Title:
IRRITABLE BOWEL SYNDROME AND BASAL SERUM TRYPTASE: THE CORRELATION BETWEEN SUBTYPE, SEVERITY AND COMORBIDITIES. A PILOT STUDY

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Irritable bowel syndrome and basal serum tryptase: correlation between subtype, severity, and comorbidities. A pilot study

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Author contribution: Constanza Ciriza de los Ríos: development of the study protocol, patient recruitment, data analysis and interpretation, manuscript preparation; Isabel Castel and Fernando Canga: patient recruitment, data analysis; M. Carmen Diéguez: development of the study protocol, control group recruitment, and basal serum tryptase analysis. Natividad de las Cuevas: basal serum tryptase analysis; Enrique Rey: data interpretation and support for manuscript preparation.
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ABSTRACT

Introduction: the activation of mast cells causes alterations in epithelial and neuromuscular function and is involved in visceral hypersensitivity and dysmotility in gastrointestinal functional disorders.

Objectives: primary: to evaluate differences in basal serum tryptase (BST) between patients with irritable bowel syndrome (IBS) and healthy controls. Secondary: BST depending on IBS subtype (diarrhea: IBS-D; constipation: IBS-C), comorbidities and correlation with IBS severity and quality of life.

Material and methods: a prospective control-case study in IBS patients (Rome IV criteria). BST (ImmunoCAP-Phadia, Sweden®), IBS Severity Score (IBSSS), pain, bloating and flatulence analogue scales, IBS quality of life (IBSQOL), and patient health status (PHQ-9) were determined. BST is the primary variable to achieve the primary endpoint.

Results: thirty-two patients were included, 21 (65.6%) with IBS-D and 11 (34.4%) with IBS-C; 32 controls were also included. Mean IBSSS: 326.6 (± 71.4), IBSQOL: 76 (± 20.3), and PHQ9: 10.2 (± 5.9). BST was 4.8 ± 2.6 in IBS and 4.7 ± 2.6 in controls (p = 0.875). There were no differences in BST between IBS subtypes (4.7 ± 2.9 in IBS-D and 5 ± 1.8 in IBS-C; p = 0.315) or IBS severity (p = 0.662). However, BST was higher in patients with IBS and extraintestinal comorbidities compared to other patients and controls (p = 0.029). This subgroup also has more severe bloating (p = 0.021). There was no correlation between BST, quality of life (p = 0.9260), and health status (p = 0.3985).

Conclusion: BST does not discriminate between IBS patients and controls. However, BST was higher in patients with IBS with extraintestinal comorbidities, which had more severe bloating. This finding is worthy of investigation.

Keywords: Basal serum tryptase. Irritable bowel syndrome. Comorbidities. IBS subtype. IBS severity.
INTRODUCTION

Mast cells are blood cells that have a modulating effect on inflammatory or allergic processes found in the mucosa and human epithelial tissue, as well as in all vascularized tissue except the central nervous system and the retina (1). Between 2 % and 3 % of inflammatory infiltration in the intestinal mucosa of healthy subjects is made up of mast cells (2). These cells contain secretory granules, which include biologically active molecules such as cytokines, histamine, protease, and proteoglycans that are liberated when mast cells are activated. This could lead to conflicting biological effects. In fact, it is believed that the role of mast cells in physiological and pathological processes goes beyond allergies. They are involved in the processes of scarring, chronic inflammation, tumor growth, and angiogenesis, and are considered a component of the immune system (3,4). As a result, mast cell-derived mediators could contribute to the pathogenesis of not only allergic, asthmatic, and mast-cell illnesses, but also others such as myalgic encephalomyelitis/chronic fatigue syndrome (CFS), fibromyalgia (FMG), coronary heart disease, and obesity among others (5).

