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Diagnostic Value of Plasma M2-Pyruvate Kinase in Egyptian Patients with Colorectal Cancer

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INTRODUCTION

Colorectal cancer (CRC) is the 3rd most frequent cancer in the United States, with around 1.4 million cases diagnosed annually and 694,000 deaths globally. By 2035, 2.4 million instances are expected to be diagnosed each year. CRC is responsible for around 12% of all cancer costs in the country. Based on the data source, the national cost of CRC treatment for a single year has been estimated at \$4.5–9.6 billion.¹

In Egypt, neoplastic lesions of the colon are a frequent health issue. One of the most prevalent cancers among Egyptians is the CRC. Patients under the age of 40 have greater rates of CRC than in the West. This has ramifications for Egypt's future epidemiological trends. Physicians in the Middle East need to be more aware of the risk of CRC in young people.²

ABSTRACT

Background: M2-pyruvate kinase (M2-PK) plays an important role in tumor metabolism, and new studies have shown that M2-PK can operate as both a protein kinase and a transcription factor coactivator. It could dynamically regulate glycolysis energy generation and synthesis processes and is a key regulator of tumor growth.

Aim of the work: to evaluate the diagnostic relevance of plasma M2-pyruvate kinase in Egyptian colorectal cancer patients.

Patients and Methods: The research has been performed on eighty (80) people who fulfilled the designed inclusion criteria. The study was conducted at the outpatient clinic of the Gastroenterology department as well as at the inpatient unit of the Gastroenterology department of Internal Medicine departments, at El-Galaa Family Military Hospital and Al-Houssein University Hospital.

Result: There had been a statistically significant difference in M2 pyruvate kinase levels between the control and patient groups. The M2 pyruvate kinase level was significantly greater in colorectal cancer than colorectal polyp than IBD.

Conclusion: Plasma M2-Pyruvate Kinase (M2-PK) levels have been significantly higher in patients with colorectal cancer (CRC) than in healthy subjects or other patients with colonic lesions and may be useful in distinguishing CRC patients from those with benign colonic lesions.

Keywords: IBD; Colorectal polyp; colorectal cancer; M2 pyruvate kinase.

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In Egypt, there is a scarcity of data on the incidence of CRC. In one study, CRC accounted for only 4.4% of recently diagnosed cancers in one study, compared to 13% in western nations. According to another study, CRC is frequent in Egypt, accounting for 10.6% of the people having symptomatic colonic illnesses. This paucity of evidence could be due to Egypt's absence of a comprehensive cancer reporting and monitoring system.³

Early diagnosis and excision of precancerous polyps can prevent the majority of CRC instances.⁴ The phase of the disease when diagnosed has a significant effect on survival.⁵

In spite of the fact that colonoscopy is the gold standard for earlier diagnosis of CRC, even in industrialized nations, the acceptability of such a costly and invasive procedure is low.⁶ Therefore, simple, non-invasive assays having high sensitivity and specificity are urgently needed.⁷

M2-pyruvate kinase (M2-PK) plays an important role in tumor metabolism, and new studies have shown that M2-PK can operate as both a protein kinase and a transcription factor coactivator. It could dynamically regulate glycolysis energy generation and synthesis processes and is a key regulator of tumor growth.⁸

Tumor M2-PK could be found in blood and faeces, which is most likely owing to increased expression in tumour cells and leakage into body fluids. Blood testing is more accessible than faecal testing, and it has a greater rate of compliance among the general public. M2-PK levels in the serum were roughly four times greater in CRC patients than in the general population.⁹

PATIENTS AND METHODS

Study Design: The main objective of such cross-sectional research was to look at the plasma levels of M2-Pyruvate Kinase (M2-PK) in Egyptian patients with CRC and compare them to those found in patients with inflammatory bowel disease (IBD), colorectal polyps and apparently healthy individuals (screening) as control group.

Sampling and Study Setting: The study was conducted on eighty (80) persons who were fulfilling the designed inclusion criteria. The study was carried out at outpatient clinic of Gastroenterology department as well as at the inpatient unit of the Gastroenterology department of Internal Medicine departments, at El-Galaa Family Military Hospital and Al- Houssein University Hospital .

