25-hydroxyvitamin D effect on cancer colon: Is visceral obesity the link?

Mohamed M. Aboelnaga
Mansoura University Faculty of Medicine
Engy Mossad Aboelnaga (engyms2007@gmail.com)
Mansoura University Faculty of Medicine https://orcid.org/0000-0002-5950-6650
Abdullah Nahed
Mansoura University Faculty of Medicine
Mostafa El Shaer
Mansoura University Faculty of Medicine

Research Article

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Abstract

Background: low 25-hydroxyvitamin have been identified in pathogenesis of colorectal cancer (CRC) with survival affection. Visceral fat tissue predisposes to chronic inflammation and release of growth factors that mediate colonic neoplasia.

Aim of the work: to evaluate effect of vitamin D status and visceral obesity on cancer colon and to report the possible link between vitamin D and visceral obesity in those patients.

Patients & Methods: Our patients were distributed in two groups; group 1 included cancer colon cases (no= 60) and 2nd group included control cases (no= 40). Clinical, anthropometric and pathological data were collected. Calculation of body mass index, visceral adiposity index (VAI) and detection of Vitamin D (25 OHD) serum level were performed to compare between groups.

Results: There were significant differences in VAI and level of 25 OHD between both groups(P=0.011). We found significant higher prevalence of vitamin d deficiency in patient' group [*32 (53.3%) versus control group 13 (32.5%)*]. There was a significant lower mean of VAI in vitamin D deficient patients versus non deficient cases (*P=0.024*). A significant different means of VAI and Vitamin D in patients' group with different TNM stages. As higher stages associated with lower level of Vitamin D (*P=0.027*) and higher VAI (*P=0.031*)

Conclusion: The vitamin D may augment the inflammatory status in visceral obesity which reported to be involved in tumourgenesis of cancer colon. Vitamin D deficiency may be a mediator between obesity and cancer and associated with higher tumour stage.

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and is one of the main causes of cancer-specific death [1]. A variety of risk factors has been recognized in pathogenesis of CRC, including low 25-hydroxyvitamin D (25-OHD) [2]. Survival of colorectal cancer is positively associated with vitamin D status [3].

Many studies tried to postulate mechanisms for this apparent protective effect of 25-OHD. Many studies tried to hypothesize mechanisms for this anti-neoplastic protective effect of vitamin D. These include impact of vitamin D on transcriptional regulation of anticancer genes which involved in cell proliferation, differentiation and apoptosis [4], and inflammatory markers [5,6] but still without conclusive results.

On the other hand, Obesity is considered one of the most important metabolic disorder of this century with serious comorbidities and has been linked to the most relevant cancers, like CRC [7]. However, Adipose tissue distribution in the body is diverse. Visceral fat tissue appears to enhance adverse metabolic outcomes [8] and thought to predispose to chronic inflammation and release of growth factors that thought to mediate colonic neoplasia [9].

In the same vein, Amato et al in 2010, individuated a novel easily applicable and sex-specific index for the evaluation of visceral adiposity dysfunction; Visceral adiposity index (VAI) combined body mass index (BMI), waist circumference (WC), high density lipoprotein -cholesterol (HDL-C) and triglycerides [10]. VAI by the combination of both functional and anthropometric parameters may be considered a valuable index for evaluation of visceral fat functional activity [11].

Relationship between circulating vitamin D levels and abdominal obesity was reported in many studies [12]. Therefore, this relationship could hypothesize the protective action of vitamin D in colorectal carcinoma and should be evaluated in CRC patients.

We aimed in our work to investigate effect of vitamin D status and visceral obesity on cancer colon among newly diagnosed cancer colon patients. Also, to evaluate the possible link between vitamin D and visceral obesity in those patients.

Patients And Methods

The current study was conducted at clinical oncology and nuclear medicine department and internal medicine specialized hospital at Mansoura university hospital, from July 2019 to June 2020. Our patients were distributed in two groups; 1st group included colon cancer cases and 2nd group included control cases participated in the study. We enrolled sixty patients with newly diagnosed colon cancer cases, and forty participants in control group. Controls were matched according age, gender, weight, waist, height, and BMI. All these subjects were BMI < 40 as we exclude obesity in order to ensure BMI homogeneity in both participants groups.

All the participants were informed about the nature of the study and provided their written consent. The study was approved by our Ethics and Research Committee in the Mansoura University, Egypt.

