Original Article

Metabolic Syndrome Frequency in Inflammatory Bowel Diseases

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ABSTRACT

Background/Aim: Metabolic syndrome (MetS) is a clinical condition characterized by central obesity, elevated triglycerides, low–high density lipoproteins, impaired fasting glucose, and hypertension. There is insufficient data on the prevalence of MetS in patients with inflammatory bowel disease (IBD). This study sought to determine the prevalence of MetS in a Turkish cohort of patients with IBD and the association between insulin resistance (IR) and the MetS parameters, in this population. **Patients and Methods:** A total of 177 patients over 18 years of age (62 with Crohn's disease (CD) and 115 with ulcerative colitis (UC)) were enrolled in the study. The presence of at least three criteria of the International Diabetes Federation (IDF) was accepted for the diagnosis of MetS. The Homeostasis Model Assessment (HOMA) was used to determine IR. HOMA values < 1 were considered normal and values > 2.5 indicated a high probability of IR. **Results:** MetS frequency was higher in patients n=34 (29.5%) with UC than in patients n=11 (17.7%) with CD ($P < 0.01$). MetS was detected in 12 of the 117 patients (10.3%) with IBD, under 45 years of age, and in 33 of 60 patients (55%) over 45 years of age. HOMA value in n=31 patients (27%) with UC was > 2.5. Body mass index, insulin ($P < 0.001$), waist circumference, fasting plasma glucose, leukocyte count ($P < 0.01$), triglycerides, C-reactive protein, and uric acid values ($P < 0.05$) were significantly higher in UC patients with IR than those without IR. **Conclusion:** Frequent occurrence of MS with increasing age in IBD, particularly in UC, showed the importance of early diagnosis and treatment of cardiovascular disease risk factors in the long-term follow-up of these diseases.

Key Words: Inflammatory bowel disease, insulin resistance, metabolic syndrome, obesity

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Metabolic syndrome (MetS) is defined as abdominal obesity, elevated blood pressure, glucose intolerance, and atherogenic dyslipidemia. Recognition of this syndrome is important in that it represents a prothrombotic and proinflammatory process.[1] İnflammatory bowel disease (IBD) is comprised of two major disorders, ulcerative colitis (UC) and Crohn's disease (CD). These disorders have distinct pathological and clinical characteristics. The pathogenesis of these diseases remains poorly understood.[2] Type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) may affect the disease course and prognosis in patients with IBD. Increased mortality has not been observed in the population-based studies.[3-8] Bernstein *et al*.,[9] reported an increased risk of cardiac artheroembolic disease in IBD. Obesity is known to increase the risk of developing colorectal cancer,[10,11] a serious concern for IBD patients with longstanding disease, who are already at risk for developing colorectal cancer.[12,13] Obesity may also influence disease activity in IBD patients.[14,15] Recent evidence suggests that in CD, hypertrophied mesenteric adipose tissue contributes to increased disease activity and development of complications.[16–19] In this study we sought to determine the prevalence of MetS in patients with IBD, as well as the association between IR and the MetS parameters in this population.

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PATIENTS AND METHODS

Patient population

A total of 177 patients, followed due to IBD diagnosis, aged 18 years and older (62 with CD, 28 women and 34 men, 36.7 ± 13.8 years of age; 115 with UC, 49 women and

66 men, 43.9 ± 13.5 years of age) were enrolled in the study. The study protocol was approved by the Local Ethics Committee (approval date and number: 02-06-2009, No: 57). The patients with known malignancy, thyroid disease, those receiving hormone replacement therapy, corticosteroids in the past six months, pregnant, with abdominal mass, ascites, chronic obstructive pulmonary disease (COPD), liver cirrhosis, Stage 3 – 4 cardiac failure or chronic renal failure were excluded.

