

RESEARCH ARTICLE

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Metabolic Syndrome and the Risk of Gastrointestinal Cancer: a Case-Control Study

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Abstract

Background: The metabolic syndrome and its concomitant complications are a major public health challenge worldwide. Growing evidence implies associations with cancer development and progression. Since there has been no report on this subject in South Khorasan, we studied metabolic syndrome components in gastrointestinal (GI) cancer patients for comparison with a control group in this province. **Materials and methods:** This case-control study was performed on 68 patients with histopathologically proven gastrointestinal cancers, referred to the oncology center in Birjand city (capital of South Khorasan province, Iran) in 2016-2017, and 100 control subjects without disease. Patients and control subjects completed a researcher-made questionnaire covering demographic characteristics, physical activities and food intake. Also, blood samples were obtained from both patients and control subjects after overnight fast. Anthropometric measurements of height, weight, body mass index, waist circumference and blood pressure were additionally performed. **Results:** Significant differences in the levels of blood glucose and serum HDL were noted between the two groups ($P \leq 0.001$). Also, the percentage of pre-diabetic and diabetic patients in the case group was higher than the control group (17.6 and 16.2% vs. 10.3 and 2.9%) ($P=0.009$). Multiple logistic regression showed that the risk of gastrointestinal cancer in people with high blood glucose was 3.35 times that in those with normal blood glucose (OR3.35, 95%CI,1.41-7.94; $P=0.006$), 2.37 times higher in subjects with lower HDL (OR 2.37, 95%CI,1.18-4.78), 10.4 times higher in overweight people (OR10.4, 95%CI,2.23-48.5) and 4.3 times higher in individuals with an opium addiction (OR4.3, 95%CI, 1.6-11.5) than those without. The mean consumption of fish ($P=0.03$) and vegetables and fruits ($P=0.027$) in the case group was significantly lower than in the control group. **Conclusion:** Emerging evidence indicates that the metabolic syndrome or its individual components may be important in the etiology and progression of GI cancer. Research to work toward preventing cancers should thus focus on nutritional and lifestyle modifications which may alleviate the metabolic syndrome.

Keywords: Metabolic syndrome- Gastrointestinal cancer- High blood glucose- High density lipoprotein- odds ratio

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Introduction

Metabolic syndrome is now a major public health challenge worldwide. Clustering of several cardiovascular risk factors including abdominal obesity (increased waist circumference), elevated triglycerides and high low density lipoprotein (LDL) cholesterol, low high density lipoprotein (HDL) cholesterol, high blood pressure and high blood glucose is recognized as metabolic syndrome (Mendonça et al., 2015). Prevalence of metabolic syndrome has been reported from < 10% to as much as 84% worldwide depending on region, sex, age and ethnicity of the population studied and definition of the syndrome used (Kaur, 2014; Kolovou et al., 2007). There

have been several definitions for metabolic syndrome depending on the diagnostic criteria including World Health Organization (WHO), the European Group for the study of Insulin Resistance (EGIR), The National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) and American Association of Clinical Endocrinologists (AACE) but one of the most commonly used criteria for definition is International Diabetes Federation (IDF). IDF estimates prevalence of metabolic syndrome is one-quarter of the world's adult population (Kaur, 2014)

Metabolic syndrome is considered as a state of chronic low grade inflammation, which is associated with elevated levels of inflammatory markers such as C-reactive protein

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(CRP) and interleukin-6 (IL-6). In addition, cardiovascular diseases in several meta-analysis and cohort studies has been related to increase cancer risk in general and major effects on the gastrointestinal (GI) tract (Fujihara et al., 2012). Malignancy is recognized as the second cause of death worldwide and represents a complex interplay of genetic susceptibility and environmental risk factors (Anand et al., 2008; Mostafalou and Abdollahi, 2013). Some risk factors associated with lifestyle including low physical activity, low fruit and vegetable consumption, obesity, smoking, air pollution and alcohol consumption are risk factors for cancers (Aggarwal et al., 2009).

