Original Article

Assessment of Tumor Necrosis Factor-α, Interleukin-17, and Vitamin D3 Levels on a Group of Gastrointestinal Tumor Patients in Babylon Provence, Iraq

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Abstract

Background: Gastrointestinal (GIT) tumors refer to collection of tumor including colorectal, gastric, liver, and pancreatic tumors and other. **Objective:** The current study aims to measure the serum level of tumor necrosis factor-α (TNF-α), interleukin-17 (IL-17), and vitamin D3 among GIT tumor patients comparing with irritable bowel disease (IBD) patients and healthy control. **Materials and Methods:** Serum samples were taken from 88 participants (42 from malignant GIT tumor, 29 from benign GIT tumor, 10 from IBD (as positive control), and 7 from health individual (as negative control)). All patients admitted in GIT center of Babylon in Merjan Medical city at April up to December 2020. The TNF-α, IL-17, and vitamin D3 level were measured by Enzyme-Linked Immunoassay (ELISA). **Results:** The result showed younger men are more prevalent with malignant GIT tumor with mean age (53.39 years) than benign GIT tumor as well as IBD. There is an significant increase in TNF-α (Least Significant Difference (LSD) = 1.79) levels of malignant GIT tumor when compared with other groups (mean ± Standard Deviation (SD) = 23.7 ± 8.1, 20.4 ± 2.8, 18.9 ± 2.66, and 18.1 ± 2.78 pg/mL for malignant GIT, benign GIT, IBD, and healthy persons respectively). Results of IL-17 level also reveal a significant increase (LSD = 13.2) of malignant GIT tumor when compared with other groups (mean ± SD = 222.2 ± 73.5, 128.2 ± 35.5, 201.5 ± 39.4, and 164.2 ± 44.1 pg/mL for malignant GIT, benign GIT, IBD, and healthy persons, respectively). Inverse results were documented for vitamin D3 level, in which a significant decrease (LSD = 23.45) in the levels of malignant GIT tumor was observed when compared with other groups (mean ± SD = 204.2 ± 24.3, 306.1 ± 97.2, 453.2 ± 78.2, 368 ± 78.0 pg/mL for malignant GIT, benign GIT, IBD, and healthy persons, respectively). **Conclusion:** The current study concluded that early age men get affected with malignant GIT tumor in Iraqi population giving a hint to that the population at high risk to involved with such tumor as well as other tumor types with elevated level of TNF-α and IL-17 and decreased level of vitamin D3. More and more studies with large number of patients should be recommended to exclude the factors in which that may lead to such conditions.

Keywords: TNF-α, IL-17 and vitamin D3, GIT tumors, IBD

Introduction

Gastrointestinal (GIT) tumors form a term representing a collection of tumors including esophageal, gastric, liver, colorectal, and pancreatic carcinomas responsible for highest percentage of prevalent and cancer-related deaths worldwide.[1] Incidence and mortality rate of GIT tumors compile 30%–40% of cancers worldwide.[2] Gastric cancer is fifth prevalent (more than 1 million newly diagnosed cases each year) and third cancer-related death causative globally.[3] Esophageal cancer order is

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eighth in prevalence and sixth leading cause of cancer-associated death.[4] Liver cancer is fifth in cancer incidence (6% of total cancer cases) cases and second order (9% of total cancer cases) in cancer-related death worldwide.[5,6] Although pancreatic cancers come last within top ten incidence cancers, those are regarded the seventh leading cause of cancer-related deaths worldwide.[7] The third incidental (approximately 2 million) and second common cause of death (approximately 1 million) due to cancers was assigned for colorectal cancers in 2020.[8]

Balancing between intestinal cell death and proliferation must be maintained to prevent tumor formation and tumor necrosis factor-α (TNF-α) plays such crucial role.[9] TNF-α modulates numerous signaling pathways and occupied in tumor formation and development especially gastric cancer.[9-11] Upregulation of TNF-α gene was seen in gastric cancer patients.[12] Interleukin-17 (IL-17) role in angiogenesis-mediated by T-cell was well defined and proposed to enhance carcinogenesis, proliferation, and invasion, and overexpression of IL-17 gene was documented in GIT tumors.[13,14] Vitamin D3 controlling numerous cellular pathways engaged in cancer expansion and progression. Deficient level of vitamin D3 can increase the risk of GIT tumors whereas many studies reported inhibitory effect of active form of vitamin D3 [$1,25(OH)_2D_3$] for the growth of gastric cancer cell.[15-17] The current study aims to measure the serum level of TNF-α, IL-17, and vitamin D3 among GIT tumor patients compared with Irritable bowel disease (IBD) patients and healthy control.

