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Determination of Resistin, Apelin, Visfatin and Lipid Profile Levels Incolon Cancer Patients

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Abstract. According to a report by the National Cancer Institute, colon cancer is still one of the most common leading causes of cancer death worldwide and the second cause of mortality from cancer. Colon cancer is often recognized very late for successful therapy.. It is linked to various reasons such as socioeconomic status, dramatic changes in the dietary habits, chemical preservatives, the presence of refrigeration and the environmental changes. Our study aimed to estimate resistin, apelin and visfatin concentrations and lipid profiles levels in colon cancer patients.. The study group included (74) patients with colon cancer and a control group of (60) healthy subjects. The biochemical assays include resistin,apelin, visfatin, total cholesterol (T-Cho), triacylglycerol (TAG),low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and very low density lipoprotein cholesterol(VLDL-C). The results showed significant increase at ($P \leq 0.0001$) in serum resistin,apelin,Visfatin, T-Cho, TAG, LDL-C and VLDL-C in the colonic cancer patients compared with the control group, while blood serum HDL-C showed a significant decrease ($P \leq 0.05$) in colonic cancer patients when compared with the control group. The patients also were divided into four groups according to colon cancer stage, the results revealed no any significant differences ($p > 0.05$) between the stages in the concentrations of parameters under study except there was significant differences ($p<0.05$) in concentration of resistin when comparing stage 3 versus stage 4. The aim of the study was to find the relation between hormones(Resistin,Apelin,Visfatin) and lipid profile in patients with colon cancer.

Key words: *resistin, apelin,visfatin, colon cancer, lipid profile.*

Introduction

Colorectal cancer (CRC) is one of the most common cancers worldwide with more than one million new cases every year. CRC considered third most common malignancy andthe second leading cause of cancer death worldwide(1). An increase in colorectal cancer incidence has occurred in younger people (aged below 50 years)(2,3). Over time, the incidence of CRC increases in younger patients. One of the primary risk factors for colorectal cancer is obesity typically assessed using the body mass index (BMI)(4). The other risk factors in the onset of cancer include host immunity, poor dietary patterns, smoking, low physical activity levels and inflammatory bowel disease(5). Carcinogenesis is a complex, long and gradual process; the prognosis for colon cancer patients is correlated with pathological stage at the detection time and it is very important to find markers that would detect a malignant tumor as early as possible(6). This is the reason to search for new biochemical markers in blood serum.Resistinisaproteinofabout(12.5)Kda producedby macrophages,peripheralbloodmononuclear cells, pancreatic cells and bone marrow(7). Increased serum resistin level has been linked to an elevated incidence

