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Effect of Insulin Resistance on Colorectal Cancer: The Role of Plasma Adiponectin Level

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Abstract

Background: Despite clinical and different basic investigations, the role of plasma adipokines, such as adiponectin as a precise predictor of the risk of colorectal cancer (CRC) is still conflicting.
Objectives: This study investigated the association between CRC and insulin resistance, obesity, and plasma adiponectin level for the first time in Iran.
Methods: A total of 80 subjects (including 45 CRC patients and 35 healthy individuals) were enrolled in this case-control study. Demographic, anthropometric, and clinical data were recorded, and serum levels of adiponectin, insulin, and glucose were evaluated using enzyme-linked immunosorbent assay and glucose oxidase technique, respectively. Insulin resistance index (HOMA-IR) was measured as well.
Results: The mean±SD plasma adiponectin concentration in the CRC patients (7.98±0.64 ng/ml) was not significantly higher, than the control group (8.05±1.14 ng/mL). However, the mean±SD of HOMA-IR and plasma glucose levels (1.81±0.61 and 7.64±1.34 mm/L, respectively) of the CRC group were significantly higher (P<0.05), compared to the control group (1.37±0.3 and 119±1.1 mg/dL, respectively); though, plasma insulin wasn't significantly different in the two study groups. Following the stratification of CRC patients according to the tumor site, a significantly lower level of adiponectin (7.36 ±1.1 ng/ml) (P<0.05) and a significantly higher level of HOMA-IR (2.08±0.44) were observed in patients with colon cancer (P<0.005), compared to the controls. Regression among the plasma adiponectin and the plasma insulin and HOMA-IR was negative in the control and CRC groups.
Conclusion: Insulin resistance has an important role in the development of CRC, especially in the genesis colon cancer, regardless of the change it causes in plasma levels of adiponectin.

Keywords: Adiponectin, Colorectal cancer, Insulin resistance, Obesity

1. Background

The third most common cancer in men and the second of women throughout the world, and the second leading cause of death among cancers is colorectal cancer (CRC)(1). Every nine minutes, one-person dies due to CRC (2). Obesity especially around your waist with sedentary lifestyle, family history of diabetes, are risk factors to metabolic disorders such as hyperinsulinemia, insulin resistance, hypercholesterolemia, hypertension, and hyperglycemia.

Additionally, hyperinsulinemia is a component of the most threatening agents in development of CRC (3-6). Studies have shown insulin elevates the cellular proliferation and decreases apoptosis that leads to malignant proliferation in earlier cells of colorectal adenoma tissue (7, 8). Some studies have demonstrated a direct relationship between insulin levels and the risk of developing CRC (9). In the other hand, the insulin receptors is expressed in human adenosine cells in greater numbers, which in turn increases the sensitivity of these cells to insulin (10).

Insulin has significant effects and promotes malignant modification of cells and increases (insulin- like growth factor number-1) IGF1 (11, 12). IGF1, like insulin, has an anti-apoptotic effect and stimulates cell growth and increases development of CRC (13). Adiponectin, is exclusively released from adipose tissue (14) and increases uptake of plasma insulin by peripheral tissue cells such as liver, muscle, adipose tissues, so higher risk of colorectal cancer is expected (15).

Therefore, if uptake of plasma insulin by peripheral tissue elevates, a reduced risk of CRC can be expected (16). Consequently, more studies on hormone adiponectin and its association with cancer are required (17, 18). Adiponectin has revers correlation with obesity and hyperinsulinemia and insulin resistance (15, 19). In the other hand, some studies have demonstrated that adiponectin is inversely related to the progression of CRC (20, 21) but some other studies have reported no association between adiponectin and risk of CRC (22). Therefore, more study is needed on the hormone adiponectin and its association with cancer (23).

For this reason, this clinical and laboratory investigation was designed to assess the probable relationship of plasma adiponectin levels with the risk of the CRC development in Iranian people. Furthermore, the possible associations between adiponectin and insulin levels, and between adiponectin level and insulin resistance and obesity were compared between the individuals with CRC and the healthy control.

