

Elevation in histamine and tryptase following exercise in patients with mastocytosis

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Clinical Implications

- Patients with mastocytosis exhibit an increase in serum levels of mast cell–related mediators with exercise and therefore should be guided regarding the management of mast cell–associated symptoms to improve safety and quality of life.

TO THE EDITOR:

Mastocytosis is a disorder of clonal mast cell proliferation with clinical features that include episodic flushing, pruritus, abdominal pain, diarrhea, and syncope.¹ The clinical manifestations of mastocytosis are thought in part to be a result of the effects of mediators released from activated mast cells.² Physical factors, such as heat, mechanical stimulation, and exercise, have been reported to increase symptoms. In some patients with mastocytosis, exercise has been reported to provoke anaphylaxis.³

Elevated baseline serum tryptase levels are observed in patients with indolent systemic mastocytosis (ISM) and generally correlate with clinical severity of the disease.⁴ Although increases in both histamine and tryptase have been reported in association with systemic allergic reactions, the effect of physical exercise on the release of mast cell mediators in patients with mastocytosis has not been explored. We thus sought to determine whether exercise could trigger release of mast cell mediators in patients with systemic mastocytosis and compare these results to mediator levels following exercise both in a patient with cholinergic urticaria (CU) and in normal volunteers (NVs).

Following informed consent on National Institutes of Health protocols 09-I-0126 and 02-I-0277, 8 patients diagnosed with ISM (based on the World Health Organization criteria⁵), 1 patient with CU (verified before testing), and 2 NVs underwent treadmill exercise challenge (see Table 1 for patients' demographic characteristics). Before the challenge, an intravenous catheter was placed in the basilic vein of the forearm. Blood was serially drawn at baseline and at designated time points during and up to 2 hours following exercise challenge (Figure 1, A). Blood samples were drawn into serum separation tubes, with serum aliquots stored at -20°C until analyzed. All subjects performed treadmill running/jogging or walking for a minimum of 25 minutes. Subjects were monitored to increase their heart rate to more than 50% maximum (50% of $220 - \text{age}$) as well as for visible perfuse facial sweating. Serum histamine was measured using a competitive enzyme immunoassay (SPI-Bio/Bertin Pharma, Montigny-le Bretonneux, France). Serum tryptase was measured using the ImmunoCAP 100 System (Phadia Inc, Uppsala, Sweden).

The absolute mean increase from baseline in serum histamine following challenge was greater in patients with ISM for all time points compared with NVs (Figure 1, B). As a positive control, we included a patient with CU who exhibited papular urticaria and a sharp rise in serum histamine levels as has been reported following exercise challenge.⁶ We similarly found that there was a significant difference (Wilcoxon matched-pairs signed rank test, $P = .0078$) in the serum histamine postexercise peak among patients with ISM when compared with baseline (Figure 1, C), an observation not seen in the NVs. The absolute mean increases in tryptase following exercise were less striking than with histamine, although patients with ISM did exhibit an increase in tryptase postexercise (Figure 1, D). Similar to histamine, postexercise peak values of serum tryptase in patients with ISM were significantly higher ($P = .0234$) compared with baseline (Figure 1, E). Furthermore, when using the Mast Cell Activation tryptase index (20% plus 2 ng/mL over the baseline level), 2 of the 8 patients (ISM-2, ISM-4, Table 1) with ISM exhibited an increase in serum tryptase levels following exercise that would meet criteria for the diagnosis of systemic mast cell activation⁷ that was not detected in patients with CU or NVs. Although patient number 4 with ISM (ISM-4, Table 1) exhibited the most dramatic increase in serum histamine and tryptase levels following exercise, the differences between baseline and postexercise peak mediator levels remain significant when removing this subject from the ISM patient data set (histamine, $P = .0078$ with #4, $P = .0156$ without #4; and tryptase, $P = .0234$ with #4, $P = .0469$ without #4). Consistent with this, patient number 4 with ISM has been avoiding strenuous exercise because of increase in symptoms. As expected, we found a significant correlation between the absolute change from baseline to postexercise peak levels of serum histamine and that of tryptase (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org; $r = 0.9628$; $P = .0001$).

We next investigated whether histamine and tryptase release parallels mastocytosis severity and found that the extent of mast cell bone marrow infiltration was associated with absolute postexercise serum mediator level increases (see Figure E2, A and B, in this article's Online Repository at www.jaci-inpractice.org). Other manifestations of systemic mastocytosis such as osteoporosis did not show any evidence of association with higher increases in histamine or tryptase levels following exercise (Figure E2, C and D). Patients described the various symptoms that were experienced either during or directly after exercise challenge (Table 1). We found that there was a trend toward an association between a greater absolute increase in serum histamine/tryptase levels and gastrointestinal symptoms as well as pruritis following exercise (Figure E2, E-H).

