ORIGINAL ARTICLE

Fasting Hyperglycemia and Insulin Resistance in Colorectal Adenomatous Polyps

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ABSTRACT

OBJECTIVES: To investigate fasting glucose, glucose tolerance, insulin resistance and insulin–like growth factor 1 in patients with or without colorectal polyps.

MATERIALS AND METHODS: In this cross-sectional study, we evaluated fasting glucose, insulin, insulin–like growth factor 1 (IGF-1), lipid profile and glucose tolerance test in 103 patients undergoing colonoscopy (52 normal and 53 with Adenomatous polyps). We also estimated homeostasis model assessment insulin resistance index (HOMA-IR) in two groups. Statistical analyses were performed using the Student T-test and Chi-square test. For all tests a P value ≤ 0.05 was considered to be statistically significant.

RESULTS: The mean of waist circumference ($P < 0.01$), waist to hip ratio ($P < 0.01$), fasting serum glucose ($P < 0.05$), total cholesterol ($P < 0.05$), and LDL ($P < 0.05$) were significantly higher in patients with adenomatous polyps. The mean of HDL was significantly lower in patients with adenomatous polyps ($P < 0.01$). There was no relation between fasting serum insulin, IGF-1 and glucose tolerance test with adenomatous polyps. Hence HOMA-IR was higher in patients with adenomatous polyps (2.9 ± 2.6 vs. 2.82 ± 2.1), this difference was not significant statistically.

CONCLUSION: Fasting hyperglycemia could be a risk factor to adenomatous polyps' development. Although this study did not show any relation between insulin resistance index and adenomatous polyps, further studies are needed for more evaluation.

KEYWORDS: Hyperglycemia, Insulin Resistance, Colorectal Polyps.

INTRODUCTION

Several clinical characteristics which are comprised in metabolic syndrome including obesity, dyslipidemia, and impaired glucose tolerance, have been linked to an increased risk for colorectal cancer in several epidemiologic studies (1-5). Insulin resistance, which is considered as a primary factor in the mechanisms of metabolic syndrome, is also known to raise the risk of cardiovascular disease and cancer, which are the leading causes of death worldwide (6-7).

The findings of recent studies have not been consistent regarding the hypothesis that plasma glucose (8), insulin (9) and IGF-1 (10)

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maybe causative factors in colorectal neoplasm. In some studies insulin was associated with colorectal cancer or adenoma (11-13) whereas in another studies there was no statistically significant association of insulin with colorectal cancer (14). Fasting and/or post–load glucose were associated with colorectal cancer in some studies (12,15,16), while in others there was no association of plasma glucose with either colorectal cancer (11,17), or adenoma (11).

Increased levels of IGF ligands and/or over-expression of IGF receptor have been observed in many cancers and have been shown to affect proliferation, differentiation, migration and apoptosis of cancer cells (18-21).

The aim of the present study was to study the association between serum fasting glucose, post–load glucose, fasting insulin level, IGF-1, HOMA-IR and lipid profile, with the presence of colorectal adenomatous polyps in patients who were submitted to colonoscopy.

MATERIALS AND METHODS

Patients and Evaluation Methods: This is a cross-sectional study on a series of subjects who had undergone colonoscopy for colorectal evaluation at the gastrointestinal clinic, in Arak, Iran, from August 2009 to February 2010. This study was approved by the Institutional Review Board of Arak University of Medical science. The exclusion criteria were a history of diabetes mellitus, acromegaly, colorectal cancer, prior colonic surgery or colon polypectomy; a medical history of severe renal, liver, lung, hematologic, or connective tissue disorders and other malignancies. All the colonoscopy procedures were performed by a single endoscopist (Gahramany R) using a videoscope (Olympus PCF 200, Tokyo, Japan). After the initial examination of the specimens under a conventional microscope, patients with adenomatous polyps were selected for further study, whereas those with hyperplastic polyps, inflammatory polyps, or other kinds of tumors were excluded.

A total of 103 subjects were recruited for this study including 51 patients with colorectal adenomatous polyps and 52 with normal colonoscopy who comprised the control group. All subjects were voluntarily consented to participate in this investigation.

BMI; obtained by dividing the individual's weight in kilograms by height in meters squared.

