ABBERANT GLYCOSYLATION OF IGA MEASURED BY HELIX ASPERSA LECTIN BINDING OR GALACTIN-8 BINDING ASSAYS DOES NOT PREDICT PROGNOSIS IN SWEDISH PATIENTS WITH IGA NEPHROPATHY

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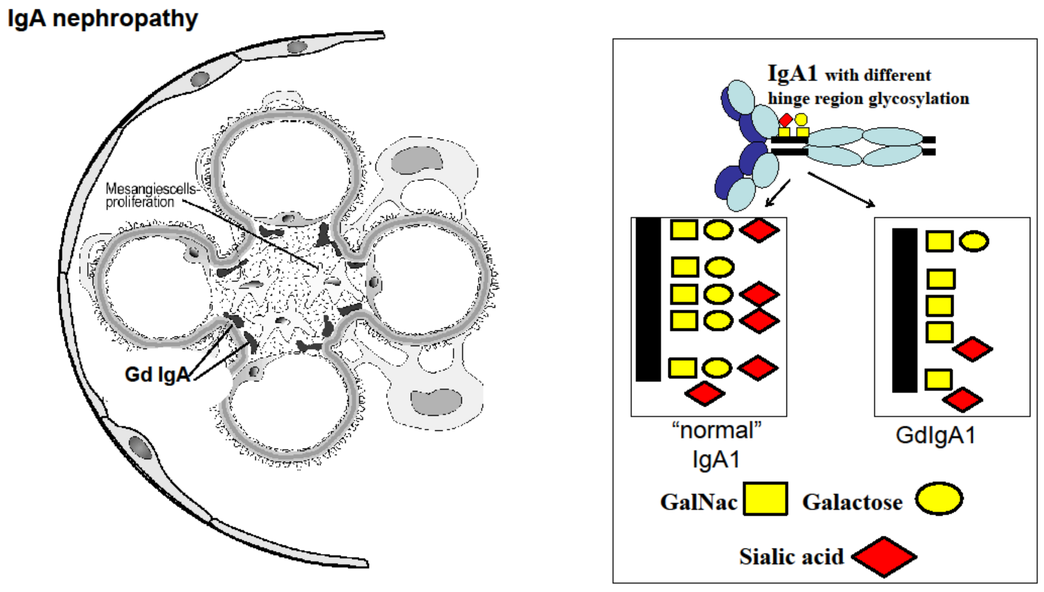


Figure 1. **The IgA1 molecule is heavily glycosylated in the hinge region. Early termination of the carbohydrate chain leads to the production of galactose deficient IgA1 (GdIgA1), which tend to accumulate in the mesangium in IgA-nepharopathy.**

Background

Deposition of galactose deficient IgA1 (GdIgA1) in the mesangium is a hallmark of IgA nephropathy (IgAN) and established as an early step in the pathogenesis (Figure 1). There are, however, conflicting results regarding the predictive value of circulating levels of GdIgA1 for prognosis. Few studies have examined the longitudinal stability of GdIgA1 levels.

Table 1. Basal characteristics of study participants

	Men	Women	Total
Numbers	97	43	140
Age years	34.4 (27.0-48.2)	36.6 (29.7-48.)	35.3 (28.3-48.3)
BMI m^2/kg	25.5 (23.4-28.7)	24.7 (21.8-26.8)	25.0 (23.1-28.2)
Blood pressure (MAP) mmHg	98 (92-104)	97 (90-102)	97 (92-103)
U-albumin g/24 hour	0.30 (0.1-1.0)	0.16 (0.03-0.8)	0.26 (0.06-0.97)
eGFR ml/min/1.73m^2	75.0 (62.2-88.4)	77 (66-92)	75.6 (62.3-89.9)
HSP/IgAN	13/84 (13%)	5/38 (12%)	18/122 (13%)

Methods

We analyzed plasma GdIgA1 at baseline in a cohort of 141 patients with IgAN and eGFR ≥ 50 ml/min/1,73m² who had been followed for a median time of 92.6 months (IQR 63.8-125.0).18 patients (13 %) had exhibited systemic features and were classified as Henoch-Schönlein purpura (= HSP). Results were correlated with urinary albumin excretion at baseline and decline in GFR during follow-up (mean eGFR slope -1.4ml/min/year). GdIgA1 was measured by non-binding to a human galactin-8 (Gal8) affinity coloumn and a Helix aspersa (HA) lectin binding assay. Gal8 binds 2-3 sialyated galactosides while HA binds terminal GalNac (***Figure 1 left***).

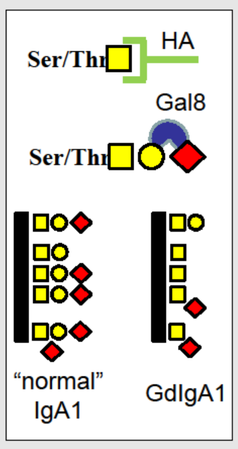
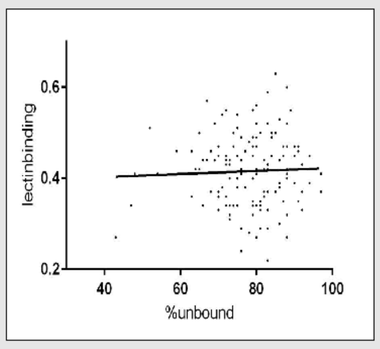


Figure 1. Left. *HA (green) binds GalNac which gets exposed when GalNac not bound to sialic acid or galactose. Gal8 (in blue) binds fully galactosylated and sialyated IgA.*

Right. *Correlation between the Gal8 assay assay on the x-axis and the HA binding assay on the y-axis.*
The low correlation between the assays demonstrate the diversity in glycation patterns among IgAN patients.