Inclusion Criteria: Egyptian patients aged more than 18 years.

Inclusion criteria for apparently healthy individuals performing screening colonoscopy: confirmed diagnosis was ascertained using endoscopies and histopathology. **Inclusion criteria for IBD patients:** confirmed diagnosis of IBD ascertained by clinical, endoscopic, radiological and histopathological criteria. **Inclusion criteria for colorectal polyp patients:** confirmed diagnosis ascertained by endoscopic and histopathological Criteria. **Inclusion criteria for CRC patients:** confirmed diagnosis ascertained by endoscopic and histopathological criteria.

Exclusion Criteria: Patients who declined to take part in the research, underwent surgery for CRC, previously received chemotherapy or any treatment for CRC, having any cancer other than CRC and sepsis

Study groups: Eighty (80) individuals involved in this study and classified into four groups:-

Group I: Including 20 apparently healthy individuals (screening) as control group, **Group II:** Including 20 patients known to have IBD (consist of; 19 patients with UC and one patient with CD), **Group III:** Including 20 patients known to have colorectal polyp (consist of; 18 patients with adenomatous polyp and two patients had

non adenomatous polyp), **Group IV:** Including 20 patients known to have CRC.

Methodology: The following procedures were performed on all patients:

A complete history is taken, as well as a comprehensive clinical examination and laboratory examinations, which include : Complete blood count (CBC), Fasting blood sugar (FBS), Liver function tests: Alanine aminotransferase (ALT) and aspartate aminotransferase (AST), serum albumin, bilirubin total and international normalized ratio (INR), Kidney function tests: blood urea and serum creatinine, Acute phase reactants: Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), *Tumor marker :* Carcinoembryonic antigen (CEA) and special test: M2-Pyruvate Kinase (M2-PK).

Imaging: Pelvi-abdominal ultrasound, CT abdomen & pelvis with contrast

Other: Metastatic work up for CRC patients to assess the staging of CRC including Chest x ray, CT chest etc.

Colonoscopy.

Biopsy samples: Biopsies have been collected from the lesions as well as the adjacent normal colonic mucosa in all groups examined.

Measurement of Plasma M2-PK Activity

A Sandwich ELISA using two monoclonal antibodies that specifically react with M-2PK and will not cross-react with the other pyruvate kinase isoforms (Type L, R, M1, and M2) was used to determine this metabolic marker.

Statistical analysis:

To code, enter, and analyze data obtained during the history, basic clinical exam, laboratory examinations, and result measurements, the Microsoft Excel program was used. The data was then analyzed using the Statistical Package for the Social Sciences (SPSS) version 20.0 software. As per the sort of data, qualitative data is represented as numbers and percentages, quantitative data is represented as a mean \pm SD, and the following tests have been employed to test for significance: The Chi-square test (χ^2) was used to determine the difference and relationship of qualitative variables. Differences between quantitatively independent two groups using the t test and many groups using ANOVA or Kruskal-Wallis, correlation using Pearson's correlation or Spearman's For significant outcomes, the P value has been set at <0.05, and for highly significant outcomes, it has been set at <0.001.

Data has been collected and statistical analysis was performed. The following statistical tests and variables have been employed (Mean, Standard deviation (SD),

The chi square (χ^2)

RESULTS

We studied 4 groups (20 patients each) with a mean age of 46.6±6.15, 31.9±9.92, 45.5±12.6

and 49.35±12.03 respectively, and in terms of gender distribution, males dominated all groupings except the 2nd group.