All subjects underwent blood tests and were evaluated for fasting glucose, total cholesterol, triglycerides, low density cholesterol (LDL), high-density lipoprotein (HDL) cholesterol, insulin and IGF-1 in the same laboratory. Fasting glucose and lipid profiles were measured with a commercially available enzymatic method (Roche Diagnostics) on the Hitachi 7600 automated chemistry analyzer (Hitachi). Levels of IGF-1 were measured by immunoradiometric method with IGF-1 IRMA (Immunotech, Marseille, France). Insulin levels were measured by immunoradiometric method with INSI-CTK IRMA (Dia Sorin), Homeostatic model assessment of insulin resistance (HOMA-IR) has emerged as a practical and simple method for estimating insulin resistance. This index was extensively validated in comparison with the gold-standard method for the evaluation of insulin resistance, the hyperinsulinemic euglycemic glucose clamp technique (22). Homeostasis model assessment of IR (HOMA-IR) was calculated as insulin (milliunits per liter) x glucose (millimoles per liter)/22.5 (23). The optimal cut-off point of HOMA-IR for the diagnosis of insulin resistance in our population was estimated to be 1.775 in non-diabetics (24).

Statistical analysis was performed using SPSS 11.0 for Windows (SPSS, Chicago, IL). The χ^2 test of independence was used to examine whether there was an association between any two categorical variables. The independent-samples T-test was used for comparison of the mean insulin and IGF-1 levels of two groups. The nonparametric Mann-Whitney U test was used for comparison of the mean HOMA-IR levels of two groups. Variables with a P value ≤ 0.05 in our univariate analysis were subsequently in a logistic regression multivariate analysis. $P \leq .05$ was considered statistically significant for every test.

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RESULTS

Demographic characteristics of the study participants are shown in Table 1. The study group was composed of 52 males (50.5%) and 51 females (49.5%). Their ages ranged from 15 to 81 years (mean 49.3 ± 15.8 years).

The univariate analysis indicated that high fasting blood sugar ($P < 0.05$); total cholesterol ($P < 0.05$); LDL cholesterol ($P < 0.05$); and low HDL cholesterol ($P < 0.01$) occurred significantly more often in patients with adenomatous colorectal polyps than those with normal colonoscopy. Laboratory data and HOMA-IR level of the study groups are summarized in Table 2.

There was no significant difference between the groups with or without adenomatous colorectal polyps in fasting insulin, the IGF-1 or the HOMA-IR. In addition, there was no significant difference between two groups concerning the 2 hour post-load glucose.

Multivariate analysis demonstrated that fasting glucose, LDL cholesterol, HDL cholesterol and waist to hip ratio were independently associated with adenomatous colorectal polyps (Table 2).

DISCUSSION

Colorectal adenomatous polyp is a premalignant lesion that tends to develop into colorectal cancer via the traditional adenoma-carcinoma sequence. There are several studies providing evidence that obesity is associated with colorectal neoplasm (25-27). Several hypotheses explain the mechanisms of carcinogenesis in obesity or diabetes through inflammation, oxidative stress, and insulin resistance (28).

Classic insulin-sensitive tissues include muscle, liver, and fat, and these tissues display insulin receptors. The most common neoplasms arise from epithelial cells, and express both the gene encoding the insulin receptor and the gene encoding the IGF-1 receptor (29).

Insulin resistance, which represents a reduced

Table 1- Demographic characteristics of the study participants

Variables	Colorectal Polyps (mean ± SD)(n = 51)	Normal Colonoscopy (mean ± SD)(n = 52)	*P* Values
Age (yrs)	51.7 ± 14.7	46.9 ± 1.7	0.31
Male/Female %	51	50	0.53
Weight (kg)	71.8 ± 10.2	68.3 ± 15.1	0.24
Height (cm)	168.3 ± 8	166 ± 10.5	0.45
BMI* (kg/m2)	24.9 ± 4.24	24.2 ± 4.71	0.57

* Body Mass Index

Table 2- Results of unvariate and multivariate logistic regression analysis of the studied groups

