PLT, WBC, NEUTRO, LYMPHO, MONO, EOSINO and BASO are represented as median and interquartile range (25%-75%). Groups bearing (a) initial are significantly different from control group. Groups bearing (b) initial are significantly different from Inflammation group. Groups bearing (c) initial are significantly different from benign tumor group.

Haematological Finding	Control N=10	Inflammation N=7	Benign tumor N=8	Malignant tumor N=91
Age:	20-49 yrs	25-68 yrs	22-59 yrs	19-69 yrs
Chronicity:	0	3-7 mth	2-4 mth	2 mth-3 yrs
HB% (11.5-15.5)	13.2 ± 1.2	11.1 ± 2.1[a]	12.8 ± 1.4	11.4 ± 1.9[aa, c]
RBS (4.3-5.7)	4.7 (4.6-5.2)	4.6 (4.5-5.1)	4.7 (4.1-5.2)	4.4 (4.0-4.9)[a]
HCT (39-49%)	38.9 (38.0-42.4)	34.9 (32.3-36.6)[a]	38.3 (34.1-40.1)	35.4 (32.6-38.7)[a]
MCV (81-100 fL)	81.1 (78.5-82.1)	75.1 (67.5-78.7)[a]	82.6 (79.8-85.7)[b]	81.1 (74.7-84.6)
MCH (27-34 pg)	27.2 (25.9-28.1)	24.7 (19.0-25.4)[a]	27.7 (27.1-29.8)[b]	26.2 (23.3-28.3)
MCHC (32-36 g/dL)	33.3 (32.3-34.3)	32.3 (28.5-32.8)	33.8 (32.9-34.5)[b]	32.4 (31.1-33.3)[a,c]
PLT (150-440 k/µL)	255.5 (238.3-346.5)	479.0 (350.0-583.0)[aa]	228.5 (127.3-285.0)[a,bb]	270.0 (206.0-378.0)[b,c]
WBS (4.5-11 k/µL)	6.9 (5.1-7.4)	8.9 (7.4-12.7)a	4.4 (3.3-6.2)[a,b]	6.7 (5.2-9.2)[b,c]
NEUTRO (35-80%)	55.1 (49.8-62.5)	65.4 (55.2-68.9)	58.2 (43.9-62.9)	58.0 (50.6-65.9)
LYMPHO (18-44%)	35.2 (26.0-41.0)	23.0 (21.2-33.3)	28.4 (26.3-39.4)	29.5 (22.7-36.2)
MONO (0-10%)	5.0 (4.8-6.5)	8.5 (6.5-10.2)[a]	9.2 (6.9-11.1)[a]	8.8 (6.0-11.7)[aa]
EOSINO (0-3%)	1.0 (1.0-2.0)	1.0 (0.8-2.8)	2.7 (1.5-4.4)[a]	2.4 (1.4-3.9)[a]
BASO (0-1%)	0.0 (0.0-0.1)	0.3 (0.1-0.5)[a]	0.4 (0.1-0.6)[a]	0.2 (0.0-0.4)[aa]

*p value ≤ 0.05 significant while **p value ≤ 0.01 highly significant.

In **Tables 5 and 6**, data showed vary between each stage of CRC, Taurine show its strong ability to differ between each stage or its sensitivity to any malignant change, it can distinguish between precancerous and cancer stage, also with high accuracy differ between stage 1 and 2. As in previous studies, tau cutoff value 20 µmol/l between cancerous and precancerous stages means any patient with Tau below that value means cancer wherever the body. As in **Table 5** CEA and CA19.9 measurements enhanced after surgical treatment (postoperative) in almost stages their value return to normal range, while tau indicated that patients not fully get better and they need more care and special dosages of Tau as a supplementary dose according to their stage. In stage 1 specific used markers dropped to normal range CEA:0.6 and CA19.9: 2 which show disappear of tumor, but taurine value was about 30 µmol/L which means the patients still in high risk zone, so the accuracy of measuring Tau also showed in follow up after surgical treatments.

