شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم

HANAA ALY

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جامعة عين شمس

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قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار

HANAA ALY

INTRODUCTION

Podocytes are unique cells with a complex cellular organization with respect to their cytoarchitecture, podocytes may be divided into three structurally and functionally different segment: cell body, major processes and foot processes. The foot processes of neighboring podocytes regularly interdigitate, leaving between them the filtration slits that are bridged by an extracellular structure, known as the slit diaphragm ***(Asanuma, 2015).***

The slit diaphragm is covered by a thick surface coat that is rich in sialoglycoproteins including podocalyxin, podoendin and others, which are responsible for the high negative surface charge of the podocyte ***(Schadde et al., 2000; Hober et al., 2001).***

Podocytes cover the outer aspects of the glomerular basement membrane they therefore form the final barrier to protein loss ***(Asanuma, 2015).***

Podocalyxin is a sialoglycoprotein, is thought to be the major constituent of the glycocalyx of podocytes in the glomerulus (Bowman's Capsule) ***(Kershaw et al., 1997).*** It is a member of the CD34 family of transmembrane sialomucins ***(Nielsen and McNagny, 2008).*** It coats the secondary foot processes of podocytes. It is negatively charged and thus, function to keep adjacent foot processes separated, there by keeping the

urinary function barrier open ***(Gartener et al., 2007).*** Podocalyxin has an essential role in podocyte morphogenesis ***(Doyonnas et al., 2001; Nielsen and McNagny, 2009).***

It has another role in the opening of vascular lumens and regulations of vascular permeability ***(Stritic et al., 2009; Debruin et al., 2014).***

Nephropathy is a major complication of diabetes and it is the leading cause of end stage renal disease; it is clinically charactarised by proteinuria and progressive renal insufficiency ***(Wright, 2008).*** Human podocytes have been demonstrated to be functionally and structurally injured in the natural history of diabetic nephropathy ***(Wolf et al., 2005).***

Recently an increase in foot process width has been identified in patients with diabetes and proteinuria, foot process width has been shown to correlate directly with the urinary albumin excretion rate ***(Berg et al., 1998).*** Further more, the number and density of pods have been reported to be markedly reduced (podocytopenia) in patients with diabetic nephropathy and other glomerular disease ***(Pagtalunan et al., 1998).***

Pods are located outside the glomerular basement membrane because of the proximity of the apical region of pods to the urinary space, pathological events occurring in this region are expected to be more easily detectable in urine than those occurring in the basal or slit diaphragm regions of pods ***(Hara et al., 1995; Hara et al., 2005).***

AIM OF THE WORK

To asses the value of urinary podocalyxin as an early marker for podocyte injury in patient with diabetic nephropathy as well as other glomerular disease and its use in comparison between diabetic nephrophathy and glomerular disease.

Chapter 1

EPIDEMIOLOGY, UPDATED CLASSIFICATIONS AND PATHOGENESIS OF GLOMERULONEPHRITIS

Epidimiology:

Identification of the profile of glomerular disease in a certain geographical region is very important academically, clinically and epidemiologically. It helps in the identification of specific risk factors and for adequate prevention ***(Barsoum and Francis, 2000).***

Racial factors is also very important, not only in the incidence, but also it define the pattern, severity and progression of the glomerular disease, environmental factors may also be involved as modifiers of the glomerular pathology in different geographical regions, of particular interest is the role of heavy metal and hydrocarbon pollution, the epidemiological significance of which remains to be elucidated. For these reasons, it is of considerable interest to identify the patterns of glomerular disease in specific regions ***(Barsoum and Francis, 2000).***

GN varies in incidence among the different geographical areas due to socioeconomic conditions, ethnicity, genetic variability and environmental factors. Recent studies suggested a changing pattern of incidence of GN in the different parts of the world ***(Ibrahim et al., 2012).***

IgAN was the most common primary GN in young adults Caucasians (Europe and USA) ***(Zaza et al., 2013)***, and some countrieis in Asia as described in reports from China, Japan and Korea, and is the most common cause of end-stage renal disease (ESRD), while it was rare in African Americans, focal and segmental glomerulosclerosis (FSGS) remained more common in African American ***(Zhou., 2009),*** brazil, india and most of Asia ***(Zaza et al., 2013).***

In the Middle East Lupus nephritis is the most frequent among the secondary Forms. In the Saudi Arabian Registry, FSGS is the most frequent renal disease, followed by MPGN.