Diagnosis of MetS

Patients with MetS, have been defined by the International Diabetes Federation (IDF) criteria. These criteria were based on the presence of central obesity (waist circumference ≥ 94 cm for men and ≥ 80 cm for women) and two or more of the following; blood pressure ≥130 / 85 mmHg (or treatment of previously diagnosed hypertension), fasting plasma glucose (FPG) ≥100 mg / dl (or previously diagnosed T2DM), raised triglycerides level ≥150 mg / dl (or specific treatment for this lipid abnormality), and reduced high density lipoprotein cholesterol (HDL-C) cholesterol < 40 mg / dl in males and <50 mg / dl in females (or specific treatment for this lipid abnormality).[20]

Sitting blood pressure measurements were performed with conventional mercury sphygmomanometers in both arms after at least 10 minutes of rest, using the Korotkoff Phase I and Phase V sounds. A second measurement was performed in the arm with a higher reading. The average systolic and diastolic blood pressure (SBP and DBP) measurements were calculated with the measurements at least three minutes apart. Waist circumference was measured at the smallest circumference between the rib cage and anterior superior iliac spine iliac crest, with the subject in the standing position and during slight expiration. Body mass index (BMI) was calculated using the Quetlet index (weight / height 2, kg/m^2).[21]

Biochemical measurements

The venous blood samples, taken after 12 hours of overnight fasting, were centrifuged (2500 rpm) and the sera were separated. Glucose, uric acid, total cholesterol (total-C), HDL-C, low-density lipoprotein cholesterol (LDL-C), and triglycerides were measured with enzymatic methods. Insulin was measured using an electrochemiluminescence immunoassay (ECLIA) (Roche E170). Insulin sensitivity was determined by Homeostasis Model Assessment (HOMA-IR).[22] HOMA values < 1 were considered normal and values > 2.5 indicated a high probability of IR.

Statistical analysis

Data were evaluated by the SPSS 15.0 statistical analysis software using Chi square, *t*-test, one way analysis of variance, Tukey test, and the Pearson correlation analysis.

RESULTS

One-hundred seventy seven patients with IBD were enrolled in this study, 115 (65%) with UC, and 62 (35%) with CD. The mean age of the patients with UC was 43.93 ± 13.59 years and the mean age of the patients with CD was 36.74 ± 13.88 years; 42.6% of the UC patients (n=49) were female (mean age 40.56 ± 12.79), 57.4% of the UC patients (n=66) were male (mean age 46.32 ± 14.39), 45.2% of the CD patients (n=28) were female (mean age 40.29 ± 14.55), and 54.8% of the CD patients (n=34) were male (mean age 33.82 ± 12.79). No significant difference was found between the duration of IBD, gender, and frequency of MetS ($P > 0.05$). Details of patient characteristics are shown in Table 1. MetS frequency was significantly higher in UC patients n=34 (29.5%) compared to CD patients n= 11 (17.7%) ($P < 0.01$). Comparison of patients in terms of the MetS criteria count is depicted in Table 2 and Figure 1.

MetS was confirmed in 12 of the 117 (10.3%) IBD patients, under 45 years of age, and in 33 of the 60 (55%) patients over 45 years of age ($P < 0.001$) [Table 3]. Cigarette smoking was significantly higher in CD patients compared to UC patients ($P < 0.001$). However, among the groups there was no difference in terms of alcohol usage.

Waist circumference values of UC patients were significantly higher, both in male ($P < 0.01$) and female patients ($P < 0.05$), than in the CD patients. In the UC patients, SBP and DBP ($P < 0.001$), BMI, total-C, LDL-C levels ($P < 0.01$), and HOMA levels ($P < 0.05$) were significantly higher than in CD patients. There was a positive correlation between BMI and waist circumference in male patients with UC and MetS criteria 3 and above (n=22) ($P < 0.01$), and in female patients (n=12) ($P < 0.05$).

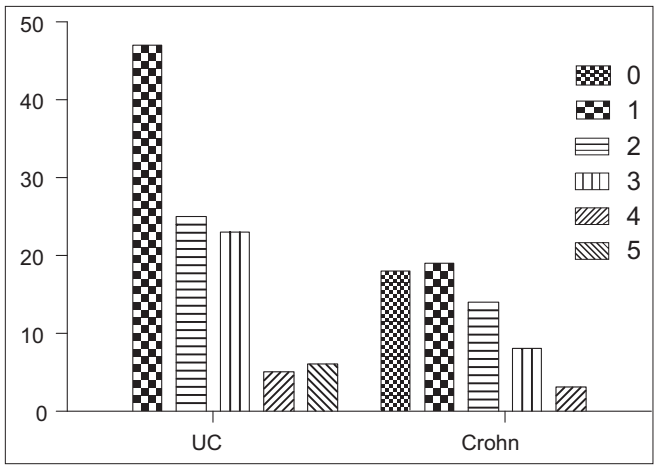

Figure 1: Comparison of patients with UC and CD in terms of the MetS criteria count