Discussion

In Egypt, a population-based study in Garbiah, Egypt has shown high rates of CRC in patients aged 40 years and younger; these rates were slightly higher than rates of the same age group in the United States [9]. Otherwise it is most often found in those aged 50 years or older worldwide [4,5]. In this study there are one-hundred patients, aged from 19-69 years, attend to NCI by gastrointestinal troubles, abdominal pain and or melena, most of them were referred from private clinics and non-specialized hospitals, 26.5% of patients aged younger than 40 years and 22.6% aged between 40-50 years by other mean about 50% of patients are young. The data shows that the major group of CRC patients diagnosed as grade II (No=68), grade III and metastasis (No=12), While grade I (No=6), inflammation group (No=7) and benign group (No=8); this is referring to lack of medical self-care, no awareness of periodically checkup or follow up for

Table 3 CEA (Carcinoembryonic Antigen) and CA19.9 (Carbohydrate Antigen 19-9) are represented as Median and interquartile range (25%-75%), while Tau. (Taurine) is represented as mean ± SD. Groups bearing (a) initial are significantly different from control group. Groups bearing (b) initial are significantly different from Inflammation group. Groups bearing (c) initial are significantly different from benign tumor group.

Tumor markers, TAU	Normal range	Control N=10	Inflammation N=7	Benign tumor N=8	Malignant tumor N=91
Age:	--	20-49 yrs	25-68 yrs	22-59 yrs	19-69 yrs
Chronicity:		0	3-7 mth	2-4 mth	2 mth-3 yrs
CEA Pre	CEA up to 2.5 ng/mL	0.0 (0.0-0.4)	5.1 (1.5-9.2)[aa]	8.5 (2.9-15.2)[aa]	712.6 (311.0-940.0)[aa,bb,cc]
CEA Post				2.1 (0.9-5.3)	3.0 (1.4-11.3)
CA19.9 Pre	CA19.9 up to 22.3 µ/mL	2.0 (0.9-2.0)	4.2 (2.0-21.5)[aa]	19.9 (15.9-29.0)[aa]	258.0 (152.0-485.0)[aa,bb,cc]
CA19.9 Post				6.7 (4.0-14.9)	9.3 (2.0-22.5)
Tau. Pre	Tau up to 70 µmol/L	60.6 ± 6.7	34.8 ± 2.7[aa]	23.4 ± 2.6 [aa,bb]	13.6 ± 1.9[aa,bb,cc]
Tau. Post				33.4 ± 1.5	27.3 ± 4.1[cc]

*p value ≤ 0.05 significant while **p value ≤ 0.01 highly significant.

Table 4 This table shows the accuracy of tumor markers, Tau in detective of CRC in various stages and comparing sensitivity between disease's different stages.

Group interactions	Main parameters	Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
Control and Inflammation	Tau	51.33	100%	100%	100%	100%	100%	100%
	CEA	0.5	100%	100%	100%	100%	100%	100%
	CA 19.9	2.0	71%	100%	100%	83%	88%	81%
Control and Benign tumor	Tau	51.33	100%	100%	100%	100%	100%	100%
	CEA	0.5	100%	100%	100%	100%	100%	100%
	CA 19.9	2.0	100%	100%	100%	100%	100%	100%
Control and Malignant tumor	Tau	51.33	100%	100%	100%	100%	100%	100%
	CEA	0.5	100%	100%	100%	100%	100%	100%
	CA 19.9	2.0	100%	100%	100%	100%	100%	100%
Inflammation and Benign tumor	Tau	31.0	100%	100%	100%	100%	100%	100%
	CEA	9.2	50%	86%	80%	60%	67%	66%
	CA 19.9	12.3	88%	71%	78%	83%	80%	77%
Inflammation and Malignant tumor	Tau	31.0	100%	100%	100%	100%	100%	100%
	CEA	20.18	96%	100%	100%	64%	96%	99%
	CA 19.9	64.5	96%	100%	100%	64%	96%	98%
Benign tumor and Malignant tumor	Tau Pre	20.2	100%	100%	100%	100%	100%	100%
	Tau Post	30.7	73%	100%	100%	24%	75%	91%
	CEA Pre	27.6	96%	100%	100%	67%	96%	97%
	CEA Post	6.2	31%	100%	100%	11%	36%	64%
	CA 19.9 Pre	47.0	97%	100%	100%	73%	97%	97%
	CA 19.9 Post	20.7	27%	100%	100%	11%	33%	54%

Table 5 CEA and CA19.9 are represented as Median and interquartile range (25%-75%), while Tau. is represented as mean ± SD.

