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Predictors of abdominal pain severity in patients with constipation-prevalent irritable bowel syndrome

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Abstract

Background: Symptoms of irritable bowel syndrome (IBS) have been associated to altered colonic motility and sensation. Smoking affects pain perception and is a risk factor in the development of post-infectious IBS, but its effect on abdominal pain and colonic transit remains to be elucidated in IBS.

Methods: Forty patients with IBS-C and 28 with IBS-M were selected based on Rome IV criteria. Colonic transit time was studied and smoking habit was recorded. Presence of mild or severe abdominal pain and the prevalent pain characteristics (diffuse or localized, chronic or acute, with cramps or gradually distending) were recorded. Data were analyzed by univariate and stepwise multiple logistic regression analysis to verify the risk association between pain and all other variables.

Results: IBS-C patients had a longer transit time in the right colon and scored more chronic pain than IBS-M patients. When severity of abdominal pain was used as discriminating factor, a significant number of subjects reporting severe pain were males and smokers (16/30 vs. 4/38 and 20/30 vs. 4/38, both $p<0.001$). Multivariate analysis confirmed that smoking was an independent factor associated with severe abdominal pain (OR 14.3, CI 2–99, p=0.007). Smoking was not associated with colonic transit times and colonic transit was not associated with IBS symptoms' severity (both p=N.S.)

Conclusions: Smoking was the only factor independently associated with severe abdominal pain. As smoking does not seem to affect colonic transit time, we suggest that smoking may influence visceral perception and symptoms severity in IBS patients.

Keywords: abdominal pain; colonic transit; constipation; irritable bowel syndrome; smoking.

Introduction

Irritable bowel syndrome (IBS) is common worldwide, being one of the most frequently encountered chronic functional gastrointestinal disorders (FGIDs). It is characterized by the presence of abdominal pain or discomfort and altered bowel habit in the absence of structural and/or biochemical abnormalities that might explain these symptoms [1]. Although the presence of diarrhea or constipation is relevant to guide diagnostic and therapeutic choices, abdominal pain represents the hallmark symptom of IBS [2] as it is associated with patients' overall distress [3, 4], and it is more strongly related to the impairment in quality of life (QOL) and to the interferences with work, school activities and social relationships rather than bowel pattern *per se* [5–9].

Several factors have been claimed to be involved in symptoms generation in IBS, including motility abnormalities, visceral hypersensitivity, changes in gut-microbiota and intestinal barrier functions, immune response dysregulation, mucosal low-grade inflammation and, finally, an abnormal central nervous system processing [10–12]; however, the relative contribution of each of these factors on the individual symptoms is still far to be identified.

Smoking has been recognized as an important risk factor for the development of post-infectious IBS [13]. Moreover, a recent systematic literature review shows a significant increase risk of FGIDs for current compared with never smokers [14] and in a recent Swedish population-based cohort of 16.840 FGIDs patients (including functional abdominal pain,

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functional bloating, constipation and IBS), former and current smoking were found to be associated with functional abdominal pain [15]. However, the relationship between smoking and IBS subtypes has been rarely explored.

Smoking modulates the autonomic function [16, 17], it delays mouth to cecum transit time [18, 19] and it has been reported to represent an independent risk factor for chronic pain syndromes [20].

It could be speculated that smoking may increase the risk or worsen the course of IBS, since a negative effect of smoking on gastrointestinal functions, especially colonic motility, has been documented [21–25]. On the other hand, some effects of smoking on colonic function may even reinforce tobacco use in patients with IBS. More than half of patients with IBS–constipation subtype or chronic constipation who smoke, attribute a stool-softening effect to cigarette smoking [26, 27].

Altogether, these observations lead to the hypothesis that smoking might modulate abdominal pain in IBS and that this might be associated with an effect either on bowel habits, visceral perception and/or colonic transit.

Thus, the aim of our study was to investigate the effect of smoking in a population of IBS patients with constipation and mixed bowel habit and to evaluate its impact on bowel pattern and colonic transit times.