2. Objectives

The present investigation aimed to investigate the relationship between CRC and insulin resistance, obesity, and plasma adiponectin level for the first time in Iran.

3. Methods

3.1. Patients

This randomized clinical investigation studied 80 subjects aged> 34 years old that underwent colonoscopy at therapeutic centers of Qom University of medical sciences (QUMS) and Arak University of medical sciences (AUMS). Among all of the exanimated subjects, eighty subjects were diagnosed with CRC and the remained subjects included as healthy controls. All of subjects that were enrolled from 2018 A.D until 2020 A.D in this investigation were from Iran and were not related together genetically.

All of subjects who were enrolled for this investigation, underwent colonoscopy either for gastrointestinal manifestations including: loss of weight, habitual change of defecation, specific pain, or for threats of developing CRC. Also subjected were recruited in accordance with exclusion criteria of diabetes type II, gastrointestinal diereses, inflammatory bowel disease, other malignancy, adenomatous polyps, or other polyp types. The definite inclusion criteria were only the positive pathologic description for development of CRC.

Demographics, clinical characteristics, weight, length, body mass index (BMI), and physical test outcomes of all of subjects were gathered. Informed consent was obtained from all of the participants for enrollment to the study. All of clinical protocols and procedures were designed in accordance to the regulations of the ethics committee of QUMS and AUMS, and it was conducted according to the principles of the Helsinki Declaration. BMI was calculated based on this formula: weight (kg)/height squared (m^2).

3.2. Biochemical assay

After about twelve to fourteen hours overnight fasting of 170 subjects, the blood samples were obtained in EDTA (anticoagulant), inside microtubes. The samples at 4°C were centrifuged and immediately the plasma was separated and kept at -80°C (24). The plasma level in form of unit of ng/ml of insulin and adiponectin were calculated by Enzyme-linked immunosorbent assay (ELISA) kit (Mercodia, Sweden, and Technique, Finlanl, respectively). Glucose was measured by method of glucosoxidase (Pars Azmoon Co., Iran). Value of HOMA-IR was calculated by this formula: fasting insulin (microU/L) multiplied by fasting glucose (nmol/L)/22.5 (25).

3.3. Statistical Analysis

SPSS software version 25 was used for descriptive and analytical statistics. Independent t test, logistic regression, chi-square test, were used for comparison of the variables among the control, CRC, colon and rectal cancer groups. T test was applied for comparison between two groups. For adjusting the confounding factors including age, BMI, and the other variables (not presented in this article) the logistic regression was used. The Pearson correlation coefficients method was applied for measuring the correlations between constant variables.

4. Results

From 45 patients involved to CRC were studied, thirty-one (68.1 %) of them with colon cancer was male and fourteen (38.9%) of them was female. Also seventeen (54%) of them with rectal cancer was male and 14(45%) of them was female. The average age of the Control group was 58.16±8.4 and CRC group was 65.7±11 years. Also twenty one (60%) of males and fourteen (40 %) of females were among the 35 control subjects. No significant difference statistically was distinguished in term of their sex, sedative NSAID intake and smoking. Characteristics of the subjects studied such as values of age, BMI, and HOMA-IR of the CRC and the control groups in according with normal weight and overweight, have been summarized in Table 1. The fasting adiponectin plasma levels (7.98±0.64 ng/ml), of the CRC group were not statistically significant in comparison with the control group (8.05±1.14 ng/ml) (Figure 1). The insulin plasma levels of two groups did not show significant difference. HOMA-IR (1.81±0.61) and the plasma levels of glucose (7.64 ± 1.34 mm/l) of the CRC group were higher significantly ($p<0.05$) compared to the control group (1.35± 0.26, 6.12 ± 0.99 mm/l respectively), but plasma insulin plasma wasn't significant between 2 groups

After stratifying individuals of CRC in according to tumor site, lower significant level of adiponectin (7.36±1.1 ng/ml) ($p<0.05$) (Figure 1), and higher of HOMA-IR (2.08±0.44) with more significant difference was observed ($p<0.005$) in individuals with the colon cancer compared to individuals of the control group (8.05 ± 1.34 µg/ml, 1.35± 0.26 respectively).