Malignant tumor		G1 N=6	G2 N=68	G3 N=17	p value
CEA	Pre	8.7 (5.0-47.5)	692.4 (392.1-772.7)	1420.0 (1107.3-3082.9)	0.001**
	Post	0.6 (0.6-1.6)	3.0 (1.5-7.5)	11.3 (2.5-79.0)	0.01*
CA19.9	Pre	33.7 (5.6-87.0)	252.9 (160.7-307.4)	2067.0 (1433.3-2412.4)	0.001*
	Post	2.0 (2.0-10.8)	9.7 (2.6-22.6)	15.0 (2.0-28.8)	0.3
Tau.	Pre	18.0 ± 0.5	13.9 ± 0.7	10.7 ± 1.2	0.001**
	Post	30.0 ± 2.3	27.9 ± 4.0	23.7 ± 2.2	0.001**

*p value ≤ 0.05 significant while **p value ≤ 0.01 highly significant.

Table 6 This table indicate the ROC curve, the Stages in malignant tumor group.

Stage	Main parameters	Tau. Pre	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
G1 and G2	Tau Pre	17.0	100%	100%	100%	100%	100%	100%
	Tau Post	27.0	50%	100%	100%	15%	54%	68%
	CEA pre	82.0	93%	100%	100%	55%	93%	99%
	CEA post	1.3	78%	83%	98%	25%	78%	86%
	CA19.9 Pre	96.0	93%	100%	100%	55%	93%	98%
	CA19.9 Post	3.2	71%	83%	98%	20%	72%	69%
G1 and G3	Tau Pre	17.0	100%	100%	100%	100%	100%	100%
	Tau Post	27.0	94%	100%	100%	86%	96%	100%
	CEA pre	82.0	100%	100%	100%	100%	100%	100%
	CEA post	2.6	76%	100%	100%	60%	83%	94%
	CA19.9 Pre	96.0	100%	100%	100%	100%	100%	100%
	CA19.9 Post	3.2	65%	83%	92%	45%	70%	66%
G2 and G3	Tau. Pre	12.4	100%	99%	94%	100%	99%	100%
	Tau. Post	27.8	100%	50%	33%	100%	60%	80%
	CEA Pre	937.6	94%	90%	70%	98%	91%	89%
	CEA Post	36.5	47%	93%	62%	88%	84%	72%
	CA19.9 Pre	752.5	94%	97%	89%	99%	96%	94%
	CA19.9 Post	14.7	53%	65%	27%	85%	62%	53%

those positive family histories, in our patients there is about 14% positive cancer family history. The incidence of CRC is expected to continue to rise in most regions in the coming decades, due to population growth and changes in demographic structure. The global CRC burden is expected to increase by 60% to more than 2.2 million new cases and 1.1 million deaths by 2030, correlating with human development levels and with the adoption of western lifestyles [14].

Colonoscopy invasiveness, associated discomfort and potential risks of complications needed for the screening itself represent marked disadvantages [20]. Also, tumor biomarkers such as CEA, CA19.9 and FOBT have been clinically utilized. However, their sensitivity and specificity are unsatisfyingly [21,22]. CA19-9 has been used as a marker for CRC, but it is less sensitive than CEA [23]. Data showed the vary between each stage of CRC, taurine show its strong ability to differ between each stage or its sensitivity to any malignant change, it can distinguish between precancerous and cancer stage, also with high accuracy differ between stage 1 and 2. As in previous studies, Taurine cutoff value is 20 µmol/L between cancerous and pre-cancerous stages means any patient with taurine below that value means cancer wherever the body [43].

