Bone Mineral Content in Patients with Anaphylactic Reactions, Signs of Mastocytosis and Elevated Basal Serum Tryptase Levels

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Abstract:

Introduction: To examine the relationship between elevated basal serum tryptase levels (BST), a marker of total mast cell mass, and bone mineral density (BMD) in patients with anaphylactic reactions and signs of mastocytosis.

Methods: Retrospective evaluation of patient charts at an allergy unit. Patients with BST levels above 20 ng/ml were eligible if clinical and follow-up data and results of dual X-ray absorptiometry (DXA) were available. Patients with previous use of anti-osteoporotic medications and with osteoporosis not caused by mastocytosis were excluded. Spearman's rank correlation, Mann-Whitney test and receiver operating characteristic curve (ROC) was used for analysis.

Results: 24 patients were included. The main presenting symptom (17 of 24 patients) was anaphylactic reactions to insect stings. BST levels ranged between 21 and 158 ng/ml (median 48 ng/ml). Study participants with Z-score values below -1.0 had a median BST level of 46 ng/ml, the patients with Z-score values above or equal to -1.0 had a median BST level of 27 ng/ml. ROC analysis of the patient group with BST values between 30 and 100 ng/ml revealed a best cut-off value of BST to detect a low BMD when BST level would be at least 27 ng/ml resulting in a sensitivity of 92% and a specificity of 70%.

Conclusion: Patients with moderately elevated BST levels seem to be at increased risk for low BMD.

Key Words: Insect venom allergy, mastocytosis, urticaria pigmentosa, osteoporosis, low bone mass.

INTRODUCTION

Mastocytosis, a heterogeneous disease, can cause accumulation of mast cells in one or more organs. It is one of the causes of secondary osteoporosis. Skeletal changes in patients with mastocytosis may be generalised or localized. Osteoporosis, osteosclerosis, or a combination of osteolytic and osteosclerotic lesions may be found [1-4]. In the late 1990's, measurement of total serum tryptase values became available. Levels of serum tryptase measured outside of episodes of anaphylaxis (hence corresponding to 'basal' blood values) are thought to represent the total mast cell burden of an individual and are usually elevated in patients with systemic forms of mastocytosis [5]. A basal serum tryptase (BST) value above twenty nanograms per millilitre is considered a minor criterion for the diagnosis of systemic mastocytosis [6].

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There are various possible pathophysiologic links between mastocytosis and low bone mass. For example involvement of the gastrointestinal tract may cause malabsorption leading to bone loss. Involvement of the bone marrow is found very often in patients with urticaria pigmentosa but can also be observed in patients without skin manifestations [7]. There are many different metabolites produced by mast cells such as heparin or prostaglandins which may facilitate bone resorption. Other metabolites such as cytokines influence the maturing of osteoblast and osteclasts, thus impacting also on bone mass itself [2]. In contrast, it is uncommon to find osteoporosis as the main clinical manifestation of mastocytosis [1]. Recently, recommendations for the use of bone densitometry have been published [8-10]. According to the official positions of the International Society for Clinical Densitometry (ISCD) measurement of bone mineral density (BMD) using Dual X-ray Absorptiometry (DXA) should be considered in women 65 years of age and older, in postmenopausal women under the age of 65 with risk factors, and in men 70 years of age an older. Additionally, patients with diseases or conditions associated with a low bone mass

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or bone loss and patients taking medication associated with these findings should be considered to undergo BMD testing [8-10]. Patients presenting in the allergy unit of the university hospital Zurich with mastocytosis and/or elevated BST levels were often, but at the time of this study not routinely referred for BMD testing. DXA was especially performed if there were additional clinical signs or risk factors for osteoporosis (in particular older age, postmenopausal status, bone pain/ back pain, positive family history for osteoporosis, and use of corticosteroids).

The objective of this retrospective study was to examine the relationship between BST levels and BMD as measured by DXA and to assess the long-term outcome in these patients with anaphylaxis and other signs of mastocytosis, respectively. Furthermore, follow-up regarding the use of anti-osteoporotic medications and occurrence of non-traumatic fractures was assessed.