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of obesity related cancers, such as colon and breast cancers, although the resistin level cannot considered as predictor factor (8).Highlevelsof plasmaresistinhavebeenassociatedwithincreaseing risk of non-obesity related malignancies, such as lung and coloncancers (9,10). Also,highresistinlevelsin blood serum ofbreastcancerpatientsshowed positivecorrelationwith metastasis, size andstageof tumor(11). Moreover,anegativecorrelationof BMI with serum resistin levels has been reported (12).Apelin is an adipokine considered as a ligand of the angiotensin like receptor 1 (APJ) (13).Apelin is expressed in various tissues including :the central nervous system, adipose tissue, gastrointestinal tract, lung, heart, and liver (14), thus suggesting the involvement of apelinin several biological processes. Apelin behave similarly to insulin as well as pro-inflammatory properties and has a role in blood pressureregulation(15). In addition, apelinmight contribute to obesity related disorders (16)andcancers (14,17).apelin increased in many kinds of cancers, where it might act as a potentially pro-angiogenic factor(14,17,18).Theprevious studies pointedoutsignificantlyhigher tissue and serumlevelsofapeliningastroesophageal (GEC) cachecticpatientsthan in healthy control. Moreover, apelin has been suggested a possible role ingastroesophagealcancer. Visfatin is an adipokine has a molecular weight about 52 KDa secreted by visceral adipose tissue. It was discovered as the enzyme catalyzing rate-limiting step in nicotinamide adenine dinucleotide (NAD) biosynthesis , therefore, visfatin designated as nicotinamide phosphoribosyltransferase (NAMPT) (19). Visfatin is a pro-inflammatory adipokine and its circulating levels correlate positively with insulin resistance(IR), metabolic syndrome, cardiovascular disease and diabetes (20). Besides, a positive correlation has been reported between high visfatin levels and obesity and cancer risk (21), BMI and the size of visceral fat deposits (20). Visfatin overexpressed in several cancers, such as the colorectal, gastroesophageal, prostatic, postmenopausal breastcancer and pancreas(22).It remains unclear whether serum lipids affect colorectal cancer risk(23), lipids role in colon cancer risk and progression is of interest(24). Experimental studies showed that serum lipids may influence carcinogenesis through inflammation, insulin resistance and oxidative stress pathways(25). Animal models illustrated that increased lipolysis which stimulates insulin release also reduces insulin sensitivity that might enhance carcinogenesis(26).Low density lipoprotein cholesterol (LDL-C) enhances intestinal inflammation and colon cancer progression through activation of ROS and signalling pathways (27). Cholesterol stimulated (CRC) cell proliferation and inhibited cell apoptosis (28).Nevertheless, epidemiological findings on colon cancer and serum lipids have been conflicting(29). Studies reported an enhanced risk of colon cancer associated with low levels of high density lipoprotein cholesterol (HDL-C), high levels of(LDL-C) and high levels of (TAG)(30,31). A meta-analysis of 17 prospective studies reported that high levels of TG and (T-cho) were associated with enhanced risk of colon cancer, while HDL-C might be associated with a decreased risk of colon cancer(32). The associations of body mass index (BMI) was observed to be more strongly with distal than proximal colon cancer(33). A large study in Korea indicated the effects of (T-cho) might vary bycolon cancer subsites(34).A case −cohort study reported that the high levels of serum T-cho and LDL-C were significantly associated with enhanced risks of colon cancer (distal and rectal) but not proximal colonic cancer(35). At present, several investigations havedemonstrated consequences of lipid metabolism disregulation in cancer not only sustain tumor growth but also promote cellmigration, invasion and angiogenesis (36)The aim of the present study was to estimate the levels of resistin, apelin, visfatin and lipid profile in blood serum of colon cancer patients and in healthy control group, as well as compare the levels of measured parameters between the two groups couldleadtonewdiagnostic markers for colon cancer.

Materials and methods:

Patients and controlSamples:

This study includes (74) colon cancer patients whom diagnosed and proved by colonoscopy and biopsy. Samples were collected over the period january 2020 to july 2020 from the patients treated in Mosul oncology and nuclear medicine hospital and Ibn-Sina teaching hospital/ Mosul/Iraq. Clinical diagnosis in

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each case was established according to the oncologist.. All patients were aged (25 -76) years. The patients in the study were 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 disease. Female cases were not pregnant or lactating. Control group consisted of (60) normal healthy individuals with negative finding to any benign or malignant colonic disease of any type, who were free from signs and symptoms of cancer or chronic diseases, matched in age with patients, and had no history for any gastrointestinal problem. Both patients and controls gave informed, written consent for participation.