As in **Table 5**; CEA and CA19.9 measurements enhanced after surgical treatment (postoperative) in almost stages their value return to normal range, while taurine indicated that patients not fully get better and they need more care and special dosages of taurine as a supplementary dose according to their stage. In stage 1 specific used markers dropped to normal range CEA: 0.6 and CA19.9: 2 which show disappear of tumor, but taurine value was about 30 µmol/L which means the patients still in high risk zone, so the accuracy of measuring taurine also showed in follow up after surgical treatments.

So, this investigation is to show how much accuracy and sensitivity of serum taurine for detection of pre-cancerous and CRC stages that represented in **Figures 1-3**. The data reveal that taurine can distinguish between inflammatory disease, benign tumor and malignant tumor, as shown in **Table 4** and **Figures 1-3**. According to previous studies, [44] this can leads to possibility of using taurine in reclassification for patients, first normal range for healthy person 50-70 µmol/L, below that to 45 µmol/L it can called save margin, to above 40 µmol/L risk area, 40-30 µmol/L highly risk area highly susceptible for cancer, above 20 µmol/L precancerous stage, below 20 µmol/L it means cancer. And in **Table 5** there is variation between different stages of CRC, in parallel with another new study. The same observation was recorded in different stages of HCC [53]; we suspect the pathological condition of any patient is stage I when taurine level between 20-16 µmol/L and stage II when taurine level ranged

from 12-16 µmol/L, but taurine level exhibited value lower than 12 µmol/L stage III of CRC is highly suspected, so taurine level also can be possibly used in classification of cancer grades.

Current studies have proposed that changes in systemic taurine levels can be used to predict the formation and malignant transformation of certain tumors. Taurine as an effective antioxidant may hinder increase of Reactive Oxygen Species (ROS) in tumors, leading to a delay of the development of cancer [49].

In addition, taurine could play a role in the process of anti-tumors by down-regulating Matrix Metalloproteinase-2 (MMP-2), up-regulating N-acetylgalactosaminyltransferase [50]. It is said that taurine may induce apoptosis in cancer cells. So, Taurine significantly inhibited cell proliferation of colon. The induction of apoptosis in human breast cancer cell lines MCF-7 and MDA-MB-231. MCF-7 is p53 proficient (p53+/+) and MDA-MB-231 is a p53 null mutant (p53-/-). Taurine is a potent candidate for the chemotherapy of breast cancer through increasing PUMA expression independent of p53 status [52]. Lately, it has been used as an antipyretic and anti-inflammatory agent to treat liver and Gallbladder disease, Cardiovascular disease, Diabetes and Cataract [38-42].

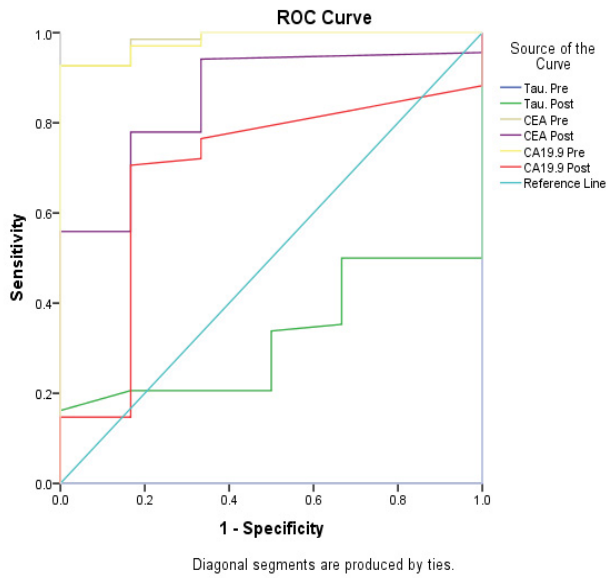

Figure 1 G1 and G2 stages of ROC curve.