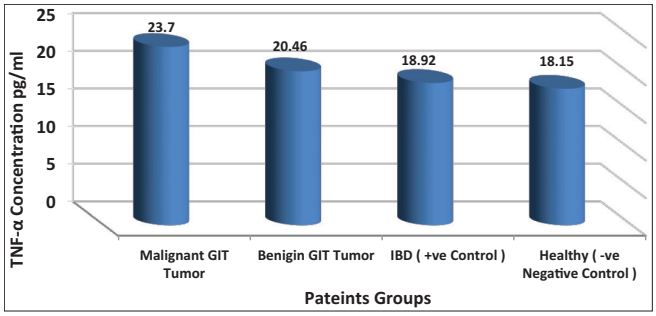

Figure 1: The TNF-α level among GIT tumor patients in comparison with controls

Materials and Methods

Patients and sample collection

Eighty eight participants were involved to evaluate the serum level of TNF-α, IL-17, and vitamin D3 among (42) malignant GIT tumor,[29] benign GIT tumor,[10] IBD (positive control),[7] and healthy individual (negative control). Serum samples were collected from all participants. Patients with GIT tumors were confirmed by a GIT specialist by endoscopy and biopsy section. All patients were admitted in GIT center of Babylon in Merjan Medical city from April up to December 2020.

Measurement of TNF-α, IL-17 and vitamin D3

The three parameters (TNF-α, IL-17, and vitamin D3) were measured by sandwich Enzyme-Linked Immunoassay (ELISA) assay according to manufacturer recommendations (Elabscience/China).

Statistical analysis

SPSS (version 26.0; IBM Corp., Armonk, New York) was used in the statistical analysis of descriptive statistic and (Least Significant Difference) LSD value.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number 3342 (including the number and the date in March 7, 2020) to get this approval.

Results

The result of TNF-α level showed that increased level in patients with malignant GIT tumor in comparison with benign GIT tumor as well as positive control (IBD) and negative or healthy control, at mean ± Standard Deviation SD (23.7 ± 8.1, 20.4 ± 2.8, 18.9 ± 2.66, and 18.1 ± 2.78 for malignant GIT, benign GIT, IBD, and healthy persons, respectively), the LSD value (1.79) as shown in Figure 1. The female patients have TNF-α level more than male patients and control, in mean ± Standard Deviation SD (20.6 ± 2.57, 22.8 ± 9.0, 17.5 ± 2.98, and 18.9 ± 2.43 for

Table 1: Distribution of TNF-α level according to gabender

Descriptive		*N*	Mean	Std. deviation	Minimum	Maximum	LSD value
TNF-α level	Male	42	20.6416	2.57633	14.92	26.27	2.25
	Female	29	22.8404	9.02710	15.76	66.27	
	Male control	10	17.5763	2.98747	13.90	25.25	
	Female control	7	18.9831	2.43660	16.10	23.39	
	Total	88	20.8860	5.79133	13.90	66.27	

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malignant GIT, benign GIT, IBD, and healthy persons, respectively), at LSD value (2.25) as shown in Table 1.

The result of IL-17 level showed increased level in patients with malignant GIT tumor in comparison with benign GIT tumor as well as positive control (IBD) and negative or healthy control, in mean ± SD (222.2 ± 73.5, 128.2 ± 35.5, 201.5 ± 39.4, and 164.2 ± 44.1 for malignant GIT, benign GIT, IBD, and healthy persons, respectively) at LSD value (13.2) as shown in Figure 2. The male patients have IL-17 level more than female patients and control, in mean ± SD (205.0 ± 66.1, 174.4 ± 95.7, 197.6 ± 83.9, and 116.5 ± 12.4 for malignant GIT, benign GIT, IBD, and healthy persons, respectively) at LSD value (24.55) as shown in Table 2.

The result of vitamin D3 level showed lower level in patients with malignant GIT tumor in comparison with benign GIT tumor and lower than positive control (IBD) and negative or healthy control, in mean ± SD (204.2 ± 24.3, 306.1 ± 97.2, 453.2 ± 78.2, and 368 ± 78.0 for malignant GIT, benign GIT, IBD, and healthy persons, respectively), the LSD value (23.45) as shown in Figure 3. The male and female patients revealed lower level of vitamin D3 than male and female control, and female patients have lower level than male patients, at mean ± SD (308.8 ± 133.8, 287.5 ± 108.0, 384.8 ± 82.0, and 345.2 ± 71.0 for malignant GIT, benign GIT, IBD, and healthy persons, respectively) at LSD vale (36.41) as listed in Table 3.