Tryptase is a serine protease that is primarily produced and stored in mast cells, it being the most abundant protein component of human mast-cell secretory granules. It is less abundant in blood basophils. In tissue mast cells, tryptase is produced and released in a constitutive manner, regardless of the organ location of mast cells, maturation stage, or subtype of mast cells. Mature tissue mast cells also store larger quantities of the enzyme in their metachromatic granules. Two major forms of tryptase are produced in mast cells, alpha and beta. Whereas the alpha form is produced and released constantly in mast cells, the beta form is primarily stored in mast cell granules (6). Determination of human serum tryptase by immunoassay measures the total concentration of both alpha and beta forms. As there is no distinction between tryptase subtypes, current tryptase determination depends on both the size and activation status of an individual’s mast cell population, although it is not directly informative on the contribution of any of these factors. Despite this, serum tryptase is considered a biomarker in daily practice for different diseases (6).
The basal serum tryptase level (BST) in healthy individuals results from the constant release of the enzyme from mature tissue mast cells (6). Elevated basal serum tryptase concentration is associated with an increased prevalence of multiple, predominantly functional and clinical phenotypes, including recurrent cutaneous symptoms, symptoms of autonomic instability, functional gastrointestinal disorders, and connective tissue abnormalities (7).

In the intestines, mast cells are found in the lamina propria of the mucosa in healthy patients, and represent 3 % of cellularity, regulating the intestinal barrier by acting in the blood flow, the contraction of smooth muscle, peristalsis, and immune response (2,8). There are specific characteristics of mast cells in the bowel, different to those of mast cells in other locations, as can be seen in morphological and immunohistochemical studies (9,10).

Mast cells are known to provoke a disruption of epithelial and neuromuscular function, as well as to generate visceral hypersensitivity. Furthermore, they alter intestinal motility patterns in functional gastrointestinal disorders (4) such as irritable bowel syndrome (IBS), a functional somatic disorder characterized by abdominal pain and disrupted defecation, and frequently accompanied by abdominal swelling/bloating (11).

Recent studies show an increase in small-intestine inflammatory cells, particularly in the colon of some IBS patients after a previous bout of gastroenteritis (12,13). In cases of IBS patients with abdominal pain and specifically in relation to severity, a larger quantity of mast cells, T-lymphocytes and degranulation of mast cells have been found around the nerve fibers of the colon, giving way to tryptase release (14,15). Moreover, IBS is also associated with digestive and extraintestinal comorbidities such as FMG and CFS, which are also related to mast cell disruption (5,7).

Therefore, the hypothesis of this study was that basal serum tryptase (BST) levels could be increased in IBS individuals, and could represent an inflammatory marker in IBS. This could also aid in the identification of susceptible patients for the subsequent improvement in symptoms with mast cell-stabilizing drugs, such as cromoglycate.

The main objective of this study was to evaluate whether an increase in BST exists in IBS patients compared to controls. The secondary objectives were to investigate the
possible differences in BST depending on IBS subtype, constipation (IBS-C) or diarrhea (IBS-D). Furthermore, BST was studied according to associated comorbidities and its correlation with IBS severity and quality of life.

MATERIAL AND METHODS
A prospective case-control study was performed at the 12 de Octubre University Hospital from June 2017 to May 2018.

Patients and control group
Patients were consecutively and prospectively included with a diagnosis of IBS who complied with the following inclusion criteria: 1) patients of both sexes over 18 years of age diagnosed with IBS according to Rome IV criteria (16); 2) normal laboratory study including hemogram, biochemistry, thyroid hormones, celiac disease study, C-reactive protein, fecal calprotectin range, and negative parasite study; 3) normal colonoscopy up to 2 years previously in patients over 50 years of age.