IgAN accounts for only 6.5%, while Lupus nephritis is the most common secondary form ***(Pesce and Schena, 2010).***

The prevalence of Membranous nephropathy secondary to infection varies in accordance with the epidemiology of the infections. In countries where Hepatitis B, and malaria are endemic, secondary MN is the leading cause of NS among children and young adults ***(Segelmark and Hellmark, 2010).***

FSGS is currently the most common primary glomerular disease causing end-stage renal disease ***(Kumagai et al., 2012).***

However, some of GN may be over estimated due to relapses and prevalent cases being counted as incident. There is variation in biopsy policy between countries, which affects the incidence rates found.

The reported incidence rates are likely to underestimate true rates of IgA nephropathy as this disease can exist sub clinically and may never be detected.

Incidence in older people appears to have increased over time, this is considered to be due to greater inclusion of this age group in referrals for biopsy rather than due to a genuine increase in disease occurrence ***(McGrogan et al., 2011).***

Classification of Glomerulonephritis (GN):

GN is usually divided into primary (PGN) and secondary forms. It may be restricted to the kidney in PGN or be a secondary to a systemic disease in secondary GN. A diagnosis of primary GN was considered if it was not associated with any systemic disease, negative serology for hepatitis B and C, HIV and anti-nuclear antibodies, and no report of familial haematuria all of these conditions at the time of biopsy, it could be due to different factors including population genetics, demographical characteristics and environmental factors ***(Jiang et al., 2013).***

Primary GN is present in about half of all native renal biopsies, this is reported by publication from many renal biopsy databases and it is one of the leading causes of end-stage renal failure in Western countries ***(Segelmark and Hellmark, 2010).***

Also it is the third leading cause of end stage renal disease (ESRD) in the USA and still major causes of chronic kidney disease in China and worldwide ***(Jiang et al., 2013).***

Secondary forms of GN are much less common in the industrialized countries than in the tropics. The infection is a major cause, some of the infective agents have been identified such as Streptococcus, schistosomiasis and malaria. Others are only speculative, being suspected from the strikingly high prevalence of proliferative GN, the prototype lesion of such etiology ***(Polito et al., 2010).***

The secondary GN is divided into four groups:

a) GN associated with systemic diseases such as systemic lupus erythematosus, Henoch-Sch¨onleinpurpura, anti-glomerularbasement membrane disease, rheumatoid arthritis, Sj¨ogren syndrome, mixed connective tissue disease, pregnancy nephropathy, malignancies, liver diseases and multiple myeloma ***(Polito et al., 2010).***

b) GN associated with metabolic diseases (diabetic nephropathy, amyloidosis, monoclonal Ig deposit disease, mixed cryoglobulinaemia and dense deposit disease).

c) GN associated with infectious diseases/postinfectious glomerulo-nephritis (endocarditis, hepatitis B and C)

d) GN associated with vascular diseases (systemic vasculitis, benign/malignant nephrosclerosis, haemolytic–uraemic syndrome, thrombotic microangiopathy, systemicsclerosis and pauci-immune crescentic GN) ***(Zaza et al., 2013).***

The classification of PGN is debatable and confusing. A major cause of confusion is the poor correlation between histological and clinical findings, causing considerable overlaps between diseases defined by clinical features and diseases defined by histological features ***(Segelmark and Hellmark, 2010).***

Primary GN was classified according to ***Zaza et al. (2013);*** into**,** immune globulin A GN (IgAN), membranous nephropathy (MGN), focal segmental glomerilosclerosis (FSGS), minimal change disease (MCD), membranoproliferative glomerulo-nephritis (MPGN), mesangioprolioferative glomerulonephritis (Mes GN) and crescentic GN**.**

The etiology of GN can be classified by their clinical presentation (nephrotic, nephritic, rapidly progressive GN, chronic GN) ***(Khanna, 2011).***

There is another classification of GN according to non proliferative glomerulonephritis and proliferative glomerulonephritis (Fig 1).