Patients and methods

Subjects and study design

Sixty-eight consecutive patients with IBS (48 women; median age: 38 years; age range: 18–69) with constipation (IBS-C) or with mixed bowel habit (IBS-M) according to the Rome IV diagnostic criteria were recruited from the clinic outpatients at a single tertiary referral center (University Hospital "Federico II" of Naples). In all the study participants organic causes that could account for the symptoms were excluded based on laboratory tests (inflammatory markers, thyroid function, celiac screening, fecal calprotectin) and diagnostic investigation (colonoscopy) as appropriate.

Smoking habit was investigated by a dedicated interview and patients were classified as habitual smokers, if consuming more than 10 cigarettes per day for more than 3 years. Bowel movements were recorded with a one-week diary and stool form was evaluated by using the validated Bristol Stool Form (BSF) recorded on the same diary. After baseline assessment, all patients underwent the evaluation of colonic transit time (see below). All patients gave their written informed consent to participate to the study.

Symptoms assessment

Each patient was asked to complete the validated PAC-SYM questionnaire consisting of 12 items assessing three domains: abdominal symptoms [4 items: 1–discomfort in your abdomen, 2–pain in your abdomen, 3–bloating in your abdomen, and 4–stomach cramps], rectal symptoms [3 items: 5–painful bowel movements, 6–rectal burning during or after a bowel movement, 7–rectal bleeding or tearing during or after bowel movement] and stool symptoms [5 items: 8–incomplete bowel movement like you did not finish, 9–bowel movement that were too hard, 10–bowel movement that were too small, 11–straining or squeezing to try to pass bowel movements, 12–feeling like you had to pass a bowel movement but you could not] [28]. Symptoms' severity score was graded on a Likert scale from 0 (absent) to 5 (severe). Also, the prevalent features of abdominal pain, defined as diffuse or localized, chronic or acute, with cramps or gradually distending were recorded.

Finally, the impairment of quality of life was evaluated with a self-administered questionnaire (PAC-QOL) consisting of 28 items exploring the effects of constipation on the patient's quality of life. The PAC-QOL questionnaire investigates the following four dimensions: physical discomfort (4 items), psychosocial discomfort (8 items), treatment satisfaction (5 items), and finally worries and/or discomfort (11 items). Response choice is a Likert scale from 0 to 4. Higher scores suggest higher negative effects on quality of life [29].

Colonic transit study

Total colonic transit time (CTT) was assessed according to Metcalf et al. [30]. Briefly, three sets of distinctive markers were ingested at the same time of the day on three subsequent days. Abdominal X-rays were obtained on days 4 and 7 at the same time as the markers were ingested. Patients with markers still present on day 7 underwent an additional abdominal X-ray on day 10. The markers were counted on the abdominal X-ray films. Colonic transit time, expressed as the number of hours taken for the markers to pass through the entire colon, was calculated according to our previous report [31]. The transit was considered to be delayed when longer than 70 h [32].

Statistical analysis

Age, body mass index (BMI) and colonic transit time in IBS-C or in IBS-M patient subgroups were compared using Student's t-test for unpaired data. Chi-square testing was used in order to compare gender, smoking habit, presence/severity, localization and features of abdominal pain between the two subgroups. Stepwise multiple logistic regression analysis was also used to evaluate the risk association between demographic characteristics, smoking, stool form and severity of symptoms, mainly abdominal pain. Odds ratio (OR) with 95% confidence interval (CI) were computed. Differences were considered to be significant at the 5% level. Statistical evaluations were performed using specialized software (SPSS®, Inc., Chicago, IL).

Results

IBS phenotype, clinical characteristics and colonic transit

The demographic features and the clinical characteristics of the 28 patients with IBS-M and 40 patients with IBS-C are

Table 1: Demographic features of IBS-M and IBS-C patients.