METHODS

Selection of Patients

Patients undergoing blood measurement of BST levels between January 1998 and June 2003 were selected from the files of the Allergy Laboratory of the Department of Dermatology. Patients were included in this retrospective study if they had had at least once a BST level above 20 ng/ml, and if DXA measurements and clinical follow-up data were available (from patient charts and by telephone calls). Only patients were included, for which could be ascertained that tryptase levels were true basal levels, and not determined during an anaphylactic reaction. All of the eligible patients agreed to be included into the study and gave their informed written consent ('study participants'). Exclusion criteria were prior use of bisphosphonates or other anti-osteoporotic agents within the previous five years and obvious secondary causes of osteoporosis such as long-term use of high doses of corticosteroids, use of antiepileptic drugs, malabsorption, malnutrition, chronic alcohol abuse, endocrine disorders (like hypogonadism, hyperthyroidism, Cushing's Syndrome), and malignant bone disease (e.g. multiple myeloma). Patients were also excluded when treated with interferon alpha 2b and if the BST values normalised during follow up. The following data were collected from the patient chart: age, body mass index, presenting symptoms, symptoms of mastocytosis, laboratory values use of alcohol and cigarettes, medications, past history, family history, and other risk factors for osteoporosis.

BST Measurements

BST was measured on the CAP system according to the recommendations of the manufacturer (Phadia Diagnostics, Uppsala, Sweden). This assay measures both the alpha- and the beta-tryptase ('total tryptase'). The alpha-protryptase is constitutively secreted and is the type of tryptase found in the serum of normal, healthy individuals [5]. Therefore, the level of the alpha-protryptase constitutes the 'basal serum tryptase level' and is thought to reflect the total mast cell burden [11]. Mature beta-tryptase can be measured in serum during systemic allergic reactions and indicates degranulation of mast cells. In all of our patients tryptase was determined at least three days after an anaphylactic reaction and, therefore, corresponds to BST levels [12, 13]. Normal BST values are below 11.4 ng/ml according to the manufacturer.

Measurement of BMD

DXA is considered being the reference standard for determination of bone mineral density (BMD) and was used in all of our patients [8-10, 14]. The lumbar spine measurement was taken from dorsal projection. The regions of interest (ROI) at the lumbar spine were in the vertebral bodies L2 – L4. In the hip ROI were total hip, neck, trochanteric region, and Ward`s triangle. If measurement was not possible at the lumbar spine or hip, an additional measurement of the non-dominant forearm was acquired according to the Official Positions of the ISCD [8-10]. Measurements were done with a Hologic QDR 4500 A and C™ device (Hologic Inc., Waltham, MA). For quality control of the DXA devices, a spine phantom was used on a daily base according to the recommendations of the manufacturer. 0.5% variability from the mean value was considered a tolerable variation of the DXA measurements for the longitudinal control. DXA measurements in four of the 24 participants were undertaken at two large district hospitals in the German-speaking region of Switzerland, using Lunar equipment (GE Medical Systems, Madison, Wisconsin, USA). BMD was given as absolute values in g/cm^2, and as Z- and, T-score values. The Z-score value corresponds to the number of standard deviations from the mean value that was defined by the range of BMD of an ethnically comparable, age- and gender-matched reference population. A Z-score value of -2.0 or lower indicates a low BMD for chronologic age. The T-score value corresponds to the number of standard deviations from the mean BMD of a gender-matched reference population of young adults defined as the Peak Bone Mass. In agreement with ISCD guidelines, osteopenia or osteoporosis were defined as the lowest measured value in either spine or hip. Osteopenia, as defined by the WHO classification, corresponds to a T-score value between -1.0 and -2.5. Osteoporosis was defined as a T-score value of -2.5 or lower. Low bone mass is defined as all T-score values indicating osteopenia or osteoporosis.

Follow Up Assessment

In April and May 2007, all participants were contacted by telephone and interviewed about use of anti-osteoporotic medications, occurrence of fractures and the course of the symptoms of mastocytosis. Follow-up determinations of BST and DXA were collected.

Statistical Analysis

Analysis of data was done with the SPSS statistical package, version 12.0 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics (rate, mean/standard deviation, median, range) were used to characterize the groups. Because of the relatively low mean and median age of study participants Z-score values served for statistical comparison as suggested in the Position Statement of the International Society for Clinical Densitometry [9]. Linear regression was applied to further investigate the relationship between BST and Z-score values. Spearman's rank correlation was done for correlation analysis between two continuous variables. Mann-Withney test served for the comparison between male and female pa-

Table 1. Characteristics of Study Participants (Patients with DXA)

