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Evaluation of insulin resistance and beta cell activity in patients with inflammatory bowel disease

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Abstract. – OBJECTIVE: Insulin resistance is an important risk factor for developing metabolic syndromes that cause morbidity diseases such as diabetes and cardiovascular diseases. Interestingly, in chronic inflammatory diseases, some inflammatory mediators can play, either directly or indirectly, a pivot role in the development of insulin resistance. This can be considered as an additional factor causing increased mortality and morbidity in these patients. In this paper, we want to investigate and compare the insulin resistance status in patients with Inflammatory Bowel Disease (IBD) and healthy control, as well as different stages of patients with Ulcerative colitis (UC) and Crohn's Disease (CD).

PATIENTS AND METHODS: A total of 180 patients were enrolled in this study; while 95 patients had inflammatory bowel disease [Crohn's Disease (n): 47, Ulcerative colitis (n): 48], 85 people were healthy controls. Insulin resistance status was evaluated with the HOMA-IR (hemostasis model of assessment of insulin resistance) index. $p < 0.05$ was accepted as significant.

RESULTS: The mean HOMA-IR levels were found to be similar for both IBD and control, and Crohn's disease and control ($p = 0.174$, $p = 0.96$, respectively); but the mean HOMA-IR score in ulcerative colitis, one of the IBD subgroups, was significantly higher than the control group ($p < 0.039$).

CONCLUSIONS: This study clearly showed that insulin resistance is increased in ulcerative colitis. Consequently, patients with ulcerative colitis should be followed and closely monitored for developing insulin resistance, metabolic syndromes, diabetes, and cardiovascular diseases. Consequently, all of them can cause an additional risk of morbidity and mortality in these patients.

Key Words:
Inflammatory bowel disease, Insulin resistance, Crohn's Disease, Ulcerative colitis, HOMA-IR score.

Introduction

Inflammatory bowel diseases (IBD) are chronic inflammatory diseases of unknown etiology that involve different locations and layers of the gastrointestinal tract and manifest themselves with different clinical pictures, such as periods of remission and acceleration[1]. Due to the inflammatory properties of these diseases, some serum inflammatory markers such as tumor necrosis factor-alpha (TNFα), interleukin 1 beta (IL1β), interleukin 2 (IL-2), and interleukin 6 (IL-6) are elevated, especially in clinically active IBD patients[2]. As recently learned, these mediators, either directly or indirectly, can play a pivot role in the development of insulin resistance[2]. This insulin resistance also plays an important role in the atherosclerosis process that is responsible for the development of metabolic syndromes, diabetes, and atherosclerotic heart diseases[3,4]. Consequently, all these factors can cause additional risks in increasing morbidity and mortality in patients with IBD, regardless of the course of the disease itself[1]. These comorbid conditions caused by insulin resistance in IBD can lead to a decrease in the quality of life, worsening of the emotional state, and disrupt the patient's struggle with the disease control[5,6]. This relationship has been demonstrated in reverse fashion; in some animal studies, it has been shown that TNFα levels are increased in the blood and adipose tissue and insulin resistance is treated by the normalization of the TNFα[7].

Traditionally, extra-intestinal manifestations of IBD, such as arthritis, psoriasis, premalign lesions and uveitis, were the first to show that IBD was causing problems outside the lumen through the markers of inflammation[8,9]. The relationship between inflammation and insulin resistance has just been discovered by physicians. In recent years, "an urgent call for action[10]" has been made for this situation in many review articles in order to reduce morbidity and mortality due to increased insulin resistance in patients with

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IBD[1,2,7]. Starting from this point, in this study, we want to investigate and compare the status of insulin resistance between IBD patients and healthy control group as well as IBD subgroups (Crohn's Disease and Ulcerative colitis).

Patients and Methods

Patients and Control Group

Patients, followed up by gastroenterology clinics of Hisar Intercontinental Hospital and Umraniye Training and Research Hospital, who had inflammatory bowel disease diagnoses (Ulcerative colitis or Crohn's Disease) and those who had not been going on drugs, such as steroids and metformin, which cause changes in insulin and glucose metabolism, in the last 6 months were included in the study. The exclusion criteria were chronic steroid using, chronic disease histories, such as diabetes, hypertension, and ischemic heart disease. Patients who applied to our polyclinic for dyspepsia complaint with no history of chronic diseases were included in the control group. Our study consisted of 48 patients with ulcerative colitis, 47 patients with Crohn's disease, and 85 healthy controls. Detailed information about the study design was shared with three different groups and ethics committee consent (number 4873) was taken. Blood samples were taken from patients and controls for measuring fasting plasma glucose, insulin, cholesterol parameters [triglyceride, LDL (low-density lipoprotein), HDL (high-density lipoprotein), VLDL (very low-density lipoprotein), blood count, sedimentation, C-reactive protein, and HbA1c levels]. HOMA-IR levels were calculated using fasting glucose and insulin values.

