

# Significance of anti-glomerular basement membrane antibodies in type 2 diabetic patients

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## ABSTRACT

**Objective:** Diabetic glomerulosclerosis is a common cause of proteinuria in patients with type 2 diabetes mellitus (DM), however, primary glomerulonephritis can superimpose on it. The aim of this study is to evaluate the significance of anti-glomerular basement membrane (GBM) antibodies in type 2 DM.

**Methods:** We choose 60 well known Saudi patients with type 2 DM diagnosed according to American Diabetes Association criteria attending the medical outpatient clinic at Al-Noor Specialist Hospital in Makkah, Kingdom of Saudi Arabia between July 2004 and December 2004, after written consent and divided them into 3 groups according to the degree of albuminuria, either normal, micro albuminuric or with diabetic nephropathy. We choose 20 healthy subjects as

the control. We checked anti-GBM serum level by indirect solid phase immunosorbent assay (ELISA).

**Results:** There was significant increase in anti-GBM serum levels in diabetic patients compared with the control subjects, mainly in the normal and micro albuminuric patients groups, but not in patients with diabetic nephropathy.

**Conclusion:** Anti-GBM antibodies are a significant predictor of diabetic nephropathy especially in the early phases, however, we need further studies to document its clinical importance in such common, important diabetic complications.

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Diabetic glomerulosclerosis is a common cause of proteinuria in patients with a long standing history of diabetes mellitus (DM). Primary glomerulonephritis, such as IgA nephropathy can superimpose on a background of diabetic glomerulosclerosis.<sup>1</sup> In 1998, Tejinder et al,<sup>2</sup> reported a case of anti glomerular basement membrane (GBM) nephritis superimposed on diabetic nephropathy in a 57 year old man. Then in 1999 Merlin et al<sup>3</sup> reported simultaneous presentation of Goodpasture's disease and insulin dependent diabetes mellitus. Dizard et al,<sup>4</sup> in 2004 reported a patient with type 1 DM and Hashimoto's

thyroiditis and membranoproliferative glomerulonephritis (MPGN). So, our aim is to study the significance of anti-GBM antibodies in type 2 diabetic patients and to ascertain whether we can consider anti-GBM antibody serum level as a significant predictor of diabetic nephropathy in type 2 DM.

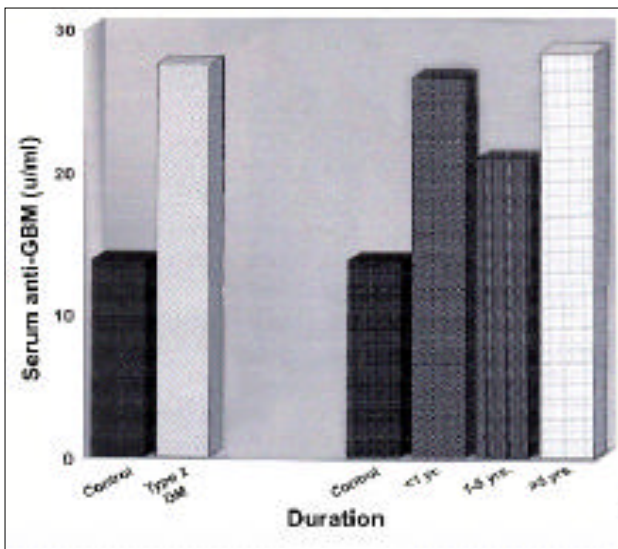
**Methods.** Sixty well known Saudi patients with type 2 DM attending the medical outpatient clinic at Al-Noor Specialist Hospital in Makkah, Kingdom of Saudi Arabia from July 2004 to December 2004,

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**Figure 1** - The histogram shows the relationship between anti-GBM serum level and durations of diabetes.

diagnosed according to the American Diabetes Association (ADA) criteria were chosen and their written consent was obtained to participate in the study. Twenty healthy subjects were chosen as the control group. Both the cases and the control group were between 35-65 years old. A full history was taken, and thorough examination was carried out for both groups. The cases were of type 2 DM of more than 5 years duration, with normal serum urea and creatinine, as well as normal fundoscopic examination. The control groups were not known diabetics with normal fasting and post 75 gm glucose serum level. The investigations were conducted by a PhD Pathologist. Glucose estimation was carried out principally by enzymatic colourimetric test based on Trinder-reaction, according to Tietz<sup>5</sup> using a commercial kit of SIMAT on Roch-Hitachi.

Microalbuminuria was examined by nephelometric method according to Larry,<sup>6</sup> using commercial kits of Roch. A serum level of anti-GBM was estimated by indirect solid phase enzyme immunometric assay (ELISA). The lower detection limit is 1 u/ml using commercial kits of DRG diagnostics (DRG Instrument GmbH-Germany) EIA-36030.

**Statistical analysis.** Data were analyzed using the student's T-test, where the difference between the mean values for each variable among patients and controls was tested, and  $p$ -values  $<0.05$  were considered significant.<sup>7</sup>

**Results.** The results revealed that the mean serum level of anti-GBM for healthy subjects was  $13.8 \pm 6$  u/ml, while that for type 2 diabetic patients

**Table 1** - Relationship between serum level of anti-GBM in different albuminuric groups (NA, MA and DN) in 80 subjects.