The result of Figure 4 show that the more risk age to affected with malignant GIT tumor are the patients in five decade of live at mean SD (53.39 years old), while benign GIT tumor at fourth decade at (47 years old), the IBD are early started at third decade (34.36 years old) in comparison with healthy control, the LSD value (1.86).

The result at Table 4 that the younger male patients are more affected with malignant GIT tumor in comparison with female and control at mean age (43.64, 50.4, 35.5, and 36.28 years old) at LSD vale (7.32).

In the result of correlation between studied parameters, there is a negative correlation between age range and vitamin D3 level as well as TNF-α level, whereas direct correlation between TNF-α and IL-17. This result might show that the vitamin D3 level gradually decreased with age prognosis, and increased TNF-α may lead to a decrease in vitamin D3 level among patients affected with GIT tumor. In contrast increased interferon might be leading to increase in TNF- α level. The results are mentioned in Table 5.

Discussion

Cytokines are believed to play a significant role in the pathogenesis of multiple types of neoplasms, including those malignancies that originate from the GIT tract and they appear to hold promise as targets for anti-cancer therapy. The tumor necrosis factor TNF-α plays an important role in the process of inflammation, infection, and tumors and has central importance in the early stages of gastric cancer; as TNF-α is needed for the proper functioning of the immune system by playing a striking role for the regulation of this balance in the gut. Depending on the cellular conditions, on the one hand TNF-α is able to mediate cell survival by activating NFκB signaling. On the other hand, TNF-α might trigger cell death, in particular caspase-dependent apoptosis but also caspase-independent programmed necrosis. By regulating these cell death and survival mechanisms, TNF-α exerts a variety of beneficial functions in the intestine. However,

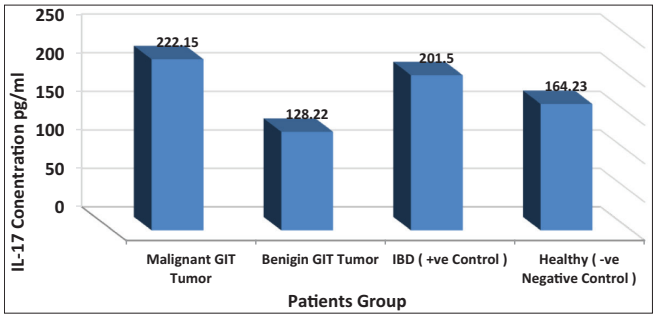

Figure 2: IL-7 level among GIT tumor patients in comparison with controls

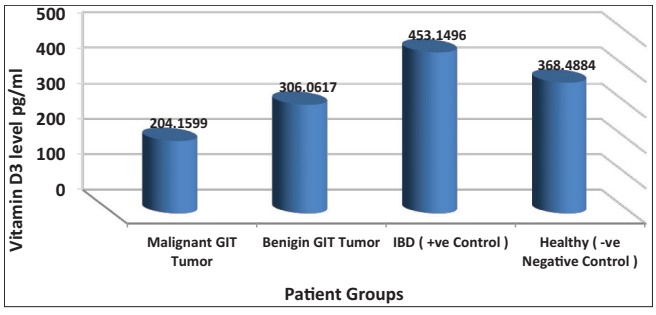

Figure 3: Vitamin D3 level among GIT tumor patients in comparison with controls

Table 2: Distribution of IL-17 level according to gender

Descriptives		*N*	Mean	Std. deviation	Minimum	Maximum	LSD value
IL-17 level	Male	42	205.00	66.1	99.00	788.00	24.55
	Female	29	174.48	95.7	96.00	546.00	
	Male control	10	197.60	83.9	96.00	546.00	
	Female control	7	116.54	12.4	96.00	135.00	
	Total	88	187.02	43.78	96.00	788.00	

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Table 3: Distribution of vitamin D3 level according to gender

Descriptive		*N*	Mean	Std. deviation	LSD value
Vitamin D3 level	Male	42	308.7985	133.84678	36.41
	Female	29	287.5807	108.02630	
	Male control	10	384.7807	82.07065	
	Female control	7	345.2138	71.07601	
	Total	88	313.3373	118.92496	