	IBS-M (n.28)	IBS-C (n.40)	p
Gender (M/F)	10/18	10/30	N.S.
Age	38 ± 17	42 ± 16	N.S.
BMI	26 ± 10	26 ± 7	N.S.
Smoking habit	8 (29%)	14 (35%)	N.S.

summarized in Tables 1 and 2, respectively Gender prevalence, age and BMI were similar in IBS-M and IBS-C patients as well as the prevalence of smokers in the two groups. The prevalence of all gastrointestinal symptoms investigated was not significantly different in the compared groups as well as the presence, severity, type and localization of abdominal pain. Only chronic pain was more frequently scored by IBS-C patients than IBS-M (40 vs. 7% respectively, OR 4.7, 95% CI 1.2–17.8, p<0.05).

Table 2: Clinical characteristics of IBS-M (28) and IBS-C (40) patients.

PAC-SYM score	IBS-M (mean ± SD)	IBS-C (mean ± SD)	p
Abdominal symptoms			
Discomfort	1.46 ± 0.84	1.6 ± 1.08	N.S.
Pain	1.64 ± 1.13	1.62 ± 1.50	N.S.
Bloating	1.46 ± 0.88	1.65 ± 1.4	N.S.
Stomach cramps	1.68 ± 1.05	1.3 ± 1.22	N.S.
Rectal symptoms			
Painful bowel movements	2 ± 1.44	1.4 ± 1.10	N.S.
Rectal burning	1.5 ± 1.14	1.52 ± 1.24	N.S.
Rectal bleeding or tearing	1.75 ± 1.36	1.38 ± 1.13	N.S.
Stool symptoms			
Incomplete bowel movement	1.21 ± 1.10	1.3 ± 1.02	N.S.
Too hard bowel movement	1.53 ± 1.35	1.45 ± 1.06	N.S.
Too small bowel movement	1.71 ± 1.44	1.6 ± 1.22	N.S.
Straining or squeezing	1.5 ± 1.23	1.88 ± 1.36	N.S.
Bowel movement mistake feeling	1.5 ± 1.2	1.58 ± 1.17	N.S.
PAC-SYM total score	**1.58 ± 0.89**	**1.52 ± 0.88**	**N.S.**
PAC-QoL total score	**2.53 ± 0.26**	**2.6 ± 0.19**	**N.S.**
	IBS-M 28 (%)	**IBS-C 40 (%)**	**p**
Type of pain			
Acute	10 (36)	12 (30)	N.S.
Chronic	2 (7)	16 (40)	<0.05
Localized	16 (57)	26 (65)	N.S.
Diffuse	8 (28)	12 (30)	N.S
Pain severity			
Mild	10 (36)	12 (30)	N.S.
Moderate	12 (43)	18 (45)	N.S.
Severe	6 (21)	10 (25)	N.S.

N.S. = not significant.

A normal CTT was found in 80% of the overall population; in fact, only 14 patients (20%) had a delayed transit time (8 IBS-C and 6 IBS-M, respectively). Total colonic transit time was not significantly different in IBS-C and IBS-M patients, while the segmental colonic transit in the right colon was significantly longer in IBS-C than in IBS-M (22.9 ± 4.1 vs. 17.4 ± 3.9 h; p<0.05) (see Figure 1).

Smoking, equally distributed in the two IBS subtypes, was not significantly associated with colonic transit times both in IBS-C and IBS-M (both p=N.S). Stool consistency expressed by BSF score was significantly correlated with total CTT (r=−0.3604, p=0.036). On the contrary, the severity of abdominal, rectal and stool symptoms, as scored by PAC-SYM questionnaire, as well as the impairment of the quality of life, as scored by the PAC-QOL questionnaire, were not significantly associated with delayed transit (all p=N.S.)

PAC-SYM/PAC-QoL questionnaire and abdominal pain severity evaluation

The results of PAC-SYM and PAC-QoL analyses are shown in Table 2. In both IBS groups, PAC-SYM evaluation reported symptoms severity score of mild-moderate degree (mean PAC-SYM total score: 1.58 ± 0.89 vs. 1.52 ± 0.87 in IBS-M and IBS-C, respectively); while PAC-QoL scores suggested moderate impairment of the quality of life (mean PAC-QoL total score: 2.53 ± 0.25 vs. 2.59 ± 0.19 in IBS-M and IBS-C, respectively). Moreover, PAC-SYM subscores analysis revealed that IBS-M scored more the fifth item (painful bowel movement; mean score 2 ± 1.44); while in IBS-C the highest score was related to straining or squeezing to try to pass bowel movements (mean score 1.87 ± 1.36). Contrary, the highest PAC-QoL subscores were associated with the 23rd item (feeling that your body is not working properly) in both IBS subtypes (mean score 4 ± 0.72 vs. 4.2 ± 0.68 in IBS-M and IBS-C, respectively).