A prospective study on 1,318 colorectal cancer patients in 2016 demonstrated that metabolic syndrome with focusing on hyperglycemia, have been recognized as a potent predictor of colorectal cancer mortality (Goulart et al., 2017).

In a meta-analysis of cohort studies on 9,492 gastric cancer patients; overweight and obesity were associated with increased risk of gastric cardia cancer among Asian and non Asian population (Kulig et al., 2010).

Furthermore, a study in 2010 showed that metabolic syndrome had a positive link with a significant increase of hepatic metastasis and tumor recurrence (Shen et al., 2010).

In a population based study on 140,000 adults (63,585 male, 77,228 female) elevation of fasting plasma glucose during 8.4 years follow up was found to be associated with cancer development (HR 1.2; 95% CI 1.03-1.39 in male, 1.28 95% CI 1.08-1.53 in female) and the strongest association was found with Hepatocellular cancer in men (Berster and Göke, 2008). In a study with 10 year follow up of 1298385 Korean adults including (829,770 male, 468,615 female), fasting glucose levels were found to be in association with increase in pancreas, liver and renal cancers (Jee et al., 2005).

The hypothesis of this study was to confirm association between metabolic syndrome components and gastrointestinal cancer patients in South Khorasan. Identification and education of individuals at risk of metabolic syndrome can be useful in prevention of GI cancers.

Materials and Methods

This case-control study was performed on patients with GI cancers and the subjects without disease in Birjand, the capital of South Khorasan province in Iran, from March 2016 to September 2017. The sample size was calculated on the basis of the formula for comparing the two ratios and the results of the study by de Santaet al (Santanaet al., 2008) on 59 people in each group. Considering 15% probability of dropping samples, the final sample size was calculated 68 in the case group. Eventually, 68 consecutive patients with gastrointestinal cancers (esophageal, gastric, colon, rectum) referred to the oncology center in Birjand city that had positive pathological examinations and 100 control subjects (without disease) referred to health centers were studied.

The patients referred to Vali-e-Asr Hospital of Birjand University of Medical Sciences for endoscopy and

colonoscopy and pathologists confirm a GI cancer were included in the study. Following approval of the University medical ethics committee (Ethical approval registration number ir.bums.1394.327), written informed consent was obtained from each patient.

The control group were selected randomly from healthy individuals referring to three health centers in northern, southern and central parts of Birjand city who were referred for health care (Mother and child health, Vaccination, Environmental and Occupational health). Samples in both groups were matched for age and sex.

The inclusion criteria were patients with new diagnosis of gastrointestinal cancers. Subjects undergone surgery, receiving chemotherapy or radiotherapy treatment were excluded from the study.

The participants in this study were informed that all identifying information would be kept confidential. Following an initial assessment, patients with gastrointestinal cancers and control subjects completed a researcher make questionnaire including demographic characteristics (age, gender, job, history of Cigarette smoking and opium and heroin addiction). Also, asked about physical activity and intake of foods with high cholesterol and saturated fat such as meat, egg and dairy products, fast foods, and also healthy foods consumption such as fish, fruit and vegetables.

To determine the content and face validity of the questionnaire, the content validity index (CVI) and content validity ratio (CVR) were used. For this purpose, a panel of 10 experts including gastroenterologists, nutritionists, health educationists, physiologists and epidemiologists was formed. The questionnaire was given to these faculty members and was revised based on their comments. The mean CVI was 82% and the mean CVR equaled to 85%.

Then, the reliability was assessed using Cronbach's alpha coefficient. The modified questionnaire was completed by 25 persons referring to the health center that were not included in the sample people and its Cronbach's alpha was obtained as 0.71. After validity and reliability of the questionnaire was confirmed, it was completed via interview for both the case and control groups.