	Patients with DXA (n=24)
Males / females	9 / 15
Proportion of females (%)	63
Age (years)	
median	48.2
mean ± SD	49.4 ± 14
Basal serum tryptase (ng/ml)	
median	38.0
mean ± SD	49.5 ± 35.5
Total IgE (Units/liter)	(n=17)
median	16.6
mean ± SD	33.0 ± 52.5
Presenting symptoms (n (%))	
Insect sting allergy	17 (71)
Systemic mastocytosis	1 (4)
Urticaria pigmentosa	2 (8)
Chronic urticaria	1 (4)
Quincke's edema	1 (4))
Osteoporosis	1 (4)
Idiopathic anaphylaxis	1(4)

There were no patients with food allergy or airway disease; SD= Standard Deviation

tients. Receiver operating characteristic curve (ROC) was performed to evaluate the discriminative power of BST levels for the identification of a low BMD (Z-score = -1.0 or lower) at lumbar spine and hip.

RESULTS

Patient Selection

133 patients with a BST above 20 ng/ml could be identified in the time period between January 1998 and June 2003. 32 of these 133 patients were excluded because blood samples had been sent from external laboratories and clinics outside the Department of Dermatology and, consequently, no clinical data was available. Six patients (of whom one with DXA measurement) were excluded because their BST returned to normal during follow up. Another two patients were excluded because it was not clear whether their elevated tryptase levels were true basal values. One patient was excluded because of use of anti-osteoporotic medication.

Data on BMD as determined by DXA could be retrieved for 24 eligible patients ('study participants'). Characteristics of these 24 patients are shown in Table **1**. The group of patients undergoing DXA was similar with respect to age and presenting symptoms to the patients not undergoing DXA. In both groups more than seventy percent of patients had been referred for anaphylactic reactions to insect stings. The 17 patients presenting with insect sting allergy had already previous allergic reaction to insect stings, but underwent evaluation for mastocytosis for the first time. The median BST level of study participants was 53% higher than the median BST of patients without DXA (38.0 vs. 24.9 ng/ml). This reflects the appreciation of an elevated BST value to possibly be a risk factor for low bone mass.

Description of Study Participants

Characteristics of the 24 study participants are shown in Table **2**. All patients were of white Caucasian ethnicity. 83% of study participants had been referred for anaphylaxis, occurring mainly following bee and yellow jacket stings (Table **1**, presenting symptoms). There was no difference for the measured BST levels between male and female patients (p= 0.34). There was a considerable variation among participants with respect to age (range 24 – 83 years), body mass index (range 19.1 – 43.2 kg/m2), clinical symptoms of mastocytosis, BST-values (range 21.2 – 158 ng/ml) and results of DXA.

All but two patients (patient 43 and 74) had persistently elevated tryptase levels and/or positive bone marrow and/or skin biopsy. Patient 43 was documented with two BST values of 21.5 and 25.8 ng/ml determined with a 7 week interval. Patient 118 was found to have slowly increasing BST values (July 1999 13.0 ng/ml, June 2000 16.7 ng/ml, August 2002 21.7 ng/ml, and February 2003 23.0 ng/ml). In some participants with persistently elevated BST values, biopsy results were non-conclusive (patients 1 and 47) or even negative (103, 13, 14, 88). None of the patients had signs of haematological malignancy.

Measurement of BMD

14 of 24 study participants (58%) had T-score values below -1.0 (osteopenia), and 6 patients (25%) values below -2.5 (osteoporosis) (Table **2**). Z-scores were on average lower for the lumbar spine as compared to the hip measurements (p=0.001). There was important variability of Z-score values in the lumbar spine region among study participants ranging from -3.3 to 2.3. Four patients with age between 24 and 48 years had a Z-score value of -2.0 or below indicating a low BMD for chronologic age. There was no difference for the measured Z-score values between male and female patients (lumbar spine: p=0.47; total hip: p= 0.49).

Characteristics of study participants with Z-score values below -1.0 are shown in Table **3**. Subjects with Z-score values below -1.0 had a median age of 43 years, the patients with Z-score values above or equal to -1.0 49 years. Study participants with Z-score values below -1.0 had a median BST level of 46 ng/ml, the patients with Z-score values above or equal to -1.0 had a median BST level of 27 ng/ml. The study participants with Z-score values below -1.0 were more likely to have urticaria pigmentosa (42% versus 25%) and for a positive bone marrow biopsy. Seven out of nine participants with a positive bone marrow biopsy had Z-score values below -1.0. Two participants with negative or non conclusive results of bone marrow biopsies (patients 103 and