Blood Sampling

Blood samples were collected using a 20 gauge needle between 08:30-10:30 a.m, following a fasting period of 8-12 hours.

Studying the Blood Samples

Glucose, insulin, triglyceride, LDL, VLDL, hemogram, sedimentation, CRP and HbA1c levels were analyzed in the Clinical Biochemistry and Microbiology Laboratory of Umraniye Research and Education Hospital the same day.

Evaluation of Insulin Resistance

HOMA-IR (Homeostatis model assessment insulin resistance) index, which was developed by Matthews et al[6] in 1985, was used to evaluate insulin resistance in patients and control groups. Insulin was measured as IU (International Unit)/ml and glucose is measured as mg/dl in our laboratory. The HOMA-IR score was calculated using this formula; fasting plasma glucose (mmol/L) x fasting plasma insulin (mU/L) / 22.5. It has been detected that high HOMA-IR score and insulin resistance are parallel. HOMA-IR that has relevant results when compared with euglycemic and hyperglycemic clamp in different studies was chosen for its advantages such as its being cheap and easy, sampling once is enough[5,7].

Statistical Analysis

All data collected from this study were analyzed using the SPSS (SPSS Inc., Chicago, IL, USA), version 11. ANOVA (the one-way analysis of variance) method was used for comparing the mean values of variables in more than 2 groups, *t*-test was used for comparing the groups and comparing the values of pre-treatment and post-treatment. The difference between genders was analyzed with the Chi-square test. Correlation analyses between groups were made with Pearson Correlation Analysis for parametric values and Spearman Correlation Analysis for nonparametric values. $p<0.05$ was accepted as significant.

Results

A total of 180 patients were enrolled in this study: 95 patients had inflammatory bowel diseases and 85 people were healthy controls group. Their demographic data are shown in Table I. No statistically significant difference was detected between patients and control groups regarding age, gender, body mass index (BMI), serum fasting insulin levels, serum triglyceride levels, and all other parameters.

The mean HOMA-IR levels were found to be higher in the patient group (2.17 ± 2.41) compared to the control group (1.82 ± 0.096), but this difference was not statistically significant ($p = 0.174$). Also, no statistically significant difference was detected between HOMA-IR levels of Crohn's patients (1.83 ± 1.48) and the control group (1.82 ± 0.96) ($p = 0.96$). Interestingly, the HOMA-IR levels were found to be higher in patients with ulcerative colitis (2.50 ± 3.02) compared to those in the control group (1.82 ± 0.96) and this difference was statistically significant ($p< 0.039$) (Figure 1).

In Table II, the status of the HOMA-IR score has been compared and shown between different

Table I. Basic demographic data of all study groups.

	Healthy control	IBD patients	p
Number	85	95	
Age	37.59 ± 9.62	39.12 ± 10.96	0.324
Sex			
Female/Male (n)	42/43	41/54	0.401
Disease duration (month)		54.79±49.5	
BMI (kg/m^2)	26.33 ± 10.9	25.15 ± 5.35	0.092
Glucose (mg/dl)	90.83 ± 9.55	95.42 ± 13.43	0.007
Insulin (IU/dl)	8.01 ± 3.95	8.99 ± 9.52	0.346
Total cholesterol (mg/dl)	189.60 ± 35.47	179.64 ± 44.89	0.045
Triglycerides (mg/dl)	112.41 ± 63.47	122.91 ± 80.69	0.315
CRP (mg/dl)	0.45 ± 0.31	1.08 ± 2.44	0.010
Fibrinogen (mg/dl)	342.25 ± 34.98	393.95 ± 127.91	0.424
Vitamin B12 (pg/dl)	310.71 ± 116.55	338.06 ± 226.66	0.371
Ferritin	55.06 ± 47.33	44.33 ± 43.24	0.558

Note: Values are presented with mean and standard deviation. IBD: Inflammatory Bowel disease.

groups. The HOMA-IR levels were similar in groups of sex, ulcerative colitis involvement, disease duration, BMI (Body Mass Index) in all IBD groups, (all p-values > 0.05). Solely, HOMA-IR score was found to be significantly higher in those with BMI > 25 ($p < 0.016$).

