

# Serum resistin level in patients with colorectal cancer

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## ABSTRACT

Resistin adipocyte-secreting adipokine, it is positively correlates with the development colorectal cancer, Resistin shares several features with proinflammatory cytokines and can play a role in the regulation of inflammation and immunity. The majority of epidemiologic studies had indicated that in vivo hyper-resistinemia is associated with some obesity-related malignancies such as colon cancer and prostate cancer, the aim of this study was to find associated resistin and other biochemical parameters (T.P ,Albumin , GSH,MDA and BMI) with colorectal cancer risk for males and females patients, in addition the effect of chemotherapy treatment on the study parameters , the cases divided in two groups after and before chemotherapy compared with control group and the results show compared between cases before and after chemotherapy. The results: mean value of (resistin, MDA and BMI) levels, show significant increase before and after chemotherapy compared with control group for females and males while significant decrease in (T.P, Albumin and GSH) compared with control group, beside the effects of chemotherapy on increase of (MDA, T.P) and significant decrease on (Resistin ,Albumin and GSH) when compared with the results before chemotherapy for females, on the other hand the results for males after chemotherapy significant decrease in (Resistin and GSH) levels, and significant increase in (MDA) level compared with the results before chemotherapy treatment .

**Key words:** colorectal cancer , resistin , adipose tissue , obesity .

**Abbreviations:** CRC: Colorectal cancer, BMI: Body mass index , GSH: Glutathione , TP: Total proteins , MDA: Malondialdehyde .MS: Metabolic syndrome , MM: Multiple myeloma

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## INTRODUCTION

Colorectal cancer is the third most common type of cancer in men and the second most common type in women worldwide, accounting for approximately 10 % of cancer incidence in both men and women [1]. There is a pronounced gradient in incidence rates between developing and developed countries, with highest rates in Australia/New Zealand and Western Europe and lowest rates in Africa and South- Central Asia [1]. The high prevalence of obesity has been hypothesized to be among the factors responsible for the high incidence of colorectal cancer in most developed countries [2][3].colon and rectum cancers are together termed as colorectal cancer (CRC), which is one of the most common malignancies with high mortality and morbidity rates worldwide. Nearly 1 million newly diagnosed cases are observed every year [4] . As in many cancer types, the patient's characteristics and familial predisposition as well as additional factors such as nutritional factors, alcohol, smoking, and obesity play a role in the development of CRC [5].

Resistin, adipocyte-secreting adipokine. Recent studies have indicated that the plasma levels of resistin are increased in many inflammation-related disorders such as atherosclerosis and arthritis[6]. Increasing evidence has also revealed that serum resistin positively correlates with the development and metastasis of malignancies [7] . Although the studies have some discrepancies, the circulating levels of serum resistin may serve as biomarkers for the pathogenesis and progression of many cancers, in particular CRC. However, information is lacking about the detailed regulatory mechanisms of resistin in CRC development [8].

Obesity, particularly central obesity, is a risk factor for colorectal cancer [9]. A meta-analysis found a relative risk of 1.45 for the association between colorectal cancer and a relatively large waist circumference [10]. Several mechanisms have been proposed to explain the obesity association with colorectal cancer [11]. First, obesity leads to insulin resistance and hyperinsulinemia , and insulin levels are positively associated with colorectal cancer risk . Second , adipose tissue secretes a

variety of adipokines, and some of them are potent proinflammatory cytokines, such as interleukin (IL)-6 and TNF- $\alpha$ , which could promote tumor initiation and progression [12]. Indeed, colorectal cancer is an inflammation-associated disease—elevated risk is seen among individuals with inflammatory bowel disease or a high level of the inflammation marker C-reactive protein. Third, other adipokines produced by adipose tissue, such as leptin and adiponectin, have bioactivities affecting tumorigenesis, and some of these adipokines also play a critical role in regulating inflammation and insulin sensitivity [13].

