Published in final edited form as:

J Allergy Clin Immunol Pract. 2020 January ; 8(1): 364–367.e2. doi:10.1016/j.jaip.2019.08.045.

IgE to Galactose- α -1, 3-Galactose Wanes Over Time in Patients Who Avoid Tick Bites

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To the Editor:

Galactose- α -1,3-galactose (α -Gal) is an oligosaccharide of non-primate mammals and the target of IgE antibodies in the syndrome of delayed anaphylaxis to mammalian meat^{1,2}. The connection between IgE sensitization to α -Gal and tick bites is now well established, and in North America the α -Gal syndrome has consistently been associated with *Amblyomma americanum*^{3–7}. Case reports and clinical experience suggest that levels of IgE to α -Gal can decrease over time in some patients, particularly those who avoid additional tick exposures^{3, 8}, but the natural history of IgE to α -Gal has not been systematically examined. Here we report results of a retrospective investigation into the trend and rate of changes in α -Gal specific IgE (sIgE) and total IgE in relation to tick exposure in subjects with established α -Gal syndrome.

This study was approved by the Institutional Review Board at the University of Virginia and involved a previously reported cohort of subjects who presented for evaluation of red meat allergy and tested positive for α -Gal sIgE (>0.1 IU/mL)⁹. Subjects were included in this analysis if they had serum assayed on at least two separate occasions and had information about interval tick bites. Sixty-seven subjects met the study criteria, with some subjects having more than one set of paired samples available for analysis. Twenty-two subjects had at least one encounter without interval tick bite(s), 37 subjects had at least one encounter with reported interval tick bite(s), and 8 subjects denied tick bites in one interval but reported tick bites in a separate interval. The clinical characteristics of these subjects are shown in supplementary Table e1. Of the total cohort, the median age was 54 years, 48% were male, 90% were Caucasian and the median α -Gal sIgE level at baseline was 13 IU/mL.

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Conflicts: ECM has received grants from the National Institutes of Health (NIH), the American Academy of Allergy, Asthma and Immunology (AAAAI), and Food Allergy Research and Education (FARE), and served as a consultant for Shire, Inc.; TPM has a patent on an IgE assay to α -Gal and has received assay support from Phadia/Thermo-Fisher; the other authors report no conflicts

The baseline α -Gal sIgE level trended higher in those who denied tick bites (median 26 IU/mL [IQR 5-75]) as compared to those who reported tick bites (10 IU/mL [5-33]), but this did not achieve significance ($p=0.16$).

Because we hypothesized that tick bites would influence changes in α -Gal sIgE levels, sera samples were stratified according to tick bite status. Levels of α -Gal sIgE and total IgE were compared in paired sera using the Wilcoxon matched-pairs rank test. There were 47 encounters where subjects denied interval tick exposures and 60 encounters where subjects reported interval tick bites (Fig 1A). The levels of α -Gal sIgE and total IgE decreased over time in patients that denied tick bites ($p<0.001$ for both α -Gal sIgE and total IgE), but not in those who reported tick bites (Fig 1B). The results were similar when α -Gal sIgE was expressed as a percentage of total IgE (Fig e1A). The α -Gal sIgE titers decreased in 42 of the 47 encounters in which subjects denied tick exposure, as compared to 23 of the 60 encounters in which tick bites were reported (89% vs 38%, $\chi^2 p<0.001$). To estimate the rate at which α -Gal sIgE changed over time, we transformed data from paired samples into percentage change and this value was normalized on a per year basis. The amount of time between paired samples ranged from 2 to 413 weeks. Among those who denied tick exposure, α -Gal specific IgE levels decreased by a median of 27.3% (IQR -16 to -59%) per year and total IgE decreased by 15.5% (IQR -10 to -35%) per year (data not shown).

To further address the effect of tick exposure on α -Gal sIgE levels over time and to account for correlations among repeated measurements in the same individuals, we used a multivariable linear regression model with a general estimating equation adjusting for sex, age, and race/ethnicity. In this model we included all available α -Gal sIgE blood tests for subjects who reported any interval tick bite(s) ($n=45$) and for those who denied any tick bite(s) ($n=22$). Exploratory data analysis demonstrated that there was a significant interaction between tick bite status and time ($p=0.002$). Consequently, further analyses were stratified by tick bite status. Among those who denied interval tick bites, there was a significant decrease in log-transformed α -Gal sIgE levels over time (β coefficient -0.03, $p<0.001$), whereas there was no significant change among those who reported interval tick bites (Fig 2A).

