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The role of Adipocytokines, Vitamin D, and C in Colorectal Cancer

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Abstract

Colorectal cancer is the world's 3rd most frequent malignant neoplasm and the 4th most common cancer in Iraq. Leptin and Adiponectin are two major Adipocytokines produced by adipose cells that have opposite effects on the formation of colorectal tumors. Leptin induces tumor growth and metastasis, whereas Adiponectin inhibits it. 1,25-Dihydroxyvitamin D controls and limits cancer cell proliferation, differentiation, and survival. Vitamin C deficiency, on the other hand, has been regularly detected in cancer tissues and has potent anti-cancer properties. The purpose of this study was to look at the biochemical role of circulatory Adipocytokine levels (Adiponectin and Leptin) as well as the anti-cancer potentials of Vitamin D and C in CRC patients from Iraq. The research looked at confirmed cases of CRC who were seen at Nanakali Hospital for Blood diseases and Cancer in Erbil before their treatment sessions. A total of 35 patients with confirmed CRC cases and 36 healthy participants who were age, gender, and BMI matched were recruited. ELISA technique was used to quantify serum levels of Adiponectin, Leptin, Vitamin D, & C. The results showed a significant increase (P<0.0001) of serum Adiponectin levels (12.06±1.59) in CRC patients relative to the controls (2.05±0.96). On the contrary, the serum Leptin levels (24.09±2.92) were non-significantly lower (P=0.098) in CRC patients in comparison to controls (53.84±1.54). Furthermore, serum Vitamin D (13.14±1.21) and Vitamin C (1.03±0.10) levels in CRC patients were significantly lower (P<0.0001) when compared to controls (24.49±1.47, 5.78±2.16), respectively. The findings in the current study suggest an imperative biochemical role of Adipocytokines (Adiponectin and Leptin) and Adipose tissue dysfunction in the pathogenesis of CRC patients. Furthermore, decreased serum levels of Vitamin D and C reduce their effective anti-cancer effects, allowing Colorectal malignant neoplasms to survive and develop. Thus, the present study findings suggest Adiponectin and Leptin as potent prognostic and risk factors of CRCs. Also, Vitamin D and C deficiencies are the major risk factors among Iraqi CRC patients.

Keywords: Adipocytokines, Adiponectin, Colorectal cancer, Leptin, Vitamin D, Vitamin C.

Introduction

Colorectal cancer (CRC) is a type of epithelial carcinoma that starts in the mucosal lining of the colon or rectum. The unregulated development of epithelial cells lining the terminal parts of the digestive tract is a hallmark of CRCs [1, 2]. The CRC is a genetically heterogeneous malignancy, with around 40% of cases carrying a KRAS plus 10% carrying a BRAF oncogenic mutations [3]. CRCs are the world's 3rd most commonly diagnosed cancer and the fourth-largest cause of cancer-related deaths. Simultaneously, CRCs are the 4th most often diagnosed cancer in Iraq, according to the most recent GLOBOCAN estimates [4].

Obesity is a major risk factor for cardiovascular and metabolic diseases, along with a number of malignancies, and it is frequently associated with poor clinical outcomes. Obesity and cancer share complicated molecular processes that are still being unraveled [5]. Obesity, predominantly central obesity, is linked to Colorectal neoplasia and cancer, particularly in men. Also, obesity has been associated with a higher risk of CRC-related mortality [6]. Adipocytokines, also known as Adipokines, are hormonal polypeptides released by adipocytes and has been hypothesized as one of the potential causal mechanisms in the link between the nutritional status of the patient and the risk of CRC

carcinogenesis [7, 8]. However, not all data in the scientific literature supports these possible connections [9, 10].

The release of many hormones known as Adipocytokines, the most prominent of which are Leptin and Adiponectin, is one hypothesis that may link Obesity with CRCs [11, 12]. Several researchers have looked into the relationship between circulating Adiponectin and Leptin levels with the risk of CRCs. However, the results were inconclusive [13].