Patients were excluded from the analysis if they demonstrated:

— Presence of organic disease, such as diverticulitis, chronic intestinal inflammatory disease, tumors, hematological and/or connective tissue disease.
— Presence of important immuno-allergic diseases such as systemic and cutaneous mastocytosis, asthma, atopic dermatitis, allergic rhinitis, and IgE-mediated anaphylaxis.
— Presence of active peptic ulcer disease.
— Gastrointestinal parasite infestations.
— Lactose malabsorption.
— Celiac disease.
— Diabetes types 1 and 2
— Kidney failure or creatinine above stage 2.
— Chronic liver disease and/or elevated transaminases or bilirubin 1.5 times above normal.
— Active consumption of alcohol and drugs.
AIDS

— Use of narcotics, anticoagulants, antibiotics, or sodium cromoglycate.
— Previous abdominal surgery, except appendectomy or inguinal herniorrhaphy.
— Pregnant or lactating women.
— Patient who did not sign the informed consent.

The age- and sex-matched control group was made up of hospital workers over 18 years of age, with no prior history of digestive pathologies or other endocrine-metabolic pathologies, and no immunological, rheumatological, cardiovascular, or allergic disorders. Those patients complying with IBS Rome IV criteria (16) were included and underwent a BST determination.

The study complied with the ethical principles of the Declaration of Helsinki and the Good Medical Practice code of conduct, as well as with the legal regulations in force. All patients and subjects were fully informed and signed the informed consent containing all relevant information of the study. The study was approved by the 12 de Octubre University Hospital Ethical Committee (N.º CEI 17/124).

Clinical variables and IBS study

All patients provided epidemiological data, medical history, year of IBS diagnosis and IBS subtype, bowel habits and stool type (Bristol scale), previously performed treatments, current treatment for IBS, and comorbidities. The patients were classified into three groups according to comorbidities for analysis purposes as none, psychiatric, and extraintestinal (Table 1). The following questionnaires and scales were autocompleted by the patient: IBS severity assessment (IBSSS), considering IBSSS as moderate-severe if greater than 175 points (17); evaluation of pain and abdominal distension using the analogic scale (0-6); quality of life assessment using the IBSQOL questionnaire (validated Spanish version) (18), and health scale (Patient Health Questionnaire PHQ-9) (validated Spanish version) (19).

The primary variable was BST determination in IBS patients and controls to achieve the primary endpoint of the study, which was to investigate if BST discriminates between IBS patients and healthy controls as a potential biomarker. The secondary endpoints
were to determine if BST varies depending on IBS subtype and associated comorbidities, and BST correlations with IBS severity and quality of life.

**Determination of basal serum tryptase**

A venous blood sample was obtained from both patients and controls at 8 am after an overnight fast and rest. None of the healthy controls were taking any medication at the time of the serum tryptase detection, and the patients continued taking their regular medication for IBS if needed (Table 1). The participants were asked to avoid antihistamines, ketotifen, nedocromil, cromolyn, theophylline, β2-agonists, antibiotics, angiotensin-converting enzyme inhibitors, codeine or opioid derivatives for at least 2 weeks. Diet modifications were not requested, neither in patients nor in controls. Blood samples were centrifuged for 10 min at 4000 rpm. The supernatants were decanted to obtain the serum, which was frozen at -20 °C until tryptase detection. The study of BST level was performed with the ImmunoCAP Tryptase (Phadia, Uppsala, Sweden®) automated technique in the Allergology Department Laboratory. Tryptase detection was carried out using a Unicap 250 analyzer (Phadia, Uppsala, Sweden®), then with the sandwich-type fluoroenzymoimmunoassay technique (20). The range of normal values was 1-13.5 ng/mL, and the detection limits were from 1 to 100 ng/mL (20,21). This test measures total tryptase (alpha and beta tryptase).