Obesity is associated with a number of metabolic abnormalities, such as elevated blood pressure, abnormal glucose metabolism, and dyslipidemia, which tend to cluster (referred to as metabolic syndrome) and increase the risk to develop cardiovascular disease and type 2 diabetes mellitus. Evidence accumulating during the past decade suggests that metabolic dysfunctions also may play a role for colorectal cancer risk. Given the high prevalence of obesity and colorectal cancer, a better understanding of the pathophysiology might have important preventive implications, because it may provide a more accurate and precise characterization of individuals at risk and it may point to targets for prevention. The current article reviews the influence of obesity and related metabolic alterations on colorectal cancer risk with a particular emphasis on findings observed during the past year [3].

Resistin is a member of the newly discovered family of cysteine-rich proteins called “resistin-like molecules” (RELMs). Its gene, referred to as Retn mapping to the p13.3 band of chromosome 19, encoded a 114-amino acid polypeptide which is secreted as a disulphidlinked homodimer and circulates in two distinct assembly states: an abundant high-molecular weight hexamer and a less abundant, but more bioactive, trimer. Resistin, has been originally reported to be a hormone linking obesity with insulin resistance in rodents. However, this association has not been consistently replicated in human clinical studies [14] and at time, the role of resistin in metabolic deregulations remains controversial. Some authors indicated that increased serum resistin levels are associated with increased obesity, visceral fat, type 2 diabetes [15][16] and MS, while other groups failed to observe such correlations.

Resistin is one of white adipose tissue adipocytokines. Plasma resistin levels were reported to be associated with many inflammatory markers [17]. Resistin shares several features with proinflammatory cytokines and can play a role in the regulation of inflammation and immunity [18]. The majority of epidemiologic studies had indicated that in vivo hyper-resistinemia is associated with some obesity-related malignancies such as colon cancer and prostate cancer [19]. Elevated levels of plasma resistin have been found in females with breast cancer, and higher levels appear related to the highest histological grade. Furthermore, resistin levels are significantly higher in lymphoma patients than in patients with other hematological malignancies. Although only a few studies have analyzed resistin in patients with malignancies the general properties of resistin could contribute to tumorigenesis. Thus, the distinct possibility exists that obesity may be linked to Multiple myeloma MM through altered secretion of one of these adipokines [20].

Colorectal cancer is one of the most frequent neoplastic diseases in human population and one of the most frequent causes of death. There are a lot of pathological factors, including reactive oxygen species (ROS) involved in the process of cancer initiation and progression. Damages to DNA, protein, cell membrane and mitochondria are involved in carcinogenesis, although no specific biochemical marker has been identified yet. In addition, information on the biochemical alterations in tissue and blood, particularly of antioxidant status, and its correlation with the clinical staging of the disease, is lacking. ROS are formed in excess in chronic diseases of the gastrointestinal tract but the precise mechanisms of oxidative stress being induced in cancer cells and the role of ROS in colorectal cancer progression are still not exactly understood [21].

The present study was to assess the levels of lipid peroxidation products like malondialdehyde (MDA) such as 4-hydroxy-2-nonenal (4-HNE) in primary colorectal cancer. Moreover, we analyzed the non-enzymatic antioxidants (glutathione). Oxygen derived free radicals are: hydroxyl radicals (OH $\cdot$ ), hydrogen peroxide (H $_2$ O $_2$ ), hypochlorous acid (HOCl), singlet oxygen (O $_2$ ), peroxy nitrite anion (ONOO $^-$ ) and peroxy nitrous acid (OHOOH). The definitive effect of free radicals is related to the balance between their destruction and formation. If formation of free radicals exceeds the antioxidant defense mechanisms then a condition termed oxidative stress arises [22].

In this study include determination of GSH, GSH is a water-soluble tripeptide made up of glutamine, cysteine and glycine, the potency of GSH exists in its cysteine residue (thiol group). It is the most important thiol anti-oxidant in the organism and protects the body against electrophilic, halogenated structures and epoxides. GSH is involved in many direct and indirect protective mechanism. It is an important antioxidant that provides a balance between oxidation and reduction, as well as protecting cells from harmful effects of endogenous and exogenous oxidants. This protection is carried out by GSH S-transferase and GSH peroxidase. In addition to detoxification, reduction of ribonucleic acids to deoxyribonucleotides in the glyoxalase system as well as gene expression of various proteins are also involved through the thiol group [23].

