International Archives of Medical Research
11:1 (2019) 27-34

ORIGINAL RESEARCH PAPER

Can serum level of prolactine be a predictor of the diagnoses of irritabl bowel syndrome?

Müslüm GÜNEŞ[1]

[1] *Department of Internal Medicine, Cınar State Hospital, Cınar, Diyarbakır, Turkey*

Abstract

Background: *To determine serum prolactin levels in IBS patients and to investigate the relationship between C-IBS and D-IBS patients and healty control group PRL levels.*

Method: *In the present study, 100 patients diagnosed with IBS and 100 healthy individuals who visited the hospital for routine check-up were included. IBS was diagnosed based on the Rome III criteria, and patients with IBS-C, patients with IBS-D and healthy controls were classified into groups 1, 2 and 3, respectively. Fasting venous blood samples were collected from all the participants between 08:00–10:00 a.m. to determine their serum PRL levels.*

Results: *Of the total participants, 28 (14.0%) were excluded, and the remaining 82 (47.7%) healthy controls and 90 (52.3%) patients with IBS were included in the study. Mean serum PRL levels were 10.47 ± 5.15 ng/ml, 14.33±5.10 ng/ml, 7.38±2.36 ng/ml and 12.17 ± 5.36 ng/ml in patients with all IBS, group 1, group 2 and group 3, respectively ($p < 0.05$). Mean serum PRL level of group 1 was significantly higher than that of group 2 (95% confidence interval [CI]: 4.626–9.267; $p < 0.001$).*

Conclusion: *A statistically significant correlation was observed between serum PRL levels and presence of IBS. Thus, serum PRL level can be possibly used as a low-cost and feasible marker for the diagnosis of IBS, despite the low sensitivity and specificity. Furthermore, future studies demonstrating an improvement in the symptoms of IBS with treatments targeting serum PRL levels will be exciting.*

Keywords: *Irritable bowel syndrome, prolactin, constipation*

* Corresponding author: E-mail: muslumgunes21@gmail.com, Tel.: +90 412 5112399 , Fax: +90 412 5112424

Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterised by symptoms such as chronic abdominal pain, changes in intestinal habits (constipation and/or diarrhoea), bloating and incomplete evacuation [1,2]. Moreover, it is accompanied with a disturbance in the intestinal motility without abnormalities in routine laboratory tests [3]. The prevalence of IBS is approximately 6%–22%, although it varies between the east and West countries . It has a female predominance with a female–male ratio of 2:1[4–6].

Although the etiology of IBS is unknown, intestinal dysmotility, increased visceral sensitivity and bacterial reproduction, food sensitivity and genetic factors have been suggested as probable causes [7,8]. An impaired parasympathetic function and sympathovagal balance may be involved in the pathogenesis of IBS [9]. IBS is diagnosed based on the Rome criteria, which depends on gaita form and defecation pattern [10,11]. According to the criteria, IBS is further categorised as constipation-dominant (IBS-C), diarrhoea-dominant (IBS-D) and mixed IBS subtypes [12–14].

Prolactin (PRL), a peptide hormone, is primarily secreted by the lactotropic cells in the anterior pituitary gland, and its secretion is regulated by the hypothalamic hormones and dopamine [15]. It may also be secreted from sites containing immune cells,such as lymphocytes[16]. In addition to playing key roles in reproduction and lactation, PRL is important in immune regulation, as it is a strong cytokine [17]. PRL secretion increases in pregnancy, breastfeeding and stress.

The pathogenesis of IBS is not known exactly, also there is no marker to be used in diagnosis[18]. But ıt is known that some intestinal hormones increase in IBS. Cholecystokinin (CCK) is the one of these hormones. In some studies, CCK levels were found to be high in IBS patients [19]. Furthermore, high CCK levels in patients with IBS reportedly lead to an increase in serum PRL levels by increasing the prolactin releasing peptide (PrRP) levels [20].

The aim of this study was to determine serum PRL levels in patients with IBS and to investigate the relationships between the patients with IBS-C, patients with IBS-D and healthy controls, based on their serum PRL levels. We hypothesised that serum PRL levels can be used as a marker for the diagnosis of IBS.

Materials and Methods

The study was conducted at the Cinar State Hospital, Diyarbakir, Turkey. It was approved by the ethics committee of Gazi Yasargil Training and Research Hospital (decision no:189/2018) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all the participants included in the study.

Patients aged between 18 and 60 years exhibiting IBS symptoms for at least 1 year were included in the study. Patients with diseases such as hypertension, diabetes, organic bowel disease and with those involving the pituitary, thyroid, liver, kidney and heart; pregnant women; breastfeeding mothers and individuals using drugs that affect serum PRL levels, were excluded from the study.