Table 1: Demographic, clinical and laboratory characteristics of patients with IBD

	Ulcerative colitis	Crohn's disease	*P* values
n	115	62	
Gender (female/male)	49/66	28/34	>0.05
Age, mean ± SD (Years)	43.93 ± 13.59	36.74 ± 13.88	>0.05
Disease duration, mean ± SD (months)	50.18 ± 55.59	47.71 ± 70.16	>0.05
Current smoker	22 (19.1%)	29 (46.8%)	<0.001
Alcohol usage	16 (13.9%)	12 (19.4%)	>0.05
BMI, mean ± SD (kg/m²)	26.27 ± 4.89	23.67 ± 5.18	< 0.01
Waist circumference (cm) Female	97.37 ± 12.55	89.82 ± 15.97	<0.05
Waist circumference (cm) Male	97.53 ± 12.69	90.47 ± 10.74	<0.01
SBP (mmHg)	122.43 ± 19.58	111.13 ± 20.96	<0.001
DBP (mmHg)	78.39 ± 11.93	71.45 ± 12.78	<0.001
FPG (mg/dl)	98.95 ± 32	91.87 ± 17.04	>0.05
Triglycerides (mg/dl)	121.26 ± 57.29	121.15 ± 63.47	>0.05
HDL-C (mg/dl) Female	61.92 ± 12.84	56.04 ± 15.56	>0.05
HDL-C (mg/dl) Male	48.53 ± 14.48	51.12 ± 14.93	>0.05
Insulin (µU/ml)	8.81 ± 5.30	7.34 ± 5.39	>0.05
HOMA-IR	2.20 ± 1.57	1.69 ± 1.27	<0.05

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, FPG: fasting plasma glucose, HOMA-IR: Homeostasis model assessment of insulin resistance

Table 2: Statistical difference between groups in terms of MetS criteria count

Groups	MetS criteria count						χ^2	*P*
	0	1	2	3	4	5		
Crohn's disease	29% (*n*=18)	30.6% (*n*=19)	22.6% (*n*=14)	12.9% (*n*=8)	4.8% (*n*=3)	0% (*n*=0)	17.43	0.004
Ulcerative colitis	7.8% (*n*=9)	40.9% (*n*=47)	21.7% (*n*=25)	20% (*n*=23)	4.3% (*n*=5)	5.2% (*n*=6)		

Table 3: Relationship between age and MetS frequency

Age group		Metabolic syndrome		χ^2	*P*
		Absent	Present		
Under 45 years of age	n	105	12	41.87	0.0001
	%	89.7	10.3		
Over 45 years of age	n	27	33		
	%	45	55		

MetS was detected in 10.3% of patients under 45 years of age and in 55% of patients over 45 years of age (*P*<0.001).

The Homeostasis Model Assessment (HOMA) value was ≥ 2.5 in *n*= 31 of the UC patients (27%) and in 16.1% of the CD patients (*n*=10). 24.5% (*n*=12) of the female and 28.8% (*n*=19) of the male UC patients had IR. 21.4% (*n*=6) of the female and 11.8% (*n*=4) of the male CD patients had IR. UC patients with IR had significantly higher BMI, insulin ($P < 0.001$), FPG, leukocyte count, waist circumference ($P < 0.01$), triglycerides, C-reactive protein (CRP), and uric acid levels compared to patients without IR ($P < 0.05$). Comparison of UC patients with IR and without IR is shown in Table 4.

C-reactive protein and leukocyte counts of patients were significantly high in CD patients ($P < 0.01$). In CD patients, BMI, FPG, leukocyte count ($P < 0.05$), and insulin values ($P < 0.001$) were higher in patients with ≥ 2.5 HOMA value. HDL-C values of female CD patients without IR were significantly higher than female patients with IR ($P < 0.05$).