Finally, as not all tick bites and not all tick species are thought to contribute to α -Gal sensitization, we were also interested in changes in α -Gal sIgE levels among subjects who reported tick bites. For this analysis we separately analyzed the rate of change in samples that increased or decreased. Interestingly, in the 23 encounters where tick bites were reported but α -Gal sIgE levels nonetheless decreased, the rate of decrease (23.8%/year [IQR 14-69]) was similar to that observed in subjects who denied tick bites (Mann-Whitney U test, $p=0.55$) (Fig 2B). Similar results were also seen for total IgE (Fig 2B) and α -Gal sIgE as a percentage of total IgE (Fig e1B).

A limitation of the current investigation is that information about tick exposure was acquired retrospectively from clinic notes, data for IgE responses to other mammalian antigens was not available, and details about specific tick species were only rarely available. The explanation for the increase in α -Gal sIgE in the 5 subjects who denied interval tick exposure is unclear but could relate to recall bias. In addition, reports of tick exposure may

not always be accurate and the paired sera were not collected at uniform time points. It is important to acknowledge that several species of ticks are common in central Virginia. In addition to *A. americanum*, *Dermacentor variabilis* and *Ixodes scapularis* are also present in this area and these ticks have not been causally-linked to α -Gal sensitization. Thus, bites from *D. variabilis* or *I. scapularis* could explain why 23 subjects reported tick bites but nonetheless experienced a decrease in their α -Gal sIgE level. Lastly, the study was not designed to assess the clinical relevance of changes in α -Gal sIgE levels (ie, decrease in symptom severity or development of tolerance upon oral exposure). Future prospective investigations are suggested to address these limitations.

In summary, this study addresses an important gap in our knowledge about the natural history of α -Gal sIgE levels in subjects with the α -Gal syndrome. The results further reinforce the connection between tick bites and the syndrome and demonstrate that most subjects (89%) will experience a decline in their α -Gal sIgE titers by avoiding tick bites. In contrast, many subjects (62%) who experience repeat tick bites will have further rises in their levels of α -Gal sIgE. The fact that some subjects experience a decline in their specific IgE despite interval tick exposure(s) is consistent with the premise that not all ticks and/or tick bites are equally effective at inducing IgE to α -Gal. The changes in total IgE, which were not entirely accounted for by IgE specific for α -Gal, are consistent with the idea that tick saliva contains Th2-promoting factors that promote IgE to tick-related epitopes in addition to α -Gal. Taken together, these findings support the view that sIgE levels to α -Gal should be reassessed at regular intervals and patients with the α -Gal syndrome should be advised to avoid tick exposure as part of their management of the disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Resource: NIH AI-R37-20565 (TPM) and K23AI123596 (ECM)

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Clinical Implications:

IgE specific to galactose- α -1, 3-galactose (α -Gal), and total IgE, decrease over time in patients with α -Gal syndrome who avoid further tick bites. These findings provide further support for the connection between tick bites and the pathogenesis of the syndrome.

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Figure 1.

(A) Schematic of the study design. (B) Change in specific-IgE to α -Gal and total IgE over time in subjects who denied or reported interval tick bites, expressed as medians with interquartile ranges (IQR) and compared with Wilcoxon matched-pairs rank test.

A

Variable	Denied tick bites		Reported tick bites	
	β -coefficient (95%CI)	p value	β -coefficient (95%CI)	p value
Time (month)	-0.03 (-0.04 to -0.15)	<0.001	-0.003 (-0.04 to 0.008)	0.56
Sex (male)	-0.43 (-1.71 to 0.84)	0.51	-0.07 (-0.78 to 0.63)	0.84
Age (year)	0.09 (-0.01 to 0.03)	0.44	0.23 (0.002 to 0.045)	0.03
Race (Caucasian)	-0.27 (-0.73 to 0.19)	0.24	omitted	

B **Figure 2.**

(A) Results of multiple variable linear regression with generalized estimating equation. (B) Rate of change in IgE levels over time (fold change as % of initial value) on a per year basis. Data were stratified by increase or decrease in rate and tick exposure history. Data expressed as medians with IQR.