We have presented evidence that patients with ISM exhibit a significant and intercorrelated rise in histamine and tryptase following exercise consistent with the conclusion that physical activity can induce mast cell mediator release. Furthermore, the increase in these mediators in circulation was associated with an exacerbation of mast cell mediator-related symptoms in the ISM cohort. Our current study in patients with ISM corroborates an accumulating body of evidence that suggests that physical exercise can trigger mast cell degranulation. Indeed, exercise is

TABLE I. Patients' demographic characteristics and results

Patient no.	Age (y)	Sex	Characteristics associated with ISM		Baseline symptoms (further increased with exercise)				Serum histamine			Serum tryptase			MCA tryptase index*
			History of anaphylaxis	Osteoporosis	GI	Headache	Pruritis	Bone pain	Baseline (nM)	Postexercise peak (nM)	Relative change† (% of baseline)	Baseline (ng/mL)	Postexercise peak (ng/mL)	Relative change† (% of baseline)	
ISM-1	30	F	✓		✓		✓		9.6	16.4	71	7.74	11.8	52.5	11.3
ISM-2	62	M		✓					12.2	15.4	26	98.2	99.5	1.3	119.8
ISM-3	60	M		✓					14	18.4	30.6	44.3	42.9	−3.2	55.2
ISM-4	41	F	✓		✓		✓		17.2	111.3	545.7	48.9	65.2	33.3	60.7
ISM-5	56	F		✓			✓		59.1	75	26.9	38.1	41	7.6	47.7
ISM-6	42	F			✓	✓	✓	✓	19.5	23.9	22.7	19.6	21.3	8.7	25.5
ISM-7	42	M	✓		✓				10.7	12.9	20.9	18	20	11.1	23.6
ISM-8	34	M		✓			✓		34.3	50.3	46.7	25.8	29.9	15.9	33
NV-1	34	M							3.9	3.5	−10.1	2.9	3.4	19.9	5.4
NV-2	56	M							5.7	9	57.9	4.4	6.7	51.8	7.3
CU-1	21	M							7.7	7.9	3.5	4.5	5.2	16.1	7.4

F, Female; GI, gastrointestinal; M, male.

Bold values indicate patients met the criteria for systemic mast cell activation (MCA).

*MCA tryptase index (baseline serum tryptase $\times$ 1.2 + 2) represents the minimum serum tryptase concentration for each patient (following an acute increase) needed in order to be considered indicative of systemic MCA.⁷

†Relative change from baseline calculated as (postexercise peak − baseline)/(baseline) $\times$ 100.