No significant differences exist between IBS-M and IBS-C patients both in the total score and in the subscales related to each items (all p=N.S.). Moreover, the multivariate regression model for the PAC-SYM and PAC-QoL results did not provide a statistically significant positive correlation with the colonic transit (all p=N.S.)

When considering the overall perceived severity of abdominal pain (Table 2), almost 68% (that is 46 out of 68 patients) reported moderate and/or severe abdominal pain, meaning that symptom significantly interferes with daily activities. Among the 30 patients complaining with moderate pain, 12 (43%) were IBS-C and 18 (45%) were IBS-M; while the 16 subjects reporting severe pain, 6 (21%) were IBS-C and 10 (25%) were IBS-M.

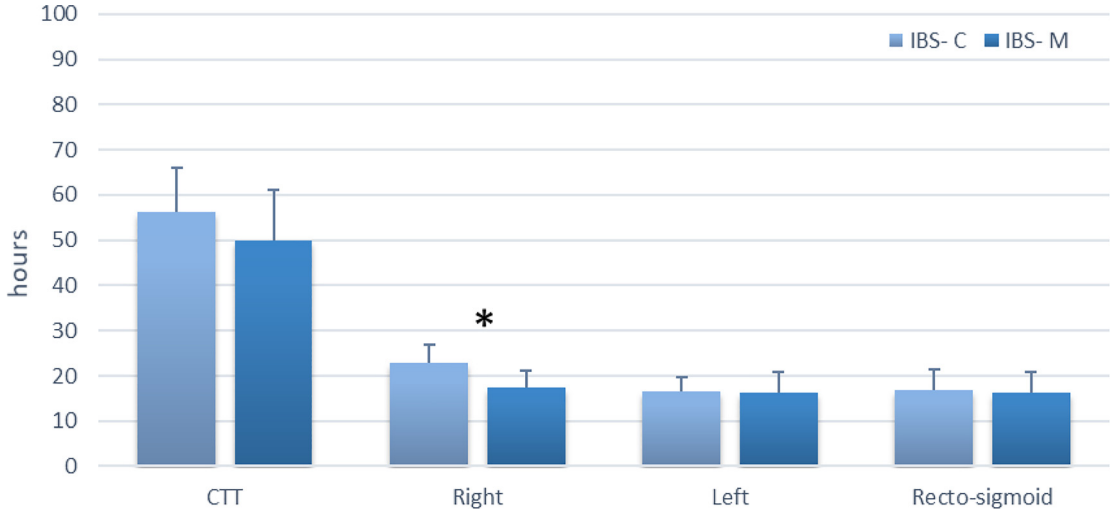

Figure 1: Total and segmental colonic transit time (CTT) in IBS-M and IBS-C patients.

The analysis of the correlation between transit time and abdominal pain yields no significant difference between delayed or normal transit, either considering the total (56.2 ± 9.7 vs. 49.9 ± 11.1 h; p=N.S.) or segmental transit time (right: 22.9 ± 4.1 vs. 17.4 ± 3.9, left: 16.5 ± 3.1 vs. 16.1 ± 4.6 and recto-sigmoid: 16.8 ± 4.5 vs. 16.4 ± 4.5 h; respectively, p=all N.S.)

However, when the perceived severity of the abdominal pain was used as a discriminating factor, a significant number of subjects in the overall population reporting severe pain were males and smokers (16/30 vs. 4/38 and 20/30 vs. 4/38, respectively, p<0.01). No significant differences were observed for all the other variables computed. Multivariate analysis confirmed that only smoking was an independent risk factor significantly associated with severe abdominal pain (OR 14.3, 95% CI 2–99, p=0.007), regardless of the prevalent bowel pattern.