			Group I	Group II	Group III	Group IV	F/ X ²	P
Age	Mean ±SD		46.6±6.15	31.9±9.92*	45.5±12.6	49.35±12.03	11.013	0.00**
	Range		37-56	19-50	19-65	23-69		
Sex	Female	N	9	16*	7	6	12.23	0.007*
		%	45.0%	80.0%	35.0%	30.0%		
	Male	N	11	4	13	14		
		%	55.0%	20.0%	65.0%	70.0%		
Family history	NO	N	14	17	16	12	3.81	0.28
		%	70.0%	85.0%	80.0%	60.0%		
	YES	N	6	3	4	8		
		%	30.0%	15.0%	20.0%	40.0%		
Smoking	NO	N	14	16	11	7	9.58	0.022*
		%	70.0%	80.0%	55.0%	35.0%		
	YES	N	6	4	9	13*		
		%	30.0%	20.0%	45.0%	65.0%		
Fat nutritional habit	NO	N	12	16	10	8	7.16	0.067
		%	60.0%	80.0%	50.0%	40.0%		
	YES	N	8	4	10	12		
		%	40.0%	20.0%	50.0%	60.0%		
Alcohol consumption	NO	N	20	20	19	18	3.81	0.28
		%	100.0%	100.0%	95.0%	90.0%		
	YES	N	0	0	1	2		
		%	0.0%	0.0%	5.0%	10.0%		
Total	N	20	20	20	20			
	%	100.0%	100.0%	100.0%	100.0%			

Table1: demographic data distribution among studied groups

This table shows:

Age was significantly younger at group II also group II was significantly associated with female regard sex distribution with no other significant difference among other groups regard age or sex, no significant association or difference among groups founded regard family history, Fat nutritional habit or Alcohol consumption but smoking was significantly associated with group IV.

	Group I	Group II	Group III	Group IV	F/ Kruskal	P
ESR	6.50±2.2 3-12	11.30±3.54 4-32	17.75±6.05 6-32	36.6±19.36 5-110	15.342	0.00**
CRP	3.75±1.03 1-6	9.25±3.85* 2-26	4.30±1.41 2-8	5.35±2.05 2-12	5.144	0.003*
HB	13.0±1.25* 11-16	11.19±1.04 8.3-12.8	10.71±1.89 7.4-16	11.41±1.87 7.2-13.5	8.035	0.00**
PLT	305.5±87.6 169-432	352.35±117.3 175-567	280.1±88.6 156-451	284.8±95.3 23-456	2.205	0.094
WBCs	6.46±1.79 4.7-10.2	6.59±2.11 4.5-11.2	5.64±1.29 4.50-10	6.59±1.28 4.7-9.6	1.517	0.217
ALT	27.3±8.05* 13-37	27.0±8.86* 11-43	32.95±6.83# 23-45	31.3±6.48# 20-45	3.004	0.036*
AST	28.1±.52 16-40	30.65±5.58 23-44	28.05±7.31 10-39	29.7±8.37 11-42	0.613	0.609
Albumin	3.98±0.42 3.3-5	3.83±0.51 3.1-5	3.91±0.33 3.4-4.6	3.87±0.62 3-5.6	0.337	0.798
Bilirubin T	0.76±0.22 0.3-1.1	0.68±0.24 0.3-1.1	0.69±0.28 0.3-1.2	0.68±0.3 0.3-1.2	0.412	0.745
INR	0.68±0.21* 0.4-1.1	0.89±0.18 0.6-1.3	0.94±0.19 0.7-1.4	1.0±0.18 0.7-1.3	10.170	0.00**
Urea	22.85±6.34 15-34	25.45±5.29 11-35	28.3±6.45 12-40	24.5±6.62 12-34	2.713	0.051
S creatinine	0.75±0.28 0.3-1.3	0.94±0.33 0.2-1.66	0.74±0.28 0.2-1.5	0.61±0.24 0.2-1.5	2.497	0.066
FBS	85.05±6.95 75-98	87.10±20.4 74-152	95.5±19.4 75-145	96.85±21.29 74-145	2.158	0.100

Table 2: LAB parameters distribution among studied groups

This table shows:

ESR was significantly higher at group IV then group III followed by group II and finally group I, regard CRP it was significantly higher at group II with no significant difference among other groups, HB was significantly higher at group I with no

other significant difference among other groups, regard ALT group I& II were significantly lower than group III&IV, Group I was significantly lower than other groups regard INR.

