Major Article

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Length and caliber of the rectosigmoid colon among patients with Chagas disease and controls from areas at different altitudes

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ABSTRACT

Introduction: In this study, we investigated radiological changes in the sigmoid colon in chagasic patients by comparing their colon lengths and caliber with those of non-chagasic living in the same region and non-chagasic living at high altitudes. **Methods:** A total of 317 individuals were evaluated using clinical, serological and radiological methods and divided into three groups: 1) one hundred and nine non-chagasic individuals from Uberaba, Brazil; 2) sixty-one non-chagasic from Puno, Peru; 3) one hundred forty-seven chagasics examined in Uberaba, being 62 without megacolon (3A), 72 with megacolon (3B) and 13 with doubtful diagnosis of megacolon (3C). **Results:** In group 2, the sigmoid colon had a significantly larger caliber ($p=0.001$) and the rectosigmoid colon was longer ($p<0.001$) than group 1. In subgroup 3A, the sigmoid colon ($p<0.001$) and rectum ($p<0.001$) had a significantly larger caliber and the rectosigmoid was longer ($p<0.001$) than that of the non-chagasic individuals. In subgroup 3B, the rectosigmoid was longer in all patients, and the caliber of the sigmoid was significantly larger than that of subjects in subgroups 3A and 3C ($p<0.001$). **Conclusions:** Morphometric analysis confirms that Chagas disease may increase the caliber and length of the rectosigmoid. Our results suggest that altitude, ethnicity and diet may have influenced the size and length of the rectosigmoid of andean patients.

Keywords: Chagas disease. Radiology. Megacolon. Sigmoid. Morphometry. Altitude.

INTRODUCTION

Human Chagas disease (HCd), which affects between 2 and 3 million Brazilians, is an important societal problem[1], with 75-90 million Latin Americans at risk of becoming infected[2].

The association between megacolon and *Trypanosoma cruzi* was reported by Chagas and Villela[3]. The etiopathogenesis of megacolon in HCd is a lesion caused by *T. cruzi* in the intramural nerve plexus of the autonomic nervous system in the large intestine. Decreased numbers of neurons (hypoganglionosis) is necessary and sufficient for development of megacolon[4,5]. Intramural denervation leads to dyskinesia of the affected segment and typically culminates in dilatation and elongation of the terminal colon, which is responsible for deposition. Moreover, secretion, absorption, and motility are altered, leading to chagasic megacolon[5].

Altitude is thought to influence colon caliber and length. A study by Frisancho[6] showed that dolichomegacolon of those living in the Andes mountains has several specific clinical, radiological, and anatomopathological characteristics as well as complications that distinguish it from other types of megacolon, particularly chagasic megacolon[7,8].

In the Andes, megacolon is common among inhabitants of the South American regions located 3,000m above sea level; this condition is thought to be unrelated to HCd. Increased colon caliber and length are attributed to racial factors, cocaine use, and vitamin B deficiency among patients in Sucre, Bolivia[9]. These morphological changes were also seen in patients in Peruvian hospitals located at altitudes >3,000m above sea level in the Andes[10]. Several possible causes of megacolon in Andean patients have been proposed, including anatomical elements, longer sigmoid colon, and aggravating factors including dietary habits, low atmospheric pressure, and racial factors.

Radiological analysis of colonic segments is difficult because of diversity in measurement methods[11,12], and no standards exist to describe normal or abnormal colopathy. Therefore, to examine variations, it is necessary to compare normal colons to those of patients with HCd. We conducted a

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radiological investigation to analyze the rectosigmoid colon and compare differences between controls and patients with HCd. The rectosigmoid colon was chosen for the analysis because it is easily accessible and generally affected by HCd. Therefore, the aim of this study was to examine the radiological alterations within the sigmoid colon in patients with HCd and compare the measurements with those in control individuals in Brazil and control individuals living at high altitudes.

METHODS

The study was conducted in region with altitude of 762 feet above sea level in Brazil, and at the mountainous region of Peru at an altitude of 3,850 feet above sea level.

