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Circulating levels of novel adipocytokines in patients with colorectal cancer

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ABSTRACT

Objective: Adipocytokines have been reported to contribute to the pathogenesis of colorectal cancer (CRC). The aim of this matched case-control study was to explore circulating novel adipocytokines, such as serum visfatin, omentin-1 and vaspin levels in patients with CRC.
Method: Serum visfatin, omentin-1, and vaspin levels were measured in 69 subjects (39 patients with colorectal cancer and 30 age- and sex-matched healthy controls) using enzyme-linked immunosorbent assay (ELISA) methods.
Results: Compared with the controls, patients with CRC had significantly higher circulating omentin-1 (203.23 vs 9.12 ng/ml, $p < 0.0001$) visfatin (4.03 vs 2.01 ng/ml, $p < 0.0001$) and vaspin (0.54 vs 0.31 ng/ml, $p = 0.015$) levels. After adjustment for covariates (age and body mass index), patients with CRC had significantly higher serum omentin-1 ($p < 0.0001$), visfatin ($p < 0.0001$), and vaspin ($p = 0.040$) levels than the control group. Furthermore, the results did not change when age and waist-to-hip ratio were considered as covariates in the general linear models.
Conclusions: The observed higher levels of omentin-1, visfatin, and vaspin in patients with CRC, independent of measures of obesity, suggest that these adipocytokines may have a potential role in the development of CRC through mechanisms other than the indirect mechanisms that are active in the association between obesity and CRC.

1. Introduction

The link between obesity and many human malignancies, including colorectal cancer (CRC), has been clearly illustrated in many epidemiological studies [1,2]. Overall, obese individuals are approximately 1.5–2 times more at risk of developing gastrointestinal cancers than normal weight individuals [1].

According to the International Agency for Cancer Research (IACR), there is sufficient evidence in humans for a causal link between overweight and obesity and cancer of the colon [3]. However, the mechanistic basis of these relationships remains incompletely understood.

Although the pathophysiological mechanisms underlying obesity in relation to CRC are likely complex, increased insulin and insulin-like growth factor signaling, intestinal microbiome, chronic inflammation, and adipocytokines have already been postulated as contributors.

Adipocytokines are protein factors that show a number of important systemic complex interactions and influence a large number of different organ systems [4]. They have recently become the focus of research on the role of obesity in carcinogenesis. Several adipocytokines, namely leptin, adiponectin, visfatin and resistin, have been under investigation in a multitude of robust in vitro and epidemiological studies carried out to clarify the association between obesity and CRC [5–12].

A decreased level of adiponectin was recognized as a strong risk factor for early CRC [6]. Two types of adiponectin receptors,

Abbreviations: CRC, colorectal cancer; IACR, International Agency for Cancer Research; AMPK, adenosin monophosphate-activated protein kinase; mTOR, mammalian target of the rapamycin; Nampt, nicotinamide phosphoribosyltransferase; PBEF1, pre-B cell-colony enhancing factor; BMI, body mass index; ELISA, enzyme-linked immunosorbent assay; HDL, high-density lipoprotein; LDL, low-density lipoprotein; WHR, waist to hip ratio; CV, coefficient of variance; GLM, general linear model; NAD, nicotinamide adenine dinucleotide; PARP, poly (ADP-ribose) polymerase; TNF, tumor necrosis factor; eNOS, endothelial nitric oxide synthase; PI3K, phosphoinositide 3-kinase; OLETF, Otsuka Long-Evans Tokushima fatty; TNM, tumor-node-metastasis; FBS, fasting blood sugar; SBP, systolic blood pressure; DBP, diastolic blood pressure.

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AdipoR1 and AdipoR2, may be intimately related to the progression of CRC [13]. Adiponectin can repress colon cancer cell proliferation through AdipoR1- and –R2-mediated adenosin monophosphate-activated protein kinase (AMPK) activation [14]. Under decreased circulating adiponectin levels, AMPK activity is suppressed, and the mammalian target of the rapamycin (mTOR) and the members downstream in the pathway are activated. These changes directly promote colonic epithelial cell proliferation and induce colorectal carcinogenesis [15].

The results of a large case-control study suggested that adiponectin might decrease the risk of colorectal neoplasia by interfering with leptin; conversely, leptin could exert a carcinogenic effect under the condition of a lower abundance of adiponectin [5]. Therefore, the concurrent assessment of adiponectin and leptin may be a helpful prognostic marker in the management of patients with CRC [16].

Visfatin, which is identical to the "pre-B cell-colony enhancing factor (PBEF1)" and "nicotinamide phosphoribosyltransferase (Nampt)," is secreted abundantly by the visceral fat of humans and mice and mimics the action of insulin [17]. There is accumulating evidence to support an interesting connection between PBEF1/Nampt/Visfatin and cancer [18,19]. PBEF1/Nampt/Visfatin may have pro-angiogenic activity, which is highly expressed in some types of tumors, including malignant astrocytomas/glioblastomas, ovarian cancers, gastric and CRC [20–23]. The results of a case-control study suggested that visfatin and resistin might be good biomarkers of colorectal malignant potential and stage progression, independent of the body mass index (BMI) [9].