The inverse correlation between body mass index BMI and albumin synthesis in cancer patients supports the possibility of a compensatory enhanced albumin synthesis in these metabolically affected patients. In the later stages of disease, malnutrition and inflammation suppress albumin synthesis. As part of the systemic inflammatory response to the tumor, pro-inflammatory cytokines and growth factors are released [24]. Serum albumin is generally used to assess the nutritional status, severity of disease, disease progression and prognosis. Serum albumin has also been described as an independent prognosticator of survival in various cancers like lung, pancreatic, gastric, colorectal and breast [24] [25].

Tumor markers are the substances specific for certain tumor or cancer cells and thus could be of appreciable diagnostic value in cancer patients. The cell surface membrane is chiefly composed of glycoproteins and glycolipids. Any intracellular micro environmental change may lead to alteration in the surface membrane constituents, releasing certain molecules in the blood of such patients [26].

In malignant cells the membrane glycoproteins and glycolipids have altered carbohydrate metabolism which could be responsible for all the abnormal behavior i.e. abnormal cell recognition, cell adherence, antigenicity and invasiveness. The glycoproteins and glycolipids can be released into the blood through increased turnover, secretion and/or shedding. Several studies have shown a positive association of glycoproteins with malignancies. Although several researchers have studied TSA, TP and TSA/TP ratio levels for the purpose of diagnosis and management of cancer [26].

#### **The aim of the study:**

The present study was the correlation and level resistin in females and male with colorectal cancer and determine biochemical parameters (GSH, MDA, T.P., BMI, S. albumin).

#### **MATERIAL AND METHODS**

Taking 75 samples from patient (35 female) and (40 male) who attend Nanakly of hematology Hospital, the province of Arbil, Iraq, between November 2014-march 2015 the samples were suffering from advanced colorectal cancer (T3/T4 with metastases or nodal status up to N3), and they required chemotherapy based on the combination (5-fluorouracil, oxaliplatin and irinotecan), they were aged between 40-70 years.

**Control group:** 90 samples (40 female and 50 male) taken from healthy people of the same age groups

#### **Blood collection and biochemistry analysis:**

Blood samples (5ml) were collected before initiating the treatment in patients. Blood samples were used to analyze (T.P and S. Albumin) commercial diagnostic kits from franc (BDH) company. Serum sample collected for estimation of Resistin were frozen at (-80) °C and were analyzed within one month the kit for estimating Resistin was obtained from My Biosource company, U.S.A. depended on ELISA.

The MDA levels in the serums of both groups were examined using Uchiyama and Mihara methods [27]. The method is based on the production of the pink compound producing maximum absorbance at 535 nm as a result of tyrosobarbituric acid's reaction with MDA. The GSH level was examined using the Ellman method [28].

The globally accepted criteria for the definition of overweight and obesity in adults are based on body mass index (BMI), calculated as weight (in kilograms) divided by height (in meters) squared divided by hundred [3].

#### **RESULTS AND DISCUSSION**

In this study show significant increase in resistin and BMI levels at ( $p < 0.001$ ) and MDA level at ( $p < 0.05$ ) for patients colorectal cancer before chemotherapy and significant decrease for (TP ( $p < 0.001$ ), Albumin ( $p < 0.05$ ) and GSH ( $p < 0.000$ )) levels compared with control group, other side the results show high significant in Resistin ( $p < 0.05$ ), MDA ( $p < 0.05$ ) and BMI ( $p < 0.001$ ), and significant decrease at ( $p < 0.05$ ) for TP and albumin at ( $p < 0.001$ ) and GSH ( $p < 0.000$ ) for females after treatment chemotherapy compared with control group as well as high significant in MDA level at ( $p < 0.001$ ) and T.P at ( $p < 0.001$ ) while significant decrease in Resistin, GSH and albumin levels at  $p < 0.05$ . and non significant in body mass index level when compared with females before chemotherapy.

