Pediatric RESEARCH

CORRESPONDENCE

Glycoprotein acetyls (GlycA) at 12 months are associated with high-sensitivity C-reactive protein and early life inflammatory immune measures

Pediatric Research (2019) 85:584–585;
https://doi.org/10.1038/s41390-019-0307-x

Inflammation and dysregulated immune responses are central pathogenic mechanisms in non-communicable diseases (NCD) such as cardiovascular disease (CVD), type 2 diabetes, and neurodevelopmental disorders.[1] These diseases have their origins in very early life,[2] so quantification of chronic inflammation in infancy and childhood is vital to understanding NCD development. Currently, childhood inflammation is determined by blood levels of high sensitivity C-reactive protein (hsCRP), but in children these reflect acute (usually infection-related) rather than chronic or cumulative inflammation.[3] Alternative markers of inflammation include the total white cell count (WCC), proportions of innate immune cells such as granulocytes, and a recently described marker of circulating glycosylated acute phase proteins; glycoprotein acetyls (GlycA).[4]

In adults, GlycA is suggested to better reflect cumulative chronic inflammation[5] and has been shown to be predictive of CVD and all-cause mortality.[4,6,7] There are limited data on GlycA in childhood, and only one report in pre-school children.[8] To better understand its use as an inflammatory marker in infants, we investigated the relationship between the inflammatory markers GlycA and hsCRP in healthy 12-month-old infants and related these to WCC and granulocyte proportions measured at both 6 and 12 months.

The Barwon Infant Study is a pre-birth cohort ($n = 1064$) with an unselected sampling frame and extensive repeated biosamples.[9] The current study was performed on a representative sub-cohort of infants with complete data and samples. In 12-month-old infants, GlycA was measured by nuclear magnetic resonance (NMR) (Nightingale Health, Helsinki, Finland), and hsCRP levels determined by the COBAS Integra 400 plus Analyser (Roche Diagnostics, NSW, Australia) ($n = 478$) on sodium heparin plasma. The WCC and differential was measured at 6 and 12 months of age. Flow cytometry of leukocytes was also performed at these ages. In brief, fresh whole blood was stained for CD3-FITC, CD4-PE, and CD45-PerCP (BD Biosciences, California, US). Granulocytes (primarily neutrophils), lymphocytes, and monocytes were gated by $CD45^+$ and differentiated by degree of side-scatter (FACSCanto II, Becton Dickinson). The proportion of granulocytes was expressed as a percentage of total leukocytes. Data were log transformed if non-normally distributed. Linear regression (adjusted for sex and 12-month weight *z*-score) was used to examine the association between 12-month GlycA and hsCRP, and between each of these inflammatory markers and the immune measures at 6 months and 12 months of age.

GlycA at 12 months (1075 ± 149 µmol/L, mean ± SD) was moderately correlated with hsCRP (0.84 mg/L, 0.24–106.84, median with range) at the same time point ($r = 0.489$, $p < 0.0001$) (Fig. 1). GlycA, but not hsCRP, was associated with the WCC count at 12 months ($p = 0.032$) (Table 1). Both GlycA ($p = 0.017$) and hsCRP ($p < 0.0001$) were associated with the cross-sectional granulocyte proportion at 12 months, but only GlycA ($p = 0.004$) was associated with the granulocyte proportion 6 months earlier (Table 1).

This is the first study to investigate the association of GlycA with other inflammatory and immune markers in infancy. Levels of GlycA at 12 months of age (measured using the same methodology) were slightly lower than reported in adults,[5,10] in keeping with GlycA reflecting cumulative inflammation across the life course. As in adults, 12 month GlycA correlated modestly with hsCRP. However only GlycA (but not hsCRP) was positively associated with inflammatory immune measures (granulocyte proportion) measured both contemperaneously and 6 months previously. This suggests that GlycA may be a superior marker of chronic cumulative inflammation in early life than hsCRP. The association of GlycA with granulocyte proportions is consistent with the previously described association between GlycA and key neutrophil-associated genes.[5]

In adults, GlycA has greater stability and less intra-individual variability than hsCRP.[11] It is a composite biomarker reflecting glycosylation of a number of major plasma proteins and may respond more consistently to diverse infectious and non-infectious pro-inflammatory stimuli than acute phase markers such as hsCRP.[12] In addition, GlycA is predictive of subsequent hospitalization and death from infection in adults, implying it may also reflect inflammatory capacity in response to microbial challenge.[5] In adolescents, GlycA is associated with increased body mass index and decreased fitness,[12] also suggesting potential as a biomarker of developing NCD risk.

Taken together the current findings indicate that GlycA may be a better general measure of pediatric inflammation and have utility as a measure of chronic inflammation from very early childhood. Repeated measures of GlycA and other inflammatory and immune biomarkers from early life, the relationship of these

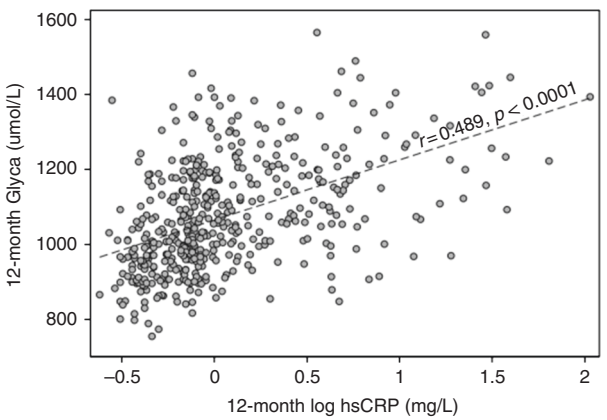

Fig. 1 GlycA and hsCRP in 12-month-old infants. Concentrations of GlycA and hsCRP in plasma samples from 12-month-old infants were modestly correlated ($r = 0.489$, $p < 0.0001$, $n = 478$)

Published online: 26 January 2019

Table 1. Associations of GlycA and hsCRP at 12 months with inflammatory immune measures, WCC and proportion of granulocytes

	GlycA (12 month)			Log_{10} hsCRP (12 month)	
	n	Regression coefficient, μmol/L (95% CI)	*p* value	Regression coefficient, Log_{10} (mg/L) (95% CI)	*p* value
Total white blood cell (WCC) count ($\times 10^6$/ml)					
6 month	397	3.82 (−1.43, 9.07)	0.153	−0.006 (−0.021, 0.008)	0.421
12 month	373	5.72 (0.49, 10.94)	**0.032**	0.009 (−0.006, 0.025)	0.242
Proportion of granulocytes (% of total WBC)					
6 month	369	2.10 (0.67, 3.54)	**0.004**	0.002 (−0.002, 0.006)	0.380
12 month	422	1.53 (0.27, 2.80)	**0.017**	0.008 (0.004, 0.012)	**<0.001**

Analyses were performed where both GlycA and hsCRP were measured, and adjusted for sex and 12-month weight *z*-score. Significance was determined by a *p* value less than 0.05 (shown in bold)
CI confidence interval, *GlycA* glycoprotein acetyls, *hsCRP* high-sensitivity C-reactive protein

measures to infectious and non-infectious pro-inflammatory stimuli and to preclinical NCD risk phenotypes are warranted.

ACKNOWLEDGEMENTS

We acknowledge the participation and commitment of the families in the Barwon Infant Study (BIS). The initial establishment work and infrastructure for the BIS was supported by the Murdoch Children's Research Institute and Barwon Health. Deakin University is now a partner organization and has provided funding and infrastructure. Funding for this particular study was provided by the National Health and Medical Research Council of Australia (1030701).

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ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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