The most crucial insulin-sensitizing adipocytokine is Adiponectin (ADP), also known as Adipocyte complement-related protein (AdipoQ, Acrp30, GBP28, or apM1). It regulates glucose absorption and promotes fatty acid oxidation [10]. The ADIPOQ gene on Chromosome 3q27 encodes ADP; this is the chromosomal locus related to metabolic syndrome and cardiovascular disease susceptibility. Adipocytes produce the majority of ADP; however, it is also produced in minor amounts by other tissues [10, 14]. Adiponectin is a 30 kDa globular protein with a primary sequence of 244 amino acids that can be found in a variety of oligomers, including trimers (≈90 kDa; low molecular mass), hexamers (≈180 kDa; medium molecular mass), and multimers (≈360–400 kDa; high molecular mass) [14]. The ADP is mainly secreted in two isoforms by abdominal adipose fat tissues: non-high molecular-weight as well as high molecular-weight; nevertheless, analytical methods frequently assess the total ADP [15, 16]. Adiponectin possesses anti-inflammatory, anti-atherosclerotic, and anti-diabetic activities, as well as direct modulation of a variety of intracellular signaling pathways involved in the development of colorectal cancer [6, 17]. In numerous investigations, low plasma ADP concentrations diminished ADP receptors expression (Adipo-R1, Adipo-R2 & T-cadherin), and ADP single-nucleotide polymorphism have all been identified as key risk factors for CRCs carcinogenesis [6, 18].

Leptin is a 16 kDa polypeptide hormone with 167 amino acids which is produced by the Ob gene on Chromosome 7 that acts by interacting with the OB-R receptor. It is an Adipocytokine produced solely by adipose tissues and a key adipocytokine that controls appetite and energy expenditure. The concentration of Leptin is inversely proportional to Body mass index (BMI); hence it is higher in overweight and obese people [1, 19]. In multiple studies, Leptin has been illustrated to possess anti-apoptotic, mitogenic, and tumorigenic effects on a range of epithelial carcinoma cell lines involving colorectal, breast, lung, uterine, pancreatic, as well as thyroid cancer cells. Furthermore, Leptin and its receptors were discovered to be considerably increased in CRCs tissue compared to normal tissues, and this overexpression was linked to a more advanced tumor composition [1, 20]. Also, in colorectal cancer cells as well as normal intestinal epithelial cells, Leptin has been found to increase Carcinoma cell migration and proliferation. These studies back up the hypothesis that the expression of Leptin could be used as a risk factor and biomarker for tumor cell characteristics as well as prognosis [21].

Vitamin D is a lipid-soluble vitamin and precursor to steroid hormones that can be acquired from food and is also synthesized by skin keratinocytes utilizing ultraviolet-B (UVB) light and sunlight. The most prevalent bioactive form of Vitamin D maintained in the human body is 25-Hydroxy Vitamin D (Calcifediol), which is also the plentiful and stable metabolite that can be determined analytically in the blood. The hormonal effects of 25-Hydroxy Vitamin D on Calcium and Phosphorus homeostasis are well-recognized [22]. Vitamin D's exoskeletal role, as well as its anti-cancer effect, has recently been the subject of extensive investigation. Vitamin D has been shown in numerous studies to slow the progression of CRC carcinogenesis by affecting multiple pathways, including Wnt/β-catenin signaling, inflammation, and apoptosis [23, 24].

Vitamin C (L-ascorbic acid) is a water-soluble vitamin and an essential micronutrient that functions as a non-enzymatic antioxidant and a cofactor in a variety of enzymatic activities in humans. There are two molecular forms of Vitamin C, each with its chemical stability, half-life, and cellular transport mechanism. Glucose transporters (GLUTs) transport the oxidized form, Dehydroascorbic acid (DHA), from the extracellular media into the cells, whereas Sodium-vitamin C co-transporters (SVCT) transport the reduced form, Ascorbic acid [25]. Hypovitaminosis C and Vitamin C insufficiency are common in many malignancies, and it's been suggested that physiological Vitamin C has a powerful antitumor effect. However, the underlying mechanism of antitumor effects of Vitamin C against adenocarcinomas, including Colorectal cancer, remains to be totally elucidated [26, 27]. Ascorbic acid might act as a tactic to transport hydrogen peroxide (H_2O_2) and oxygen free radicals to the tissues, resulting in tumor cells killing through a variety of metabolic processes. Numerous research published in the previous decade found that therapeutic doses of ascorbic acid could induce cytotoxic, antiproliferative, and genotoxic effects in colon cancer cell lines, with the mechanism of action varying by cell type [28]. Therefore, the objective of this study was to investigate the biochemical impact of circulatory Adipocytokine levels (Adiponectin and Leptin) and the anti-cancer

potentials of Vitamin D and C among Iraqi CRC patients.