Table 2. Clinical Characteristics of Study Participants

Pat-Nr.	Sex	Age	Body Mass Index	Presenting With (in brackets:Mueller Grade [12])	Signs and Symptoms of Mastocytosis	Basal Serum Tryptase	T-score Spine	Z-score Spine	T-score Hip	Z-score Hip	Skin Biopsy	Bone Marrow Biopsy
1	f	43	28.7	Quincke Edema	P, F, G, N	24.3	1.4	1.7	0.4	0.6	nd	+/-
2	f	64	31.0	Urticaria pigmentosa	UP, P	114.0	-0.2	1.6	-0.2	1.0	+	nd
4	f	33	22.2	Insect sting allergy (III)	A, Dz, M	60.8	-0.8	-0.7	-0.3	-0.3	nd	+
5	f	42	43.2	Systemic mastocytosis	A, UP, P, G, M,	38.5	-2.2	-1.8	0.8	1.1	+	+
7	f	35	23.8	Insect sting allergy (IV)	A, UP, P, M, G, D	46.4	-3.4	-3.3	-2.2	-2.0	+	+
11	f	43	23.1	Insect sting allergy (IV)	A, P, F, M	158.0	-1.9	-1.9	-1.5	-1.5	+	+
13	m	54	29.0	Insect sting allergy (IV)	A, F, M, G	40.3	0.6	1.1	0.1	0.5	-	nd
14	m	44	25.4	Insect sting allergy (IV)	A, F, G, D	45.8	-2.6	-2.4	0.6	1.0	-	nd
16	f	48	26.2	Insect sting allergy (IV)	A	37.4	-1.6	-1.0	0.1	0.4	nd	nd
17	f	24	20.5	Osteoporosis	P, F, D	28.0	-3.0	-2.9	-1.1	-1.1	+	+
42	f	72	19.1	Insect sting allergy (IV)	A, M	21.2	-4.5	-1.8	-2.6	-0.6	nd	nd
43	m	46	26.9	Insect sting allergy (IV)	A	21.5	1.9	1.7	1.4	1.5	nd	nd
47	f	37	24.7	Chronic Urticaria	M, U, D	26.6	0.4	0.5	1.9	2.0	+/-	nd
49	m	70	27.0	Insect sting allergy (IV)	A, M, S	56.0	-1.8	-0.9	-0.2	0.5	nd	nd
54	m	40	31.4	Insect sting allergy (IV)	A, UP, P, F, M, G	26.5	-0.5	-0.5	0.0	0.1	+	nd
55	f	42	23.1	Insect sting allergy (IV)	A, P	25.8	0.5	0.8	-0.1	0.1	nd	nd
74	f	83	32.4	Insect sting allergy (IV)	A, M, G	25.4	-0.4	2.3	-0.2	2.0	nd	nd
88	m	62	23.2	Insect sting allergy (IV)	A	77.9	-2.6	-1.9	-0.5	-0.1	-	+
90	m	41	25.6	Insect sting allergy (IV)	A, UP	116.0	-1.4	-1.6	-0.6	-0.5	+	+
103	f	52	20.5	Insect sting allergy (III)	A, F, M	30.9	-1.1	-0.3	0.0	0.6	nd	-
115	f	58	24.5	Urticaria pigmentosa	A, UP, F	26.8	0.3	1.5	0.7	1.5	+	+
118	m	35	23.8	Insect sting allergy (IV)	A, F, P	21.7	-1.4	-1.4	-0.1	0.0	nd	nd
127	f	48	23.7	Insect sting allergy (IV)	A	76.9	-2.6	-2.0	-1.4	-1.0	nd	+
133	m	29	24.8	Idiop. Anaphylaxis	A, UP, P, F, D	50.4	-1.4	-1.4	0.2	0.3	+	nd

1) had normal lumbar spine Z-score values of -0.3 and 1.7, respectively.

Relationship Between BST and BMD

Figs. (**1a** and **1b**) show BST values by Z-score values measured at the lumbar spine and total hip. There was no strong association between BST values and BMD in linear regression analysis (r^2=0.06 for the lumbar spine and 0.16 for the hip). The slope of the regression lines was negative. However, Spearman's rank correlation revealed a significant correlation between lumbar spine BMD and BST level (p= 0.03) and between total hip BMD and BST level (p= 0.02). Table **4** and Fig. (**2**) show BMD values analysed by BST categories. There was no obvious difference between the four BST categories with regard to age and BMI. Lowest Z-score mean values were found for BST values between 30 and 100 ng/ml. Additionally, receiver operating characteristic curve (ROC) was done for the patient group with BST values between 30 and 100 ng/ml (i.e. patients 2, 11, and 90 with values above 100ng/ml were excluded). ROC revealed an area under the curve of 0.78 ± 0.11 for the identification of a low BMD at the hip (p=0.03; CI: 0.56 – 0.99) when us-

