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Correlation of GBP2 expression with histopathological and clinical findings in prevalent glomerulopathies

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Background and Aims: The most commonly observed glomerulopathy types include IgA Nephropathy (IGAN), Membranous Glomerulonephritis (MGN), Focal Segmental Glomerulosclerosis (FSGS), and Diabetic Nephropathy (DN). Diabetes and glomerulonephrities are among the primary reasons for the need for renal replacement therapies. Although the pathogenesis of glomerulopathies is known to be related to the immune system, it has not yet been fully elucidated. Research has shown that in the pathogenesis of Diabetic Nephropathy, the protein Guanylate Binding Protein 2 (GBP2), released from M1 macrophages accumulating in the glomerular and tubulointerstitial areas, inhibits the NOTCH-1 signaling pathway, leading to macrophage accumulation in the kidneys. In Lupus Nephritis, it has been demonstrated that GBP2 protein secretion in the glomeruli and tubulointerstitial areas is increased compared to normal kidneys, and GBP2 plays a role in the interferon signaling pathway. The aim of this study is to understand the effect of GBP2 expression on the histopathological and clinical prognosis of patients with the most common glomerulopathies, whose pathogenesisis still not fully understood.

Method: The study included 150 kidney biopsy cases (71 males, 81 females) diagnosed with IGAN (46), MGN (34), FSGS (42), and DN (30) at Bezmialem Vakıf University Hospital (2014–2023). Sections of 4 microns in thickness were obtained from paraffin-embedded blocks fixed in 10% buffered formaldehyde, containing sufficient tissue for hematoxylin eosin staining. The appropriate titer (1:25) for the GBP2 antibody was determined, and a 3,3-diaminobenzidine (DAB) detection kit was used to cover the tissues with a ready film. Immune cells stained with GBP2 were counted in three high-power fields with the most intense staining. H score was calculated by using chronicity (%) x intensity (1–3) (Fig. 1). Data were analyzed for correlations between GBP2 expression and histopathological markers (glomerulosclerosis, tubular atrophy, fibrosis, immune complex deposition), clinical parameters (proteinuria response, hematuria, creatinine doubling time, GFR, blood pressure), comorbidities (Hypertension, Congestive Heart Failure, Type II Diabetes, Ischemic Heart Disease), demographics (sex, age, BMI, smoking). Statistical analyses utilized Pearson Correlation and Kruskal-Wallis tests.

Results: Over a mean follow-up of 26.1 months, the mean immune cell count was 4 in DN, 2 in IGAN, and 1 in MGN and FSGS, with an overall mean of 1.717. The mean H score was highest in DN (8.9), followed by IGAN (6.4), MGN (3.9), and FSGS (3.1), with an overall mean of 5. The number of immune cells and H score were found to be significantly different among the four groups ($P = 0.0017$; $P = 0.0026$) (Graphic 1). The correlation between H Score and systolic blood pressure is found positively correlated ($r = 0.226$, $P = 0.006$). H Score and global sclerosis showed a significant positive correlation ($r = 0.191$, $P = 0.019$). A negative correlation is found between H Score, immune cell count and follow-up duration ($r = -0.175$, $P = 0.033$; $r = -0.168$, $P = 0.040$). Positive correlation was found between immune cell count and hematuria ($r = 0.188$, $P = 0.021$). In patients with DN group, H Score and creatinine doubling time exhibited a strong negative correlation ($r = -0.745$, $P = 0.034$). Among MGN group, immune cell count and hypertension showed a significant positive correlation ($r = 0.428$, $P = 0.012$). Immune cells count or H score showed no significant difference among the proteinuria response ($P = 0.9$).

Conclusion: GBP2 expression varies across glomerulopathies. GBP2 expression was found to be positively correlated with hematuria, systolic blood pressure, and global sclerosis. Additionally, GBP2 expression showed a negative correlation with follow-up duration. In Diabetic Nephropathy, GBP2 expression may have a shortening effect on the creatinine doubling time. GBP2 expression is found not significantly influencer on proteinuria response. Further studies are needed to elucidate GBP2's role in glomerulopathy pathogenesis and prognosis.

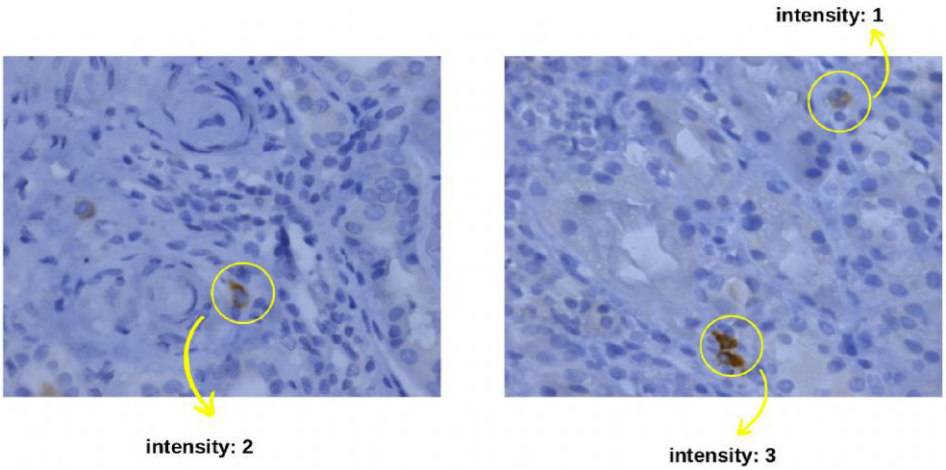
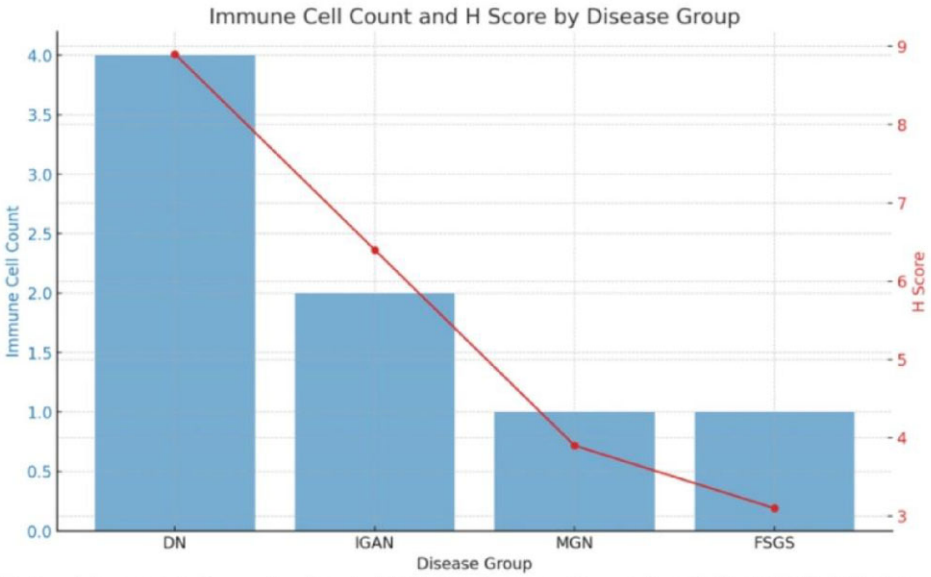


Figure 1: Immunhistochemistry GBP2 staining.



(FSGS:Focal Segmental Glomerulosclerosis, MGN: Membranous Glomerulonephritis, IGAN:IgA Nephropathy, DN: Diabetic Nephropathy)

Graphic 1: Immune cell count and H score by disease group.