DISCUSSION

MetS is a major worldwide health problem and is a risk factor for CVD and T2DM.[23] MetS increases the risk of cardiovascular morbidity thrice, morbidity three times, mortality two times and T2DM five times. The reason for the increased incidence and prevalence of MetS in children can be attributed to the obesity epidemic in this population.[24,25] MetS prevalence increases with abdominal obesity and is approximately 27% in the United States, 13% in France, 31 – 40% in Pakistan, 33 – 29% in Turkey, and 40% in India.[26,27]

Similar to many western populations, abdominal obesity and MetS prevalence are increasing in Turkey as well. In Turkey, MetS prevalence was 33.0% and 38.8%.[26,28] In a study carried out by the Metabolic Syndrome Association (METSAR), MetS prevalence was found to be 33.9% and it was 40% in women and 28% in men. Prevalence was 6.7% in the age group of 20 – 29 years and 43.5% in the age group of 60 – 69 years. MetS was 53% in coronary heart patients.[29] Even as prevalence increases with age and BMI, it decreases with increasing educational level and physical activity. It is also more frequently found in women.[25]

Table 4: Comparison of UC patients with and without insulin resistance

	IR+UC	IR-UC	*P* values
n	31	84	
Gender (female/male)	12/19	37/47	>0.05
Age, mean ± SD (years)	48.32 ± 13.01	42.31 ± 13.51	<0.05
Disease duration, mean ± SD (months)	52.97 ± 51.28	49.15 ± 57.35	>0.05
BMI, mean ± SD (kg/m²)	29.85 ± 5.75	24.95 ± 3.79	<0.001
WC (cm) Female	105.75 ± 10.217	94.65 ± 12.136	<0.01
WC (cm) Male	104.74 ± 15.369	94.62 ± 10.254	<0.01
SBP (mmHg)	128.06 ± 23.72	120.36 ± 17.52	>0.05
DBP (mmHg)	80.97 ± 14.45	77.44 ± 10.79	>0.05
FPG (mg/dl)	114.74 ± 57.07	93.12 ± 10.07	<0.01
Triglycerides (mg/dl)	140.94 ± 69.62	114.00 ± 50.58	<0.05
HDL-C (mg/dl) Female	59.83 ± 14.295	62.59 ± 12.473	>0.05
HDL-C (mg/dl) Male	45.00 ± 13.760	49.96 ± 14.675	>0.05
Insulin (μU/ml)	15.38 ± 5.27	6.39 ± 2.55	<0.001
Uric acid (mg/dl)	5.06 ± 1.36	4.47 ± 1.43	<0.05

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, FPG: fasting plasma glucose, HDL-C: High density lipoprotein cholesterol, WC: Waist circumference

There is a lack of data on the prevalence of MetS in patients with IBD. In a study reported in Japan, there was no difference in the prevalence in MetS in IBD patients compared to the general population over the age of 40 years.[30] This study found that MetS was more common in IBD patients with advancing age.

Higher MetS frequency in IBD patients, over 45 years of age, enrolled in the study could be explained by the addition of a long-term inflammatory effect to the current risk factors.

The etiology of IBD is unknown, but the condition seems to be the result of a combination of environmental, genetic, and immunological factors, where an uncontrolled immune response within the intestine leads to inflammation in genetically predisposed individuals.[31] Dysfunctions of the intestinal immune system and cross-reactivity against host epithelial cells have been implicated as major mechanisms by which inflammation occurs.[32]

Early atherosclerosis is a clinical feature common to several inflammatory and immunological diseases, in which atherothrombotic complications represent one of the most important causes of mortality and morbidity.[33] Parameters such as inflammation, and IR, which are considered clinical markers of early atherosclerosis, are accepted as predictors of cardiovascular events.[34,35]

A number of prospective studies indicate that those with CVD and impaired glucose metabolism have a significantly greater cardiovascular morbidity and mortality compared to those with normal glucose metabolism.[36] IR and hyperinsulinemia are considered the primary events that lead to atherosclerosis.[37] The role of insulin in the development of atherosclerosis could be direct – through the stimulation of vascular smooth muscle cell proliferation and arterial wall lipid deposition, or indirect – through promoting the development of hypertension and dyslipidemia.[38,39] Bregenzer *et al.* reported an increase in IR in CD.[35] Capristo *et al.* , however, found that glucose uptake in IBD was similar to that in the control group.[40] In our study, the HOMA value above or equal to 2.5 was found in 27% and 16.1% of UC and CD, respectively. The UC patients with IR had significantly higher BMI, insulin, FPG, leukocyte count, TG, CRP, uric acid levels, and WC values compared to patients without IR. BMI, FPG, leukocyte count, and insulin levels of the CD patients were high in those with HOMA values ≥ 2.5. HDL levels of female CD patients without IR were significantly higher compared to female CD patients with IR.

