Serum Leptin Levels and Irritable Bowel Syndrome
A New Hypothesis

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Goals: This study was undertaken to investigate the relationship between serum leptin levels and the development irritable bowel syndrome (IBS).

Background: Stress has been known as an important causative factor in IBS. Various studies have indicated the relationship between serum leptin levels and stress levels. So searching the relationship between the production and level of this hormone and development of IBS may help to understand the pathophysiology of the disease.

Study: This was a case-control study. Eighty IBS patient and 80 controls were recruited. All participants were asked to fill in a questionnaire included demographic information and medical history and also a stress questionnaire. Serum leptin level was measured by enzyme-linked immunosorbent assay method. Chi-square, Student *t* test, Pearson correlation and logistic regression were used for investigating the relationships between variables.

Results: Mean serum leptin levels were 7.41 and 19.33 ng/mL in IBS and control groups, respectively ($P < 0.001$). Participants in IBS group had significantly higher stress levels than controls ($P < 0.001$). Multivariate logistic regression analysis showed that adjusted odds ratios (ORs) for serum leptin level (OR: 0.9; 95% confidence interval: 0.85-0.94) and stress level (OR: 1.15; 95% confidence interval: 1.09-1.23) were nearly the same as crude ones.

Conclusions: This study indicated the relationship between leptin and IBS for the first time. Our results show that serum leptin level is significantly lower in IBS group than controls and this relationship is independent of other variables such as stress levels, body mass index, etc. This may help in better understanding of the pathogenesis of IBS and consequently lead to the development of more effective treatments.

Key Words: irritable bowel syndrome, leptin, stress

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Irritable bowel syndrome (IBS) is a functional disorder of gastrointestinal system,[1] characterized by altered bowel habits and abdominal pain in the absence of detectable structural abnormalities.[2] Prevalence of IBS is 10% to 20% all over the world, 70% with present mild manifestations of the disease, 25% and 5% present on moderate and severe types, respectively.[2,3] The disease is more common in developed countries but its prevalence is increasing in developing world.[4] In the United States, 8 billion dollars is spent for this disease annually. IBS is diagnosed by ROME II criteria.[2] One may develop the disease on any period of life, for example, similar manifestations have been detected in children but investigating therapeutic methods in adults has some priority in research topics. According to recent research, women are more predisposing to IBS than men.[3]

Unfortunately, despite having high prevalence and so many social and economic complications, the etiology and pathogenesis of the disease has not been clearly known.[5–7] Psychologic stress,[8] female sex,[2,9] young ages,[2] abuse (physical and psychologic), neonatal maternal deprivation, neonatal colonic irritation (inflammatory stimuli), neonatal colonic pain (rectal distension),[10] *Blastocystis hominis*,[11] dysbiotic changes in the large and small intestines after enteric infections,[12] trauma,[5] and heredity[13] have been proposed as some probable etiologic factors of IBS.

The interface of psychiatry (anxiety disorders, depressive disorders, and somatoform disorders) and IBS has been well established,[9] with psychiatric comorbidity approaching 20% to 60%.[5] Stress is an important causative factor in IBS.[14] It remains unknown whether stress-related changes in gut function are mediated by altered autonomic efferent gut-specific innervation.[14] Patients with IBS show heightened visceral sensation, suggesting involvement of a different regulatory mechanism, either central or peripheral.[14]

Various studies have indicated that by increasing catecholamine and stress, serum leptin level changes significantly.[15,16] So, searching the relationship between the production and level of this hormone and development of IBS may help to understand the pathophysiology of the disease. Leptin (derived from Greek word leptus that means thin) is a peptide hormone and was discovered in 1994 for the first time.[15] This hormone weights 16 kd and is produced by obesity gene. Obesity gene is expressed in white fat, placenta, etc. It was known as modulator of receiving and consuming energy, and controlling body weight. Its function depends on its receptors in feeding center of hypothalamus.[16] Recent studies have indicated that leptin has various effects on other organs and body systems too; these include immune system, gynecology system, gastrointestinal system and specially central nervous system, and peripheral nervous system. Recently, leptin expression has been detected in gastric epithelium, but the physiologic role of gastric leptin remains unknown.[17]

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With regard to the above information, the theory of relationship between leptin and IBS can be offered. So, this study was undertaken to investigate this relationship for the first time.