References

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Conclusions

In this cohort of patients with IgAN we found no correlation between prognosis and baseline levels of GdIgA1, and the levels of GdIgA1 tended to be stable over time, in both stable and progressing patients. Our data are consistent with the notion that elevated plasma GdIgA is a genetically determined risk factor for IgAN; and that other factors, effecting later stages in the pathogenesis, are more important for the prognosis.

Results

In line with other studies we found that IgAN patients had increased plasma levels of IgA compared to healthy controls and that the increase consisted mainly of aberrantly glycosylated IgA1, measured both with Gal8 and HA assay (Fig 1). However the correlation between the assays was low and HSP patients tended to have less GdIgA1.

There was **no correlation** with levels of GdIgA1 and baseline **proteinuria** (HA assay r = -0.02; Gal8 assay r = 0.02) or **GFR slope** (HA assay r = -0.05; Gal8 assay r = -0.01).

During follow-up 13 patients lost over 50% of their baseline GFR while 72 patients lost less than 10%. There was no difference between these groups with the HA assay (1.46 ± 0.69 units, vs 1.46 ± 0.55units, p = 0.95) or the Gal8 assay (2.67 ± 1.13 g/l, vs 2.82 ± 1.12, p = 0.65) (***Figure 3***)
Subgroup analysis based on age, GFR at onset, steroid therapy (before or after sampling) and proteinuria did not reveal any links between GdIgA1 and prognosis.

A total of 80 follow-up samples from 25 patients were analyzed with the HA assay (mean FU 6 years, range 0.5-16 years). 11 patients with stable GFR (median change +0.16 ml/year) had a median change in the HA assay of 0.017 units per year (IQR -0.004 – 0.022), while 14 patients with progressive GFR loss (median change -3.2 ml/year) exhibited a median change in the HA assay of 0.015 units/year (IQR -0.027 – 0.031)

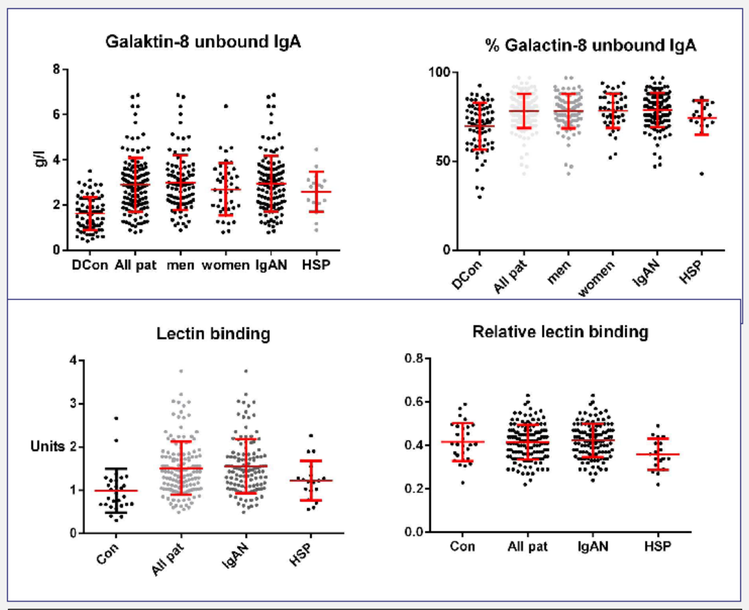

Figure 2. *Levels of galactose deficient IgA measured by Gal8-binding assay expressed in absolute values (A, g/L) and relative terms (B, % unbound), and HA-binding assay in absolute terms (C, units) and relative terms (D, units).*

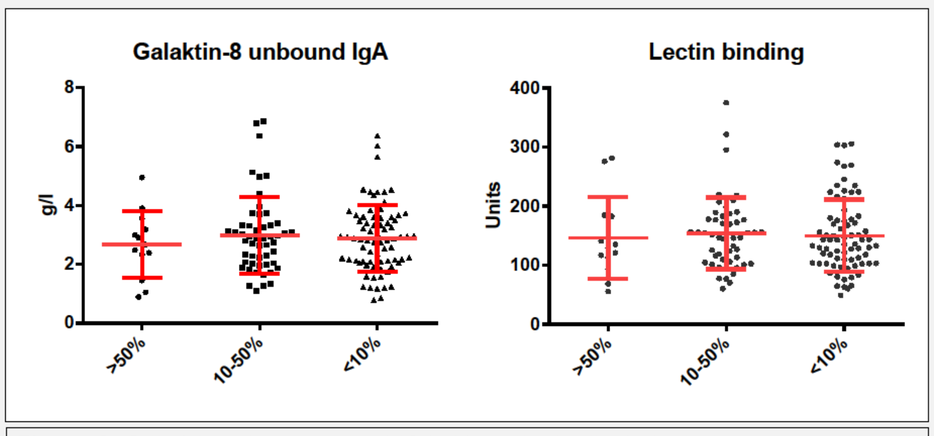

Figure 3: GdIgA1 and prognosis. 140 IgAN patients divided into three groups based last GFR as function of baseline GFR: rapid progression, moderate progression and stable GFR.

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