			Group				X ²	P
			Group I	Group II	Group III	Group IV		
Abdominal pain	-VE	N	2	12	1	18	12.76	0.005*
		%	100.0%	60.0%	85.0%	90.0%		
	+VE	N	0	8*	3	2	13.29	0.004*
		%	0.0%	40.0%	15.0%	10.0%		
Bleeding per rectum	-VE	N	2	15	1	13	13.29	0.004*
		%	100.0%	75.0%	50.0%	65.0%		
	+VE	N	0	5	1	7	2.05	0.56
		%	0.0%	25.0%	50.0%	35.0%		
Constipation	-VE	N	2	20	1	19	2.05	0.56
		%	100.0%	100.0%	95.0%	95.0%		
	+VE	N	0	0	1	1	34.28	0.00**
		%	0.0%	0.0%	5.0%	5.0%		
Diarrhea	-VE	N	2	10	2	20	34.28	0.00**
		%	100.0%	50.0%	100.0%	100.0%		
	+VE	N	0	10	0	0	16.87	0.001*
		%	0.0%	50.0%	0.0%	0.0%		
Weight loss	-VE	N	2	17	1	10	16.87	0.001*
		%	100.0%	85.0%	85.0%	50.0%		
	+VE	N	0	3	3	10	6.58	0.087
		%	0.0%	15.0%	15.0%	50.0%		
Alternation (constipation, Diarrhea)	-VE	N	2	16	1	16	6.58	0.087
		%	100.0%	80.0%	70.0%	80.0%		
Total	+VE	N	0	4	6	4	6.58	0.087
		%	0.0%	20.0%	30.0%	20.0%		
		N	2	20	2	20		
		%	100.0%	100.0%	100.0%	100.0%		

Table 3: clinical picture distribution among studied groups

This table shows:

Abdominal pain and Diarrhea was significantly associated with group II, bleeding per rectum was significantly associated with group II, III and IV and weight loss was significantly associated with group IV.

			Group				X ²	P
			Group I	Group II	Group III	Group IV		
Ascites	N	N	2	2	20	1	2.85	0.211
	O	%	100.0%	100.0%	100.0%	90.0%		
Colonic mass	Ascites	N	0	0	0	2	0.71	0.889
		%	0.0%	0.0%	0.0%	10.0%		
Hepatomegaly	N	N	2	1	17	1	4.62	0.098
	O	%	100.0%	80.0%	85.0%	90.0%		
HFL	Hepatomegaly	N	0	4	3	2	5.01	0.076
		%	0.0%	20.0%	15.0%	10.0%		
Total	N	N	2	2	20	2		
	O	%	100.0%	100.0%	100.0%	100.0%		

Table 4: Radiological finding distribution among studied groups

This table shows: No significant difference founded among groups.

	Group I	Group II	Group III	Group IV	F/ Kruskal Walis	P
CEA	1.91±0.37	2.86±1.26	3.08±1.39	274.51±84.6*	20.374	0.00**
	0.7-1.66	0.6-8.5	0.15-10.7	14.8-839.0		

Table 5: CEA distribution among studied groups

This table shows: Group IV was significantly higher regard CEA with no other significant among other groups

	Group I	Group II	Group III	Group IV	F/ Kruskal	P
Plasma M2 PK	1.27±0.49	3.94±1.25	6.71±2.14	14.36±4.44	69.010	0.00**
	0.5-2.1	1.9-8.0	3.4-11	3.5-24.0		

Table 6: Plasma_M2_PK distribution among studied groups

Group IV was significantly higher than group III then group II and finally Group I

DISCUSSION

Colorectal cancer (CRC) is an extremely frequent and fatal disease. It is the world's third most prevalent cancer type, after lung and breast cancer. Following lung cancer, it is the second most prevalent cause of death.¹⁰ CRC, on the other hand, is regarded as among the most avoidable cancers

since it can arise from a variety of mechanisms, including polyps and inflammatory bowel disease (IBD), in addition to the hereditary pathogenesis that has become well documented in this illness.¹¹

The American Cancer Society (ACS) recommends starting screenings at the age of 45. The recommendations for regular screening of individuals aged 45 and older are strong, and they

continue for average-risk people in great health with an average lifespan of more than 10 years until the age of 75. CRC screening options include a faecal immunochemical test each year, a high-sensitivity, guaiac-based faecal occult blood check each year, a multitarget stool DNA check every three years, a colonoscopy every ten years, a CT colonography every five years, and a flexible sigmoidoscopy every five years.¹²