Blood collection:

Ten milliliters of venous blood was taken from patients and control indivituals and left for (15) minutes at room temperature for coagulation, then serum was separated by centrifugation at (3000 xg) for 10 minutes, and divided in (4) aliquots and kept frozen at (-20°C) untill analysis.Resistin, Apelin and Visfatin were measured via enzyme-linked immune sorbent assay (ELISA) by using the commercial kit (Bioassay laboratory technology ,ELISA kit, Human, Shanghai, China) and the procedures were followed as given in the kit catalog. Lipid profile (Total Cholesterol, Triglycerides, High density lipoprotein cholesterol (HDL-C)) were quantified by followed the given procedure with the kit (biolabs, France), Low density lipoprotein cholesterol (LDL-C) wascalculated using Fried ewald's formula:

LDL-C (mg/dl) =Total cholesterol- (HDL-C + TG/5)

Very low density lipoprotein cholesterol (VLDL-C) estimation by the following equation:

VLDL-C= TG/5 (37)

Statistical analysis:

The data analysis was performed using the ready-made statistical package SPSS 20 (SPSS Software, SPSS Inc., Chicago, Illinois,USA)(38). Allresultswereexpressedasthemean±standarddiviation.For the comparison of significance between groups, The results were analyzed statistically using t-test to find the significant differences between the study groups and the probability level $p \leq 0.05$ was considered significant while, $p > 0.05$ was considered non significant, as well as the correlation coefficient was used. (Pearson's moment correlation) for the purpose of determining the existence of an effective correlation between the studied variables. Dataformultiplevariable comparisons were analyzed by one-way analysis of variance (ANOVA).

Results:

colon cancer patients were classified into two groups according to their (age, sex, smoking behaviour, treatment type , stages of cancer, history of family). Detailed clinic pathological characteristics of the patients are given in **TABLE 1**

TABLE 1. The clinical characteristics of patients with colon cancer

Variable	number	Percentage (%)
Total number of patients	**74**	**100**
• **Age** **a) (25-50)** **b)(51-76)**	 **33** **41**	 **44.6** **55.4**
• **Gender** **a) Female** **b)Male**	 **36** **38**	 **48.6** **51.4**

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• **Family History of colon cancer** **a) With** **b)Without**	 **3** **71**	 **4** **96**
• **Stage of tumordiagnosis** **Stage:** **Ⅰ** **Ⅱ** **Ⅲ** **Ⅳ**	 **3** **3** **32** **36**	 **4** **4** **43** **49**
• **Smoking** **a) Smoker** **b)Non-smoker**	 **5** **69**	 **6.8** **93.2**
• **Drug** **a) Chemotherapy treatment** **b)Without treatment** **c)surgical treatment**	 **23** **30** **21**	 **31** **40.5** **28.5**
• **Obesity** **a) Obese** **b)Non-obese**	 **19** **55**	 **25.6** **74.4**

The results in the **TABLE 2** showed a significant increase inResistin,Apelin, Visfatin,T-cho, TAG, LDL-C, VLDL-C concentrations in patients compared with control while HDL-C level shows a significant decrease in patients compared with control.

TABLE 2. Resistin, Apelin, Visfatin and lipid profile levels incolon cancer patients and controls**.**

Parameters	**Control(n=60)**	**Patient (n=74)**	**P-value**
Resistin(ng/L)	**5.45±1.37**	**20.33±8.45**	**0.0001**
Apelin(ng/L)	**204±23.97**	**694.8±40.39**	**0.0001**
Visfatin(ng/ml)	**5.53±3.78**	**8.65±4.97**	**0.001**
T-cho(mg/dl)	**147.46±14.47**	**164.88±21.11**	**0.0001**

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TAG(mg/dl)	**94.46±16.277**	**148.94±13.95**	**0.0001**
HDL-C(mg/dl)	**38.54±9.11**	**33.59±7.74**	**0.0001**
LDL-C(mg/dl)	**95.122±22.949**	**100.523±28.99**	**0.0001**
VLDL-C(mg/dl)	**15.809±3.255**	**29.788±2.79**	**0.0001**