In this prospective cross-sectional study, patients who reported to the internal medicine outpatient clinic of our hospital with complaints for at least 1 year were diagnosed with IBS, based on the Rome III criteria [21]. Patients with psychiatric or organic bowel diseases were screened for a definite diagnosis. A total of 90 patients with IBS and 82 healthy controls who visited the hospital for routine check-up were included in the study. Patients with IBS-C, patients with IBS-D and healthy controls were classified into groups 1, 2 and 3, respectively.

Fasting venous blood samples were collected from all the participants between 08:00–10:00 a.m. These were placed in standard tubes and centrifuged. Serum PRL levels were determined in our laboratory using the fourth-generation device (Abbott ARCHITECT i1000SR Immunoassay Analyser, California, USA) and the original kits (Abbott ARCHITECT Prolactin) provided by the manufacturer, with the normal range for serum PRL level in the device being 5–26 ng/ml.

Statistical analysis

We performed a post hoc analysis of serum PRL levels among the groups. Our study power was 100% with an α error of 0.05. The G Power version 3.1.7 was used for sample size analysis. The data were summarised as the mean and standard deviations (SD) and as percentages for discrete variables. The Kolmogorov–Smirnov one-sample test was used for the assumption of normal distribution of continuous variables; therefore, the central tendency was expressed as the mean (± SD). Continuous variables were compared using Mann–Whitney Utest and Kruskal–Wallis test. Demographic data were analysed by descriptive statistics. Spearman correlation analysis was used to determine the correlation between the age of the participants and their serum PRL levels. Receiver operating characteristic (ROC) analysis and the area under the curve (AUC) were used to examine the patients' serum PRL levels to predict presence of IBS. Sensitivity and specificity values were calculated and the optimal cut-off levels for serum PRL were defined. Differences were considered significant at $p < 0.05$. Statistical analysis was performed using the SPSS 22 (Chicago, Illinois, USA).

Result

Of the total 200 participants enrolled in the study, 28 (14%) were excluded. Thus, the study included 82 participants (47.7%) in group 3 (healty controls) and 90 (52.3%) patients with IBS, further divided into groups 1 and 2 comprising patients with IBS-C and IBS-D, respectively. The characterisitics of all patient groups are shown in Table 1. Mean age of all the participants was 32.07 ± 11.62 (18–60) years, with 89 (51.7%) and 83 (48.3%) of them being males and females, respectively.

Table 1 Demographic data of the patients. Data are presented as the median or number of patients (%).

Characteristic	**Group 1 (IBS-C)**	**Group 2 (IBS-D)**	**Group 3 (HC)**
Age (year)	34.25±11.47	35.54±11.47	28.90±11.06
Gender n (%) Female	26 (65)	20 (40)	43 (52.4)
Male	14 (35)	30 (60)	39 (47.6)
Prolactin Values (ng/ml)	14.33±5.10	7.38±2.36	12.17±5.36
Total n (%)	40 (23.3)	50 (29)	82 (47.7)

mean ± standard deviation; n : Patient number; C-IBS: Constipation dominant Irritable bowel syndrome; , D-IBS: diarrhoea dominant Irritable bowel syndrome; HG: Healty group.

Mean serum PRL levels were 10.47 ± 5.15 ng/ml, 14.33±5.10 ng/ml, 7.38±2.36 ng/ml and 12.17 ± 5.36 ng/ml in patients with all IBS, group 1, group 2 and group 3, respectively ($p < 0.05$). Mean serum PRL level was significantly higher in group 1 than in group 3 ($p < 0.05$). Furthermore, mean serum PRL level in group 1 was significantly higher than in group 2 (95% confidence interval [CI]: 4.626–9.267; $p < 0.001$; Table 2). Additionally, there was a statistically significant correlation between the age of the participants and their serum PRL levels ($r = -0.187$, $p < 0.017$).

Table 2 Comparison of groups according to prolactin levels

Groups		**Mean Difference**	**p**	**95% Confidence Interval (Lower-Upper)**
Group 1	Group 2	6.9465	0.001	4.626-9.267
	Group 3	2.1557	0.05	0.046-4.266
Group 2	Group 3	-4.7908	0.001	-6.754--2.828

Table 3 Multivariate Linear Regression Model Patients to predict prolactine values according to independent variables (Age, Gender, Presence of IBS, Study groups)

Characteristics	**Regression coefficeint**	**p**
Constant	15.437	< 0.001*
Age	-0.118	0.082
Gender	-0.197	0.003*
Presence of IBS	0.990	< 0.001*
Study groups (1,2,3)	-0.982	< 0.001*

ROC analysis for predicting IBS demonstrated that the AUC for serum PRL levels was 0.593 (95% CI: 0.507–0.679; $p < 0.05$; Figure 1), and the optimal cut-off level was 9.75 ng/ml, with a sensitivity and specificity of 57.3% and 56.6%, respectively.