**Statistical analysis**

A sample size of 20 patients and 20 controls was estimated in order to achieve a statistical power of 80 %, with a confidence interval of 95 % based on the mean and standard deviation (SD) previously reported, in which twenty-three newly-diagnosed IBS-D patients and 14 healthy volunteers were examined (IBS-D: 5.52 (SD: 2.01; 95 % CI: 4.52 to 6.53); H: 5.40 (SD: 2.15; 95 % CI: 3.96 to 6.85) μg/L) (22). Eventually, 32 patients were included with a control group of 32 healthy subjects. Age, sex, and BST values were recorded for the control group. Qualitative values are described with their frequency distribution and are summarized with the mean and standard deviation (SD), as well as a confidence interval (CI) at 95 %. The normality of continuous quantitative variables study was performed using the Kolmogorov-Smirnov and
Shapiro-Wilk goodness of fit tests.
The association between qualitative variables was evaluated using the chi-square test or Fisher’s exact test. The characteristics of the distribution of variables and whether they complied with the conditions of normal distribution were determined. The differences in variables studied between groups were analyzed using Student’s t-test, variance analysis (ANOVA), and intergroup analysis with contrast studies (Scheffé test). If the distribution was not normal, non-parametric tests were used (Kruskal-Wallis, Wilcoxon’s). Correlations were analyzed with the appropriate test according to the presence of a normal distribution. Cohen’s kappa index was used in order to calculate agreement between variables.

RESULTS
Thirty-two patients were included, 30 (93.7 %) females with a mean age of 48 years (± 15.3). The control group was formed of 32 healthy subjects, of whom 29 (90.6 %) were female. The mean age of the control group was 46.5 years (± 15.3). No differences were found between patients and the control group regarding age and sex distribution (p = 0.667 and p = 0.644, respectively).
The clinical characteristics of the patients are shown in table 1. Mean time to IBS diagnosis was 61.7 months (± 61.4). Mean severity according to the IBSSS questionnaire was 326.6 (± 71.4), and mean days with pain was 12.2 days (± 2.77) and 13.1 (± 1.90) with bloating. Pain severity was 3 (± 1.15) and 3.7 (± 1.3) for bloating. Mean score for quality of life was 76 (± 20.3), and the PHQ9 scale was 10.2 (± 5.9). A statistically significant positive correlation was observed between BST and age, although it was not pronounced (p = 0.022).
BST values were similar in both patients and controls (4.8 ± 2.6 and 4.7 ± 2.6, respectively; p = 0.875). Moreover, there were no differences in IBS subtype function; 4.7 ± 2.9 in IBS-D and 5 ± 1.8 in IBS-C, respectively; p = 0.315, or between BST and IBS severity (p = 0.662), degree of abdominal pain (p = 0.769), or abdominal bloating (p = 0.066). However, when subdividing the group of patients depending on any kind of comorbidity, BST was greater in patients with IBS and extraintestinal comorbidities compared with other groups (p = 0.029) (Fig. 1). When analyzing clinical characteristics
and comorbidity, this group presented a greater severity of bloating (p = 0.021) and there were no differences with regard to other characteristics (Fig. 2). The increase in BST did not correlate with worse quality of life (p = 0.9260) (Fig. 3), nor with health status (p = 0.3985), either in general or considering IBS subgroups according to comorbidity (p = 0.863 and p = 0.206, respectively).
DISCUSSION