Table 1. Clinical and demographical characteristics of individuals of CRC and Control groups with normal wieght and overweight

Variables	Control		P value	CRC		P value
	Normal Weight (n=53)	Overweight /obesity (n=35)		Normal Weight (n=16)	Overweight /obesity (n=66)	
Age (y)	56.79 ± 6.81	59.54 ± 10.13	0.91	65.56 ± 13.5	64.59 ± 11.7	0.774
Height (m)	168.41 ± 9.63	168.65 ± 7.98	0.91	167.93 ± 10.53	168.30 ± 8.50	0.883
Weight (kg)	64.67 ± 9.46	74.91 ± 7.27	0.001	71.18 ± 10.98	75.05 ± 7.51	0.096
BMI (kg/m²)	22.60 ± 1.76	26.29 ± 1.07	0.001	23.84 ± 0.89	28.71 ± 2.05	0.001
Adiponectin (µg/ml)	8.31 ± 1.4	7.98 ± 1.34	0.08	8.26 ± 1. 8	7.86 ± 1.1	0.568
Glucose (mmol/L)	5.92 ± 0.98	6.34 ± 1.02	0.06	7.45 ± 1.44	7.83 ± 1.24	0.334
Insulin	5.17 ± 1.24	5.67 ± 1.41	0.86	5.67 ± 1.08	5.75 ± 1.20	0.819
HOMA	1.30 ± 0.26	1.43 ± 0.26	0.027	1.80 ± 0.40	1.82 ± 0.31	0.939

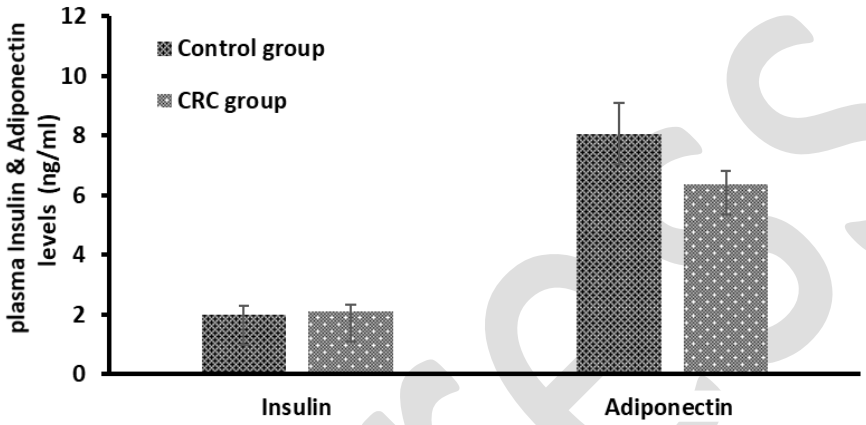

Figure 1. levels of fasting plasma insulin and, adiponectin between colon cancer and control. All of data has shown as Mean ± se. *p<0.05

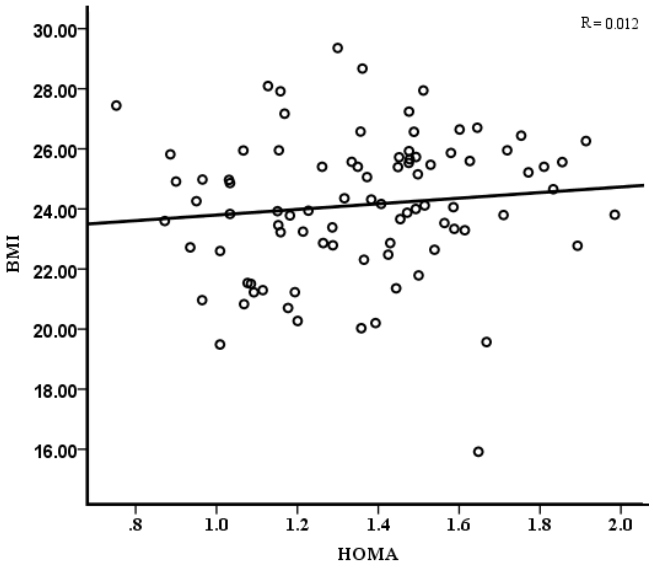

Figure 2. Regression between HOMA and BMI in the control group with values of R=0.012

BMI values of the CRC group (26.22± 1.4) was significantly (p<0.01) higher in comparison with the control group (24.4± 1.8).