The colon cancer patients were sub-classified into four groups according to disease stages, stage Ⅰ, Ⅱ, Ⅲ and Ⅳ. The results revealed non significant differences ($p>0.05$) between the stages except there was significant differences ($p<0.05$) in the concentration of Resistin when comparing stage Ⅲ versus stage Ⅳ as shown in **TABLE 3**. As can be seen, for all four subgroups of patients, serum resistin levels were significantly higher as compared to controls ($P<0.01$ for stage Ⅰ, Ⅱ and $P<0.001$ for Stages Ⅲ and Ⅳ), ($P<0.01$, stage Ⅰ, Ⅱ carcinoma vs. Controls; NS, stage Ⅰ, Ⅱ vs. Stages Ⅲ and Ⅳ, $P<0.001$, Stages Ⅲ and Ⅳ vs. controls) apelin and visfatin serum concentrations were non significantly increased in patients four stages ($P>0.05$). Moreover, a significant posative correlation was present between resistin and disease stage ($r=0.238$, $P=0.011$), however no correlation was noticed between the other measured parameters concentrations and tumor stage.

TABLE 3. The concentrations of measured parameters in the sera of patients according to tumor stage.

Parameters	**Stage Ⅰ (n=3)**	**Stage Ⅱ (n=3)**	**Stage Ⅲ (n=32)**	**Stage Ⅳ (n=36)**
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Resistin(ng/L)	10.3±8.4	13.9 ± 9.7	27.4 ± 70*	35.8 ± 5.6*
Apelin(ng/L)	614.8±33.9	684.53 ± 29.54	691.8 ± 25.68	783.25 ± 11.35
Visfatin(ng/ml)	8.5±4.97	8.61 ± 3.79	8.91 ± 6.8	9.22±1.4
T-cho(mg/dl)	150.53± 12.4	156.53± 15.2	160.53± 13.9	169.53±31.5

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TAG(mg/dl)	140.80± 12.7	142.40± 11.3	151.82± 9.54	154.20±1 3.9
HDL-C(mg/dl)	40.33±8. 45	38.69±6.25	31.43±2.56	30.59±1.79
LDL-C(mg/dl)	88.8±10. 9	94.68±11.6	99.21±13.3	110.2±12.5
VLDL-C(mg/dl)	28.16±2 .54	28.48±3.0	30.1±2.1	31.5±2.78

***(p<0.05)**

In addition the present study showed significant posative correlation between Resistin with Apelin,Visfatin and T-cho in both groups patient with colon cancer and control **TABLE 4**,while there was a significant negative correlation between Resistin and HDL-C (r=-0.555)whereas there were no any correlation between Resistin with TAG,LDL-C and VLDL-C in patients under study

TABLE 4. correlation between Resistin and parameters under study in colon cancer patients and control

parameter	**Patients(n=74)**		**Control(n=60)**	
	Resistin(ng/L)		**Resistin(ng/L)**	
	r value	**P-value**	**r value**	**P-value**
Apelin(ng/L)	**0.446**	**0.001***	**0.54**	**0.001***
Visfatin(ng/ml)	**0.54**	**0.032***	**0.5**	**0.001***
T-cho(mg/dl)	**0.498**	**0.041***	**0.499**	**0.001***
TAG(mg/dl)	**0.093**	**0.565**	**0.221**	**0.245**
HDL-C(mg/dl)	**-0.555**	**0.011***	**-0.489**	**0.023***
LDL-C(mg/dl)	**0.121**	**0.317**	**0.211**	**0.362**
VLDL-C(mg/dl)	**0.094**	**0.571**	**0.231**	**0.249**