Patients

A total of 317 individuals were examined and divided into 3 groups as follows: *Group 1*: one hundred nine individuals with negative serological results for HCd from *Triângulo Mineiro* and Alto Paranaíba, State of Minas Gerais, Brazil (35 men with a median age of 45 years and 74 women with a median age of 42 years); *Group 2*: sixty-one individuals with negative serological results for HCd from the region of Puno, Peru (40 men with a median age of 37 years and 21 women with a median age of 36 years); and *Group 3*: one hundred forty-seven patients with HCd from *Triângulo Mineiro*, Brazil (median age, 58 years; 62 without megacolon [subgroup 3A], 72 with megacolon [subgroup 3B], and 13 with an unconfirmed diagnosis of megacolon [subgroup 3C]).

Patient selection

The Brazilian individuals were selected from among patients with chronic HCd who were seeking outpatient services. The patients underwent a clinical examination in which all data were collected in a standard form prepared for this study. They were then subjected to a series of complementary examinations such as repeated serology for HCd, blood cultures for *T. cruzi*, and tests to characterize the clinical form of HCd.

Control individuals (Group 1), were from several clinical departments from Clinics Hospital, and did not have complaints related to HCd. Subjects from high-altitude regions (Group 2) were selected from those living within Puno, Peru. These individuals were chosen from employees and patients at the Puno's Hospital; their family members were also selected. Individuals in both groups with diarrhea, constipation for >3 days, or evidence of inflammatory or tumor-like intestinal lesions and those who were <20 or >60 years of age were excluded from the study.

A clinical evaluation was previously conducted in patients and controls to rule out secondary causes of megacolon dysfunction, such as congenital or toxic megacolon, intestinal parasitic disease, cancer, or metabolic causes (diabetes mellitus and hypothyroidism).

Serological exams for human Chagas disease

Blood samples were collected from all patients, and serological reactions such as indirect hemagglutination (IHA), indirect immunofluorescence reaction (IFR), and enzyme-linked immunosorbent assay (ELISA) were conducted to diagnose HCd. Only samples that were positive for at least 2 of the 3 performed tests were considered seropositive.

Blood samples of the patients from Puno were acquired via finger prick, collected on Whatman® qualitative filter paper, Grade 1 (Sigma-Aldrich, USA), and tested using the same serological tests.

Radiological exams

Colopathy was diagnosed by measuring the caliber and length of the rectosigmoid colon.

Thoracic teleradiography was used to evaluate the heart. Conventional radiography of the abdomen with the patient in the supine position was used to evaluate the distribution of intestinal gas before administration of opaque enema. These tests were performed using medium-sized devices at 500mA and 125kVp without an image intensifier.

In Group 1, the colon test was preceded by intestinal preparation with administration of a laxative the day before and an aqueous enema 4h before the test. In all other groups, contrast colonoscopy (opaque enema) was conducted without intestinal preparation, according to the simplified technique reported by Ximenes et al.[13]. In all patients, 300mL of barium sulfate was diluted in 900mL of water for a total volume of 1,200mL. Radiography was performed for each patient in the supine, prone, and side positions for a total of 3 radiographs each. The technique reported by Ximenes et al.[13] was also used in Puno.

To diagnose megacolon, we determined whether the colon was enlarged by dilatation or elongation. We identified different sigmoid parameters and classified them as I, II, III, or undetermined based on the Farrar guidelines to determine the morphology of the sigmoid colon in control individuals in Uberaba[11].

To measure the length of the rectosigmoid colon, a curvimeter was used and passed through the central axis of the colon using a backward motion from the anus up to the left iliac crest, which was assumed to be the beginning of the sigmoid colon. The caliber and length of the sigmoid colon and rectum were measured using a ruler based on the results of the side radiograph of the rectum. These measurements were always conducted at the level of the third sacral vertebra or where the sigmoid colon had a larger diameter. The caliber of the rectum was measured below the S3 level to the sigmoid colon. All measurements were conducted twice at different time points by the same investigator so that reproducibility of this method could be ensured.

Statistical analysis

Quantitative variables are expressed as medians. Those measurements were compared among groups (Groups 1, 2, 3A, 3B, and 3C) using the Kruskal-Wallis, non-parametric analysis of variance (ANOVA) test, and Dunn's multiple comparison test or the Mann-Whitney *U* test wherever appropriate. The possible effects of age or height on the measured rectosigmoid parameters were evaluated using Spearman's correlation, while the effect of gender in each group was evaluated using the Mann-Whitney *U* test.