Table 3. Comparison of Study Participants with Z-Score Values < -1.0 in the Region of the Lumbar Spine with Study Participants with Z-Score Values ≥ -1.0

	All patients	Lumbar Spine Z-Score Value ≥ -1.0	Lumbar Spine Z-Score Value < -1.0
Male / female	9 / 15	4 / 8	5 / 7
Proportion of females (%)	63	50	58
Age (years)			
mean ± SD	49 ± 14	52 ± 15	44 ± 13
median (range)	48 (24 - 83)	49 (33 - 83)	43 (24 - 72)
Body-Mass-Index (kg/m2)			
mean ± SD	26 ± 5	27 ± 4	25 ± 6
Urticaria pigmentosa (%)	33	25	42
Anaphylaxis (%)	83	75	92
Basal Serum Tryptase (ng/ml)			
mean ± SD	50 ± 36	40 ± 27	60 ± 42
median (range)	38 (21 - 158)	27 (22 - 114)	46 (21 - 158)
Bone marrow biopsy (n (%))			
positive	9 (38)	2 (17)	7 (58)
negative / non conclusive	2 (8)	2 (17)	0 (0)
not done	13 (54)	8 (66)	5 (42)
Z-score value Lumbar Spine			
mean ± SD	-0.6 ± 1.6	0.7 ± 1.1	-2.0 ± 0.6
Z-score value Total Hip			
mean ± SD	0.3 ± 1.0	0.8 ± 0.8	-0.3 ± 1.0
Z-score value Total Hip Neck			
mean ± SD	0.0 ± 1.1	0.7 ± 0.9	-0.6 ± 1.0

n = number of patients; age = age at time of first BST measurement; SD = standard deviation

ing a BST cut-off value of ≥20ng/ml and an area under the curve of 0.74 ± 0.13 for the identification of a low BMD at the lumbar spine (p= 0.02; CI: 0.49 – 0.98) (Fig. **3a** and **b**). Using a cut-off point of ≥30 ng/ml for the BST level, the sensitivity to detect a low BMD at the lumbar spine or hip was 83% and the specificity 70%. Based on our limited patient population the best cut-off value of BST to detect a low BMD would be a BST level of at least 27 ng/ml resulting in a sensitivity of 92% and a specificity of 70%.

Follow-up Assessment of Participants

There was a median duration of clinical follow up of 6.6 years (range 4 to 9 years) after determination of the first BST value above 20 ng/ml. Median duration of BST follow up was 2.3 years (mean 3.0 years, range 1 to 8 years), and median number of BST determinations per patient was 3 times (range 1 to 7). In most of the patients, BST follow-up values remained in a similar range to the initial value, as one would expect for patients with indolent systemic mastocytosis.

Seven patients were prescribed bisphosphonates (patient-numbers 7, 14, 17, 42, 88, 90, 127) for duration of between 2 and 7 years. Patient 17 was changed to calcitonin nasal spray after two years of bisphosphonate therapy. Eight patients reported having been prescribed calcium and vitamin D supplements. The only patient who reported radiologically documented fractures was patient 17, a physically active young woman. She had acquired several fractures of finger bones when snowboarding during wintertime, and reported a traumatic 'fissure' of the proximal tibia of one side. A non-traumatic fracture did not occur in any of the patients. She was the only patient in our study who presented with osteoporosis. Additionally, this patient suffered from chronic diarrhoea for duration of four years. She was first misdiagnosed as having Crohn's disease, but later her symptoms were attributed to gastrointestinal involvement of mastocytosis. It is well known that gastrointestinal involvement with mastocytosis can lead to malabsorption which may cause bone loss.