Inclusion criteria were as follows: Age above 18, both sex, histopathological diagnosis of adenocarcinoma of colorectal carcinoma, all stages, normal hepatic and kidney functions. Whereas exclusion criteria were; other pathological types, patients on vitamin D supplements, patients on medications that could affect vitamin D levels, disorder which could affect vitamin D levels such as malabsorption disorders, patients with autoimmune diseases, endocrinopathies associated with hypovitaminosis D level or obesity including diabetes mellitus also excluded from study, and anti-obesity drugs use at time of diagnosis or previous six months, hepatic or renal disease failure.

The following data were recorded: clinical and anthropometric data (age - gender – height- weight and waist circumference). Pathological data (stage of disease, nodal staging, pathological type, neurovascular invasion and site of tumour). Body Mass Index (BMI) was calculated according to the standard formula: BMI = (weight in kg divided by square height in m). Waist circumference was measured as the smallest circumference around the abdomen at the level of the umbilicus without any clothing.

Visceral adiposity index (VAI) was calculated according to formula, where triglyceride level and HDL cholesterol were expressed in mmol/L, waist circumference in cm and BMI in Kg/m2 [10].

$$VAI = \left(\frac{waist}{36.68+(1.88\times BMI)}\right) \times \left(\frac{Triglyceride}{1.03}\right) \times \left(\frac{1.31}{HDLc}\right) \quad \text{for male}$$

$$VAI = \left(\frac{waist}{36.58+(1.89\times BMI)}\right) \times \left(\frac{Triglyceride}{0.81}\right) \times \left(\frac{1.52}{HDLc}\right) \quad \text{for female}$$

Morning venous blood samples were drawn after a 10 to 12h overnight fast. The serum was separated by centrifugation immediately frozen at − 80 °C until analysis. Serum glucose, cholesterol, triglycerides, HDL cholesterol (HDL-C), and C-reactive protein (CRP) were measured. LDL cholesterol (LDL-C) was calculated using the Friedewald equation. Vitamin D (25 OHD) serum level was detected using enzyme-linked immunosorbent assay (ELISA). 25(OH) vitamin D level below 30 ng/ml are considered as insufficiency while values lower than 20 ng/ml as deficiency.

Data analysis

The SPSS statistical version 23.0 was used for data analysis, the results were given as the mean ± Standard Deviation for continuous variables and as percentage for categorical data. We used independent T test for comparison of continuous variables between patients and control groups. But for categorical data, Chi-square test was used. The analysis of variance (ANOVA) for independent samples were used to compare the differences in means between the different patients' grades. Generally, a P value less than 0.05 was considered to be statistically significant for all tests.

Results

Sixty patients with newly diagnosed cancer colon were enrolled in this case control study. Patients' ages ranged from 39–65 years (mean age 56.97±5.58 years). Forty participants matched according age, height, weight, waist and BMI as control group were compared to the patients' group. In spite of non-significant difference in weight, height, waist, and BMI between patients and control groups, there were significant differences in VAI, HDL and triglyceride levels. Also, level of 25 OH vitamin D was significantly lower in patients' group (P=0.011). In addition, we found significant higher prevalence of vitamin d deficiency in patient group 32 (53.3%) of patients than control group 13 (32.5%) (P= 0.032). Other details of both groups' characteristics were presented in table 1.

In patients' group, we compared clinical, anthropometric and laboratory parameters in 28 patients with vitamin D deficient versus 32 non-deficient patients. There was a statistically significant lower mean of VAI in vitamin D deficient patients versus non deficient cases (P=0.024). However insignificant differences in other parameters were found (Table 2).

Tumor characteristics of the 60 colon cancer patients were posted in Table 3. In this study, we found a statistically significant different means of VAI and Vitamin D in patients with different TNM stages. As higher stages associated with lower level Vitamin D (P=0.027) and higher VAI (P=0.031). No significant differences in means of VAI and Vitamin D were found when comparing the pathological type, nodal staging, tumor location and neurovascular invasion in patients' group (table 4).

Discussion

In spite of extensive research evaluated the relation of obesity with cancer colon, the relationship of obesity with cancer colon is still inconsistent. In this study, we wanted to highlight the potential role of visceral fat functional activity of in colon cancer. In addition, we evaluated the link between visceral obesity activity and vitamin D status in cancer colon patients.