Our study shows that BST is similar between IBS patients and healthy controls, and therefore is not a useful marker for IBS. BST was not significantly different depending on IBS subtype but higher levels were found in IBS patients who also had extraintestinal comorbidities and more severe abdominal distension. BST did not correlate with the severity of disease or with quality of life and health status. IBS is a complex heterogenic disorder with a wide variety of symptoms of varying severity and frequency, as well as a potential influence of other both somatic and psychological comorbidities. The diagnosis of IBS is currently performed by means of symptom-based diagnostic criteria, but there is interest in developing biomarkers that could simplify the diagnosis and the assessment of severity of the disease. Biomarkers would be useful to identify the presence of IBS pathophysiological mechanisms. Among them, local and systemic immune activation is significant, which leads to a state of microinflammation. In some IBS patients, an increase has been shown of colonic inflammatory cells, such as mast cells (23,24). This low-grade inflammation could be responsible for the peripheral sensitization and visceral hypersensitivity associated with the pain suffered by IBS patients (25). In fact, degranulation of mast cells, close to colonic nerve fibers with histamine and tryptase release, could be correlated with the severity of abdominal pain (12). This could activate the Protease Activated Receptor 2, which is related to visceral pain in the colon and favors the recruitment of inflammatory cells. Under non-anaphylactic conditions, tryptase levels reflect the total body mast-cell burden, which is used to diagnose and monitor mast-cell diseases. Serum levels generally reflect the extent of mast cell activation either by IgE- or non-IgE-mediated mechanisms. High levels of BST have also been recorded in 4-6% of the general population, which also increases with age (7,26), and was confirmed in our study. However, differences have not been found between IBS patients and control subjects, or IBS-C and IBS-D subtypes. The latter recorded a greater alteration in mast cells in IBS-D patients, findings which are unconfirmed by other studies. For example, a greater expression of tryptase mRNA in colon biopsies was found in both IBS-D and IBS-C patients, although there were no differences between either subtype in healthy subjects (27). Guillarte et al. (20) reported similar
serum tryptase concentrations, within the normal range, in both IBS-D patients and controls. There was no correlation in our study between BST, greater IBS severity or abdominal pain intensity. However, greater BST values were observed and there was a tendency to present more severe abdominal bloating. When evaluating BST according to comorbidity, IBS patients with extraintestinal comorbidities had higher values than patients with no comorbidities or only psychiatric comorbidities. Furthermore, this subgroup presented abdominal bloating, which was believed to be more severe. The majority of extraintestinal comorbidities were FMG, CFS, and unspecific arthralgia-myalgia not complying with connective tissue disease criteria, with frequent overlapping of different somatic functional disorders such as IBS, FMG, and CFS in the general population (28). Many of these disorders have stress as a precipitating factor, which favors the release of the corticotropin-releasing hormone, causing the activation of mast cells (29). Moreover, these and many other entities, such as chronic prostatitis, interstitial cystitis, migraine, cardiovascular disease, etc., are considered neuroinflammatory diseases with mast cell implication (26,29). This could explain why increased BST is found in this subgroup of patients.

On the other hand, there was no correlation between BST and a greater involvement in quality of life or general health status, or by subgroups according to comorbidity. The quality of life or state of health as perceived by the patient most likely involves other factors such as psychiatric comorbidities and other parameters such as degree of anxiety and sleep disorders, which were not specifically analyzed in our study.

The greatest limitation of this study was its sample size, which could be considered insufficient to observe clear differences in the data obtained. The "activation" of mast cells is usually inferred by the release of their mediators, centering mainly on the increase of tryptase serum levels. However, these levels could be inadequate or deceiving, and could lead to false positive results, as they are affected by various conditions such as the rheumatoid factor or a delay in measuring serum tryptase for 0.2-4 hours after the appearance of symptoms (5), which could affect the recording of the presence of rheumatoid factor in the patient group. The ideal situation would be to have a BST and serial tryptase measurements available for cases with a greater intensity of symptoms. However, the data available for BST and IBS are scarce and only
studies with a small number of patients are available. Different variables that can affect BST such as circadian rhythms or diet were not taken into account (20). Therefore, an initial study was performed on this topic, as there is a lack of information published in real clinical practice, but it seems that BST is not a useful biomarker for inflammation in IBS. Therefore, this coincides with another study in which serum tryptase levels were similar between patients with Crohn’s disease and controls (30). Nonetheless, the authors considered that the measurement of serum tryptase is a reliable, non-invasive diagnostic approach to estimate the burden of mast cells in patients with mastocytosis, which may involve diarrhea and abdominal symptoms, and to distinguish between categories of disease.