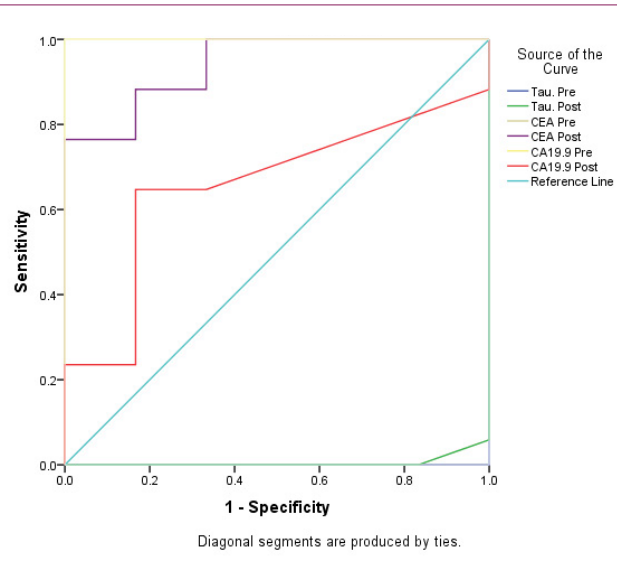

Figure 2 G1 and G3 stages of ROC curve.

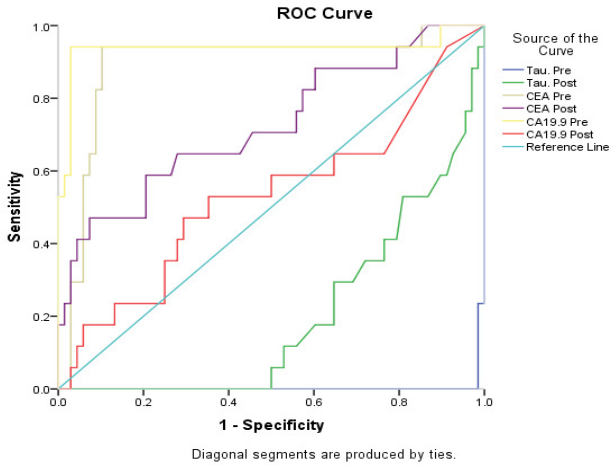

Figure 3 G2 and G3 stages of ROC curve.

Recently, Taurine can be used as an early biomarker as in Breast cancer, Uterus cancer, Diabetic retinopathy, Liver fibrosis, Hepatocellular Carcinoma (HCC) [43-47]. Newly, taurine was used to ameliorate hepatotoxic effect of dinitrotoluene in rats [48].

So, from this result we can use serum Taurine level as a pre-early marker and a biomarker for detection of any malignant change, also for staging CRC and for better follow up after surgical treatments. It is already used for enhancing immune system and induce apoptosis and inhibit cell proliferation.

Conclusion

Serum taurine results in our study showed that, besides CRC biomarkers; it is most attractive, more precious and more accurate biomarker for early detection of any malignant change which may lead to CRC by other mean it is the most sensitive and more specific tumor marker for CRC. So, we can recommend measuring its level regularly with other prognostic tumor biomarkers and screening examination for all people with abdominal and gastrointestinal problems and for pre-cancerous patients as a pre-early biomarker for Colorectal carcinoma and give supplementary dose (protective dosage) of taurine for all patients presented with gastrointestinal troubles and those who were diagnosed as Chronic inflammatory disease or Crohn's diseases and for those who their taurine level were less than 40 µmol/L and after surgical treatment to decrease side effects of chemotherapy and radiotherapy as taurine is an effective

antioxidant, may hinder the increase of Reactive Oxygen Species (ROS) in tumors, leading to a delay of the development of cancer. So, it needs more further studies to confirm that observations on large scale of population as it obvious the small sample size in early stage and lack data due to limited financial resources and it needs more efforts to collect first and pre-cancerous stages patients, to prove our investigation aim, may it help in decline CRC rises and specially in young patients.

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