Often referred to as central or abdominal obesity, periomental or visceral excess fat is a component of MetS and is associated with the increase of CVD risk. Central obesity hyperinsulinemia is associated with clinical conditions such as IR, diabetic dyslipidemia, hypertension, albuminuria, and proinflammatory-prothrombotic proinflammatory and prothrombotic.[41,42] In a study where obese young women were enrolled, there was a correlation between waist circumference and both plasma insulin and IR.[43] Lifestyle changes to prevent CVD were expected to reduce not only the risk of CVD, but also the risk of dysplasia and colorectal cancer development in IBD patients.[10,11,44,45] Furthermore, a case report suggested that reducing body weight might also contribute to decreasing disease activity in UC.[46] Holtmann *et al.*,[47] recently showed improved outcomes in UC patients treated with azathioprine, with a lower BMI maintained under,[18] suggesting the benefit of body weight control in IBD patients. In our study, a positive correlation between BMI and waist circumference was established in male and female UC patients, with MetS criteria count ≥3. The BMI of UC and CD patients with IR was significantly higher compared to patients without IR. Furthermore, the waist circumference values of female and male UC patients with IR were significantly high compared to the female and male UC patients without IR.

Chronic inflammation is related to both MetS and future CVD. In recent years, markers of systemic inflammation and certain components of the hemostatic system have been found to predict atherosclerotic risk. CRP was found to be independently associated with body weight, IR, and SBP. White blood cell count and fibrinogen were associated with obesity and IR.[48]

C-Reactive protein is an inflammatory marker and is produced in the liver by the stimulation of cytokines

generated at IL-1, IL-6, and TNF-alpha. The association between MetS and CRP is related to the release of cytokines through the adipose tissue. IR can cause elevated levels of CRP release and this effect is similar to the effect of insulin on the hepatic acute phase protein synthesis.[49] Festa *et al.* revealed that chronic subclinical inflammation is a part of the IR syndrome.[50] Fröhlich *et al.* determined high levels of CRP and IL-6 in patients with MetS.[51]

The strong association between CRP levels and IR determined by the HOMA-IR formulation was revealed in a study evaluating the relationship between CRP level as an inflammatory marker and other CVD risk factors, which comprised of 1025 subjects aged between 35 and 60 years, without any known health condition.[52] Chronic activation of the innate immune system may also underlie the formation of MetS, and chronic inflammation can explain the formation of T2 DM and CVD as well.[48] The serum CRP level correlates with the BMI and the waist-to-hip ratio in both non-diabetes and patients with T2 DM[53] In our study, the CRP and leukocyte levels of UC patients with IR were significantly higher than those in patients without IR. In patients with CD, the leukocyte count was higher in those with HOMA value > 2.5. There was no difference between the BMI and waist circumference or CRP and leukocyte values in male and female patients with UC.

It is known that there is a relationship among elevated serum uric acid levels, CVD, hypertension, MetS, coronary artery disease, cerebrovascular disease, vascular dementia, pre-eclampsia, and kidney disease.[54] In subjects with high MetS risk, uric acid is thought to be the determinative variable for the development of T2DM.[55] In the eight-year prospective study by Kekalainen *et al.*,[56] it was found that while dyslipidemia, HT, and uric acid levels were associated with IR; hypertension and very-low-density lipoprotein cholesterol were associated with impaired first phase insulin secretion. In IR patients, plasma uric acid concentrations were higher due to the decrease of uric acid renal clearance. Nonetheless, the plasma uric acid level was not a very sensitive indicator of IR. Normal uric acid levels did not necessarily mean insulin sensitivity.[57] In our study, the uric acid levels of UC patients with IR were significantly higher than those without IR.

CONCLUSIONS

MetS is a preventable, but poorly recognized chronic inflammatory disease with high prevalence and usually treated inadequately. Insulin resistance is an important parameter in the relationship between MetS and CVD. Although, due to insufficient comparable worldwide data, this study may conclude the importance of MetS and IR in IBD patients. In terms of prevention of cardiovascular morbidity and mortality and avoiding colorectal cancer, strategies toward preventable risk factors that will increase insulin sensitivity, such as, weight control, normalizing lipid levels, and blood pressure, seem to be important issues in IBD treatment.

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