MATERIALS AND METHODS

This was a case-control study. The study population was consisted on patients who were referred to gastroenterology clinic of 5th Azar Hospital (Gorgan, Iran) during period 2005 to 2006 and presented with symptoms compatible with IBS based on ROME II criteria,[2] identified by gastroenterologists (after exclusion of any disease proposed as differential diagnoses of IBS). Eighty of these patients were selected randomly. A consent form was taken and they were referred to Golestan Research Center of Gastroenterology and Hepatology. In this center, the study was explained to them and they were asked to fill in questionnaire included demographic information, medical history, and some selected clinical manifestations. Eighty healthy controls were selected from individuals who referred to optometric clinic of 5th Azar Hospital. Controls had no history of gastrointestinal disorders and in clinical examination done by a gastroenterologist; they were free of any gastrointestinal signs and symptoms. A consent form was taken again and they were also asked to fill in the questionnaire. Individuals with chronic diseases (diabetes mellitus, hypertension, asthma, renal and hepatic failure, history of gastrointestinal surgery, anorexia, psychiatric problems treated by antipsychotic drugs) and also pregnant and breast feeding women were excluded from both case and control groups. With regard to confounding effect of stress in the relationship between leptin level and IBS, stress levels were evaluated in case and control groups by standard perceived stress scale 10 (Perceived Stress Scale 10) questionnaire.[18] It includes 10 questions which are of a general nature and hence are relatively free of content specific to any subpopulation group. It has been translated into Persian and the reliability of the translated version was evaluated by test retest method during a pilot study ($\kappa = 0.76$). In the next step, 5 cm^3 of (8 h) fasting blood sample was taken from the case and control groups in morning. Serum samples were preserved in $-70^{\circ}C$ till the time of processing. Leptin level was measured by enzyme-linked immunosorbent assay methods using Biovendor leptin kit (Czech Republic). Data were entered into the computer and were analyzed by SPSS13 software. Chi-square, Student *t* test, Pearson correlation, and logistic regression were used for investigating the relationship between variables. *P* values of less than 0.05 were considered as significant. This project was approved by ethics committee of Golestan University of Medical Sciences.

RESULTS

Eighty IBS cases with mean ± SD age of 31.83 ± 10.89 years and 80 controls with a mean ± SD age of 32.38 ± 13.55 years participated in our study. Participants in IBS group had alternate constipation and diarrhea type IBS. The severity of IBS in almost all of them was moderate. The characteristics of participants and the comparison between 2 groups are shown in Table 1. No significant relationship was found among the distribution of age, body mss index (BMI), sex, education level, and marital status between IBS and control groups (Table 1).

TABLE 1. Sociodemographic Properties of IBS Patients and Controls

Variables	IBS Group	Control Group	*P*
Mean of age (y)	31.83	32.38	0.78*
Mean of BMI (kg/m^2)	25.1	25	0.89*
Sex			
Male	42.5%	38.8%	0.75†
Female	57.5%	61.2%	
Education			
High	63.8%	70.9%	0.4†
Low	36.2%	29.1%	
Marital status			
Married	68.8%	75%	0.48†
Single	31.2%	25%	
Mean of stress level (PSS scores)	21.74	15.31	< 0.001*
Mean of serum leptin levels (ng/mL)	7.41	19.33	< 0.001*

*Student *t* test.
†χ^2 test.
BMI indicates body mass index; IBS, irritable bowel syndrome; PSS, Perceived Stress Scale.