The main result in this study was that patients of colon cancer associated with higher functional activity of visceral obesity and lower 25 OH vitamin D levels in comparison with age, height, weight, waist and BMI matched control subjects. In addition, the activity of visceral fat correlate with staging of cancer colon patients. These results augment the hypothesis of role of pro-inflammatory status associated with visceral obesity in development of colon carcinoma. In addition, the hpovitamonosis D associated with higher visceral fat functional activity may hypothesize for a speculated mechanism for tumourgenesis in carcinoma of colon via visceral obesity.

In our study, we found that colon cancer patients had a higher VAI index denoting higher functional activity of adipose tissue in comparison with matched subjects. Moreover, advanced stage of colon cancer had higher VAI. These results concluded that activity of adipose tissue was more linked with cancer than obesity itself defined by BMI or visceral obesity defined by waist.

Many studies evaluated relationship between obesity and CRC. Nevertheless, the findings have been inconsistent regarding this relationship [13]. Mounting evidence indicates that obesity may be associated with the risk of colon cancer by a large number of studies and review paper [2,14-17]. However, other studies suggested that obesity was a greater risk for cancer colon in males but not females, thus providing inconclusive results regarding their relationship and gender effect [18]. Therefore, the magnitude of the association has varied widely across studies. In addition, no overall quantitative estimate has previously been reported due to different sociodemographic characteristics of participants and methodologies used to assess obesity in each individual study. In contrast to the consistent and strong evidence linking obesity with carcinoma of colon, few studies did not find association between obesity and CRC [19, 20].

The mechanisms that link excess body fat and carcinogenesis are not fully elucidated. However, few mechanisms have been postulated to explain the obesity correlation with colon neoplasia. First, obesity leads to hyperinsulinemia and insulin resistance was proposed, which consequently reduces Insulin-Like Growth Factor Binding Protein (IGFBP-1) levels while elevating levels of insulin-like growth factor-1(IGF-1) [21]. IGF-1 is responsible for cancer promoting effects, favoring tumor growth, increases cell proliferation

and inhibits apoptosis, increasing cell migration, and ultimately may lead to metastasis [22,23] . Second mechanism, a variety adipokines secreted by adipose tissue have potent proinflammatory cytokines, such as interleukin (IL)-6 and TNF-α, these cytokine hypersecretion result in a state of chronic inflammation which could promote tumor initiation and progression by acting as mitogens for normal and neoplastic colon cells[24,25]. thirdly, as a hormonally active tissue, obesity alters adipose tissue-derived adipokines levels, such as adiponectin, leptin, and resistin [26]. Leptin has tumorigenic bioactivity, acts as a potent mitogen and regulates angiogenesis or apoptosis through several signaling pathways [27]. Adiponectin could reduce cell proliferation rate and induce cells apoptosis as demonstrated in many studies [28]. In the same vein, it was reported recently that higher plasma levels of resistin in connection with insulin resistance play a role in susceptibility to colorectal carcinoma [29]

Adipose tissue is very heterogeneous and current evidence suggest that visceral adipose tissue associate with more obesity-related comorbidity and mortality than subcutaneous fat tissue [30]. This could partially be explained by the unique architecture of visceral adipose tissue. visceral is high vascular, cellular organ, and contains cells with inflammatory and immunological functions. In addition, the close proximity of visceral fat to the portal vein causes excess free fatty acids drainage and inflammatory cytokines directly to the liver, therefore could affect metabolism [31]. Sex-based differences in VAT may relate to different sex hormones profile [32].

The characteristic in our studies is the comparison of functional activity of VAT in colon cancer patients with anthropometric parameters matched control subjects. The use of VAT by combination of both anthropometric and functional parameters. Moreover, VAI has different formula for both genders. With consideration of gender effect on visceral obesity, VAI may be more predictive in evaluation of central obesity risks than anthropometric parameters alone. In addition, we reported that vitamin D levels tend to be lower in patients' group. Also, Vitamin D deficient patients had higher VAI than non-deficient patients in spite of non-significant difference in BMI and waist.

A protective effect of vitamin D in CRC has been reported more than three decades ago, many extensive studies and meta-analysis linked vitamin D level with incidence of CRC and survival [33- 36]. In the same vein, inverse association of vitamin D intake and CRC incidence was reported [37]. Our results were in concordance with previous studies results. On the other hand, few exceptional studies reported absence of this association [38,39]. Furthermore, a seven years study reported no effect for seven years vitamin D supplementations on the incidence of colorectal cancer [40].