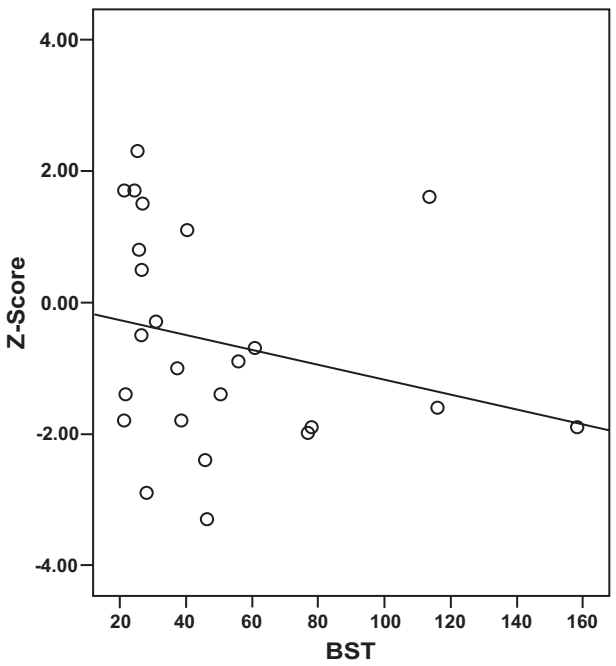

Fig. (1a). Correlation of basal serum tryptase levels (BST, in ng/ml) and bone mineral density Z-score values (Z-Score) of the lumbar spine region.

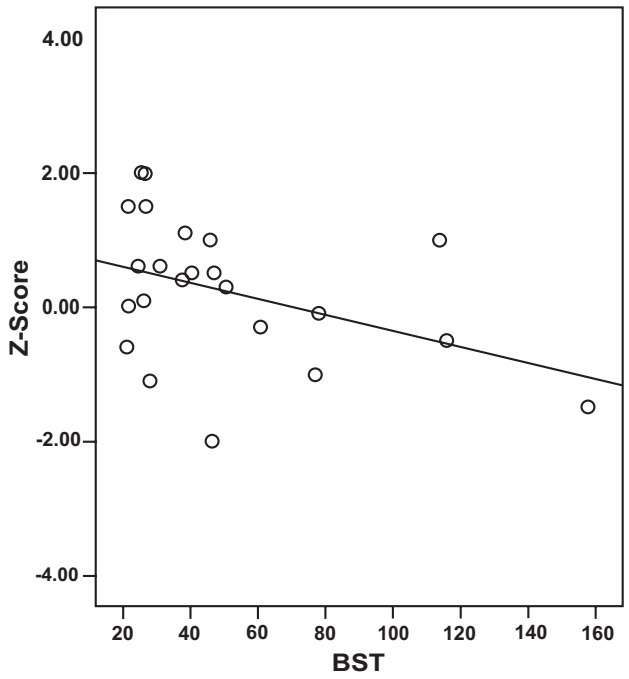

Fig. (1b). Correlation of basal serum tryptase levels (BST, in ng/ml) and bone mineral density Z-score values (Z-Score) of the hip region.

DISCUSSION

The results of this study show, that the prevalence of osteopenia (58%) and osteoporosis (25%) is high in patients with elevated BST levels presenting with severe anaphylactic reactions and other signs of mastocytosis. The group of Dean Metcalfe from the NIH examined the relationship between BST levels and Z-score values in different categories of patients with mastocytosis, including less severe (cutaneous mastocytosis, indolent systemic mastocytosis; ISM) and more aggressive forms (smoldering systemic mastocytosis, systemic mastocytosis with associated haematological monoclonal disease (SM-AHNMD) [15]. In contrast to our results, they found a positive correlation between BST values and Z-score values, which was significant for the femoral neck Z-score values. The lowest values were measured in the group of 14 patients with indolent systemic mastocytosis (ISM). This group had a mean BST value of 107.2 ng/ml. Patients with more severe forms of mastocytosis and higher mean BST values (256.7 for SSM, and 238.7 ng/ml for SM-AHNMD, respectively) were found to have higher BMD in

Table 4. Study Participants According to Basal Serum Tryptase Categories

Categories	All	BST 20-30	BST 30.9-50	BST 50.4-100	BST >100
	(n=24)	(n=10)	(n=6)	(n=5)	(n=3)
Age (years)					
mean (median)	48 (44)	48 (43)	49 (48)	43 (41)	49 (43)
BMI (kg/m2)					
mean	26	26	28	24	27
Z-score values (means)					
Lumbar spine	-0.6	0.2	-1.2	-1.5	-0.6
Hip	0.3	0.6	0.3	-0.3	-0.3
Femoral neck	0.0	0.5	0	-0.8	-0.6