Because the ideal biomarker for CRC has yet to be found, there is an urgent requirement for dependable, less invasive, highly sensitive, and specific indicators of individualized and optimized patient therapy at the earliest illness phase possible.¹³

The current cross-sectional study sought to evaluate the plasma levels of M2-Pyruvate Kinase (M2-PK) in Egyptian patients having CRC and compare such levels to those acquired from patients having IBD, colorectal polyps, and seemingly healthy people, as well as to determine its specificity and sensitivity as a non-invasive biomarker in the diagnosis of these patients

As regards age in our study, the age varied from 19 to 50 years for IBD patients, with an average value of 31.9 ± 9.92 years, and from 19 to 65 years for colorectal polyp patients, with an average value of 45.5 ± 12.6 years, and from 23 to 69 years for CRC patients, with an average value of 49.35 ± 12.03 years, and from 37 to 56 years for normal healthy individuals (screening group), with an average value of 46.6 ± 6.15 .

¹⁴ they reported that the majority of IBD cases occur in individuals between the ages of 15 and 35, with up to 25% of patients developing IBD by adolescence. A bimodal distribution seems to exist; with a second peak of 10% to 15% developing IBD following the age of 60. Unlike¹⁵, who reported that the majority of UC patients are diagnosed between the ages of 40 and 50, the maximum age of onset for CD patients is between the ages of 30 and 40.

As regard gender in our study it was found that group II was significant associated with female regard sex distribution with no other significant difference among other studied groups, in IBD group females (80%) are more common than males while males are more common in colorectal polyp and cancer groups 65% and 70 % respectively.

Likewise¹⁶, reported that until the age of 45, the prevalence of UC did not show significant differences between female and male patients; after that, males exhibited a significantly greater prevalence of UC than females, and in general, there is a slight female predominance in Crohn's disease.

¹⁷ reported that men have a higher total prevalence of bowel cancer than women. A variety of biological and gender-related (behavioral) variables can contribute to men's higher vulnerability to CRC development.

As regards CRP in our study, CRP show a significant difference between the studied groups mainly elevated in IBD group.

The role of CRP as a predictor of survival in CRC is controversial. Their study showed that plasma inflammatory indicators, which include CRP, have not been significantly linked to CRC risk in men and that the null relationship between plasma CRP level and CRC risk noted in this research is consistent with the majority of prior research by.¹⁸

In contrast, in¹⁹ of their studies, they found that CRP levels are increased in those with CRC and that inflammation is a risk factor for the progression of colon cancer in people at average risk.

The current cross-sectional study's aim was to look into the plasma levels of M2-PK in Egyptian CRC patients. We measured enzyme levels in EDTA-plasma samples as this is the best sample for determining the tumor marker's diagnosis. An ELISA can be used to detect and quantify tumor M2-PK in stool samples.

As regards plasma M2-PK, the present study showed that plasma M2-PK levels were greater in CRC patients (14.36 ± 4.44 U/ml) than in other groups (p-value <0.00). In colorectal polyp, IBD, and normal people, the average plasma M2-PK was 6.71 ± 2.14 , 3.94 ± 1.25 and 1.27 ± 0.49 U/ml, respectively.

Our results are in agreement with those conducted by²⁰ which found significantly higher serum M2-PK in CRC patients compared to adenoma, non-adenomatous polyps, IBD and normal population.

²¹ in his study found that the carcinoma group had much greater plasma M2-PK levels than the adenomatous colorectal polyps groups and the area under the curve was 0.664 the sensitivity was 35% and the specificity was 99.33%.

CONCLUSION

From this study we can conclude the following:

Plasma M2-Pyruvate Kinase (M2-PK) levels were significantly higher in patients with colorectal cancer (CRC) than in healthy subjects or patients with other colonic lesions and may be useful in distinguishing CRC patients from those with benign colonic lesions. Also, plasma M2-PK can differentiate between functional and organic colonic lesions.

This suggests that plasma M2-PK is a potential rapid, non-invasive biomarker for CRC early diagnosis and may be considered as a CRC screening indicator to reduce unnecessary endoscopic examinations that could be painful and uncomfortable for the patient as well as time-consuming and costly healthcare services.

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