To compare categorical variables among groups, the χ^2 test with Yates's correction was used as needed or Fisher's exact test was employed. Probabilities < 5% ($p < 0.05$) were considered statistically significant.

Ethical considerations

This study was approved by the Institucional ethics committee of our Federal University. The study participants were informed of the tests to be performed and provided written consent.

RESULTS

A total of 317 patients with HCd and controls were divided into 3 groups and examined from 2000 to 2005. Analysis of subject age showed that individuals with Chagas tended to be older than controls ($p < 0.005$). There was no age difference between the HCd subgroups.

In control individuals (Group 1), the caliber of the sigmoid colon was 2-6cm with a median of 3.1cm. There was a significant gender-related difference ($p = 0.029$) in caliber (median, 3.3cm in males vs. 3cm in females). The caliber of the rectum was 2.5-8.5 cm with a median of 4.5cm. Individual gender, age, and height did not affect caliber. The length of the rectosigmoid colon was 32-75cm. The median length was 57cm and was significantly influenced by patient gender, age, and height **(Table 1)**.

Based on the tests performed on 109 control individuals (Group 1) and using a 99% percentile for comparison with other groups, we considered the following as the upper normal limits: sigmoid caliber, 4.5cm; rectum caliber, 7.4cm; and rectosigmoid length, 74cm.

In control individuals (Group 2), the caliber of the sigmoid colon was 3.2-8.0cm with a median of 5cm. The caliber of the rectum was 2.5-8cm with a median of 4cm. In 15 (24.6%) individuals, the rectum had a higher caliber than that of the sigmoid colon. The length of the rectosigmoid colon was 45-84cm with a median of 65cm **(Table 1)**. None of these measurements were influenced by gender, age, or height.

In the radiological exam of the sigmoid colon and rectum of 147 patients with HCd (Group 3), we diagnosed megacolon in 72 (49%) patientes. Thirteen (8.8%) had a unconfirmed diagnosis, whereas 62 (42.2%) did not have megacolon.

In patients with HCd but without megacolon (subgroup 3A), the caliber of the sigmoid colon was 2.5-5.0cm with a median of 3.4cm. The caliber of the rectum was 3.0-7.6cm (median, 5.4cm). The length of the rectosigmoid colon in subgroup 3A was 31-86 cm (median, 65cm) **(Table 1)**.

We observed that the caliber of the sigmoid colon was significantly greater in subjects from Puno than in those from Uberaba (5.0cm and 3.1cm, respectively; $p=0.001$). Moreover, their rectosigmoid colons were larger (65cm in Puno vs. 57cm in Uberaba; $p<0.001$) (**Table 1** and **Figure 1**).

The measurements of only 3 (2.7%) patients in this group exceeded the limits established for Group 1, whereas 41 (66.1%) individuals in Group 2 had measurements that exceeded the normal limits **(Table 1)**.

Calibers of the sigmoid colon (3-4cm) and rectum (5-45cm) and the length of the sigmoid colon (65cm) of the patients with HCd but without megacolon (subgroup 3A) were significantly higher than those of the control individuals from Group 1, who had measurements of 3.1, 4.5, and 57cm, respectively (**Table 1** and **Figure 2**).

All 72 patients diagnosed with megacolon (subgroup 3B) had increased rectosigmoid colon length. The calibers of the rectums were measured in 54 patients with megacolon and were 3.0-13.5cm (median, 6.1cm). The calibers of the rectums were 3.5-10cm (median, 6.3cm). No patients had a caliber <3.5cm, and the caliber did not exceed 7.4cm in 39 (72.2%) patients **(Table 2)**.

TABLE 1 - Comparisons between non-chagasic individuals examined in Uberaba, State of Minas Gerais, Brazil, (group 1) and in Puno, Peru, (group 2) and between non-chagasic individuals of Uberaba (group 1) and chagasics without megacolon (subgroup 3A).