Anthropometric measurements of height (cm), weight (kg), Body Mass Index (BMI) (kg/m^2), waist circumference (cm) and blood pressure (mm Hg) for each patient or the control subject was performed. Blood pressure was measured in a quiet and calm environment by a mercury sphygmomanometer (Diplomat, Riester, Germany) and a stethoscope (4064, Riester, Germany). Blood pressure measurement was performed once the participants had sat on a chair for ten minutes. Individuals' weight was determined in wearing light clothes and no shoes by a scale (Seca, Germany). Also, Individuals' height was measured without shoes, using a digital scale. Waist circumference (WC) was measured with a relaxed abdomen using a metric tape on a horizontal plane above the iliac crest and BMI was calculated using the formula $\text{weight (kg)} / (\text{height})^2$ Individuals' classified as underweight ($\text{BMI} < 18.5 \text{ kg}/\text{m}^2$), normal ($\text{BMI} 18.5\text{-}24.9 \text{ kg}/\text{m}^2$), overweight ($\text{BMI} 25\text{-}29.9 \text{ kg}/\text{m}^2$) and obese ($\text{BMI} \geq 30 \text{ kg}/\text{m}^2$).

Following the questionnaire completion and

anthropometric measurements, the patients and the control subjects were sent to central lab of the University for blood tests. Blood samples (5ml) were obtained from each patient or control subject after 12 hours overnight fast by left brachial vein puncture under aseptic condition for measurement of serum fasting blood glucose (FBS), LDL-C, HDL-C, triglyceride levels by the (Cobas, Hitachi Japan, type 6000).

Then data was entered and analyzed by Statistical Package for Social Sciences (SPSS) 16 software and were reported as mean± standard deviation (SD) or as numbers and percentages for quantitative variables. At first, the normal distribution of the data was assessed through running the Kolmogorov-Smirnov test. The independent t-test and Mann-Whitney statistical tests were used to determine the significant differences between the two groups. Chi-Square test was used to compare diabetes status in the case and control groups. Odds ratios (ORs) and 95% CIs were calculated using multiple logistic regressions to estimate the association between gastrointestinal cancers and various components of metabolic syndrome. Adjusted ORs were derived after adjusting the covariates. A P-value of < 0.05 considered statistically significant for all statistical tests.

Table 1. Comparison of Metabolic Syndrome Elements in GI Cancer and Control Group

Variable	GI cancer mean ± SD	Control mean ± SD	P - value
Glucose (mg/dL)	103.22 ± 28.69	88.69 ± 18.09	≤0.001*
HDL cholesterol (mg/dL)	38.84 ± 9.11	46.53 ± 11.45	≤0.001*
Triglycerides (mg/dL)	103.61 ± 42.22	117.18 ± 58.82	0.12
LDL cholesterol (mg/dL)	106.79 ± 35.73	114.28 ± 31.59	0.19
Waist circumference (cm)	83.17 ± 12.61	86.67 ± 13.04	0.11
BP systole (mmHg)	115.22 ± 14.18	118.8 ± 18.84	0.32
BP Diastole (mmHg)	72.83 ± 10.78	74.55 ± 9.37	0.33

* P<0.05 is significant

Results

This study was conducted on 68 patients with gastrointestinal cancer and 100 controls. Mean age in case group was 65.35± 13.03 years and in control group was 64.6±10.43 years. T-test showed no significant difference in the mean age of the two groups (P=0.23). Also, chi-square test showed no significant difference on sex between the two groups in case and control groups (P=0.22). Table 1 show that there were significant differences in the levels of blood glucose and serum HDL