Correlation of BMI with the plasma insulin level was positively in the control group (r=0.636, P < 0.001), in the patients with colon (r=0.902, P <0.001), in the patients with rectal (r=0.891,P< 0.001) cancer and in the patients with CRC (r=0.918, P < 0.001).

Correlation between BMI and the HOMAR was positively in the control and CRC group that their regressions (R) are illustrated in figures 2 and 3. Correlation among the plasma adiponectin and the plasma insulin and also HOMA were negatively in the control and CRC groups.

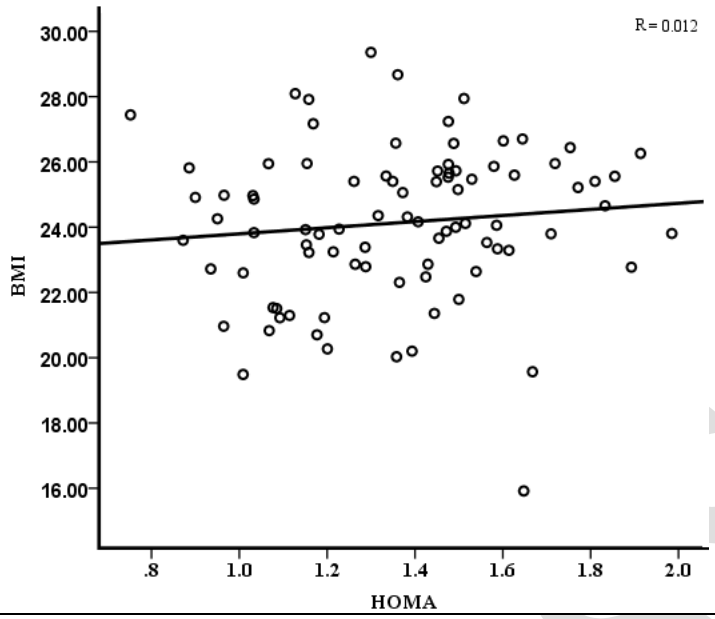

Figure 3. Regression between HOMA and BMI in the colorectal (CRC) group with values of R= 0.002

After dividing the subjects into two groups, individuals with normal BMI and individuals with higher BMI, no significant difference was found between adiponectin levels of these two groups. In our study, individuals with CRC who were overweight or obese had a higher insulin resistance index than individuals with normal weight.

BMI was positively correlated with insulin in the controls (r =0.636, P < 0.001), in the patients with colon (r =0.902, P <0.001), in the patients with rectal (r =0.891,P < 0.001) cancer and in the patients with CRC (r =0.918,P < 0.001).

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Correlation between BMI and the HOMAR was positively in the control and CRC group that their regressions (R) are illustrated in figure 2 and 3. Correlation among the plasma adiponectin and the plasma insulin and also HOMA were negatively in the control and CRC groups

5. Discussion

This study was conducted for the first time in Iranian population. The plasma glucose levels, HOMA-IR and BMI were significantly higher in the group of CRC. However, the plasma levels of adiponectin and insulin did not show significant difference between the two groups. On the other hand, after stratifying patients according to the location of malignancy, it was observed the lower plasma levels of adiponectin and higher HOMA-IR were more common in the patients with rectal tumor compared to the control group, the finding that is reporting for the first time.

It has been conflicted interpretations about role of adiponectin in development of CRC. Ming-Wei Chen et al. (26) measured plasma adiponectin in 165 men with colorectal cancer and 102 non-colorectal men. They reported that adiponectin levels in patients with colorectal cancer were lower than subjects of control and introduced the decreased adiponectin as an important risk factor for colorectal cancer. In the other hand, In study conducted by Demir et al. no significant difference in the serum adiponectin levels between the groups of colorectal adenoma and control was reported that our results are consistent with this study (20).