	Median	Group 1 (n = 109)	Group 2 (n = 61)	P value Groups (1x2)	Subgroup 3A (n = 62)	P value Groups (1x3A)
Caliber of the sigmoid		3.1cm	5cm	0.001	3.4cm	0.013
	<3.5cm	73 (67%)	2 (3.3%)	0.001	32 (50%)	0.271
	>4.5cm	1 (0.9%)	39 (63.9%)	>0.001	5 (8%)	<0.001
Caliber of the rectum		4.5cm	4cm	0.008	5.45cm	<0.001
	<3.5cm	12 (11%)	2 (3.3%)	0.142	3 (4.8%)	0.001
	>7.4cm	1 (0.9%)	1 (1.6%)	0.749	2 (3.2%)	0.276
Length of the rectosigmoid		57 cm	65 cm	<0.001	65 cm	<0.001
	<50cm	18 (16.5%)	1 (1.6%)	0.007	7 (11.3%)	0.481
	>74cm	1 (0.9%)	12 (19.7%)	<0.001	10 (16.1%)	<0.001

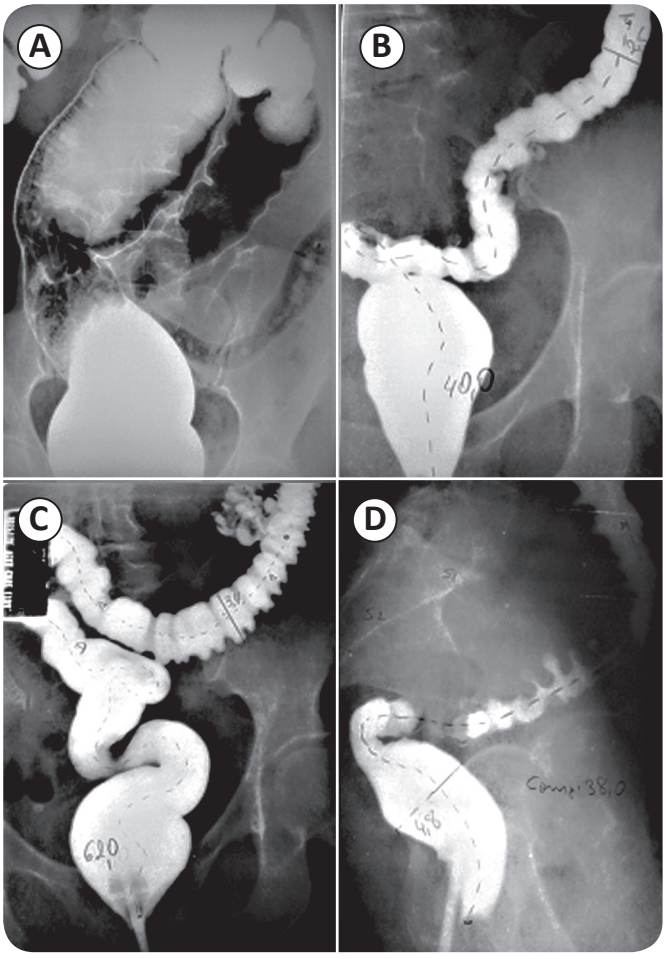

FIGURE 1 - Different morphologies of the rectosigmoid colon: increased sigmoid caliber and length (A), increased rectum caliber only (B), increased rectum caliber with normal sigmoid caliber (B) and (D), and elongated sigmoid (C).

