Longitudinal association of the anti-inflammatory serum marker GDF-15 with serum IgA and IgG in apparently healthy children

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Introduction

Both the innate and adaptive immune responses are deregulated in individuals with obesity and are a key driver of its associated metabolic alterations. Although the anti-inflammatory growth differentiation factor 15 (GDF-15) is a candidate protein against obesity, its mechanisms regulating the immune responses are not fully understood.

Methods

We examined whether serum GDF-15 was related to serum levels of immunoglobulins in a cohort of healthy children recruited at the primary health care centers of Girona, in Northeastern Spain (204 Caucasian children, 101 girls and 103 boys). Children were assessed longitudinally at baseline (8.5 ± 1.8 years) and follow-up (13.0 ± 1.9 years, Table 1). At baseline, children were classified according to BMI (above/below median BMI z-score =0.62 ± 1.4) or renal fat (above /below median).

Results

GDF-15 positively associated with IgA and IgG levels and the IgA*IgG product in apparently healthy children at both baseline and follow-up (Figure 1). The associations were more pronounced in heavier children (those with BMI-SDS above the median) as well as in children with higher accumulation of renal fat (those with renal fat-to-height ratio above the median), in whom they remained significant after correcting for possible confounding variables (Table 2). Serum GDF-15 levels accounted for up to 16% of the variance of IgG levels and 14% of the variance of IgA*IgG product at follow-up.

Table 1. Descriptive analysis of the studied parameters in all children.

Baseline	**N=204**
Female/male sex (n)	101/103
Overweight (n)	62
Age (years)	8.5 ± 1.8
Weight (kg)	37.8 ± 14.7
Weight-SDS (z-score)	0.82 ± 1.45
Height (cm)	135.4 ± 12.9
Height-SDS (z-score)	0.69 ± 1.13
BMI (kg/m2)	19.9 ± 4.7
BMI-SDS (z-score)	0.62 ± 1.40
Renal fat (cm)	0.20 ± 0.04
Renal fat-to-height ratio (cm/m)	0.15 ± 0.03
IgA (mg/dL)	108 ± 52
IgG (mg/dL)	982 ± 220
IgA*IgG product x10^3	110 ± 71
GDF-15 (pg/mL)	99.3 ± 28.0
Follow-up	
Overweight (n)	61
Age (years)	13.0 ± 1.9
Weight (kg)	59.1 ± 19.9
Weight-SDS (z-score)	0.84 ± 1.51
Height (cm)	158.6 ± 12.1
Height-SDS (z-score)	0.42 ± 1.03
BMI (kg/m2)	23.2 ± 6.0
BMI-SDS (z-score)	0.76 ± 1.58
Renal fat (cm)	0.12 ± 0.04
Renal fat-to-height ratio (cm/m)	0.07 ± 0.02
IgA (mg/dL)	135 ± 59
IgG (mg/dL)	1006 ± 223
IgA*IgG product x10^3	140 ± 82

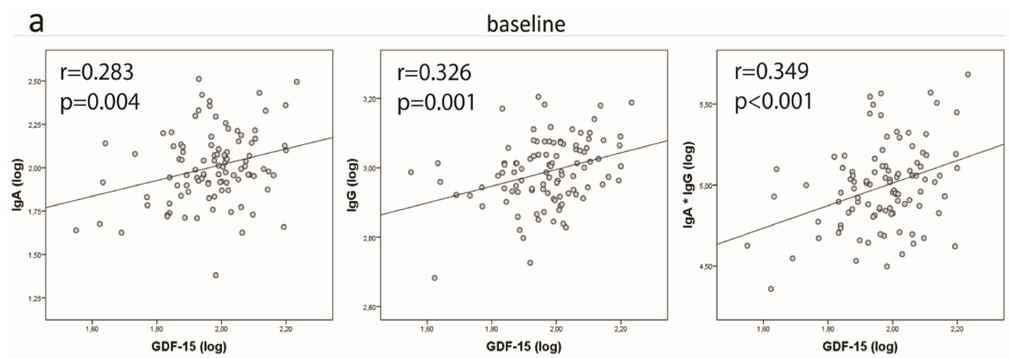

Figure 1. Correlation graphs between circulating GDF-15 and the studied IgA, IgG and IgA*IgG product in children with higher renal fat-to-height ratio at a) baseline and b) follow-up.

Table 2. Multivariate analyses between circulating GDF-15 and the studied parameters at baseline (age 8.5 years old) and follow-up (age 13 years old) in children with higher renal fat-to-height ratio (those above the median value, N=102).

	Baseline						**Follow-up**					
	IgA		**IgG**		**IgA*IgG product**		**IgA**		**IgG**		**IgA*IgG product**	
	β	**P**	**β**	**P**	**β**	**P**	**β**	**P**	**β**	**P**	**β**	**P**
Baseline GDF-15	0.192	0.03	0.283	0.003	0.259	0.003	0.241	0.013	0.404	< 0.001	0.333	< 0.001
Sex (female/male)	-0.189	0.03	-0.296	0.002	-0.261	0.003	-0.162	ns	-0.244	0.009	-0.214	0.019
Baseline age	0.396	0.001	0.207	ns	0.395	< 0.001	0.186	ns	0.044	ns	0.164	ns
Baseline BMI	0.019	ns	-0.026	ns	0.006	ns	0.163	ns	-0.001	ns	0.129	ns
Model R^2	*0.235*		*0.189*		*0.302*		*0.178*		*0.199*		*0.229*	
GDF-15 R^{2*}	*0.028*		*0.097*		*0.058*		*0.051*		*0.164*		*0.144*	

**Step-wise method.*

Conclusion

The longitudinal associations of the anti-inflammatory GDF-15 with IgA, IgG and the IgA*IgG product in children with higher BMI or higher renal fat accumulation suggest a role of GDF-15 in human obesity through the regulation of the adaptive immune system.

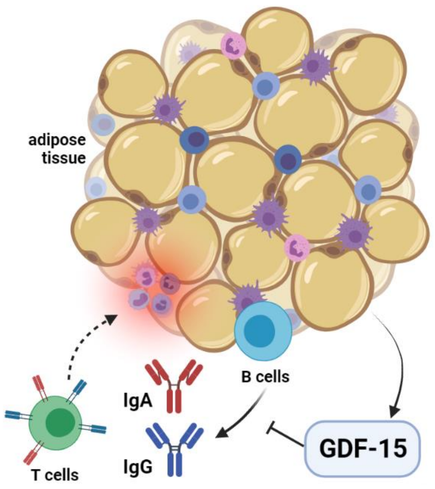

Figure 2. Plausible mechanism of immune system regulation by GDF-15.

In obesity, both B cells and T cells are recruited into the adipose tissue and promote an inflammatory response (increased IgA and IgG , among others). GDF-15 secreted by the adipose tissue could regulate this adaptive immune response (Figure 2).

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