Variable	Controls (n = 20)	NA (n = 20)	MA (n=30)	DN (n=10)
Anti-GBM u/ml (mean)	13.8 u/ml	27.5 u/ml	24.7 u/ml	12.9 u/ml
$\pm$ SD	$\pm 6$ u/ml	$\pm 3.5$	$\pm 3.7$	$\pm 1.7$
SEM	1.3	0.87	0.77	0.54
P1 (NA/C)		$<0.05$ S		
P2 (MA/C)			$<0.05$	
P3 (DN/C)				$>0.05$

The table shows significant increases in anti-GBM within NA and MA than controls where  $p < 0.05$  (significant) and in DN  $p > 0.05$  (non-significant). GBM - glomerular basement membrane, P - probability, NA - normo-albuminuric, MA - micro albuminuric, DN - diabetic neuropathy, C - control.

was  $25.7 \pm 6.4$  u/ml, and there was a statistical significant difference between type 2 diabetic patients and control (Figure 1). There was a significant increase in serum level of anti-GBM mainly in the normo- and microalbuminuric patients non-significant correlation in patients with diabetic nephropathy when compared to the control group (Table 1). According to the duration of diseases, Figure 1, shows a positive significant correlation of anti-GBM and duration of type 2 DM.

**Discussion.** Previous reports show that immune complex glomerulonephritis can superimpose on diabetic glomerulosclerosis. Idiopathic membranous glomerulonephritis, lupus nephritis and amyloidosis can all occur with diabetic nephropathy.<sup>8</sup> Glomerulonephritis mediated by antibodies against GBM is a prototype of human glomerular disease produced by pathogenic antibodies to intrinsic glomerular component. The principle target of human anti-GBM antibodies directs against the auto-antigen 3 type IV collagen of the GBM.<sup>9</sup> In this study we used a highly specific ELISA assay based on microplates coated with highly specific and purified GBM proteins with high sensitivity detection, as low as 1 u/ml. In our study, there was significant increase in anti-GBM antibody serum level in diabetic patients compared with control subjects. Moreover, there was a statistically significant correlation between diabetes duration and anti-GBM serum levels (Figure 1). We can compare these results with a report of a 57-year-old Caucasian with type 2 diabetes mellitus and hypertension, who developed anti-GBM nephritis.<sup>11</sup> Moreover, Nicoloff et al<sup>8</sup> in 2002 reported a high

correlation of IgG and IgM antibodies to collagen IV basement membrane proteins and duration of DM of >6 years in their study.

Microalbuminuria is an early marker for renal involvement in diabetics with a significant correlation with the progress of nephropathy.<sup>10</sup> In our study, serum level of anti-GBM antibody showed a significant increase in diabetic patients with either normo- or microalbuminuria when compared to the control group, while anti-GBM level did not show a significant difference in patients with macro-albuminuria as compared with the controls. This increase of anti-GBM antibodies in the early stages of diabetic nephropathy may be due to increased production followed by deposition on its target antigen (GBM) as an autoimmune complex with obliteration of the capillary loops and sclerosis. Also, synthesis of anti-GBM may cease after consumption of its target antigen. We can support these results with another recent study by Imgrad et al<sup>11</sup> in 2003, who performed histopathological examination of renal biopsies for idiopathic glomerulonephritis with immune deposits. They found that the degree of disease was proportionate to the amount of IgG immune deposits, but with disease progress, they could no longer detect the immune deposits. They concluded that the immune complex might be a time dependent phenomenon and IgG deposits were more evident in the early stages.

In 2004, Dizard et al<sup>4</sup> reported a patient with type 1 DM who developed membranoproliferative glomerulonephritis (MPGN) and Hashimoto thyroiditis with low complement 3 and 4 and negative other immunological screen. The renal biopsy of that patient showed duplication of basement membrane characteristic of MPGN and they observed by immunofluorescence, deposits of IgG, IgM and C3. On the basis of the present study, we can consider anti-GBM antibody serum level a

significant predictor of diabetic glomerulonephritis during the follow up of type 2 DM, especially in the early phases when diagnosis and treatment of nephropathy is promising. We recommend further studies, with a large sample size in different populations.

## References

1. Mak SK, Wong PN, Tong GM. IgA nephropathy superimposed on diabetic glomerulosclerosis in type 2 DM. *Nephrol Dial Transplant* 2001; 16 :1183–1188.
2. Tejinder SA, Ahuja MD, Velasco A. Diabetic nephropathy with Anti-GBM antibody nephritis. *Am J Kidney Dis* 1998; 131; 1: 127-130.
3. Merlin C, Thomas A, Robert J. Simultaneous presentation of Goodpasture disease and IDDM. *Nephrol Dial Transplant* 1999; 14 : 1997-1998.
4. Dizard O, Serkan K, Gultekin G. Membranoproliferative glomerulonephritis associated with type 1 DM and Hashimoto thyroiditis. *Nephrol Dial Transplant* 2004; 19: 988.
5. Tiez NW. Clinical Guide to Laboratory Tests, Philadelphia (PA): WB Saunders Company; 1995. p. 266-273.
6. Larry J. Principles of immunochemical techniques. In: Teitz NW, editor. Fundamentals of clinical chemistry. 5th ed. Philadelphia (PA): WB Saunders; 2001. p.192.
7. Goldstone LA. Understanding Medical Statistics. 1st ed. London: William Heinemann Medical Books Limited; 1983. p. 49.
8. Nicoloff G, Baydanaff S, Shrisov CH. Serum antibodies to collagen type IV and the development of vascular complication in type 1 DM. *Vasc Pharmacol* 2002; 38: 143.
9. De Angelo AJ, Lancaster WK, Eliason, Worthman WJ. Diabetic nephropathy with interstitial nephritis presenting with a false positive anti-GBM antibodies. *Clin Nephrol* 2002; 57: 381-385.
10. Newman DJ, Thakav H, Gallaghev H. Progressive renal disease: Does the quality of proteinuria matter or the quantity? *Clin Chim Acta* 2000; 279: 43-54.
11. Imgrad N, Heinz R, Renate K. Glomerular immune deposits are associated with increased proteinuria in patients with ANCA associated nephritis. *Neph Dial Transplant* 2003; 18: 524.