Discussion

In this study, the status of insulin resistance was examined in all study populations and also compared between patients with IBD and healthy control groups, as well as IBD sub-groups (Crohn's Disease and ulcerative colitis). The HOMA-IR levels were used to measure insulin resistance in 85 healthy controls and 95 patients with inflammatory bowel diseases (47 with Crohn's disease and 48 with ulcerative colitis).

The mean HOMA-IR scores were compared and found similar between Crohn's disease patients (1.83 ± 1.48) and the control group (1.82 ± 0.96) and this was statistically significant (p = 0.096). The mean finding of this study was that

Table II. Comparison of the mean HOMA-IR levels among the different groups. When all patient groups were evaluated according to BMI (< 25 or > 25), the mean HOMA-IR score was found to be significantly higher in those with BMI > 25 ($p < 0.016$).

Variables	HOMA-IR	p
Sex		
• Female	1.88 ± 0.24	0.280
• Male	2.40 ± 0.38	
Ulcerative Colitis Involvement		
• Pancolitis	2.06 ± 1.56	0.36
• Partial Involvement	2.86 ± 0.66	
Ulcerative Colitis (Truelove Witts Score)		
• Mild	2.58 ± 0.55	0.9
• Moderate	2.61 ± 0.90	
Disease duration (IBD) (month)		
• < 120	2.23 ± 0.26	0.476
• > 120	1.68 ± 0.26	
BMI (Body Mass Index) (all groups)		
• < 25	1.49 ± 0.10	**0.016**
• > 25	2.46 ± 0.23	
BMI (Body Mass Index) (IBD groups)		
• < 25	1.63 ± 0.15	0.32
• > 25	2.40 ± 0.38	

Note: Values are presented with mean and standard deviation. The difference between the groups was checked by Student's t-test.

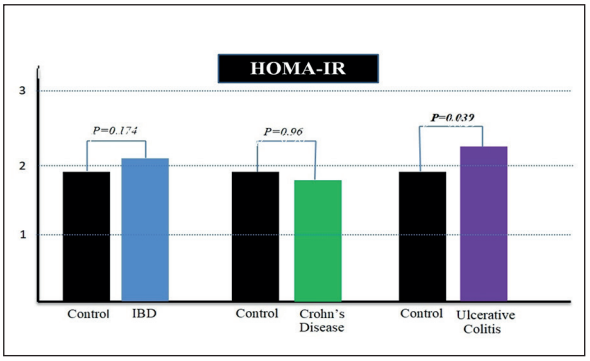

Figure 1. The mean HOMA-IR score was similar between IBD patients and the control group, as well as also Crohn's disease. The HOMA-IR levels were found to be higher in patients with ulcerative colitis (2.50 ± 3.02) compared to those in the control group (1.82 ± 0.96) and this difference was statistically significant ($p < 0.039$).

the HOMA-IR levels were found to be higher in patients with ulcerative colitis (2.50 ± 3.02) compared to those in the control group (1.82 ± 0.96), and this difference was statistically significant ($p < 0.039$). These findings indicated that the risk for developing insulin resistance, metabolic syndrome, and type 2 diabetes was increased. In other studies mentioned above[1,9] the risk for developing metabolic syndromes and atherosclerotic diseases was increased in patients with ulcerative colitis and this finding is in accordance with our results.

There are two ways to cause insulin resistance *via* the activation of the inflammatory signal pathways by the cytokines[11]. In the first place, intracellular pathways, which are activated by the serine phosphorylation of insulin receptor substrate 1 (IRS1) *via* inflammatory signals, cause resistance in insulin-sensitive cells such as hepatocytes and myocytes[12]. In the second place, cytokines and TNFα, which are secreted due to infiltration of inflammatory cells in adipose tissues, decrease insulin sensitivity by changing the lipid metabolism[13]. Fatty acids are activated by the Jun-N terminal kinase (JNK) activator protein 1 (AP-1) and I-kappa kinase (IKK)/nuclear factor kappa beta (NF-κβ) pathways, which are activated *via* the pro-inflammatory response. JNK and IKK signal pathways activate and aggravate insulin resistance[14].