Table (2) show the results significant increase in resistin level at  $p < 0.001$ , MDA level at  $p < 0.05$  and BMI at  $p < 0.000$ , and significant decrease in T.P, Albumin at  $p < 0.05$  and GSH at  $p < 0.000$  for male with colorectal cancer before chemotherapy

when compared with control group , on the other hand the result for male with chemotherapy when compared with control group it show high significant in levels of ( Resistin at  $p<0.05$ , MDA at  $p<0.001$  , BMI at  $p<0.001$  and significant decrease in albumin at  $p<0.05$  , T.P , MDA at  $p<0.001$  and GSH at  $p<0.000$ ), aside from the results show when compared males before and after chemotherapy significant increase in resistin and MDA levels at  $p<0.05$  but there is significant decrease in GSH at( $p<0.001$ ) and resistin at( $p<0.05$ ) , and no significant in T.P , Albumin , BMI .

The results show signification increases in resistin levels in patients (females and males) with CRC, increasing epidemiological evidence has demonstrated that obesity and metabolic syndrome are associated with an increased risk of cancer especially CRC[29][30], Recently, adipocytokines produced by adipose tissue have been suggested as novel risk markers not only of MS but also of different type of cancers, particularly obesity-related cancers [31].

**Table (1) Resistin and some biochemical parameters for females (mean ± SD)**

Parameter biochemical group	Resistin ng/ml	T.P g/dl	Albumin g/dl	GSH μmol/l	MDA μmol/l	BMI %
Control N=40	6.72±1.21	6.81±0.15	4.315±0.53	8.17±0.74	1.76±0.081	29±1.7
Patients with (colorectal cancer) before chemotherapy N=15	8.31±1.31 **	4.81±0.25 **	3.35±0.87 *	3.86±0.51 ***	3.03±0.031 *	34.11±2.31 **
Patients with (colorectal cancer) after chemotherapy N=20	7.04±1.20 *#	5.11±0.28 *#	2.88±0.08 ***#	2.64±0.88 ***#	4.044±0.451 *##	33.45±1.99 **

\*= $P<0.05$ , \*\*= $P<0.001$ , \*\*\*= $P<0.000$ (Statistically significant when compared with control)

#= $P<0.05$ , ##= $P<0.001$ , ###= $P<0.000$ (Statistically significant when compared between patients before and after chemotherapy)

**Table (2) Resistin and some parameter biochemical for males (mean ± SD)**

Parameter biochemical group	Resistin ng/ml	T.P g/dl	Albumin g/dl	GSH μmol/l	MDA μmol/l	BMI %
Control N=50	7.8±1.74	7.33±0.12	4.25±0.41	9.34±0.34	1.99±0.46	30.7±2.12
Patients with (colorectal cancer) before chemotherapy N=20	9.16±0.53 **	5.82±0.73 *	3.84±0.5 *	5.51±0.66 ***	3.81±0.61 *	35.31±1.02 ***
Patients with (colorectal cancer) after chemotherapy N=20	8.77±1.32 *#	5.33±0.51 **	3.41±0.25 *	3.25±0.56 ***##	4.23±0.95 *##	34.11±0.98 **

\*= $P<0.05$ , \*\*= $P<0.001$ , \*\*\*= $P<0.000$ (Statistically significant when compared with control)

#= $P<0.05$ , ##= $P<0.001$ , ###= $P<0.000$ (Statistically significant when compared between patients before and after chemotherapy)

It is clear that little is known about the resistin-CRC link , resistin may be a good biomarker of CRC independently from BMI which is constant with our results , in humans, resistin is mainly produced by macrophages and monocytes, and it is only moderately detectable in adipocytes. Although the pattern of resistin expression in humans has been clarified, its precise physiological function is far from being elucidated and data regarding the regulation of blood resistin levels in humans are scarce. We thus performed a correlation between resistin, metabolic and inflammatory parameters [14].