Discussion

In this study we found increase in the Resistin concentration of colon cancer patients when compared with healthy control group.These results are in agreement with other studies which found increased levels of resistin in patients with colorectal (39), breast (40) lung cancer (41)and endometrial cancer patients (42). Nakajima et al. reported that resistin levels were significantly higher in colorectal cancer patients than those in controls independent of the BMI, and these levels gradually increased with progression in tumor stage (43). In our study, colon cancer patients displayed increased serum resistin levels,also we obtain signifigant posative correlation between serum levels of resistin and tumor stage.Resistin is a proinflammatory cytokine and has a role in many inflammatory disorders,despite of studies demonstrating increased serum resistin in colon cancer patients, its role on colon cancer cells is yet to be investigated. In addition, the absence of a definite resistin receptor on cancer cells poses challenges in deciphering its mode of action.It has been suggested that high resistin levels are related to cancer associated chronic inflammation. Data indicate that stimulation of macrophages in vitro with endotoxin or proinflammatory cytokines leads to a marked increase in resistin production and vice versa,also resistin strongly upregulate TNF–alpha and IL–6 production (44).In colon cancer which is highly prevalent resistin level correlate with this disease risk (45). This association generates curiosity to investigate the plausible interrelation between the two. More than half of the colon cancer patients have a mutation and/or loss of function in p53. It was found that cells with loss of p53 or mutated p53 exhibited

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decrease in proliferation upon resistin treatment whereas in cells having functional p53 protein, resistin treatment did not change growth pattern.It has been reported that about 50% of the solid tumor mass is contributed by tumor associated macrophages (46). Along with the stage of the tumor, the macrophage infiltration increases and macrophages secrete resistin (47). Based on these reports findings it is conceivable that the increase in serum resistin with the increase in stage of colon tumor is likely to be a function of extensive macrophage infiltration , the level of plasma apelin in obese men with colon cancer was significantly increased compared to healthy individuals (48). Moreover, tumor-associated apelin has positive correlation with apelin receptor concentration, while both expression levels were higher in colon cancer as compared to healthy tissue (49). Additionally, apelin can stimulate tumor growth and proliferation of several types of cancer, including lung cancer (50), ovarian cancer ,prostate cancer (51) and cholangiocarcinoma (52). Numerous studies have indicated that the apelinergic system can be involved in migration and invasion of cancer cells, however the mechanism of its precise action is still unclear (53).Apelin has been shown to stimulate the migration of gastric cancer cells (54), oral squamous cell carcinoma cells (55) and human lung adenocarcinoma cells (56). Moreover, apelin-13 induce lymph node metastasis of implanted apelin-overexpressing melanoma cells in mice (57).The increase in visfatin levels in colon cancer patient's agreement with (58).Visfatin appears to be involved in the regulation of cancer cell angiogenesis. Visfatin stimulates malignant tumors and related to the worst clinical factors ; previous study (59)reported that extracellular visfatin increase the growth of cancer cells and capability secondary growth of cancerous tumors through activation two factor or proteins important in incidence cancer(60) whomreported that high serum visfatin level was associated with poorer survival of cancer patient. A high level of serum visfatin was associated with malignant cancer behavior and the level of serum visfatin could offer a means for prognosis in cancer (61)suggested that increased expression of visfatin resulted in a more aggressive phenotype in CRC patients(62).Though the precise mechanism remains undetermined, these findings will help to better understand the roles of visfatin on the progression of CRC and indicate that visfatin might be a valuable target for CRC therapy(63). The increase in cholesterol, TG, LDL- C, concentrations agreement with , who reported that chol, TG, LDL-C, increased in colorectal cancer patients also pointed that there is a relationship between increase cholesterol levels and infected with cancer. There is a relationship between cell growth and cholesterol biosynthesis, cancer stimulate cholesterol increasing because it activate tumor spreading and growing (52). Reported that a high LDL-C level increases the risk of colon cancer. HDL-C showed a significant decrease in colon cancer patients as compared with control group and this agreement with (49). HDL-C inhibits the uptake of the LDL-C from arteries walls and therefore facilitates cholesterol transport from peripheral tissues to liver (60). High LDL-C concentration may produce from lipid peroxidation which increase in cancer patients, these results in oxidation and cellular injuries (49). High VLDL-C level might be due to increasing the oxidation in the body that causes decreased activity of lipoprotein lipase which leads to increase VLDL-C (52). In conclusion: visfatin levels increase in colon cancer patients and this may relate with high lipid profile in these patients.

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