Table 2. Odds Ratio and 95% Confidence Intervals for GI Cancer

Variable		Case N (%)	Control N (%)	OR (95%CI)	P-Value
Diastolic blood pressure	Normal	62 (91.2)	56 (82.4)	1 ^a	
	Abnormal	6 (8.8)	12 (17.6)	0.45 (0.16-1.28)	0.13
Systolic blood pressure	Normal	64 (94.1)	59 (86.8)	1:00 AM	
	Abnormal	4 (5.9)	9 (13.2)	0.41 (0.12-1.4)	0.15
Blood Pressure	Normal	61 (89.7)	54 (79.4)	1:00 AM	
	Abnormal	7 (10.3)	14 (20.6)	0.44 (0.17-1.18)	0.1
Waist Circumference	Normal	38 (55.9)	35 (51.5)	1:00 AM	
	Abnormal	30 (44.1)	33 (48.5)	0.84 (0.43-1.64)	0.61
Fasting Blood Sugar	Normal	45 (66.2)	59 (86.8)	1:00 AM	0.006*
	Abnormal	23 (33.8)	9 (13.2)	3.35 (1.41-7.94)	
Triglycerides(mg/dL)	Normal	56 (82.4)	54 (79.4)	1:00 AM	0.66
	Abnormal	12 (17.6)	14 (20.6)	0.83 (0.35-1.95)	
HDL(mg/dL)	Normal	21 (30.9)	35 (51.5)	1 ^a	0.016*
	Abnormal	47 (69.1)	33 (48.5)	2.37 (1.18-4.78)	
LDL(mg/dL)	Normal	51 (75)	51 (75)	1 ^a	
	Abnormal	17 (25)	17 (25)	(0.46-2.17)	1
BMI(kg/m ²)	Normal	55 (83.1)	37 (54.4)	1 ^a	
	Overweight	10 (14.9)	17 (25)	10.4 (2.23-48.5)	0.003*
	Obesity	2 (3)	14 (20.6)	4.12 (0.77-21.9)	0.098
Cigarette Smoking	No	54 (79.4)	57 (83.8)	1 ^a	
	Yes	14 (20.6)	11 (16.2)	1.34 (0.56-3.22)	0.51
Opium Addiction	No	48 (70.6)	62 (91.2)	1 ^a	
	Yes	20 (29.4)	6 (8.8)	4.3 (1.6-11.5)	0.002*
Physical Activity	Yes	23 (33.8)	27 (39.7)	1 ^a	
	No	45 (66.2)	41 (60.3)	0.78 (0.38-1.56)	0.48

* P<0.05 is significant; ^a, Reference Category

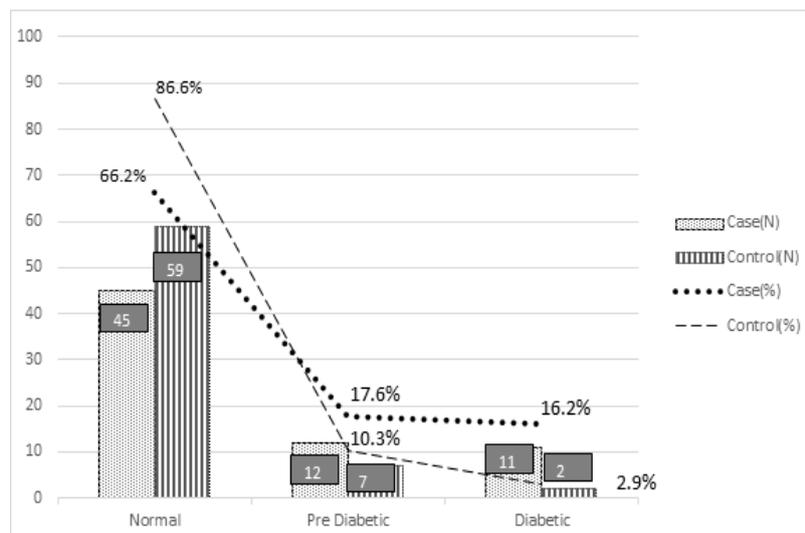


Figure 1. Comparison of Diabetes Status in the Case and Groups.

Table 3. Comparison of Mean Food Consumption Score in Both Case and Control Groups

Group	Case (N = 68)	Control (N = 68)	Mann whitney
Variable	mean ± SD	Mean ± SD	P - value
Red meat	2.35 ± 0.85	2.29 ± 0.79	0.74
Hen	1.57 ± 0.89	1.71 ± 0.88	0.26
Fish	0.29 ± 0.52	0.54 ± 0.72	0.03*
Fried Food	2.56 ± 1.1	2.57 ± 0.79	0.95
Vegetables and Fruits	2.19 ± 1.2	2.65 ± 1.1	0.027*
Cola	3.13 ± 1.3	3.34 ± 0.99	0.69
Fast food	3.89 ± 0.46	3.88 ± 0.32	0.26
Total	17.31 ± 2.8	18.84 ± 2.22	0.001*

* P<0.05 is significant.

level between the two groups (P≤0.001). However, there was no significant difference in serum level of triglyceride and LDL, as well as systolic and diastolic blood pressure between the two groups (P>0.05).