However heighten significantly in resistin level may by the associations between resistin and CRC in relation with several important potential confounders, including age, sex, smoking, alcohol consumption, exercise and menopausal status. In addition, we performed multiple stratified analysis including markers of obesity, MS and inflammation known to be associated with both CRC and resistin levels.

Resistin, as other adipocytokines, participates in regulation of systemic inflammatory response, stimulating the production of IL-6, IL-8, IL-12, and TNF- $\alpha$  in white adipose tissue [32]. Resistin induces growth, differentiation, and migration of endothelial cells, which is important in tumor genesis and angiogenesis processes [33][34]. Our results suggest that concentrations of serum resistin can increase during cytokine-stimulated inflammatory response in GEC patients.

On the other hand may be the chemotherapy (5-fluorouracil plus oxaliplatin or irinotecan) based chemotherapy administered to colorectal cancer patients decreased the concentration of resistin ,and positively affected cytokine production and decrease resistin which are proangiogenic ,promoting cancer cell proliferation [35][36].

The results show significant decrease in T.P for male and female with colorectal cancer that may be to positive association of glycoproteins with malignancies [26]. Lower serum albumin concentration may be to the production of Cytokines such as IL-6 , which modulate the production of albumin by hepatocytes , Alternatively ,tumor neurosis factor may increase the permeability of the microvasculature , thus allowing an increased trans capillary passage of albumin presence of micro metastatic tumor cells in lever may induce the kupffer cells to produce a variety of cytokines (IL-1b,IL-6) , which may modulate albumin synthesis by hepatocytes [24][37].

In females and males patients show the result indicated the significant decrease in T.P and albumin levels the reason may be duo the serum dramine oxidase activity (DAO) which is the main enzyme for the metabolism of ingested histamine [38][39], DOA is localized mainly in the small intestinal mucosa ,serum DAO activity decreased step-by-step significantly during anticancer drug therapy in human it may be to serve as a useful predictor of gastrointestinal toxicity due to anticancer drug . some studies show relationship between DAO activity and decrease in total protein and albumin in serum[40].

In addition to the results show significant decrease in GSH level for patient (female and male) with colorectal cancer the reason may be increased oxidative stress coupled with membrane damage due to lipid peroxidation antioxidant non enzymes a scavenger of oxygen radicals, might have increase as a compensatory mechanism ; an antioxidant could enhance the cytotoxic ability of macrophages to scavenger free radicals by prevent radical-induced cellular damage , in such a situation non-enzymatic antioxidant are not able to prevent oxidative modification of cell components . the GSH level decrease progression of colorectal cancer and are therefore higher in clinical stage II and lower in stage IV of colorectal cancer [21][41].

On the other side GSH level show significant decrease after chemotherapy in female and male patients the reason may be due side-effects associated with the cancer chemotherapy limit the scope of chemotherapeutic drugs [42]. some studies show the GSH and GSH metabolizing enzyme are presen at elevated levels in colonic tumors , they may serve as clinically useful biomarkers of colon cancer , and/or targets for anti-colon cancer drugs [43].

The results indicated high significant in MDA level in female and male with colorectal cancer before chemotherapy compared with control group the level of probability, Free radical related mutagenesis that can result in cancer initiation and progression is a frequent event in normal human cells. Although free radical mediated tumor promotion has not been directly demonstrated in humans, there is convincing experimental evidence that oxidative stress can differentially induce the proliferation of tumor cells [23]. Formation of reactive oxygen species is a normal consequence of a variety of essential biochemical reactions. It is also known the oxygen radicals could be formed in excess in chronic diseases of the gastrointestinal tract which might contribute to the increased risk of cancer , lipid peroxidation one of oxygen radical production, final lipid peroxidation malondialdehyd MDA , 4-hydroxynonenal , they are produceds endogenously via lipid peroxidation and prostaglandin in biosynthesis and exits in biological matrices both in the free form , and bound to SH and/or NH<sub>2</sub> groups of various biomolecules , it is a genotoxic product of enzymatic and oxygen radical –induced lipid peroxidation [44] , damage of DNA by oxygen free radicals , frequently leads to initiation and progression of human cancer related mutation ROS-induced DNA damage include[45] cross-linking through Schiff's base with DNA and DNA damage.