Materials and Methods

Study subjects

The current study comprised 71 persons in the age range (38-69) years, 35 of them were clinically and histologically diagnosed as having Colorectal malignancies with stages II and III adenocarcinomas according to the TNM staging method. The samples were collected at Erbil's Nanakaly Hospital for Blood Diseases and Cancer. Patients were screened using a comprehensive medical history to rule out any existing systemic disease or drugs that would alter the biochemical parameters to be investigated. They were compared to a control group of 36 healthy individuals who were age, gender, and BMI matched to CRC patients. The information on study subjects (patients and healthy control) are summarized in Table 1.

Table 1. The host information of the studied groups

Group	No.	Gender		Age	BMI
		Male	Female	Mean±SD	Mean±SD
Healthy Controls	35	23	12	48.58±1.23	27.06±1.05
CRC Patients	36	26	10	51.22±2.16	27.96±1.66

Specimen collection

An aliquot of 4 to 5 milliliters of venous blood specimens were collected from each subject, placed in Gel and clot activator tubes (yellow cap), left to stand at room temperature for 10 minutes, and subsequently centrifuged at (3500 rpm) for 15 minutes. The serum samples were immediately transferred to Eppendorf tubes that had been pre-labeled and coded. All study samples were preserved at –20°C for later examination. Hemolyzed serum specimens were discarded.

Determination of the Biochemical parameters

Human Leptin, Adiponectin, and Vitamin D circulatory levels were assayed using the enzyme-linked immunosorbent assay (ELISA) technique via Monobind Inc.'s AccuBind® ELISA kits (USA). Besides, the Human Vitamin C ELISA kit (SunLong Biotech, China) was used to assay the circulatory level of Vitamin C.

Statistical analysis

The study data was statistically analyzed using the GraphPad Prism version 9 computer program. The results of the statistical analysis were expressed as Mean±SD. The research biochemical parameter means were evaluated using an unpaired student's *t*-test between CRC patients and healthy control groups. Because the confidence interval (CI) of choice was 95%, all *P*-values were two-sided, and values of less than 0.05 were considered significant.

Results and Discussion

Circulatory level of Adipocytokines

The results in Table 2 show the mean comparison of serum Adipocytokines levels (Adiponectin and Leptin) between the CRC patients and healthy controls.

Table 2. The Mean±SD values of Adipocytokines level in sera samples of CRC patients and Healthy Controls

Parameters	Healthy controls	CRCs patients	*P*-Value
Adiponectin (ng/mL)	2.05±0.96	12.06±1.59	<0.0001
Leptin (pg/mL)	53.84±1.54	24.09±2.92	0.098
If the *P*-value is <0.05, it's considered statistically significant.			

Serum level of Adiponectin

Despite numerous investigations, the potential relevance of Adiponectin as a biomarker and risk factor in Colorectal cancers remains unknown. In the current study, compared to healthy controls, the concentration of Adiponectin in serum samples from the CRCs group was significantly higher. This finding is consistent with several other studies, including those by Tojek *et al.* [6], Ashktorab *et al.* [17], and Zekri *et al.* [29], all of which found a significant rise in the circulating level of Adiponectin in CRC patients as compared to healthy controls. Likewise, a recent meta-analysis by Wang *et al.* [13] uncovered that a greater level of circulatory Adiponectin was linked to a greater risk of CRCs in overweight people. On the contrary, the present study result was not in agreement with numerous studies, especially by Mhaidat *et al.* [1], Chandler *et al.* [30], and Polito *et al.* [31], as they reported a significant decrease or non-

significant difference in blood Adiponectin level in CRCs when related to healthy controls.