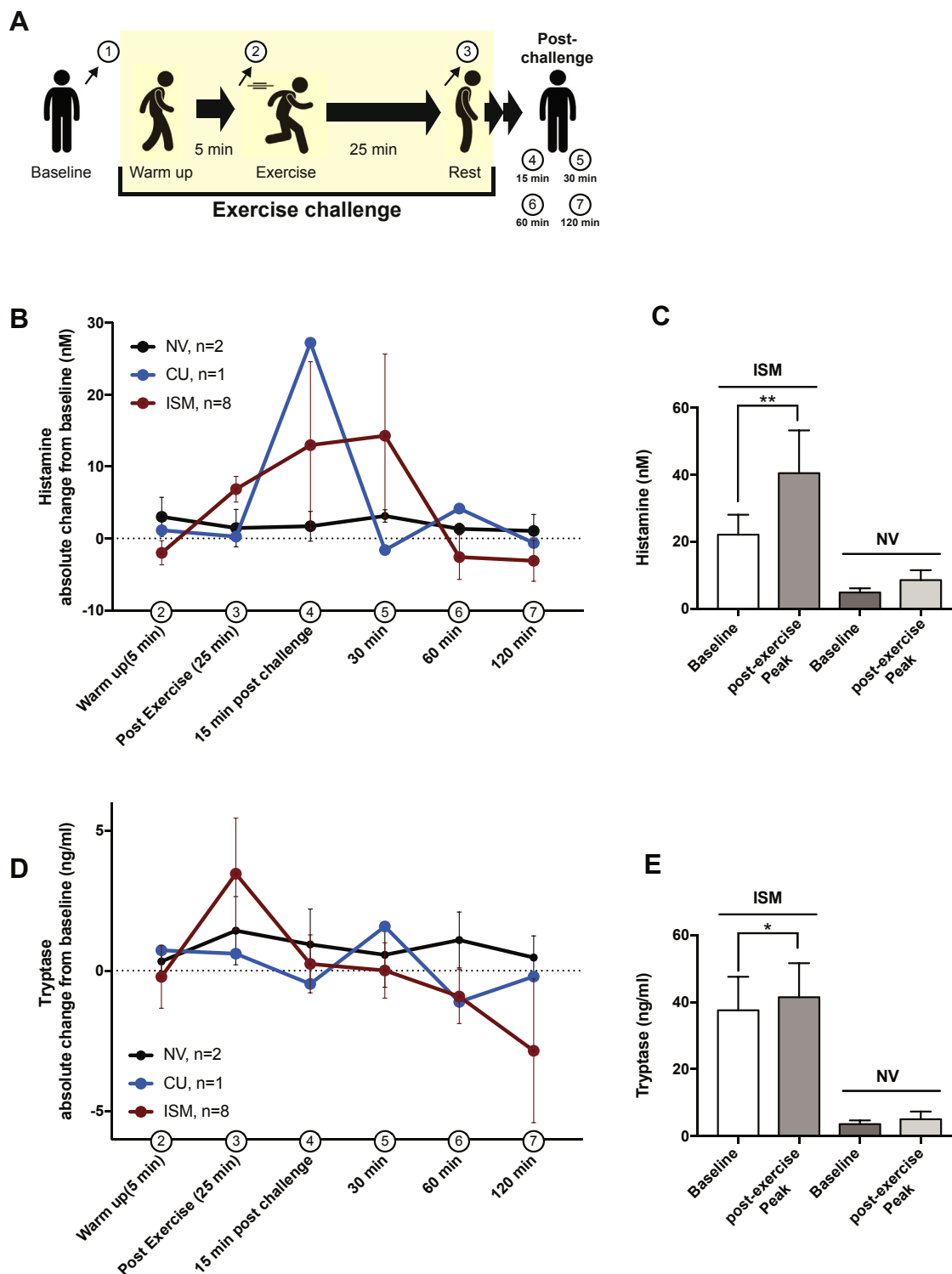


FIGURE 1. The effect of exercise on serum histamine and tryptase levels in patients with mastocytosis. **A**, Exercise challenge depicting blood draws (1-7). **B**, Mean $\pm$ SE change in serum histamine from baseline (time point 1) at time points 2 to 7. **C**, Baseline and peak postexercise serum histamine levels (mean $\pm$ SE for each group). Same for tryptase (**D** and **E**). Data were derived from 3 technical replicate measurements at each time point. A 2-tailed Wilcoxon matched-pairs signed rank test was used to compare baseline and postexercise peak levels of serum histamine (Fig 1, C) and tryptase (Fig 1, E) among individuals in the ISM patient cohort. * $P < .05$; ** $P < .01$.

considered a significant augmenting factor in as much as 10% of food-related anaphylactic reactions⁸ and has recently been reported to cause local release of histamine and tryptase from skeletal muscle.⁹ In conclusion, our findings suggest that clinicians managing patients with systemic mastocytosis should instruct their patients regarding the effects of exercise and provide guidance in the judicious use of mast cell mediator receptor antagonists that may provide relief of symptoms as well as the self-administration of epinephrine for the treatment of anaphylaxis should it occur.

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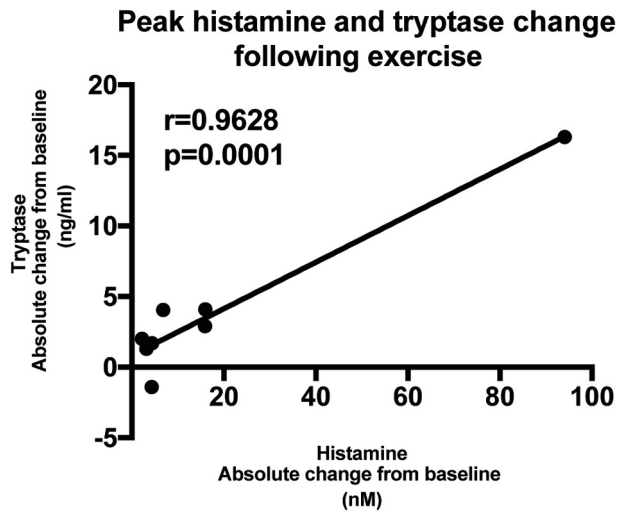


FIGURE E1. Correlation between the absolute change (from baseline to postexercise peak) in serum histamine and the absolute change (from baseline to postexercise peak) in serum tryptase among patients with ISM.