In 1996, it has been proven by Hotamisligil et al[15] that tyrosine kinase activity of insulin is decreased by an inflammatory mediator, and the TNFα has been proven to cause insulin resistance. The study by Capristo et al[3], published in 1998, is the first study to evaluate the relationship between glucose metabolism and insulin sensitivity in inflammatory bowel disease. In this study, 10 patients with inactive ulcerative colitis and 10 patients with Crohn's disease and 40 healthy controls were included and thereafter evaluated by using the euglycemic and hyperglycemic clamp test. No statistically significant difference was detected between IBD patients and control groups regarding glucose metabolism[3]. This is supposed to be a result of the diseases being in the inactive period. In 2000, Festa et al[8], with their insulin resistance atherosclerosis study (IRAS) study, showed that chronic inflammation causes insulin resistance syndrome. There is a strong relationship between CRP levels, and insulin resistance, fasting insulin levels and proinsulin levels. In 2006, in Germany, Bregenzer et al[16] evaluated insulin resistance and β cell activity with HOMA test in 17 patients with Crohn's disease and found that insulin resistance was higher in the patients' group compared to the control group. Chronic inflammation was supposed to be related to insulin resistance[17].

In 2009 in Japan, Nagahori et al[18] included 107 patients (76 UC, 31 CD) in their study. Likewise, in our study metabolic syndrome (MS) prevalence was found to be higher in ulcerative colitis (23%) compared to the Crohn's disease (7.1%). No statistically significant difference was detected when the prevalence of metabolic syndrome in inflammatory bowel diseases was compared with the general population[18]. In 2010, Dagli et al[5] studied the risk factors of atherosclerotic diseases in IBD in a study group containing 40 patients with inflammatory bowel disease and 40 controls. Mean age and gender range in the patients and the control group of their study were similar to ours and were 39.4 ± 11 and 38.1 ± 10.2 respectively. Stiffness of carotid artery, CRP, HOMA-IR, and homocysteine levels were found to be higher in the inflammatory bowel disease group compared to the control group, and this was statistically significant[5].

In 2011, in Turkey, Yorulmaz et al[19] conducted a study on the metabolic syndrome frequency in inflammatory bowel diseases, including 177 patients – 115 patients with ulcerative colitis, and 62 patients with Crohn's disease. In their work, the metabolic syndrome was detected in 34 patients with ulcerative colitis (29.5%) and in 11 patients with Crohn's disease (27%). 31 UC patients (27%) showed a HOMA-IR rate > 2.5, which is similar to our study (29%).

Our findings are similar to other studies, indicating that especially in ulcerative colitis insulin resistance levels are higher than normal people. Although HOMA-IR index increases in all of the 3 groups were related to BMI, especially in Crohn's disease with BMI $\geq$ 25, the increase in HOMA-IR was statistically significant. As expected, HOMA-IR score, an index of insulin resistance, increases together with of BMI. Our findings revelaed that no relation was detected between HOMA-IR and disease activity and gender. As the insulin resistance was found to be higher in regard to the involvement region in ulcerative colitis compared to the control group. No relation was detected in Crohn's disease. In ulcerative colitis, 28 patients with involvement of left colon and its distal components, and 20 patients with extensive pancolonic involvement were compared using index of HOMA-IR. While the mean HOMA-IR levels were found to be 2.86 ± 0.66 in the left colon and distal involvement group, a mean rate of 2.06 ± 1.56 was instead detected in the pancolonic group. Pancolonic patients are more likely to be careful in their diets and tend to have poor appetite due to inflammation and weakness, which result from the catabolic process. In this study, it has been shown that the HOMA-IR score increased in patients with bowel diseases, especially in ulcerative colitis.

Conclusions

Patients with ulcerative colitis should be closely monitored for developing insulin resistance, metabolic syndromes, diabetes, and cardiovascular diseases. Consequently, all these diseases could produce additional morbidity and mortality in patients with ulcerative colitis.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethical Approval

Detailed information about the study design was shared with three different groups and ethics committee consent (number 4873) was taken from Umraniye Training and Research Hospital Ethic Committee.

Informed Consent

The informed consent was obtained by patients.

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Authors' Contribution

Data collection: RK and AND; design: TA; Statistic: AND and RK; writing and overview: TA and RK; table and figure: TA and AND.

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