In recent years, attention has been focused on pleiotropic directions of effects exerted by vitamin D [41]. Evidence from many in vitro and in vivo researches reported that active vitamin d had immune modulation, anti-angiogenesis, anti-proliferation, pro-differentiation, pro-apoptosis. Moreover, vitamin D regulate release of cytokines, such as interleukin (IL)-6, IL-8, and microRNA regulation which participate in the anti-tumour effect of vitamin D [42]. Many studies have reported consistent link of circulating vitamin D concentration with CRC incidence and mortality, however, however this strong correlation between vitamin D and cancer colon mostly weakened after adjustment for obesity parameters [43].

Vitamin D deficiency is associated with various chronic diseases including adiposity and metabolic disorders, such as insulin resistance. An association between hypovitaminosis D and obesity has consistently been demonstrated in many studies [44]. However, the nature of this association between hypovitaminosis D and obesity remains poorly understood [44]. Some s studies speculated that active vitamin D might block the expression fatty acid synthase enzyme in adipocyte, hence, inhibit adipogenesis [45]. While other thought this inverse relationship a result of enhanced metabolic clearance in adipose tissue [46]. Another study suggested that the decreased bioavailability of cutaneous synthesis of vitamin D3 in obese individuals [47]. Recently, there is an ongoing discussion low vitamin D status may simply indicate poor health status rather than a causal factor itself [48]

In the light of our study results, we hypothesized that the vitamin D may augment the inflammatory status in visceral obesity, which reported to be involved in tumourgenesis of colon cancer. Vitamin D may be a mediator between obesity and cancer. We suggest that functional activity rather than obesity is involved in pathogenesis of this tumour.

The previous result suggests that the vitamin D may augment the inflammatory status in visceral obesity which reported to be involved in colonic tumorigenesis, and the functional activity rather than obesity is involved in tumour pathogenesis.

Our study has some limitation also warrant mentioning. Firstly, this study had a case control design, we could not evaluate the duration of visceral obesity and could not evaluate recent changes. Second, we did not evaluate Calcitriol, 1α, 25-dihydroxyvitamin D3 (1,25 (OH)2D3), the most active form of vitamin D, responsible for most of its biologic actions due to financial issue. Third, lack of radiology for precise quantification of adiposity volume as we used waist measurement to estimate visceral fat. However, waist circumference provides a simple yet effective measure of visceral fat [49]. Fourth, relatively small number of patients were recruited in our studies, larger studies will be needed for confirmation of our results.

Conclusion

We could conclude from this study that both vitamin d deficiency and visceral obesity associated with higher risk of cancer colon, but the extent of this association still not need more exploration. Vitamin D deficiency might augment the pro-inflammatory state in visceral obesity and this could be a link between vitamin D and visceral obesity in cancer colon pathogenesis. Moreover, vitamin D deficiency associated with higher tumor stage in cancer colon.

Declarations

Ethical Approval:

This study was approved by the institutional review board of Faculty of Medicine, Mansoura University.

Competing Interests:

Authors have declared that no competing interests existing.

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Tables

Table 1: Baseline characteristics of studied population.

Variables		Patients' group (n=60)	Control group (n=40)	P value
Age (year): mean ± SD		56.97±5.584	56.78±7.223	**0.882**
Gender: No (%); Male	Female	42 (708%) 18 (30%)	26 (65%) 14 (35%)	**0.378**
Height (m): mean ± SD		1.6853±07784	1.69±.07958	**0.645**
Weight (kg): mean ± SD		91.50±16.901	89.7±12.544	**0.566**
BMI (kg/m2): mean ± SD		32.1518±5.07177	31.3±3.76357	**0.849**
Waist (cm): mean ± SD		112.42±18.223	109.83±16.001	**0.467**
FBS (mg/dl): mean ± SD		100.9± 9.78	98.5±8.57	**0.207**
Total cholesterol (mg/dl): mean ± SD		241.97±54.187	226.65±38.340	**0.125**
LDL-C (mmol/L): mean ± SD		148.95±73.159	136.325±59.512	**0.188**
HDL-C (mmol/L): mean ± SD		44.2±7.804	49.25±8.451	**0.003**
Triglycerides (mg/dl): mean ± SD		244.08±51.10120	205.38±39.06218	**0.006**
VAI: mean ± SD		3.92±1.49270	3.265±1.09858	**0.019**
25 OH vitamin D level: mean ± SD		19.39±9.297	24.1±8.425	**0.011**
Vitamin D deficiency: No (%)		32 (53.3%)	13 (32.5%)	**0.032**

BMI: body mass index; **WC:** waist circumference; **HDL:** high-density lipoprotein; **LDL:** low-density lipoprotein**; VAI**: visceral adiposity index; **FBS:** fasting blood sugar.