Gender of the participant, presence of IBS and study groups (control, IBS-D, IBS-C) were found to be predictors of serum PRL levels, according to the multivariate linear regression model (adjusted $R2 = 0.291$, $R 2 = 0.555$, $R2 = 0.308$, respectively; $F = 18.599$; $p < 0.01$). Thus, the presence of IBS was positively correlated with serum PRL levels ($p < 0.001$) (Table 3). Likewise, gender of the participant and the study groups were positively correlated with serum PRL levels ($p = 0.003$ and $p < 0.001$, respectively).

Fig. 1 Receiver operating curves (ROC) for prolactine values to predict the diagnoses of IBS.: AUC:.593 (95% CI:0.507-0.679; p<0.05)

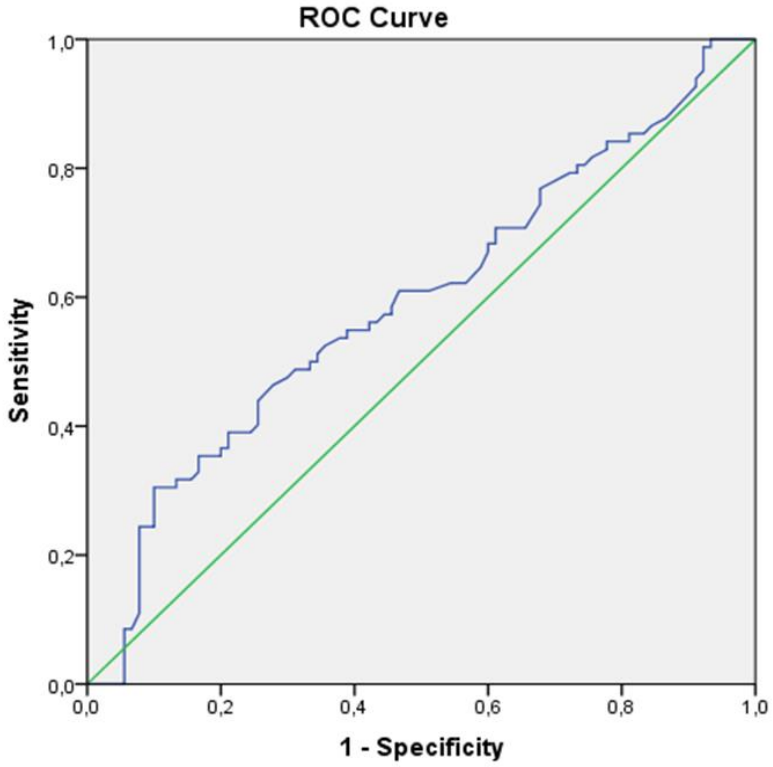
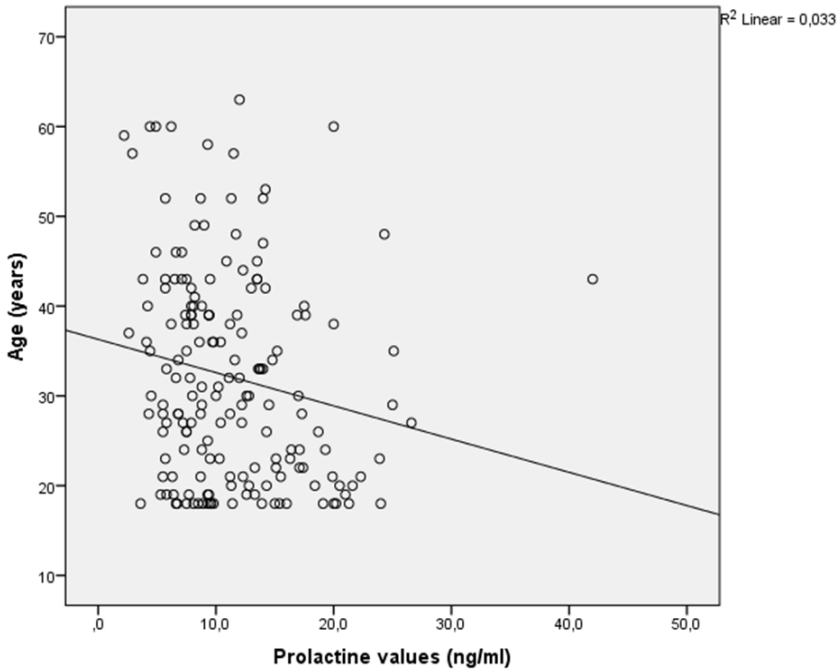