Adiponectin (ADP) is one of the most important Adipocytokines secreted by adipocytes, and because of its unique biological roles, it's also known as the "Guardian angel adipocytokine". Body fat mass and Visceral fat are inversely related to Adiponectin expression [15]. Obesity and increased adiposity have been linked to a variety of malignancies, including Breast, Prostate, Ovarian, Liver, Pancreatic, and Colorectal cancers, according to a multitude of experimental evidence [21]. Obesity affects cancer progression through adipocytokine dysregulation, which includes enhanced production of the oncogenic adipocytokine Leptin and diminished production of Adiponectin along with augmented expression of proinflammatory cytokines such as Tumor necrosis factor-α (TNF-α) along with Interleukin-6 (IL-6). Adiponectin has been demonstrated to protect against obesity-related cancers in numerous studies [13, 21]. Adiponectin suppresses adenocarcinomas by a number of mechanisms, one being the Adenosine monophosphate-activated protein kinase (AMPK) pathway, which plays a key role in this mechanism. Adiponectin activates AMPK while inhibiting the PI3K/AKT, mTOR, Glycogen synthase kinase 3-β, and Janus kinase/signal transducer and activator of transcription (JAK-STAT) pathways. It's believed that AMPK suppresses the development of Colorectal carcinogenesis by influencing cell growth signaling via the mTOR pathway. It may also reduce tumor cell adhesion and migration [10, 15, 21]. In the present study, the significant incline of circulatory Adiponectin in Iraqi CRCs patients is inconsistent with most published studies elsewhere because their results suggest low circulatory Adiponectin as a substantial risk factor for obesity-associated colorectal cancers. This disagreement results may be connected to any sort of genetic mutation in the Adiponectin receptors. This notion was earlier validated by Yu *et al.* [32] and Mhaidat *et al.* [1,] who approved that Adipo-R1 (rs1342387) and ADIPO (rs266729) polymorphism is correlated with a high-risk of Colorectal cancers. It could also be linked to ethnic disparities, certain epigenetic patterns, and the main etiological causes of Colon cancers among Kurdish and Arab Iraqi residents, as well as a small population size of CRC patients being included in the current study owing to economic constraints. Therefore, more research with a larger number of participants is needed to determine whether Adiponectin and interrelated adipocytokines augment colon neoplasia, tumor migration, and invasion among Iraqi CRC patients.

Serum level of Leptin

Leptin (LEP) is a vital adipocytokine hormone secreted by adipose cells that regulate basal metabolism and food intake, as well as playing a pivotal role in obesity. The LEP is mostly expressed in Adipose tissues; nonetheless, it has also been detected in the gastrointestinal system, brain, muscles, and even malignant cells in the tumor microenvironment. LEP and Obesity have been linked to the genesis, progression, and proliferation of various cancers in recent decades [33]. Despite the great number of clinical studies demonstrating Leptin's clinical importance in CRCs, the results remain conflicting.

Obesity is a significant epigenetic factor in Colorectal cancer. Leptin has been linked to obesity-related CRCs; however, the exact mechanism is still unknown [20, 34]. Leptin, the satiety hormone, induces cell migration and proliferation in Colorectal tumors and normal intestinal epithelial cells, according to many studies. As a result, LEP expression could be employed as a biomarker for tumor cell properties as well as prognosis. However, some data suggest a positive effect for LEP, dubbed the "obesity paradox," as well as a probable antineoplastic activity for the hormone via the activation of natural killer (NK) cells and autoimmune response [19, 20, 33].

Leptin exhibits multiple phenotypic effects due to the large number of LEP receptors recognized as Ob-R and/or LEPR, which belong to the class I cytokine superfamily receptors. Once LEP receptors are activated, they can bind to Janus kinases (JAKs) and trigger other signaling pathways. The Mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK1/2), JAK2/signal transducer and activator of transcription3 (STAT3), and Phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathways allow the long LEP receptor isoform (Ob-Rb) to fully transduce activation signals into target cells [20, 34].