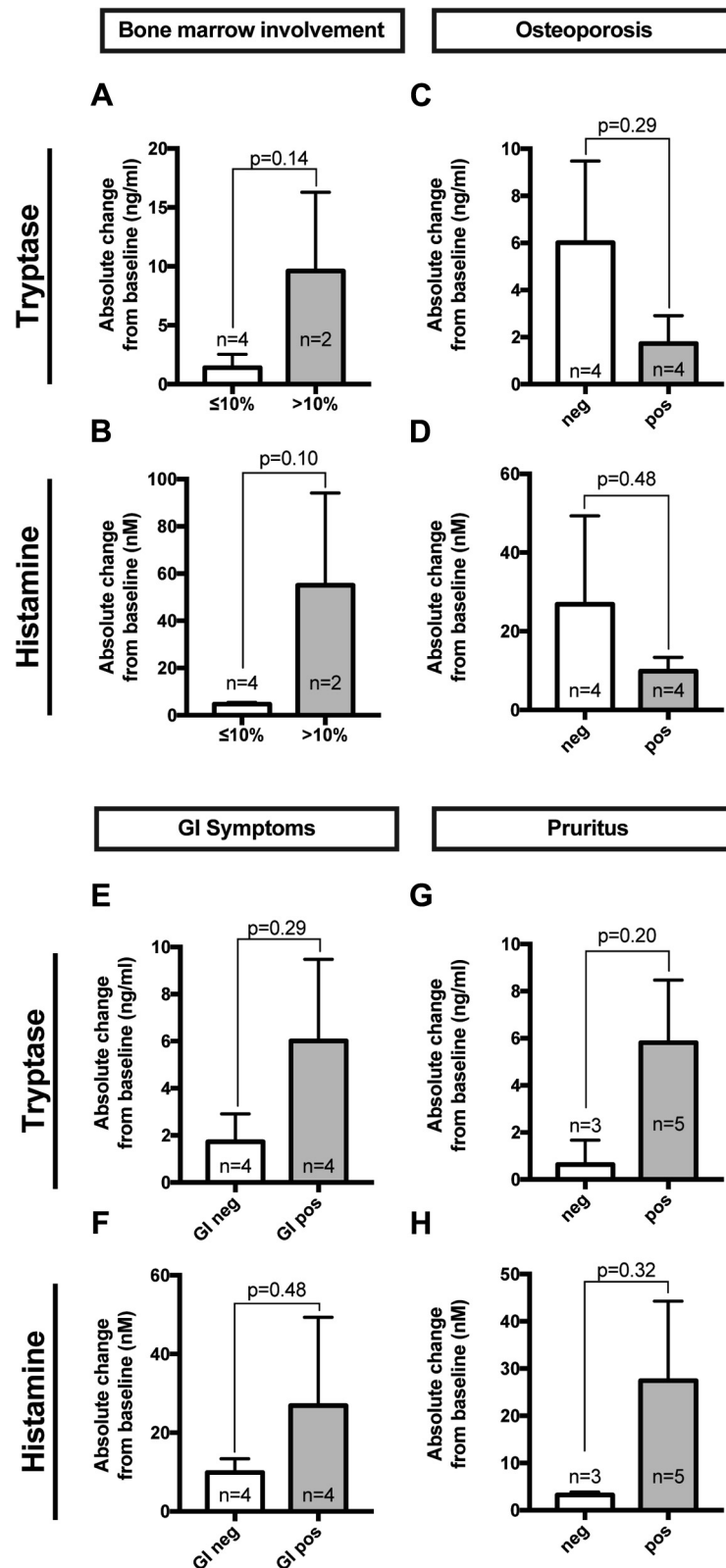


FIGURE E2. Comparison of acute serum mediator level increase following exercise in patients with ISM stratified by mastocytosis-related clinical parameters. **A-D**, Comparison of the absolute change (from baseline to postexercise peak) in serum tryptase (Figure E2, *A* and *C*) and histamine (Figure E2, *B* and *D*) among patients with ISM who exhibit clinical parameters associated with mastocytosis disease severity. **E-H**, Comparison of the absolute change (from baseline to postexercise peak) in serum tryptase (Figure E2, *E* and *G*) and histamine (Figure E2, *F* and *H*) in patients with ISM who exhibited mast cell mediator-associated symptoms (pos, positive) or not (neg, negative) during exercise. Plots represent the mean $\pm$ SE data obtained from the indicated number of patients with ISM in each category. *P* values were calculated using a 1-tailed unpaired *t* test. *GI*, Gastrointestinal.