As shown in Figure 1, the percentage pre-diabetic and diabetic patients in the case group was higher than in the control group (17.6% and 16.2% vs. 10.3% and 2.9%) and this difference was statistically significant (P=0.009).

Multiple logistic regression model indicated that the risk of gastrointestinal cancer in people with high blood glucose was 3.35 times than those of normal blood glucose (OR3.35, 95% CI, 1.41-7.94), 2.37 times higher in subjects with lower HDL (OR 2.37, 95% CI,1.18-4.78), 10.4 times higher in overweight people (OR10.4, 95%CI, 2.23-48.5) and 4.3 times higher in individual who had opium addiction than the control group (OR4.3, 95%CI, 1.6-11.5). This differences were statistically significant (Table 2).

Comparison of mean food consumption score in both the case and control groups revealed that average consumption of fish and vegetables and fruits in the case group was significantly lower than the control group (Table 2).

Discussion

The metabolic syndrome and its concomitant complications are a serious and escalating challenge and, probably, will gain even more attention in the future because surplus energy intake, increasing obesity prevalence, unbalanced diets and sedentary life habits (Braun et al., 2011).

This study showed that based on FBS levels, subjects were categorized according IDF criteria into three groups using cut off value of 100 mg/dl including normal fasting glucose (NFG)< 100 mg/dl, prediabetes 100-125 mg/dl and diabetes mellitus ≥ 126 mg/dl. Odd ratio was calculated and times risk of developing gastrointestinal cancer in subjects having elevated FBS compared with normal glucose levels.

Our findings are consistent with findings of the large cohort studies that demonstrated hyperglycemia is positively correlated with an increased risk of developing cancers associated with the gastrointestinal tract (Ikeda et al., 2009; Stattin et al., 2007). However, in one meta-analysis by Ge et al., (2011) including 4 case-controls and 17 cohort studies either incidence or mortality of gastric cancer did not show an overall higher risk of gastric cancer with diabetes mellitus when sex was not analyzed separately.

Epidemiological studies of the relationship between of diabetes mellitus and the risk of cancer are not entirely consistent and the relationship between them appears to be complex (Onitilo et al., 2012).

Hyperglycemia can be a high glucose supply for cancer cells favoring tumor growth and metabolism due to high sugar intake and elevated blood glucose levels alter the expression of genes that promote cell proliferation, migration and adhesion (Masur et al., 2011). In the cancer cells appears profound metabolic change which the most remarkable is aerobic glycolysis and is known as the Warburg effect. Glycolytic intermediates derived from glycolytic metabolism in anabolic pathways provide protein, nucleic acid and lipids needed for proliferation (García-Jiménez et al., 2014).

Additionally, HDL cholesterol levels were classified based on IDF criteria as men < 40 mg/dl and women < 50 mg/dl as abnormal levels. The present study showed that risk of gastrointestinal cancers negatively associated with HDL cholesterol levels.

Studies published by Jung et al in Korean on case-control study showed a higher incidence of stomach dysplasia with lower HDL levels (Jung et al., 2008). Report of by Wulaningsih et al., (2012) on 540,309 participants >20 years old from the Swedish Apolipoprotein Mortality Risk (AMORIS) study revealed that 84,774 had baseline LDL cholesterol, HDL cholesterol, apolipoprotein B, and apolipoprotein A-I, quartiles of HDL were negatively associated with risk of stomach cancer, but was not statistically significant. Although the prevalence of dyslipidaemia is increasing worldwide either alone or as part of the metabolic syndrome, the precise mechanism for the development of cancer by serum lipids still is unknown and contradictory results have been reported (McGrowder et al., 2010).