BST values in ng/ml; BMI = body mass index

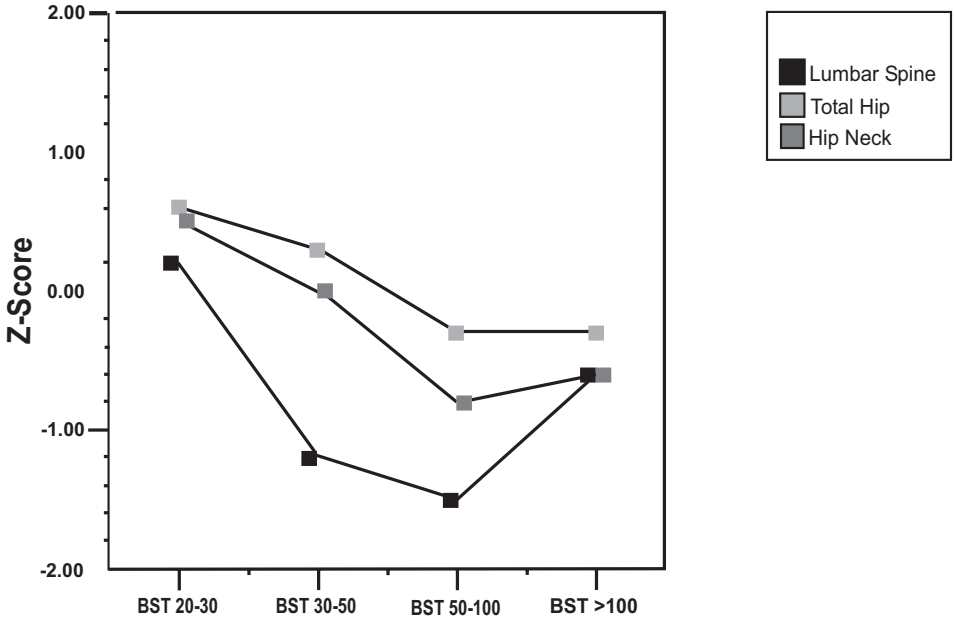

Fig. (2). Correlation of basal serum tryptase (BST) categories as shown in Table **4** and Z-score values (Z-Score) of the lumbar spine, total hip and femoral neck region.

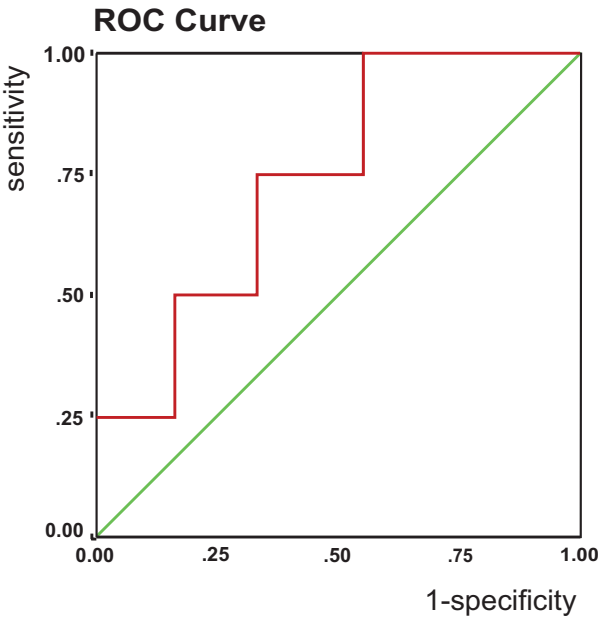

Fig. (3a). Receiver operating characteristic curve showing that the use of a cut-off value of BST level ≥20ng/ml leads to an area under the curve of 0.78 ± 0.11 for the identification of a low BMD at the hip (total hip region, p=0.03; CI: 0.56 – 0.99).

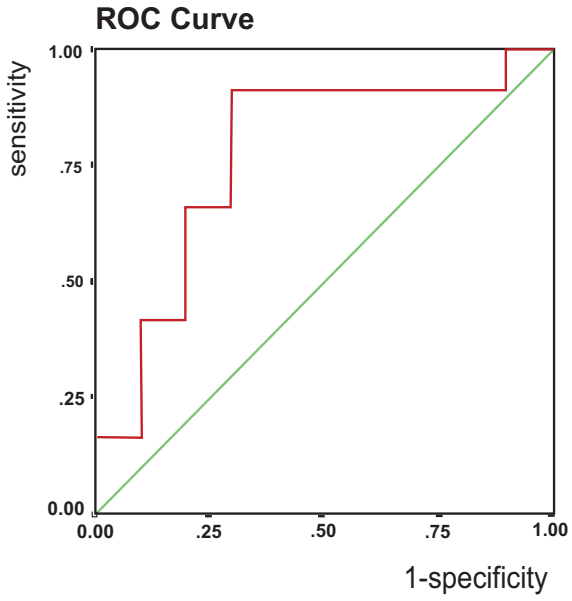

Fig. (3b). Receiver operating characteristic curve showing that the use of a cut-off value of BST level ≥20ng/ml leads to an area under the curve of 0.74 ± 0.13 for the identification of a low BMD at the lumbar spine (p= 0.02; CI: 0.49 – 0.98).