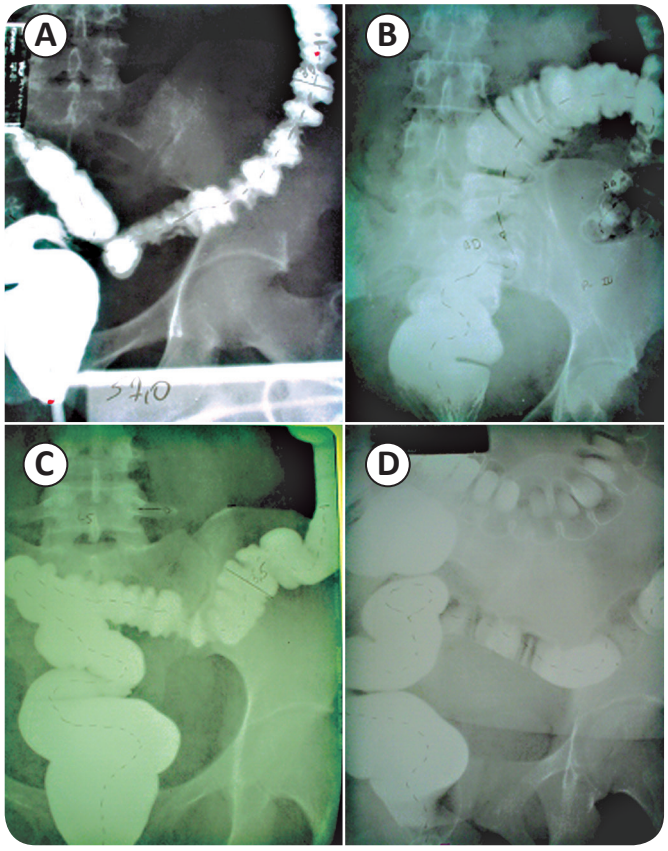

FIGURE 2 - Normal (A) and altered morphometry (B). Normal rectosigmoid colon of a patient from Uberaba (C) and a patient from Puno (D).

All patients from subgroup 3B showed a large increase in sigmoid colon length, making this measurement impossible. When there were large alterations, the calibers of both the rectum and sigmoid colon increased.

All patients with an unconfirmed diagnosis of megacolon (subgroup 3C) had a rectosigmoid length that exceeded the normal limit (74cm). None was <80cm, and the median was 88.5cm. We observed that 41.6% of the calibers of the sigmoid colon and 25% of the calibers of the rectum exceeded the maximum normal limits established in this study **(Table 2)**. The calibers of the sigmoid colon and rectum were significantly higher in subgroup 3B than in subgroup 3A ($p < 0.001$) **(Table 2)**.

When the length of the sigmoid colon increased significantly (subgroup 3B), the calibers of the rectum and sigmoid colon increased and were higher than the normal limits in 11 (20.3%)

TABLE 2 - Comparisons between chagasics without diagnosis of megacolon (subgroup 3A) and those diagnosed with megacolon (subgroup 3B) and between chagasics with megacolon (subgroup 3B) and those with doubtful diagnosis of megacolon (subgroup 3C).

	Median	Subgroup 3A	Subgroup 3B	P value	Subgroup C	
	(n = 62)	(n = 72)	Groups (3Ax3B)	(n = 13)	Groups (3Bx3C)	P value
Caliber of the sigmoid		3.4cm	6.10cm	<0.001	4.1cm	<0.001
	<3.5cm	32 (50%)	1 (1.8%)	<0.001	2 (16.6%)	0.083
	>4.5cm	5 (8%)	50 (92.6%)	0.001	5 (41.6%)	<0.001
Caliber of the rectum		5.45cm	6.3cm	<0.001	6.75cm	0.987
	<3.5cm	3 (4.8%)	0	0.293	0	-
	>7.4cm	2 (3.2%)	15 (27.8%)	<0.001	3 (25%)	1

patients. The lengths of the rectosigmoid colon were higher in subgroup 3B patients (with megacolon) than in subgroup 3C patients. Additionally, the sigmoid calibers were significantly higher in subgroup 3B patients; however, there was no difference in rectum calibers **(Table 2)**. Of the 13 patients in subgroup 3C, only 1 (7.7%) had a simultaneous increase in sigmoid and rectum calibers, while this simultaneous increase was observed in 12 (22.2%) patients in subgroup 3B. In subgroup 3C, there were 5 (41.6%) patients with calibers higher than the normal limits, while this was observed in only 3 (7.4%) patients of subgroup 3B. A caliber increase in either the sigmoid colon or the rectum was observed in 7 (58.3%) patients of subgroup 3C and in 39 (74.1%) patients of subgroup 3B.

DISCUSSION

The chronic phase of HCd includes a period of subpatent parasitemia after the first 60 days of acute infection[14]. The factors influencing the clinical variability of the phases of HCd have not been elucidated, but genetic variability of both the host and the parasite may be important[15].

The most frequently observed alterations of the digestive form of HCd include esophagopathy and colopathy, which cause swallowing difficulties and constipation, respectively[16,17]. Colopathy manifests as prolonged constipation, which may have serious complications such as fecaloma and volvulus.

This study aimed to contribute to the diagnosis of colopathy, particularly small dilatations, by proposing the standard for measuring rectosigmoid dimensions. Thus, we established normal limits for sigmoid and rectum calibers and rectosigmoid lengths.