Table 2: comparison between patients with non deficient vitamin D level versus patients with deficient vitamin D in cancer colon group.

Variables	Non deficient vitamin D (>20.00; n=32)	Deficient vitamin D (D< 20.00; n=28)	P value
Age (year)	57.93±4.371	56.13±6.414	**0.215**
Gender : Male	22 (68.8%)	20 (71.4%)	**0.5**
Female	10 (31.2%)	8 (28.6%)	
BMI (Kg/m2)	32.1234±4.86948	32.18±5.32003	**0.968**
Height (m)	1.6807±.0633	1.689±.08948	**0.671**
Weight (kg)	90.89±15.529	92.03±18.248	**0.797**
Waist (cm)	109.71±15.939	114.78±19.959	**0.286**
Total cholesterol (mmol/L)	242.82±52.605	241.22±56.364	**0.91**
LDL-C (mmol/L)	150.6429±48.27113	147.47±54.18172	**0.813**
HDL-C (mg/dl)	45.36±9.596	43.19±5.783	**0.303**
Triglycerides (mg/dl)	234.11±75.592	252.81±71.000	**0.327**
VAI	3.4751±.98931	4.31±1.74618	**0.029**
FBS (mg/dl)	101.785±9.818	100.156±9.854	**0.525**

BMI: body mass index; **WC:** waist circumference; **HDL:** high-density lipoprotein; **LDL:** low-density lipoprotein**; VAI**: visceral adiposity index; **FBS:** fasting blood sugar.

Table 3: Tumor characteristics in patients' group (no:60).

variable		No (%)
TNM stage:	I	10 (16.7 %)
	II	13 (21.7%)
	III	23 (38.3%)
	IV	14 (23.3%)
Nodal staging:	N0	19 (31.65%)
	N1	22 (36.7%)
	N2	19 (31.65%)
Pathology type:	Adenocarcinoma	
Mucoid type		41 (68.3%)
Signet ring type		12 (20%)
		7 (11.7%)
LVI/PNI:	Negative	14 (61.7%)
	Positive	37 (23.3%)
	Unknown	9 (15%)
Site of tumour:		
Right		23 (38.3%)
Left		22 (36.7%)
Transverse		11 (6.7%)
Sigmoid		4 (18.3%)

Table 4: Tumour characteristics in relation to 25 OH vitamin D level, BMI and VAI.

Variable		Vit D level	BMI	VAI
		Normal vs. abnormal	Normal vs. abnormal	Normal vs. abnormal
TNM stage: I-II		23.17±9.12	30.91±3.7	3.29±1.09
III		18.13±8.85	34.1±6.23	4.27±1.3
IV		15.25±8.51	30.96±4.01	4.36±2.01
P value				
		0.027	**0.058**	**0.031**
Nodal staging: N0	N1	21.684±10.199	30.61±3.33	3.43±1.1
N2		19.522±10.2	33.88±5.47	4.37±1.67
		16.947±6.79	31.69±5.65	3.89±1.59
P value				
		0.295	**0.106**	**0.131**
Pathology type: Adenocarcinoma		19.37±9.385	31.8350± 4.91	3.778±1.352
Mucoid type		17.67±8.731	33.0264±6.89	4.547±1.983
Signet ring type		22.428±10.31	32.5078±1.7	3.693±1.236
P value		**0.568**	**0.765**	**0.27**
LVI/PNI: Negative		15.5±9.4	32.88±4.196	3.81±1.381
Positive		20.5±8.981	32.49±5.731	4.01±1.613
Unknown		20.89±9.8	29.61±2.127	3.73±1.233
P value		**0.203**	**0.260**	**0.842**
Site of tumour:				
Right		20.695 ±10.41	32.89 ±5.18	4.14 ±1.46
Left		19.18 ±9.032	32.6±5.69	3.89 ±1.46
Transverses		19.41±8.24	30.09±3.71	3.55 ±1.87
Sigmoid		13. ±6.32	31.11±3.81	3.91 ±.849

P value	0.512	0.46	0.761