In summary, from the data obtained by this pilot study, whether BST discriminates between IBS patients and healthy subjects cannot be confirmed. Therefore, BST cannot be considered a useful inflammatory marker for IBS. BST is not different according to IBS subtype and could not predict IBS severity. However, BST is higher in IBS associated with other functional somatic comorbidities and more severe abdominal distension. This would imply that the concurrence or overlapping of various functional somatic comorbidities could exert an added effect on its pathophysiology, which would suggest a greater participation of mast cell activity. These differences observed in IBS patients who have extraintestinal comorbidities might be worthy of further investigation. More studies are needed with a larger sample size in order to distinguish between the possible uses of BST as a potential marker, particularly in patients with IBS associated with other functional somatic comorbidities. These findings appear to reinforce the hypothesis that a significant group of functional somatic comorbidities possess an inflammatory basis involving mast cells.
REFERENCES


Table 1. Clinical Characteristics of patients with IBS

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td><strong>Subtype</strong></td>
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<tr>
<td>Constipation</td>
<td>11</td>
<td>34.4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21</td>
<td>65.6</td>
</tr>
<tr>
<td><strong>Previous treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>6</td>
<td>18.8</td>
</tr>
<tr>
<td>Fiber only</td>
<td>3</td>
<td>9.9</td>
</tr>
<tr>
<td>Laxatives only</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>Antispasmodics only</td>
<td>3</td>
<td>9.4</td>
</tr>
<tr>
<td>Probiotics only</td>
<td>1</td>
<td>3.1</td>
</tr>
<tr>
<td>Laxative + Antispasmodics</td>
<td>1</td>
<td>3.1</td>
</tr>
<tr>
<td>Three or more drugs</td>
<td>10</td>
<td>21.4</td>
</tr>
<tr>
<td><strong>Current treatment (last 7 days)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– No</td>
<td>19</td>
<td>59.4</td>
</tr>
<tr>
<td>– Fibre</td>
<td>1</td>
<td>3.1</td>
</tr>
<tr>
<td>– Laxatives</td>
<td>7</td>
<td>21.9</td>
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<tr>
<td>– Linaclotide</td>
<td>2</td>
<td>6.3</td>
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<tr>
<td>– Two or more drugs</td>
<td>3</td>
<td>9.4</td>
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<tr>
<td>Diarrhea</td>
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<td></td>
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<tr>
<td>– No</td>
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<td>62.5</td>
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<td>– Rifaximin</td>
<td>7</td>
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<td>– Probiotics</td>
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<td>9.4</td>
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<tr>
<td>– Xyloglucan</td>
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<td>6.3</td>
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<tr>
<td>Pain</td>
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<td></td>
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<tr>
<td>– No</td>
<td>14</td>
<td>43.8</td>
</tr>
<tr>
<td>– Antispasmodic calcium antagonist</td>
<td>4</td>
<td>12.5</td>
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<tr>
<td>– Antispasmodic smooth muscle relaxant</td>
<td>6</td>
<td>18.7</td>
</tr>
</tbody>
</table>
- Antispasmodic anticholinergics 7 21.9
- Two or more treatments 1 3.1

Bloating
- No 21 65.6
- Probiotics 9 28.2
- Antibiotics 1 3.1
- Activated carbon 1 3.1

Comorbidity
- None 13 40.6
- Psychiatric 7 21.9
- Extraintestinal 12 37.6
  - Systemic (FM, CFS, arthralgia) 10 31.3
  - Localized (cephalea, interstitial cystitis) 2 6.3

FM: fibromyalgia; CFS: chronic fatigue syndrome.
Fig. 1. Basal serum tryptase in patients with IBS according to comorbidities and controls (*p < 0.05; Kruskal-Wallis test).
Fig. 2. Clinical characteristics of IBS patients according to comorbidities (*p < 0.05; Kruskal-Wallis test).
Fig. 3. Correlation between basal serum tryptase and quality of life scale (Cohen’s kappa index: weighted kappa: 0.145; 95% CI (-0.1122, 0.4026); BST: basal serum tryptase).