Compared to our results, studies have reported different median sigmoid and rectum values. Rezende et al.[18] found that the diameter of a normal sigmoid colon should be <6cm. Hernandez et al.[19] studied approximately 60 individuals and identified a mean sigmoid caliber of 4.38, rectum caliber of 6.2cm, and rectosigmoid length of 51.2cm; all of these values are lower than those found in this study. However, the maximum values in control individuals are similar. This similarity suggests that the differences in limits established by earlier previous studies may be due to the measurement methodology.

Occurrence of megacolon in Puno and other regions within the Andes represents a special situation that requires further study, despite studies that have already been conducted by researchers from Bolivia, Argentina, Chile, and Peru. These studies describe changes in the colon in those living in the Andes and the existence of another type of endemic non-chagasic megacolon. They draw attention to the frequency of volvulus[20,21] and changes in intestinal transit[7] in certain countries of the Andes, which motivated us to include this population in our study.

The unique significant difference in rectosigmoid measurements between patients from Uberaba and those from Puno was that the patients from Puno had rectums with smaller calibers.

The initial hypothesis that dolichomegacolon in the Andes is due to altitude appears to have no basis because there are no reports of megacolon occurrence in other populations living at the same or even higher altitudes such as in the Alps or the Himalayas[10]. However, we unexpectedly observed a higher frequency of intestinal movement in patients from Puno, with a mean interval of 0.73 days in contrast to the interval of 2 days observed in controls from Uberaba. This difference may be related to the smaller caliber of the rectum observed in Puno despite the higher sigmoid caliber. However, other factors such as diet, cocaine use, and race must be considered and investigated further.

Patients with HCd have greater calibers of the sigmoid colon and rectum and grater rectosigmoid lengths than those of control individuals. Sigmoid colon caliber was significantly greater among individuals with HCd and evidence of megacolon than among individuals without megacolon and those with unconfirmed diagnosis. A similar study by Castro[12] of 291 patients showed similar findings regarding sigmoid measurements; however, the authors observed that the mean diameters of the rectums in patients with HCd did not differ significantly from those of control individuals.

We used morphometry to confirm the presence of megacolon in both cases classified as unconfirmed and others previously considered normal. In these cases, calibers of the sigmoid colon and rectum and rectosigmoid colon lengths were significantly higher in control individuals (8%, 3.2%, and 16.1%, respectively), that were higher than normal. In 16 (25.8%) patients, morphometry showed incipient organ enlargement. Such findings show that colopathy occurs more frequently than what can be evaluated using conventional radiology.

In addition to being relevant for diagnosis, the use of morphometry revealed the importance of rectosigmoid elongation in pathophysiology of the megacolon. It showed that even in cases of advanced megacolon, sigmoid and rectum calibers may remain normal, which confirms the results of earlier studies showing that elongation may precede dilatation[22]. In contrast to the esophagus, elongation of the megacolon occurs earlier and more frequently, the fecal content is retained, and an intestinal transit delay occurs[22].

Among the 3 radiological measurements obtained, only the rectosigmoid length had increased in all radiographs with a megacolon diagnosis. Even among the 13 patients for whom diagnosis was unconfirmed after radiography, morphometry enabled detection of alterations, thus allowing the diagnosis of megacolon. The 10 patients with a colon >74cm (subgroup 3A) were considered to have incipient megacolon. However, without using morphometry, it is extremely difficult to identify such patients.

The clinical type of megacolon could be determined in 50 of the 62 patients with HCd who were diagnosed as not having megacolon and in whom measurements showed incipient megacolon. Of these, 14 were undetermined, 9 were cardiac, 10 were mixed, and 17 were digestive, with 3 (13%) showing abnormal values of the colon on morphometry. Esophagopathy was observed in 27 subjects, while an increased rectosigmoid caliber or length was seen in 10 (37%).

In summary, our results suggest that factors such as diet (corn, potatoes, and starchy foods), cocaine use, ethnicity, and altitude may have influenced rectosigmoid calibers and lengths of Andean patients. Morphometry revealed that HCd may increase rectosigmoid caliber and length. Moreover, measurement results are dependent on the observer.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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