Fig. 2 The correlation of age of patients and prolactine values . (r = -0.187, P <0.017)



Discussion

In the present study, we observed that serum PRL levels in patients with IBS-C were significantly higher than those in patients with IBS-D ($p < 0.001$). We also noted a significant difference between serum PRL levels in patients with IBS-C and those in healthy controls ($p < 0.05$). Furthermore, serum PRL levels were significantly lower in patients with IBS-D than in the healthy controls ($p < 0.001$).

As IBS is common across the world, people suffering from this disease are frequently referred to health institutions [22]. Consequently, doctors perform numerous blood tests and use imaging methods to exclude organic and other functional diseases. These procedures are costly and time-consuming for patients [23]. To overcome these drawbacks, it is necessary to aid the diagnosis of IBS with rapid, rational and inexpensive tests. Hence, more studies are needed to recognise the hormones and mediators involved the pathophysiology of IBS. The level of one of these hormones, PRL, is affected in many physiological and pathological conditions. Therefore, the use of serum PRL levels in the diagnosis and differentiation of the subtypes of IBS has been a topic of interest for some researchers.

Currently, there is a limited number of studies in the literature regarding IBS and serum PRL levels. In an earlierstudy comparing serum PRL levels in patients with IBS with those in healthy controls, no significant difference was evident [24]. Although high urine catecholamine levels were observed in patients with diseases associated with stress, such as IBS, there was no increase in serum PRL levels, despite PRL being considered as a stress hormone [25]. In this study, a different result was found according to our study results. Because serum PRL levels were examined without discriminating IBS patients as C-IBS and D-IBS group. Since constipation and diarrhea have the opposite pathophysiological mechanism that PRL levels are expected to be different.We found that serum Prolactin levels of total IBS patients were lower than control group. PRL levels were determined by differentiating C-IBS and D-IBS groups and C-IBS group had significantly higher serum PRL levels than D-IBS group. This difference can be attributed to stimulation of PRL secretion by intestinal hormones or mediators, such as CCK, which affect intestinal motility in IBS.

CCK hormone is known to have an effect on intestinal motility. Studies have reported high CCK levels in patients with IBS. In a related study, CCK levels in patients with IBS were compared with those in healthy controls, and plasma CCK levels were observed to be significantly higher in patients with IBS [19]. However, no significant difference was found among the IBS subtypes. Therefore, these results indicate that CCK does not play a role in determining the subtypes of IBS [19]. Furthermore, recent studies suggest a strong correlation between CCK and PrRP levels. Since the peripheral application of CCK has been shown to activate neurons expressing PrRP [20]. this may lead to a change in PRL levels in patients with IBS. In another study, psychological symptoms and PRL levels in patients with IBS subtypes were compared with those in healthy controls, and it was found that patients with IBS-C had higher serum PRL levels than healthy controls and patients with IBS-D [12]. They also noted that patients with IBS-C were psychologically more depressed and anxious. Since emotional stress is associated with increased serum PRL levels, it is expressed as one of the causes of PRL increase in patients with IBS-C [12]. Furthermore, this finding is similar to the high PRL levels observed in patients with IBS-C in our study. In the literature, a case with IBS-C and hyperprolactinemia has been reported, wherein IBS was reported to be recovered after treating hyperprolactinemia [26]. This result supports the findings of our study, and therefore, a relationship between IBS and PRL is evident.

Thus, according to the results of this study, we suggest that high CCK levels may affect intestinal motility and lead to IBS. Furthermore, high CCK levels can increase serum PRL levels by stimulating PrRP, which indeed, justifies the high serum PRL levels observed in patients with IBS-C in our study.

The study was a single centre study, had insufficient number of patients and the mixed group İBS was not included. In addition to the Rome III criteria for the diagnosis of IBS, invasive methods, such as endoscopy and colonoscopy, may sometimes be required for a differential diagnosis. However, no further investigations were performed to establish a diagnosis in the patients included in the study.

Conclusion

Presently, there is no biomarker for the diagnosis of IBS. Serum PRL level can be considered as a low-cost and feasible marker for the diagnosis of IBS; however, controlled studies with larger series of patients are required. Furthermore, future studies demonstrating an improvement in the symptoms of patients with IBS by treatments targeting serum PRL levels will be exciting.