Omentin-1 is a novel 34 kDa adipocytokine that is selectively and highly expressed in visceral adipose tissue compared with subcutaneous adipose tissue [4,24]. Vaspin (visceral adipose tissue-derived serpin), a member of the serine protease inhibitor family, is also a novel adipocytokine with insulin-sensitizing effects [25].

Against the background of previous research on the contribution of adipocytokines to the pathogenesis of CRC, investigating the circulating levels of novel adipocytokines, such as omentin-1, visfatin and vaspin may be useful to illustrate some pathophysiological aspects of adipose tissue involvement in the development of CRC. The present matched case-control study sought to explore for the first time the concentrations of serum omentin-1 and vaspin and assess visfatin levels in patients with CRC.

2. Methods

2.1. Patients and controls

Thirty-nine consecutive new patients (mean age ± SD 56.72 ± 9.25 years: 23 women and 16 men) who had undergone colonoscopy at Imam Khomeini University Hospital and had been histopathologically diagnosed with CRC by hospital pathologists were enrolled in the study in June 2008. All patients in the sample met the following criteria: no curative medication for CRC; no previous history of malignancy or colorectal operations; no diagnosis of any inflammatory bowel disease, including ulcerative colitis and Crohn's disease; no diagnosis of familial adenomatous polyposis or acromegaly.

We selected a healthy age- and sex-matched control group (mean age ± SD 53.03 ± 6.14 years: 15 women and 15 men) from participants in the Persian Gulf Healthy Heart Study. The Persian Gulf Healthy Heart Study, a prospective population based cohort study, was designed to determine the risk factors for cardiovascular diseases among the northern Persian Gulf population. Detailed information about the methods and procedures of this study is available elsewhere [26].

The participants in the control group had anthropometric measurements comparable with those of the CRC group (Table 1).

Venous blood was obtained from all patients and healthy controls in a fasting state. All the sera were kept frozen at −70 °C until they were used. The study was approved by the medical–ethical committee of Bushehr University of Medical Sciences, and written informed consent was obtained from all subjects.

2.2. Measurements

2.2.1. Physical measurements

Blood pressure was assessed twice at the right arm after a 15-min rest in the sitting position, using a standard mercury sphygmomanometer.

A stadiometer was used to measure height and weight. Heavy outer garments and shoes were removed before the participants' height and weight were measured. Body mass index (BMI) was calculated. Waist circumference was defined at the midway level between the costal margins and the iliac crests. Hip circumference was measured at the level of the greater trochanters. Waist-to-hip ratio (WHR) was calculated for all participants.

2.2.2. Biochemical measurements

A fasting blood sample was taken, all samples were promptly centrifuged, and sera were separated and kept frozen at −70 °C until they were used. On the day of blood collection, analyses for biochemical parameters (blood glucose, triglyceride, and cholesterol levels) were carried out at the Persian Gulf Health Research Center with a Selectra 2 autoanalyzer (Vital Scientific, Spankeren, the Netherlands). Glucose was assayed by the enzymatic (glucose oxidase) colorimetric method using a commercial kit (Pars Azmun Inc., Tehran, Iran). Serum total cholesterol and HDL (high-density lipoprotein) cholesterol were measured using cholesterol oxidase phenol aminoantipyrine. Triglycerides were measured using the glycerol-3 phosphate oxidase phenol aminoantipyrine enzymatic method. Serum LDL (low-density lipoprotein) cholesterol was calculated using the Friedwald formula. LDL cholesterol was not calculated when the triglycerides concentration was >400 mg/dl.

To detect visfatin and vaspin in the serum samples, commercially available (Cat. No. V0523EK and Cat. No. V0712EK, respectively) enzyme-linked immunosorbent assay kits (AdipoGen, Seoul, Korea) were used according to the manufacturer's instructions. The assay sensitivity for visfatin was 0.10 ng/ml; the intra- and interassay coefficients of variance were 3.8–5.5% and 6.4–9.5%, respectively. The assay sensitivity for vaspin was 0.012 ng/ml; the intra- and inter-assay coefficients of variance were 1.3–3.8% and 3.3–9.1%, respectively.

Serum omentin-1 concentrations were measured by manual omentin-1 (human) detection (ELISA kit (intelectin-1 (human) ELISA kit, Apotech Corporation, Switzerland)). The detection limit of the assay was 0.4 ng/ml (range 0.5–32 ng/ml). The mean intraassay and interassay CVs of the omentin-1 assay were 4.51–7.4% and 4.19–9.27%, respectively. The antibodies used in this kit are specific to the measurement of natural and recombinant human omentin-1.

2.3. Definitions

The cutoff points of serum total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) distributions used to assign subjects to different levels of risk were those derived from the National Cholesterol Education Program (NCEP) guidelines in the United States (Adult Treatment Panel [ATP] III) [27].

The tumor-node-metastasis (TNM) staging for colorectal cancer defined by the American Joint Committee on Cancer (AJCC), 7th