In the present study, the concentration of circulatory LEP in CRCs patients was shown to be non-significantly lower when related to healthy controls. The current study result was accordant with several studies led by Bolukbas *et al.* [35], Sălăgeanu [36], Kumor *et al.* [37], and Tessitore *et al.* [38,] who similarly reported a decline or insignificant difference of LEP circulatory concentration in CRC patients when related to healthy controls. Moreover, the results of a prospective study conducted by Woo *et al.* [39] was similar to the current study as they reported an insignificant variance of serum levels of LEP in Breast carcinoma patients. On the other hand, the current study's findings contradicted several investigations that found high blood levels and

overexpression of LEP in CRC patients as contrasted to healthy control subjects [1, 17, 33, 40, 41]. These studies denote that LEP is strongly related to the occurrence of CRCs, which could be due to the proven mitogenic, antiapoptotic, and tumorigenic properties of LEP. However, it's also known that LEP levels may be influenced by sex variations among CRC patients as well as body fat mass disparities among males and females [42]. Therefore, it's probable that sex differences played a role in the lower LEP levels seen in Iraqi CRC patients in the current study. It's also possible that these disagreeing results may be related to the small population size of the study participants and the diverse Iraqi patient population. As a result, conducting a study using rigorous procedures involving other cancer-related adipocytokines with a large number of participants is critical.

Serum level of micronutrients (Vitamins D and C)

The results in Table 3 show the mean comparison of serum Vitamin D and C micronutrients between CRC patients with healthy control subjects.

Table 3. The Mean±SD values of Vitamin D and C levels in CRC patients and Healthy Controls' serum samples

Parameters	Healthy controls	CRCs patients	*P*-Value
Vitamin D (ng/mL)	24.49±1.47	13.14±1.21	<0.0001
Vitamin C (ng/mL)	5.78±2.16	1.03±0.10	<0.0001
If the *P*-value is <0.05, it's considered statistically significant.			

Serum level of Total 25-Hydroxy Vitamin D

Obesity is described as an inappropriate or superfluous buildup of adipose tissues induced by a prolonged positive metabolic energy balance, which happens when energy intake exceeds energy expenditure, increasing the risk of developing chronic metabolic diseases, including many cancer kinds [43]. Vitamin D is a potent liposoluble vitamin well-known for its pivotal function in bone metabolism, specifically Calcium and Phosphorus homeostasis and absorption from the intestines, as well as bone remodeling. Vitamin D is essential for adipocyte physiology and glucose metabolism, which are commonly disrupted in patients with high BMI and obesity. Furthermore, it is now understood that Vitamin D impacts cell proliferation, differentiation, and adhesion, possibly leading to several types of Adenocarcinomas. Undoubtedly, research findings point to a possible link between Vitamin D levels and malignancies, as higher Vitamin D levels are tied with a lesser risk of developing many forms of adenocarcinoma tumors, including colorectal, lung, breast, as well as prostate cancers [43, 44].

The CRC is the most thoroughly researched neoplasia that has been shown to be impacted by the bioavailability of Vitamin D. Many biochemical studies reveal that the bioactive metabolite of Vitamin D, the 1,25-dihydroxyvitamin D3, also called Calcitriol suppresses proliferation as well as promotes epithelial differentiation in human colon cancer cells which expressing Vitamin D receptor (VDR) through the control of a large number of genes [45-47]. The multilayer suppression of the Wnt/β-catenin signaling pathway, whose aberrant activation in colon epithelial cells originates and promotes CRCs, is a critical function underpinning this impact. As a result, high levels of this pluripotent steroid hormone can defer CRC progression and may give a cost-effective treatment option for CRC patients [45, 46].