Participants in IBS group had significantly higher stress levels than controls ($P < 0.001$) (Table 1). In the other hand, serum leptin levels were significantly lower in IBS group than the other one ($P < 0.001$) (Table 1). The normal range for serum leptin in our laboratory was 13.48 to 19.67 ng/mL. The mean of serum leptin level in controls was within normal range. But in IBS cases it was lower than normal. Overall, there was a significant negative correlation between serum leptin levels and stress levels in all participants ($r = -0.17$, $P = 0.03$); but it was not significant separately within each of the 2 groups. Table 2 shows the relationship between serum leptin and other variables separately in IBS and control groups. In both groups, serum leptin levels were significantly higher in

TABLE 2. Relationship Between Serum Leptin and Other Variables Separately in IBS and Control Groups

	IBS Group		Control Group	
Variables	Mean ± SD of Leptin Level (ng/mL)	*P**	Mean ± SD of Leptin Level (ng/mL)	*P**
Sex				
Male	3.92 ± 3.1	< 0.001	14.57 ± 11.82	0.04
Female	10 ± 7.6		22.34 ± 17.32	
Education				
High	8.04 ± 6.99	0.27	18.75 ± 15.80	0.71
Low	6.31 ± 6.39		20.21 ± 16.25	
Marital status				
Married	6.14 ± 5.38	0.26	25.05 ± 18.39	0.06
Single	7.99 ± 7.31		17.42 ± 14.51	
BMI (kg/m^2)				
≤24.5(Normal/underweight)	5.03 ± 5.04	0.002	21.11 ± 16.14	0.4
> 24.5(Overweight/obese)	9.57 ± 7.48		18.08 ± 15.61	

*Student *t* test.
BMI indicates body mass index; IBS, irritable bowel syndrome.

TABLE 3. Relationship Between Stress Levels (Mean of PSS Scores) and Other Variables Separately in IBS and Control Groups

	IBS Group		Control Group	
Variables	**Mean ± SD of Stress Levels**	***P****	**Mean ± SD of Stress Levels**	***P****
Sex				
Male	20.35 ± 7.5	0.12	12.35 ± 5.1	0.001
Female	22.76 ± 5.7		17.18 ± 6.8	
Education				
High	21 ± 7.1	0.16	16.14 ± 6.8	0.1
Low	23.03 ± 5.5		13.43 ± 6.1	
Marital status				
Married	21.62 ± 6.8	0.81	14.93 ± 6.6	0.38
Single	22 ± 6.3		16.45 ± 6.8	
BMI (kg/m^2)				
≤24.5 (Normal)	22.05 ± 6.9	0.69	17.09 ± 6.5	0.04
> 24.5 (Overweight/obese)	21.45 ± 6.4		14.06 ± 6.5	

*Student *t* test.
BMI indicates body mass index; IBS, irritable bowel syndrome.

females than males. Serum leptin level was not significantly related with education level and marital status in the 2 groups. In IBS group, serum leptin level had a significant positive correlation with BMI ($r = 0.37$; $P = 0.001$) but the association between these variables in control group was not significant ($r = -0.1$; $P = 0.34$). Relationships between stress levels and other variables separately in IBS and control groups are shown in Table 3. Females had more stress than males in both groups, although the difference was not significant in IBS group. No significant relationship was found between stress levels and education, and marital status in IBS and control groups. Individuals with normal weight (BMI ≤24.5 kg/m^2) had higher stress levels in both cases and control groups, but the relationship was not significant in first one. We used multivariate logistic regression analysis to assess if BMI and stress levels had any confounding effects on the relationship between serum leptin levels and IBS. BMI was excluded from the model because of nonsignificant relationship. Adjusted odds ratios for serum leptin level and stress level were nearly the same as crude ones (Table 4).

DISCUSSION

IBS is one of the most common gastrointestinal disorders, characterized by abdominal pain and disturbed defecation that cannot be explained by structural abnormalities.[10] Although IBS symptoms (visceral pain, increased gut permeability, motility alterations)[10] have been clearly known, the etiology has been poorly understood. We conducted this study to determine the relationship between serum leptin levels and IBS.

We did not find significant differences in age, sex, BMI, education level, and marital status between IBS and control groups (Table 1). So, we can exclude the confounding effects of these variables on the relationship between serum leptin levels and the development of IBS.

Stress levels in IBS group were significantly more than controls. Other studies suggested similar findings.[5,14] Serum leptin levels were significantly lower in IBS than the other group. Unfortunately, we did not find any similar study in the literature review.