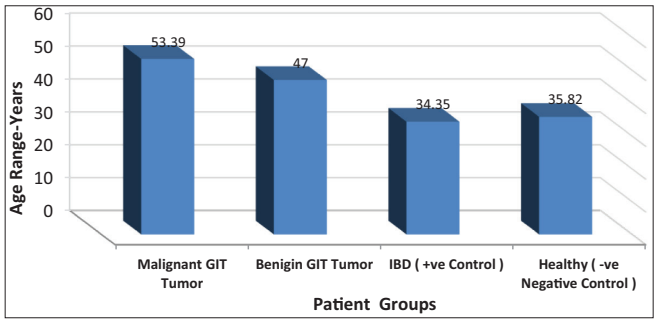

Figure 4: Mean age of patients with GIT tumor in comparison with controls

TNF-α signaling is also supposed to play a critical role for the pathogenesis of IBD, infectious diseases, intestinal wound healing and tumor formation.[9]

Interestingly, TNF-α has initially been described as a factor released by host cells to induce tumor necrosis; therefore, a role for TNF-α to regulate tumor development and growth was implicated, where circulating levels of TNF-α were positively correlated with the occurrence of colorectal adenomas. Moreover, significantly increased TNF-α serum levels were observed in colorectal cancer patients, with the highest levels in stage 4 of it.[18] TNF-α gene expression was significantly higher in GIT tumor as compared to adjacent normal tissues. Additionally, patients with low TNF-α serum levels were characterized by a higher survival rate as compared to patients with high TNF-α serum levels.[19]

IL may influence various molecular processes that are crucial for the successful development and spread of malignancies owing to their unique nature and function, and it has been demonstrated that, among a group of "inflammation-related" neoplasms, including GIT malignancies, the action of inflammatory cytokine IL-17, may be of particular significance. This concept is based on the fact that elevated tissue expression of IL-17 has been detected in colon cancer tissue samples, and this expression has been linked to outcomes in affected patients.[20] Moreover, polymorphisms in genes coding for IL-17 may have an altered risk for developing gastric cancer and in the pathogenesis of different types of gastric neoplasms in humans.[21,22]

In this study, we found that in comparison to healthy individuals, patients with GIT tumor had elevated IL-17 levels, as the concentrations of IL-17 were statistically comparable to those observed in healthy controls, findings similar to those of the study by Malek-Hosseini *et al.*,[23] also, several authors have previously demonstrated that elevated systemic levels of this cytokine are present in patients with gastric carcinoma.[24,25]

The vitamin D receptor (VDR) is expressed in various tumor tissues and is considered to mediate most of the anti-tumor effects of vitamin D. Vitamin D has been shown to regulate the proliferation, cell differentiation, invasion, and metastasis of various types of tumor cells. It was found that the VDR expression was decreased in precancerous tissues and strongly decreased in gastric cancer tissues compared to normal tissue, and the VDR expression was significantly decreased in the undifferentiated or minimally differentiated gastric cancer tissues. Therefore, the VDR may be a potential prognostic factor, or therapeutic target, for patients with gastric cancer.[26,27] Additionally, Vitamin D can inhibit the proliferation of GIT cancer cells and induce cell cycle arrest and apoptosis and to exert additive or synergistic effects with a variety of chemotherapeutic drugs used in the treatment of GIT cancer.[28]

Certain meta-analysis of vitamin D clinical trials showed that vitamin D supplementation reduced the risk of cancer death by 16%,[29,30] where VDRs are widely expressed throughout the body, and experimental evidence suggests that vitamin D has antineoplastic activity. The binding of vitamin D to the VDR results in transcriptional activation and repression of target genes, producing apoptosis, antiproliferative effects, and immunomodulatory effects that may contribute to reduced metastatic disease and fatal cancer.[31,32]

Conclusion

The early age men affected with malignant GIT tumor in Iraqi population give a hint to that the population at high risk to affected with such tumor as well as other tumor types, more and more studies with large number of patients should be recommended to exclude the factors in which that lead to such conditions.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Table 4: Gender distribution of mean age of patients and control

Descriptives		*N*	Mean	Std. deviation	LSD value
Age range	Male	42	43.6429	20.09468	7.32
	Female	29	50.4138	16.07908	
	Male control	10	35.5000	16.06411	
	Female control	7	36.2857	15.29395	
	Total	88	44.3636	18.52192	

Table 5: Correlation between all studied parameters among patients with GIT tumor

Correlations		Age range	IL-17 level	TNF-α level	Vitamin D3 level
Age range	Pearson correlation	1			
	Sig. (2-tailed)				
IL-17 level	Pearson correlation	.139	1		
	Sig. (2-tailed)	.197			
TNF-α level	Pearson correlation	.099	.101	1	
	Sig. (2-tailed)	.357	.349		
Vitamin D3 level	Pearson correlation	–.367**	.018	–.357**	1
	Sig. (2-tailed)	.000	.870	.001	

** Correlation is significant at the 0.01 level (2-tailed)

* Correlation is significant at the 0.05 level (2-tailed)

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