In the current study, the serum concentration of total Vitamin D (D2 plus D3) in CRC patients was significantly lower in comparison to healthy controls. These convincing results suggest an inverse association between serum Vitamin D and the overall risk as well as poor prognosis of colorectal cancer. According to the majority of similar published results to the current study, low serum Vitamin D levels may be associated with a poor prognosis of CRCs, whereas adequate serum levels may provide a better survival rate and prediction of CRCs among Iraqi patients. The current study result was in total agreement with numerous case-control, prospective Cohorts, randomized-controlled trials, and up-to-date meta-analysis studies conducted by many authors worldwide. Savoie *et al.* [48] reported that Vitamin D repletion appears to be a viable intervention during chemotherapy in CRC patients before and after chemotherapy. Also, Al-Ghafari *et al.* [49] stated that in the Saudi Arabian population, adequate blood Vitamin D levels were found to be important in preventing the initiation of CRCs. Moreover, Bao *et al.* [50] reported blood levels of Vitamin D were linked to overall survival in Asian CRC patients, particularly those with stage III disease on the left side of the Colon. Likewise, Zhang *et al.* [51] meta-analysis study reported that sufficient plasma circulating Vitamin D levels are linked to a reduced risk of colorectal cancer in Asian nations

populations. In an International Pooling Cohort study, McCullough *et al*. [52] reported that a higher level of circulating Vitamin D was related to a considerably lower Colorectal cancer risk in women and men. Furthermore, the recent systematic meta-analysis conducted by Boughanem *et al*. [23] demonstrated that the good nutritional status of Vitamin D is correlated to CRCs prevention. The verdicts of these studies, along with the current study, indicate that insufficient circulatory Vitamin D is convincingly interrelated with overall malignancy risk, higher risk of metastatic progression, and poor survival of CRC patients. Taking all of the pieces of evidence into account, the findings of this study suggest and confirm that Vitamin D status plays a significant role in the tumorigenesis of CRCs. Therefore, the Iraqi population needs to regularly recuperate its nutritional status and maintain a higher level of Vitamin D to reduce the overall risks and mortality ratio of CRCs. The current study proposes that Vitamin D oral supplements (Vitamin D2 "Ergocalciferol" and Vitamin D3 "cholecalciferol") should be added as a therapeutic approach in conjunction with standard chemotherapy regimens for Iraqi CRC patients.

Serum level of Vitamin C

Vitamin C (L-ascorbic acid) is an essential micronutrient for humans because it operates as an antioxidant and a cofactor for dioxygenase enzymes, which are involved in a wide range of physiological functions [26]. Vitamin C is a multi-hydroxyl molecule with a structure alike to glucose that can be produced by a variety of plants and animals. Vitamin C is an essential dietary component that should be obtained from external sources, such as fruits and vegetables, because Homo sapiens, dissimilar to most mammalian species, are unable to biosynthesize it. Vitamin C, which conducts the majority of its actions inside cells, must enter via specialized transporters through the cell plasma membranes. Vitamin C is available in two molecular forms, each having its chemical stability, *in vivo* half-life, and cellular transport route. Glucose transporters (GLUTs) transport the oxidized form, Dehydroascorbic acid (DHA), into the cell, whereas Sodium-Vitamin C co-transporters (SVCT) transport the reduced form, Ascorbic acid (AA), into the cells [26, 53].

Several pieces of research have implied that Vitamin C has anti-cancer potential and tumor-killing ability because of its favorable influences on redox imbalance (redox homeostasis), oxygen sensing control, epigenetic reprogramming, collagen production, and host immunity, all of which are implicated in tumor angiogenesis, chemotherapy resistance, or metastasis [54]. Vitamin C deficiency is common in cancerous tissues, including Colorectal neoplasms, and it has been suggested to have a significant antitumor action. However, the mechanism of Vitamin C's anti-cancer and killing effect is still not completely clear [27]. Multiple molecular mechanisms have been identified for Vitamin C's ability to inhibit tumor progression, including (a) generation of cytotoxic amounts of H_2O_2 in the tumor microenvironment; (b) Vitamin C activation of the 2-Oxoglutarate-dependent dioxygenases (2OGDDs), which controls the hypoxia-inducible factors (HIFs) responsible for DNA plus histone demethylation; and (c) amplified oxidative stress in cancer tissues induced by Dehydroascorbic acid (DHA) [55].