Overall, there was a significant negative correlation between serum leptin levels and stress levels in all participants. Results from 1 study also showed a reduction in leptin plasma levels during academic stress as compared with baseline. It seems that stress exerts a negative feedback mechanism over leptin production.[19,20]

In both groups, serum leptin levels were significantly higher in females than males. This was in agreement with other studies indicated that women had higher baseline endogenous leptin levels than men and that the slope of the correlation between serum leptin concentration and BMI was steeper in women.[15,21–26]

In IBS group, serum leptin levels were significantly higher in overweight/obese individuals than normal/underweight ones (Table 2). Previous studies showed significant positive correlation between individuals BMI and serum leptin levels ($r = 0.784$, $P < 0.001$).[27,28] Other ones suggested that serum leptin levels correlate highly with percentage of body fat, increasing exponentially with increasing BMI.[15,16,21,26,29] We did not find significant relationship between serum leptin levels and BMI in control group.

Females had higher stress levels than males in both groups, although the difference was not significant in IBS group (Table 3). Other studies reported similar results.[30] Stress levels were higher in normal/underweight individuals than overweight/obese ones but the difference in IBS groups was not significant. Karelis et al[31] found no significant relationship between stress and BMI.

We used multivariate logistic regression analysis to assess if BMI and stress levels had any confounding effects on the relationship between serum leptin levels and IBS. BMI was excluded from the model because of nonsignificant difference. Adjusted odds ratios for serum leptin level and stress level were nearly the same as crude ones (Table 4). This shows that serum leptin level is significantly lower in IBS group than controls and this relationship is independent of other variables such as stress levels, BMI, etc.

TABLE 4. Relationship Between BMI, Serum Leptin Level and Stress Level, and Irritable Bowel Syndrome

Variables	IBS Group	Control Group	Crude Odds Ratio*	CI 95%	Adjusted Odds Ratio*	95% CI
BMI (kg/m^2)	25.1 ± 4.75	25 ± 4.99	1.05	0.97-1.14	—	—
Serum leptin level (ng/mL)	7.41 ± 6.79	19.33 ± 15.8	0.89	0.84-0.93	0.9	0.85-0.94
Stress level (PSS)	21.74 ± 6.62	15.31 ± 6.64	1.16	1.09-1.24	1.15	1.09-1.23

*Multivariate logistic regression analysis.
BMI indicates body mass index; CI, confidence interval; IBS, irritable bowel syndrome; PSS, Perceived Stress Scale.

Results from animal experimentation suggest a 2-way interaction between leptin and the sympathetic nervous system, with leptin causing sympathetic activation and conversely, the sympathetic system imposing a feedback regulatory inhibitory mechanism over leptin release.[32] In contrast, down-regulation of neuropeptide Y expression in hypothalamus by leptin, results in increased sympathetic nervous system outflow.[33] In addition, leptin modifies the activity of the hypothalamo-pituitary axis in the adult rodent and inhibits the production of glucocorticoids from human and rat adrenals in vitro.[18,34] As leptin and cortisol show an inverse circadian rhythm, it has been suggested that a regulatory feedback mechanism exist between the 2 hormones.[35] Interactions between brain and gut have been known as an important underlying pathophysiologic pathway in IBS.[36] Recently, Piche et al[37] showed that fatigue had a significant correlation with serum leptin levels in IBS cases. Regarding the above-mentioned facts and also our results, it can be concluded that leptin may alter bowel movement and consequently play a role in pathomechanism of IBS by affecting sympathetic system and adrenal catecholamine release. Complementary studies are needed to prove this relationship and clearly to determine the role of leptin in development of IBS.

The limitation of this study was due to its design (case-control). That means we evaluated the relationship between IBS, leptin and stress contemporary, so causality could not be assessed in this study and more researches are needed to clarify the cause-effect relationship in this setting.

CONCLUSIONS

This study indicated the relationship between leptin and IBS for the first time. We found that serum leptin levels are significantly lower in IBS patients than control group. Our findings may help in better understanding of the pathogenesis of IBS and consequently lead to development of more effective treatments.

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