In another study, insulin and HOMA-IR indices were significantly higher than the control group (13). The results of the present study, by showing a higher HOMA-IR index in the cancer group than the control group, emphasized the results of that study and strengthened the hypothesis of the role of insulin resistance in the progression of colorectal cancer.

The results of two meta-analyzes studies in 2011 by Xi Tao XU et al. (included 3015 cases of colorectal cancer and colorectal adenoma and 3160 non-patients) and the other by wei An et al. (included 2632 cases with colorectal cancer and 2753 non-affected individuals) revealed the cases with cancer had lower levels of adiponectin compared to control group. However, a performed meta-analysis ten years later in 2021 by Yan Wang et al. (10) on 20 studies from 2003 to 2020 showed that adiponectin levels were not associated with an increased risk of colorectal cancer. The results of our study was consistent with this recent meta-analysis. They showed that the higher levels of adiponectin in men might reduce the risk of cancer. Many studies have confirmed the inverse relationship between

adiponectin hormones and the risk of colorectal cancer, and the role of this adipokine in prevention of the colorectal neoplasms has been scientifically presented (22, 27). However, the conflicting results of the last meta-analyzes investigation has caused the need to more special studies at the molecular levels with larger sample sizestudies, considering the adiponectin and the different types of adipokines and function of their receptors.

Our study showed the higher plasma insulin and lower adiponectin levels in the patients with colon cancer presenting a higher reverse relationship between them compared to control group. Chamg et al. (16) observed also a reverse correlation between the plasma insulin and adiponectin that finding of our study was supported by theirs.

In our study, after dividing the subjects into two groups, normal and abnormal BMIs, no significant difference was found between adiponectin levels in these two groups. Moreover, in our study, individuals with CRC who were overweight or obese had a higher insulin resistance index than individuals with normal weight. Body fat seems to be associated with the production of pro-inflammatory cytokines and subsequent susceptibility to colorectal cancer. Moreover, Chakraborty et al. (28) in their recent review study demonstrated an association between insulin resistance index and BMI with development of CRC. This association is a risk factor in cancer genesis , although they concluded that role of adiponectin is bifurcated.

Otani et al. (23) recently expressed that protein of adiponectin with numerous general properties and high levels in circulatory system perhaps has remarkable effects in regulation of homeostasis, and its seems unlikely to act as an anticancer protein. They hypothesized that the lower level of plasma adiponectin might leads to progression of colon cancer when the colorectal tissue is excited by carcinogenetic factors such as oxidants. Our finding about association of the lower plasma adiponectin with genesis colon cancer is supported by their study.

In another investigation, Gonolo et al. examined the association of serum adiponectin and resistin levels with insulin resistance status on patients with CRC. The adiponectin and resistin serum levels in patients with colon cancer was lower than the controls (21). So, our finding about association of the lower plasma adiponectin with genesis colon cancer is supported by their study.

6. Conclusion

The Plasma adiponectin and insulin levels showed no difference between healthy individuals and patients with CRC. However, The plasma adiponectin levels of the patients with colon cancer was lower than control group. It seems the lower plasma levels of adiponectin in association with higher HOMA-IR have an important role in development of CRC, especially in genesis colon cancer. Further investigations are needed to determine the role of adiponectin in behavior of CRC.

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Footnotes

Conflicts of Interest: All of authors state there are no conflict of interests in the present study.
Author's contribution: Seyed Jalal Eshagh Hoseini and hamid farhani: Conceptualization and methodology (Join between basic sciences and clinical sciences and role of hormoes on development of cancers) .
Amir Hamta: data analysis and interepretion
Mostafa Vahedian: Drafting the article
Mohammadreza Saadati: Data collection
Hamid Farahani: Revising and final approval of the manuscript.
Funding/support: Support of this study has been approved by grant from Qom University of Medical Sciences by code of (IR.MUQ.REC.1400.074).
Ethical statement: All of clinical protocols and procedures, were done in according with ethical codes of in accordance to Ethics committee approval from the ethics committee of QUMS and AUMS and NIH.

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