The serum content of Vitamin C in CRC patients was considerably reduced in comparison to healthy controls in this study. This compelling evidence points to a potent link between the circulatory level of Vitamin C and the overall risk, progression, as well as poor prognosis of colorectal malignancies. Low serum Vitamin C levels may be related to a poor prognosis of CRCs, but normal serum levels may provide a better survival rate for CRC patients, according to the majority of similar published research to the current study. Numerous case-control, randomized-controlled trials, and up-to-date meta-analysis studies undertaken by many worldwide authors corroborated the current study's findings. The studies conducted by Chang *et al*. [56], Mahdavi *et al*. [57], and Saygili *et al*. [58] reported significantly reduced Vitamin C levels, diminished antioxidant status, invigorated generation of reactive oxygen free radicals, and exaggerated Oxidative stress (OS) in Colorectal cancer and similar adenocarcinomas. In an intriguing study, Yun *et al*. [59] reported that large dosages of Vitamin C preferentially kill KRAS and BRAF mutant colorectal cancer cells by targeting the glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH). Moreover, Chen *et al*. [27] also demonstrated that a physiologically high dose of Vitamin C tends to kill Colorectal cancers with overexpressed metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) in a cell line-derived xenograft (CDX) model. In a mouse model study conducted by Kondo *et al*. [60], Vitamin C coupled treatment with Irinotecan anti-cancer drug delivery significantly lessened plasma levels of Reactive oxygen species (ROS) and IL-6 while increasing Collagen type I and Caspase-1 expression. In another study, Pires *et al*. [28] proved that pharmacological concentrations of AA in conjunction with antineoplastic agents

chemosensitize colorectal cancer cells as well as synergistically inhibit tumor growth. Moreover, in a clinical intervention study, Dachs *et al*. [61] reported that Vitamin C administration by intravenous infusion significantly increases tumor AA content in CRCs patients, consequently killing tumor tissues. Taking all of the pieces of evidence into account, the current study's findings indicate a significant decline in antioxidant defense mechanisms among Iraqi CRC patients, as evidenced by low Vitamin C levels, which may be related to increased usage to scavenge lipid peroxides and oxidative free radicals, as well as tumor cell sequestration. Furthermore, this study advises intravenous administration of high dosages of Vitamin C as a therapeutic strategy in conjunction with standard chemotherapy regimens to increase the overall survival of Iraqi CRC patients and reduce the adenocarcinoma risks among Iraqi residents.

Conclusions

The current study findings suggest that adipocytokines (Adiponectin and LEP) and adipose tissue dysfunction play an imperative biochemical role in the pathogenesis of Colorectal cancer among Iraqi patients. Furthermore, diminished Vitamin D and C serum levels weaken their potent antitumor effects, allowing Colorectal malignant neoplasms to survive and develop. The current study's findings point to Adiponectin and LEP as potent prognostic and risk factors for colorectal cancer. Similarly, Vitamin D and C deficiencies are major risk factors among Iraqi CRC patients. The present study suggests high doses IV administration of Vitamin C besides oral supplements of Vitamin D as a necessary therapeutic scheme in conjunction with standard chemotherapy regimens for better prognosis as well as the survival of Iraqi CRC patients.

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Authors' Declaration

-Conflicts of Interest: None.

-We hereby confirm that all the Figures and Tables in the manuscript are ours. Besides, the Figures and images, which are not ours, have been given the permission for re-publication attached with the manuscript.

- Ethical Clearance: The project was approved by the local ethical committee at Soran University.

Authors Contribution

AJM wrote the manuscript with support from HMB and PAI. AJM developed the theoretical formalism and performed the statistical analysis, paraphrasing, and manuscript proofreading. HMB supervised the project. HMB and PAI contributed to the final version of the manuscript. All authors discussed the results and contributed to the final version of the manuscript, and authors provided critical feedback and helped shape the research, analysis and manuscript.

Ethics Approval

The blood samples and information were obtained from a government hospital (Nanakali Hospital for Blood Diseases and Cancer) with oncologist physician approval and patient consent. The Faculty Council (Faculty of Science/Soran University) and the Deanery of the Faculty of Science/Soran University (Code number 1/1/142) approved the project.