The non-proliferative type of glomerulonephritis is characterized by decrease number of cell in the glomeruli (lack of hypercellularity), divided into three sub divisions:

- Minimal change disease (MCD): causes mainly 80% of nephrotic syndrome in children, visible only by electron microscope.

- Focal Segmental Glomerulosclerosis (FSGS): primary or secondary, nephrotic syndrome with impaired renal function.

- Membranous GN (MGN): thickened glomerular basement membrane without hypercellular glomerulus, diffuse granular uptake of IgG that affect the tubulus of the kidney.

The proliferative glomerulonephritis is increased the number of glomerulus cells (hypercellular) presents the nephritic syndrome and end stage of renal failure, divided into four sub divisions:

- IGA nephropathy: is the most common type of proliferative glomerulonephritis. This disease causes visible bloody urine or haematuria.

- Post infection GN.

- Membranoproliferative glomerulonephritis (MPGN): present the nephrotic syndrome although nephritic with massive progression of renal failure.

- Rapidly progressive GN or Crescentic GN: poor prognosis with rapid progression of kidney failure ***(Munni, 2016).***

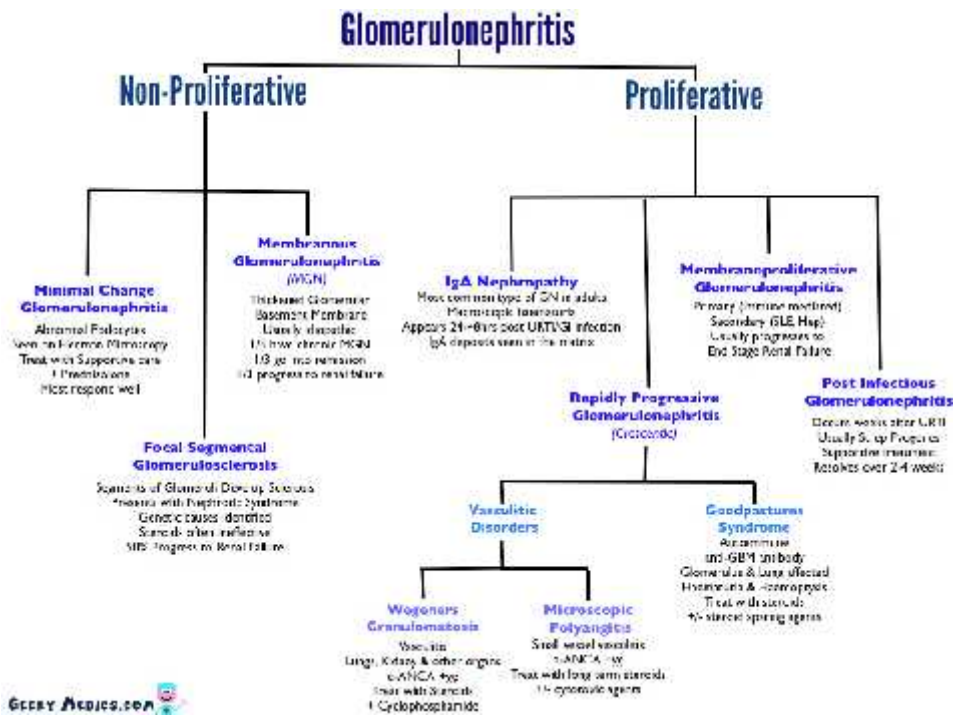

Figure (1): Classification of GN ***(Munni, 2016).***

Recent classification of GN:

- There is recent classification for GN was established in 2015 based on etiology and pathogenesis by a group of renal pathologists and nephrologists with the aim of standardizing the kidney biopsy report of GN which is classified into the following five pathogenic types each with specific disease entities ***(Sethi et al., 2015).***

  1. Immune-complex GN.
  2. Pauci-immune GN.
  3. Antiglomerular basement membrane GN.

4. Monoclonal Ig GN.

5. C3 glomerulopathy.

- This classification does not extend to other forms of glomerular diseases, such as membranous nephropathy, podocytopathies, and thrombotic microangiopathy ***(Sethi et al., 2015).***

Table (1): The recent classification of GN

Pathogenic Type	Specific Disease Entity	Pattern of Injury: Focal or Diffuse	Scores or Class
Immune-complex GN[a]	IgA nephropathy, IgA vasculitis, lupus nephritis, infection-related GN, fibrillary GN with polyclonal Ig deposits	Mesangial, endocapillary, exudative, membranoproliferative, necrotizing, crescentic, sclerosing, or multiple[b]	Oxford/MEST scores for IgA nephropathy ISN/RPS class for lupus nephritis
Pauci-immune GN	MPO-ANCA GN, proteinase 3-ANCA GN, ANCA-negative GN	Necrotizing, crescentic, sclerosing, or multiple[b]	Focal, crescentic, mixed, or sclerosing class (Berden/EUVAS class)
Anti-GBM GN	Anti-GBM GN	Necrotizing, crescentic, sclerosing, or mixed[b]	
Monoclonal Ig GN[a]	Monoclonal Ig deposition disease, proliferative GN with monoclonal Ig deposits, immunotactoid glomerulopathy, fibrillary GN with monoclonal Ig deposits	Mesangial, endocapillary, exudative, membranoproliferative, necrotizing, crescentic, sclerosing, or multiple[b]	
C3 glomerulopathy	C3 GN, dense deposit disease	Mesangial, endocapillary, exudative, membranoproliferative, necrotizing, crescentic, sclerosing, or multiple[b]	

MEST: mesangial hypercellularity, endocapillary hypercellularity, segmental sclerosis, interstitial fibrosis/tubular atrophy.
ISN/RPS: International Society of Nephrology/Renal Pathology Society.
EUVAS: European vasculitis study group.
a Some pathologists use the terms immune complex-mediated GN, monoclonal Ig-associated GN, *etc*. It is up to the discretion of the pathologist to use these terms.
b Multiple patterns include two or more patterns of injury. The patterns should be stated (*e.g.*, focal mesangial proliferative, crescentic, and sclerosing or diffuse necrotizing, crescentic, and sclerosing)

(Sethi et al., 2015)

Immune-complex GN: is characterized by granular deposits of polyclonal Ig on IF or immunohistochemistry (IHC). Complement is often co deposited along with the Ig.

The type and location of the immune deposits often point to the underlying etiology, immune-complex GN includes specific disease entities, such as IgA nephropathy, lupus nephritis, infections and autoimmune diseases other than SLE and fibrillary GN, with the understanding that fibrillary GN may not represent true immune–complex GN in the sense of antigen-antibody complexes ***(Alpers And Kowalewska, 2008).***

Infections are an important cause of immune-complex GN in both developing and developed countries. The pattern of glomerular injury is variable, and depending, in part, on the etiology, there may be no lesion by LM, mesangial proliferative, endocapillary proliferative, exudative, membranoproliferative, necrotizing and crescentic, sclerosing, or a combination of these patterns. Some forms of GN (*e.g.*, lupus nephritis) may have mixed membranous and proliferative patterns ***(Sethi et al., 2015).***

Pauci–immune necrotizing and crescentic GN is characterized by negative or few Ig deposits on IF or IHC.80%–90% of patients have serologic evidence of ANCA, and as such, this category has been referred to as ANCA-associated GN (ANCA GN) whereas the remaining patients are termed ANCA-negative GN ***(Chen et al., 2009).***