In this study levels of MDA in patients with colorectal cancer agree with the studies of Skrzydlewska E. (2005) [21] and Maia F. etal.(2014)[46].

On the other side the results indicated the MDA level highly significant for patients (female and male ) after chemotherapy some studies suggested that chemotherapy (and radiotherapy) is associated with increased formation of reactive oxygen and



nitrogen species as well as depletion of endogenous antioxidant, where tissue injury can cause reactive oxygen species generation through activated phagocytes or release of transition metal ions from injured cells, thus, reduced free radical trapping capacity of plasma, increased MDA [47]. Meanwhile, a large number of anticancer drugs have been shown to induce oxidative stress [48].

From the other side the results for BMI indicated significant increase for females and males with colorectal cancer before chemotherapy compared with control group, some potential mechanisms of the association between body fatness and colorectal cancer risk have been proposed, thus, obesity-related changes in sex hormone levels were suggested to be linked to colorectal cancer risk, for instance, high body fatness is associated with higher endogenous estrogen levels, and a prospective study among postmenopausal women observed a significant association between high a significant association between high endogenous estradiol levels and higher risk of colorectal cancer [49], the positive association was unaffected by adjustment for waist circumference, insulin, and free IGF, which led the authors to the conclusion that is independent of the pathway broadly associated with obesity, hyperinsulinemia, and IGF-1, a second prospective study of postmenopausal women observed positive association between endogenous estrone but not estradiol and colorectal cancer risk [3].

Some studies show the influence BMI on the development of some types of cancer appears to be affected by sex different and sex hormones [50][51] and the risk of colon cancer is correlated with BMI in man and menopausal women [52] BMI is commonly used in epidemiological studies to assess degree of obesity, and the BMI-colon cancer association has consistently been found to be stronger in men than in women [53].

On the other hand the results show significant increase in BMI level for (females and males) patients after chemotherapy compared with control but no significant difference show the results compared between before and after respectively, some studies have evaluated the prognostic role of weight change in stage III colon cancer patients [53].

We measured body weight change during the adjuvant chemotherapy period (before and at the last cycle of chemotherapy), obesity leads to decrease level of circulating adiponectin and increase of insulin-like growth factor1 which contribute to an increased risk of colorectal cancer [54].

**Table (3) compared between male(smoker and nonsmoker)(mean±SD)**

Parameter	N	Smokers	N	Nonsmoker	P
GSH	22	2.99±0.39	28	5.81±0.91	P<0.001
MDA	22	4.71±0.96	28	3.51±0.42	P<0.05

The results in table(3) show significant decrease in GSH levels for smokers the reason may be the smokers a rich of oxidants and it increased production of reaction oxygen species-associated with smoking may exceed the capacity of oxidant defense system, resulting in oxidative damage. oxidative stress is the result of an imbalance between the generation of reactive species (ROS) and the antioxidant system in favour of the former, the potential damage that can caused by free radicals is normally minimized by a combination of biological antioxidant systems including enzymatic and non enzymatic reaction [55], as well as the reason may be the erythrocytes from healthy cigarette smokers contain more GSH and catalase, and protect lung endothelial cells from H2O2 better than do erythrocytes from age-and gender –matched non –smokers, the results suggests that free radical inhaled in cigarette smoke are highly toxic, and impaired oxidant – antioxidant balance is a risk factor in degenerative diseases [56].

On the other hand the results indicated high significant in MDA level in smoker when compared with non smokers, smoking may enhance oxidative stress through generation of reactive oxygen species, thereby causing lipid peroxidation, one of the frequently used biomarker of lipid peroxidation is the serum MDA concentration, a byproduct of lipid peroxidation process in the present study, the serum MDA level was remarkably higher in smokers as compared to non smokers these results are in accordance with the earlier studies, showing elevated lipid peroxidation among smoker subjects [57], additions the toxicity associated with smoke could be due to oxidative tissue damage as they catalyze oxidative reactions in biological macromolecules, [58] smoker was classified as proven human carcinogen.

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