Variables	Colorectal Polyps (Mean ± SD) (n = 51)	Normal Colonoscopy (Mean ± SD) (n = 52)	Univariate analysis *P* -value1	Multivariate analysis		
				P -value1	Odds ratio	95% CI
Fasting glucose (mg/d)	105.3 ± 31.4	96.7 ± 14.9	<0.05	0.03	4.68	1.11-19.73
Post glucose load (mg/d)	137.3 ± 79	122 ± 61.7	NS			
Total cholesterol (mg/d)	194.1 ± 41.5	188.5 ± 43.1	<0.05	0.33	2.1	0.39-11.5
Triglyceride (mg/d)	159.4 ± 137	121 ± 65.7	NS			
LDL cholesterol (mg/d)	117.2 ± 37.4	111.4 ± 42.7	<0.05	0.03	0.04	0.003-0.82
HDL cholesterol (mg/d)	49.1 ± 12.8	53.2 ± 10.5	<0.01	0.03	0.18	0.03-0.87
IGF-1 * (ng/ml)	290 ± 94.5	316 ± 116.5	NS			
Fasting insulin (lU/ml)	10.6 ± 7.5	11.4 ± 7.6	NS			
HOMA-IR **	2.92 ± 2.62	2.82 ± 2.10	NS			

* Insulin –like growth factor 1
**Homeostasis model assessment insulin resistance index

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physiological response of the peripheral tissues to the action of the normal levels of insulin, is a major finding in several metabolic disorders, including obesity, type 2 diabetes and metabolic syndrome (30).

The homeostasis model assessment of insulin resistance (HOMA-IR), which is developed for application in large epidemiologic investigations (31), is an alternative to the glucose clamp and the most commonly used surrogate measure of insulin resistance in vivo. In terms of precision (reproducibility of measure), HOMA-IR is comparable to the glucose clamp technique. HOMA-IR is a possible and easy way to study with a single glucose and insulin measurement in fasting state (32).

The ethnic and racial factors are known to be significant in the etiology of insulin resistance (33). As a result of such factors, one important point in implementing the HOMA-IR method successfully is the presence of specific cut-points for the race or age of the studied population. According to Alireza Esteghamati et al., the optimal cut-off point of HOMA-IR for the diagnosis of metabolic syndrome in our non-diabetes population was estimated to be 1.775 (24).

The aim of this research was to examine if patients with colorectal adenomatous polyps have increased levels of fasting glucose, insuline, IGF-1 and HOMA-IR compared to the control group. The results of this research are consistent with the hypothesis that hyperglycema plays important roles in colorectal neoplasia. Namely, significantly higher levels of fasting glucose were found in colorectal adenomatous polyps patients than in the control group. In addition, with multivariate analysis; the present study revealed that LDL cholesterol was significantly higher and HDL cholesterol was significantly lower in patients with adenomatous colorectal polyps. Nonetheless, our study did not show any significant relation between the fasting insulin, the IGF-1, the HOMA-IR and 2 hour post–load glucose with colorectal adenomatous polyps.

In a study Andrew Flood et al. (34) followed patients with previous colorectal adenoma for 4 years and showed higher recurrence of adenoma in patients with increased serum insulin and glucose level. They concluded that patients with increased serum insulin or glucose are in greater risk of colorectal adenoma.

Marugame T et al. (35) evaluated the relation of impaired glucose tolerance and diabetes mellitus to colorectal adenomas in Japan. They resulted that impaired glucose tolerance, new type 2 DM, and known DM were associated with a modest increase in the risk of colorectal adenomas after adjustment for possible confounding factors.

In a study by Robert E. Schoen et al. (36), IGF-1 and insulin were significantly increased in subjects with adenomas compared with the controls, but they did not find any relation between visceral adipose tissue and adenomatous polyps.

Other epidemiologic studies have been done to investigate the relationship between the IGF system and colorectal neoplasm**.** While some have documented a correlation between higher levels of IGF-1 and increased risk of colorectal neoplasm, others have found no such association (37-39)

There are challenges related to the imprecision of using random or even fasting or postprandial measurements to estimate the impact of levels that fluctuate throughout the day according to nutrient consumption (40). On the other hand, substantial IGF-1 is locally produced by neoplastic tissue in an autocrine or paracrine manner, and this provides a source of these ligands supplementary to the classic ‘endocrine’ production by the liver delivered via the circulation (41).

Also present in the extracellular fluid in the cellular microenvironment are IGF binding proteins and IGF binding protein proteases, which can regulate bioavailability of IGF-1. Classically, IGF binding proteins reduce ligand bioavailability by competing with receptors for ligand (42,43).

Although cause-effect conclusions cannot be drawn from cross-sectional studies, we believe

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that this simple and non-invasive set of tests may be a useful tool in optimizing the selection of patients to proceed to a more invasive investigation. Accordingly, future prospective studies will require that relevant data be accumulated and analyzed on a more objective basis**.**

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