HDL-c particles are known for multiple biological effects in the body that is linked to their antiatherothrombotic action including anti-inflammatory and antioxidant (McGrowder et al., 2010). Several studies have been demonstrated that reduced levels of HDL as well as elevated levels of LDL have been linked to an increased activity of proinflammatory markers of TNF- α and IL-6 which may contribute to cancer development (Wulaningsih et al., 2012; Zuliani et al., 2007). Low HDL levels leads to lipid peroxidation in lipoproteins and induce cellular damage which may promote malignant transformation of normal cells. Therefore, considering of the role serum lipids on gastrointestinal cancer seems rational to improve nutrition and decrease in the risk of disease in families of the cancer patient. Health professionals can play an important role in education of healthy lifestyles to patients' families and societies.

In our study cancer patients had lower intake of vegetables, fruits and fishes than the control group.

Lifestyle changes such as healthy diet, regular exercise, smoking cessation and weight control proven to increase HDL cholesterol levels and modify risk of gastrointestinal cancer. Pan et al., (2004) showed that ovarian cancer risk inversely associated with a higher intake of vegetables and cruciferous vegetables and with supplementation of vitamin E, beta-carotene and vitamin B-complex (Ashen and Blumenthal, 2005). In our study, possibly lower intake of vegetables, fruits and fishes in cancer patients was in association with low HDL levels.

On the other hand, associations between intake of vegetables and fruits and lower gastrointestinal cancers risk have been inconsistently reported among different studies which may be related to other risk factors for colorectal cancer, such as smoking though this study showed no significant relationship between smoking and gastrointestinal cancers was found. However, several studies indicated protective effects on colorectal cancer. One possible explanation is that fruits and vegetables have constituents such as carotenoids, folate, vitamin C, flavonoids, organosulfides, isothiocyanates, and protease inhibitors, which may reduce DNA damage and mutations.

Also, fermentable fiber in fruits and vegetables decreases transit time (Michels et al., 2006). Thus, lifestyle change and improvement of nutrition can have a significant impact on reducing the disease burden and the associated healthcare costs.

Our findings on the risk of gastrointestinal cancer that was 4.3 times higher in people who had opium addiction than the control group is in agreement with previous studies that showed. Many studies have shown that opium use may increase the risk of some malignancies including upper and lower gastrointestinal cancers (Iankarani et al., 2017; Naghibzadeh Tahami et al., 2014).

One of the proposed mechanisms is opium alkaloids have mutagenic effects. In some studies pyrolysis of opium (called sukhteh locally), but not of crude opium in conjunction with dietary deficiencies of riboflavin, vitamins A and C and animal protein in north-east Iran that was associated with a high incidence of oesophageal cancer. The adverse biological effects of these pyrolysates have been demonstrated as mutations in bacteria salmonella strains, in human lymphocytes and Chinese hamster ovary cells and transformed cultured Syrian hamster embryo cells (Friesen et al., 1985).

During processing of opium, a heavy metal lead is being added to make it heavier. Lead is a toxic substance that has induced poisoning in opium addicts (Roya and Abbas, 2013). Lead poisoning may also contribute to the GI malignancy. Thus, awareness of health care professional and opioid abusers about the risks of contaminated opium is essential to prevent complications of chronic lead poisoning.

In conclusion, this study demonstrated statistically significant higher risk of gastrointestinal cancer in patients with higher FBS and diabetes mellitus and low HDL levels, the two components of metabolic syndrome comparing with the control individuals. Also in our study cancer patients had unhealthy nutrition habits which it also is in related to components of metabolic syndrome. On the other hand, growing evidence supports that metabolic syndrome or its components may be important risk factors for certain cancers, progression of some cancers as well as altering the outcome of some cancers. Therefore, regular screening serum lipid and glucose concentrations, as well as healthy lifestyle is important for the prevention and management of metabolic syndrome and GI cancers.

Limitations and Strengths

The present study has a number strength. It has a case-control design and provided information about possible confounders such as smoking status, opium addiction and duration of the GI cancer patients and control group. Also, one of the positive point this study was confirmation of cancer group based on histopathological diagnosis which minimized the possibility of bias.

Our study is not without limitations. A limitation of this study is small number of patients because low population of the province which consequently did not provide required data for certain type of gastrointestinal malignancies. Additionally, there was no information registry on cancer in South Khorasan province.

Conflicts of Interest

The authors report no conflict of interest in connection with this article.

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