the lumbar spine, upper femur and distal third of the forearm, than patients with less severe forms of mastocytosis. The characteristics of our patients correspond most closely to the group of ISM patients described by Kushnir and colleagues in 2006. Therefore, their findings of lower Z-score values in the ISM group as compared to other forms of mastocytosis, and of a negative association of BMD with hypotensive episodes (corresponding to anaphylaxis [1]), do confirm our observations.

Urine histamine metabolites have been used as surrogate marker of total mast cell burden, similar to BST levels [16, 17]. Brumsen *et al*. showed in a study of 48 men with osteoporosis (mean age 47 years) that the level of urine methylhistamine is negatively associated with BMD values, but positively with mast cell numbers in the bone marrow. Levels of urine methylhistamine were only mildly elevated (highest value 2.5 times the upper limit of the reference range). Four patients with increased N-methylhistamine levels in the urine were diagnosed to have systemic mastocytosis on the basis

of characteristic bone marrow mast cell infiltrates [18]. Studying 16 patients with varying degrees of mastocytosis as determined by the urine excretion of methylimidazoleacetic acid (highest value 8.6 times the upper limit of the reference range), Johansson et al. found lower BMD values and osteoporosis with vertebral fractures in patients with a moderately elevated mast cell mass (values between 1.4 and 4 times the upper limit of the reference range) [19]. In contrast, BMD was higher in patients with more strongly elevated mast cell mass (methylimidazoleacetic acid values 7.5 and 8.6 times the upper limit of the reference range). The overall association between methylimidazoleacetic acid excretion and BMD in the hip was positive, similar to the study of Kushnir et al., who found a positive association between BST and femoral neck BMD Z-score values.

In view of the studies discussed above the results of our study would suggest a U-shaped relationship between the total mast cell burden and BMD in the lumbar spine and hip regions [15, 18, 19]. We found the lowest BMD levels in patients with mildly and moderately elevated mast cell mass, corresponding to BST levels between approximately 30 and 100 ng/ml. In a recent paper, a patient with secondary osteoporosis due to mastocytosis was described who had a BST value of 50.9 ng/ml [20]. The patient excluded from our study because of previous treatment with anti-osteoporotic medication also suffered from secondary osteoporosis due to biopsy proven systemic mastocytosis. His BST was 40.6 ng/ml, again compatible with our finding of lowest BMD values and highest risk of osteoporosis between BST values of 30 and 100 ng/ml. In our patients no non-traumatic fractures occurred during follow-up, but several patients were treated with bisphosphonates.

This study has important limitations relating to the retrospective design, the high exclusion rate of potentially eligible patients, and the selection of patients (e.g. high proportion of females among study participants). Furthermore, there is no control group with anaphylaxis and normal BST values and we cannot provide any follow-up information of those patients from our unit with similar BST values and clinical signs but who did not undergo DXA measurement. Many parameters relevant to BMD and to exclusion of secondary causes of osteoporosis (parathormone, vitamin D, calcium, phosphorus, thyroid hormone, sex hormones, renal excretion) were not evaluated due to the retrospective nature of this study. However, our observations are in line with previous reports and underline that an increase of BST in patients with signs of mastocytosis may correlate with a loss of BMD. In patients with BST values between 30 and 100 ng/ml the prediction of a low BMD would eventually be possible with a sensitivity of 92% and a specificity of 70% when using a cut-off value of BST of 27 ng/ml. However, our this interpretation is limited because of the important variability of the association between BMD and BST observed in our study. However, this observation is based on a very limited number of patients and, therefore, large-scale prospective studies including patients with normal BST values are necessary to confirm our findings and to further investigate the hypothesis of a U-shaped association between BMD and BST.

In conclusion we confirm previous studies indicating an increased risk of low BMD values in patients with moderately elevated BST levels and anaphylaxis. Therefore BMD measurement using DXA should be considered in such patients. In this small series of selected patients we suggest a tendency of higher BMD values in those patients with the highest BST values, a finding that was described by previous authors, too.

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