Discussion

The present study shows that habitual smoking is significantly associated with a more severe abdominal pain in both IBS-C and IBS-M patients. Furthermore, our results show that this association does not depend on colonic motility, since smoking was not associated with bowel habits and/or colonic transit and no correlation between transit time and abdominal pain severity was observed.

Which factors are associated with IBS symptoms severity remains a matter of debate. Abdominal pain is often the main complaint of these patients and interferes profoundly with daily activities. In keeping with this, in the present study, we showed that more than a half of our patients reported bothersome abdominal pain, reflecting a poor quality of life of these subjects.

We found a gender difference in abdominal pain severity, with males scoring more severe pain intensity when compared to females. However, when all variables were computed in a multivariate analysis, only smoking was significantly associated with the complaining of more severe abdominal pain.

In our study population, smoking had a prevalence of 32% and was equally distributed in the two subtypes (29% in IBS-M vs. 35% in IBS-C; p: N.S.). These epidemiological data are in agreement with literature, where a recent review reported no significant difference in smoking occurrence between IBS patients and controls, with smoking prevalence in IBS ranging from 0 to 47% [33]. Further supporting this data, a recent observational study involving 553 Middle East adult subjects showed that smoking was not significantly associated with IBS, as no significant difference in IBS prevalence emerged between those who ever smoked and those who never smoked cigarettes. Interestingly, instead water pipe smoking proved to be significantly associated with a higher IBS prevalence [34].

Although we did not directly investigate the underlying mechanisms, it is reasonable to hypothesize that smoking might act both on sensory and motor functions. Nevertheless, we observed that, tobacco consumption was not associated with any significant effect on CTT and, thus, it is likely to speculate that smoking had a significant effect on visceral perception at least in our subset of patients.

Smoking may play a dual effect in painful conditions. Nicotine may provide an acute analgesic effect, thus reinforcing smoking habit [35]. On the other hand, robust epidemiologic evidences [36–39] show that smoking is a

risk factor for chronic painful conditions and that, among patients suffering from chronic pain, smokers complain of greater pain intensity. This apparent paradox could be explained by the chronic hypothalamic receptors desensitization induced by the continuous exposure to high nicotine levels, so the acute analgesic effect of nicotine may be attenuated or abnormal [40].

In addition, a certain degree of mucosal inflammation has been clearly demonstrated, in at least a subset of IBS patients [41, 42]. In keeping with this, an alternative hypothesis could be that smoking may alter visceral perception, by modulating multiple transmission pathways [43] and/or through an increased activation of immune mucosal cells [44].

Several authors have previously investigated the role of colonic transit and its putative association with IBS symptoms, yielding conflicting results. The percentage of IBS patients with altered colonic transit time ranged from 11 to up to 50%, with contrasting results when segmental CTT was analyzed [45–47]. It is unclear whether these discrepancies are related to patients' selection or the use of different techniques. In our population, delayed transit time was noticed in less than 20% of both IBS-M and IBS-C patients without significant differences between the two groups.

According to previous data we confirmed that colonic transit is indeed associated with stool form [45, 48–50] but also that an altered colonic transit does not play a major role in determining IBS symptoms [46]. A delayed transit alone was not significantly associated with both presence and severity of abdominal pain, bloating and discomfort in IBS.

In conclusion, our results suggest that smoking habit is an independent risk factor for severe abdominal pain/discomfort at least in the subgroup of constipated IBS patients and that the contribution of colonic dysmotility to symptoms generation is likely to be of minor relevance. Although further studies are needed to assess the precise mechanisms involved, it is reasonable to hypothesize that abnormal colonic transit may have only a cumulative effect on determining symptoms, as just suggested in literature [51] and that an enhancement in visceral sensitivity, rather than bowel dysmotility, may account for severe abdominal pain in IBS patients. In conclusion, the more severe abdominal complaining reported by smokers may be a result of this process.

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