References

1. Drossman DA. Irritable bowel syndrome and sexual/physical abuse history. Eur J Gastroenterol Hepatol 1997;9:327–30.

2. Talley NJ, Spiller R. Irritable bowel syndrome: a little understood organic bowel disease? Lancet 2002;360:555–64

3. Thompson WG. Irritable bowel syndrome: a management strategy. Best Pract Res Clin Gastroenterol 1999;13:453–60.

4. Kang JY. Systematic review: The influence of geography and ethnicity in irritable bowel syndrome. Aliment Pharmacol Ther 2005.

5. Müller-Lissner SA, Bollani S, Brummer RJ, Coremans G, Dapoigny M, Marshall JK, et al. Epidemiological aspects of irritable bowel syndrome in Europe and North America. Digestion 2001.

6. Chey WD, Kurlander J, Eswaran S. Irritable Bowel Syndrome. JAMA 2015;313:949.

7. Schmulson MW, Chang L. Diagnostic approach to the patient with irritable bowel syndrome. Am J Med 1999;107:20–6.

8. Svendsen JH, Munck LK, Andersen JR. Irritable Bowel Syndrome–Prognosis and Diagnostic Safety. Scand J Gastroenterol 1985;20:415–8.

9. Liu Q, Wang EM, Yan XJ, Chen SL. Autonomic functioning in irritable bowel syndrome measured by heart rate variability: A meta-analysis. J Dig Dis 2013.

10. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional Bowel Disorders. Gastroenterology 2006.

11. Thompson WG. Irritable bowel syndrome: Guidlines for the diagnosis. Gastroenterol Int, 1989:92–95.

12. Eriksson EM, Andrén KI, Eriksson HT, Kurlberg GK. Irritable bowel syndrome subtypes differ in body awareness, psychological symptoms and biochemical stress markers. World J Gastroenterol 2008;14:4889.

13. Saha L. Irritable bowel syndrome: Pathogenesis, diagnosis, treatment, and evidencebased medicine. World J Gastroenterol 2014;20:6759.

14. Mearin F, Balboa A, Badía X, Baró E, Caldwell E, Cucala M, et al. Irritable bowel syndrome subtypes according to bowel habit. Eur J Gastroenterol Hepatol 2003;15:165–72.

15. Shelly S, Boaz M, Orbach H. Prolactin and autoimmunity. Autoimmun Rev 2012;11:A465-70.

16. Ben-Jonathan N, Mershon JL, Allen DL, Steinmetz RW. Extrapituitary prolactin: distribution, regulation, functions, and clinical aspects. Endocr Rev 1996;17:639–69.

17. Vera-Lastra O, Jara LJ, Espinoza LR. Prolactin and autoimmunity. Autoimmun Rev 2002;1:360–4.

18. Spiller RC. Potential Biomarkers. Gastroenterol Clin North Am 2011;40:121–39.

19. Zhang H, Yan Y, Shi R, Lin Z, Wang M, Lin L. Correlation of Gut Hormones with Irritable Bowel Syndrome. Digestion 2008;78:72–6.

20. Lawrence CB, Ellacott KLJ, Luckman SM. PRL-releasing peptide reduces food intake and may mediate satiety signaling. Endocrinology 2002.

21. Drossman DA. The Functional Gastrointestinal Disorders and the Rome III Process. Gastroenterology 2006;130:1377–90.

22. Lovell RM, Ford AC. Global Prevalence of and Risk Factors for Irritable Bowel Syndrome: A Meta-analysis. Clin Gastroenterol Hepatol 2012.

23. Inadomi JM, Fennerty MB, Bjorkman D. The economic impact of irritable bowel syndrome. Aliment Pharmacol Ther 2003;18:671–82.

24. Sperber AD, Weisberg I, Skibin A, Neumann L, Fich A, Buskila D. Serum Interleukin1, Interleukin-2, Interleukin 6, and Prolactin Levels Are Not Associated with the Severity of Disease in Patients with the Irritable Bowel Syndrome, with or Without Concomitant Fibromyalgia. J Musculoskelet Pain 1999;7:15–27.

25. Heitkemper M, Jarrett M, Cain K, Shaver J, Bond E, Woods NF, et al. Increased urine catecholamines and cortisol in women with irritable bowel syndrome. Am J Gastroenterol 1996.

26. Seretis C, Seretis F, Liakos N, Pappas A, Keramidaris D, Gourgiotis S, et al. Constipation-Predominant Irritable Bowel Syndrome Associated to Hyperprolactinemia. Case Rep Gastroenterol 2011;5:523–7.