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دور ألاديبوسيتوكينات و الفيتامينات د و سي في سرطان القولون و المستقيم

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الخلاصة:
يعد سرطان القولون و المستقيم ثالث أكثر الأورام الخبيثة انتشارًا في العالم ورابع أكثر أنواع السرطانات شيوعًا في العراق. اللبتين و الأديبونكتين هما نوعان من السيتوكينات الشحمية الرئيسية التي تنتجها الخلايا الدهنية التي لها تأثيرات معاكسة على تكوين أورام القولون والمستقيم. اللبتين يحفز نمو الورم وانتشاره، بينما الأديبونكتين يمنع نمو الورم. ١،٢٥- ديهيدروكسي فيتامين د يتحكم ويحد من تكاثر الخلايا السرطانية والتمايز والبقاء على قيد الحياة. من ناحية أخرى، تم اكتشاف نقص فيتامين سي بانتظام في الأنسجة السرطانية وله خصائص قوية مضادة للسرطان. الغرض من هذه الدراسة هو تقييم التأثير الكيميائي الحيوي لمستويات أديبوسيتوكينات (اللبتين والأديبونكتين) في الدورة الدموية، وكذلك التأثيرات المضادة للسرطان لفيتامينات د وسي في مرضى سرطان القولون و المستقيم العراقيين. يركز البحث على الحالات المؤكدة المصابة بسرطان القولون والمستقيم الذين شوهدوا في مستشفى ناناكالي لأمراض الدم والسرطان في أربيل قبل جلسات العلاج. تم تشخيص ٣٥ مريضا المؤكد إصابتهم بسرطان القولون و المستقيم و ٣٦ شخصا من الاصحاء كمجموعة ضابطة المتطابقين من العمر والجنس و مؤشر كتلة الجسم. تم استخدام تقنية إليزأ لقياس مستويات اللبتين، الأديبونكتين، فيتامين د وفيتامين سي في المصل. أظهرت النتائج زيادة معنوية (ف القيمة<0,001) في مستوى الأديبونكتين (١٢،٠٦±١،٥٩) في دم المصابين بسرطان القولون و المستقيم بالنسبة إلى مستوياته في مجموعة ضابطة (٩٦، ٠ ± ٠٥، ٢). على العكس من ذلك، كان مستوى اللبتين في المصل أقل بشكل ملحوظ(ف القيمة<0,098) في مرضى سرطان القولون والمستقيم (٢٤،٠٩±٢،٩٢)مقارنة بمجموعة الضوابط (٥٤ ،١±٨٤ ،٥٣). علاوة على ذلك، كانت مستويات فيتامين د في الدم (١٣،١٤ ± ١،٢١) و فيتامين سي (١،٠٣ ± ٠،١) في مرضى سرطان القولون و المستقيم أقل بشكل ملحوظ (ف القيمة<0,001) مقارنة بمجموعة الضوابط (٢٤،٤٩ ± ١،٤٧ & ٥،٧٨ ± ٢،١٦)، على التوالي. وتشير نتائج الدراسة الحالية إلى دور كيميائي حيوي الحتمي لـأديبوسيتوكينات (اللبتين و الأديبونكتين) و خلل الأنسجة الدهنية في التسبب في مرضى سرطان القولون و المستقيم. إلى جانب ذلك، فإن انخفاض مستويات فيتامين د و سي في المصل يضعف آثارهما القوية المضادة للأورام ويسمح بالبقاء على قيد الحياة وتطور الأورام الخبيثة في القولون والمستقيم. وكما أن نتائج الدراسة الحالية تظهر أن (اللبتين والأديبونكتين) عوامل تنبؤية وخطورة قوية لمرض سرطان القولون والمستقيم. بالإضافة إلى أن نقص فيتامين د وفيتامين سي يعتبر من عوامل الخطر الرئيسية بين مرضى سرطان القولون والمستقيم العراقيين.

الكلمات المفتاحية: أديبوسيتوكينات، الأديبونكتين، سرطان القولون والمستقيم، اللبتين، فيتامين د، فيتامين سي.