A Dissertation on

PATTERN OF GLOMERULONEPHRITIS AND CHANGING TRENDS AT A TERTIARY CARE CENTRE

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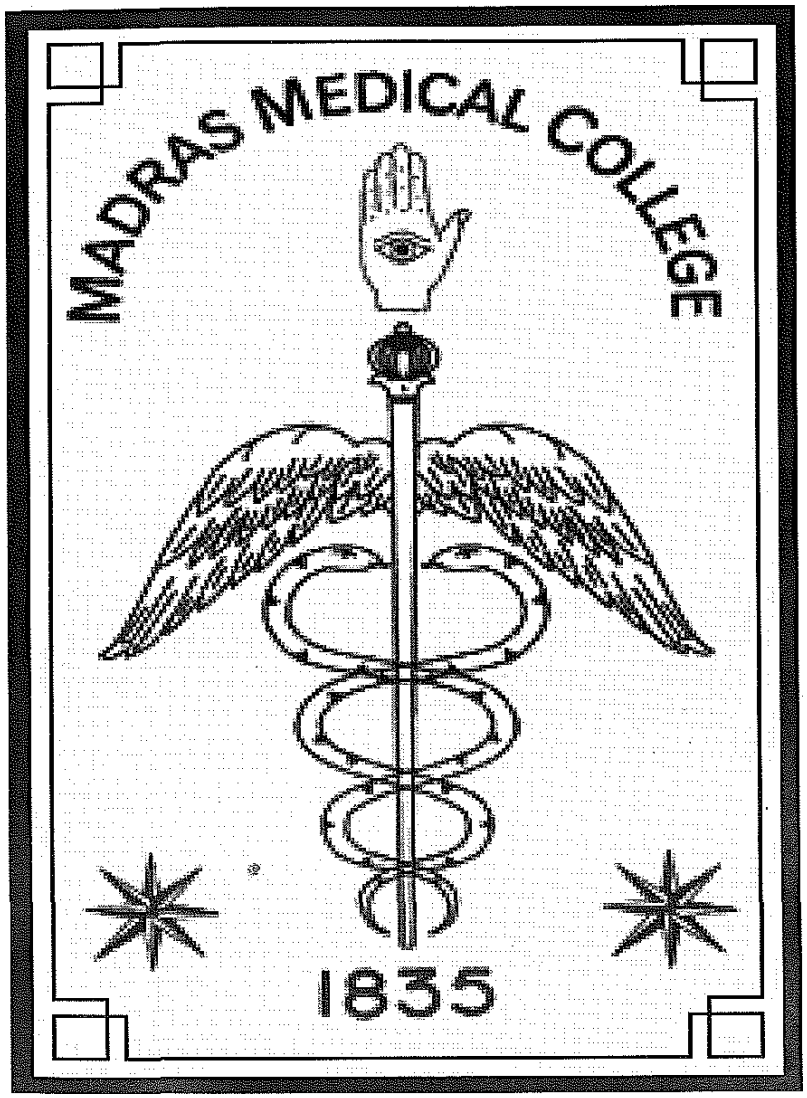

"learn to heal"

CERTIFICATE

This is to certify that the Dissertation entitled **"PATTERN OF GLOMERULO NEPHRITIS AND CHANGING TRENDS AT A TERTIARY CARE CENTRE"** presented here is the original work done by **Dr. A. EZHILARASI** in the Department of Nephrology, Government General Hospital, Madras Medical College, Chennai-600003, in partial fulfillment of the University rules and regulations for the award of D.M. Nephrology Degree under our guidance and supervision during the academic period from 2006-2009.

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CONTENTS

INTRODUCTION

Numerous inflammatory and non-inflammatory diseases affect the glomerular and lead to alteration in glomerular permeability, structure and function. Many glomerular diseases come under the genomic title glomerular nephritis (GN) which implies that there is immune pathogenesis. Not all glomerular diseases are caused by immune pathogenesis and here to be considered in its differential diagnosis, particularly important are diabetic nephropathy and amyloidosis as well as hereditary nephropathy, most commonly Alport syndrome.

Glomerular nephritis may be primary, restricted in clinical manifestations to the kidney or it may be part of multisystem disease, most frequently systemic lupus erythematosis and vasculitis. While the likelihood of a patient having glomerulo nephritis can be estimated with varying degree of confidence from the clinical setting and laboratory test it cannot ultimately be diagnosed without histological evidence of renal cortical tissue.

The underlying cause of most glomerular diseases reminds unknown since knowledge of etiology and pathogenesis is rather limited. The most reliable classification of glomerular diseases based on clinical pathological and laboratory evidence of the disease.

Different studies by various authors in western countries as well as in India have shown varying prevalence of glomerular diseases [1].

In this study of pattern of glomerular diseases (primary and secondary) an attempt has been made to study the distributions, clinical, histopathalogical profile of various glomerular diseases as they occurred in this centre (Madras Medical College, Chennai-3) between two study periods (i.e., 2000-2006 and 2007-2008).

This data has been compared with other centre in south India (CMC, Vellore and US and European data).

REVIEW OF LITERATURE

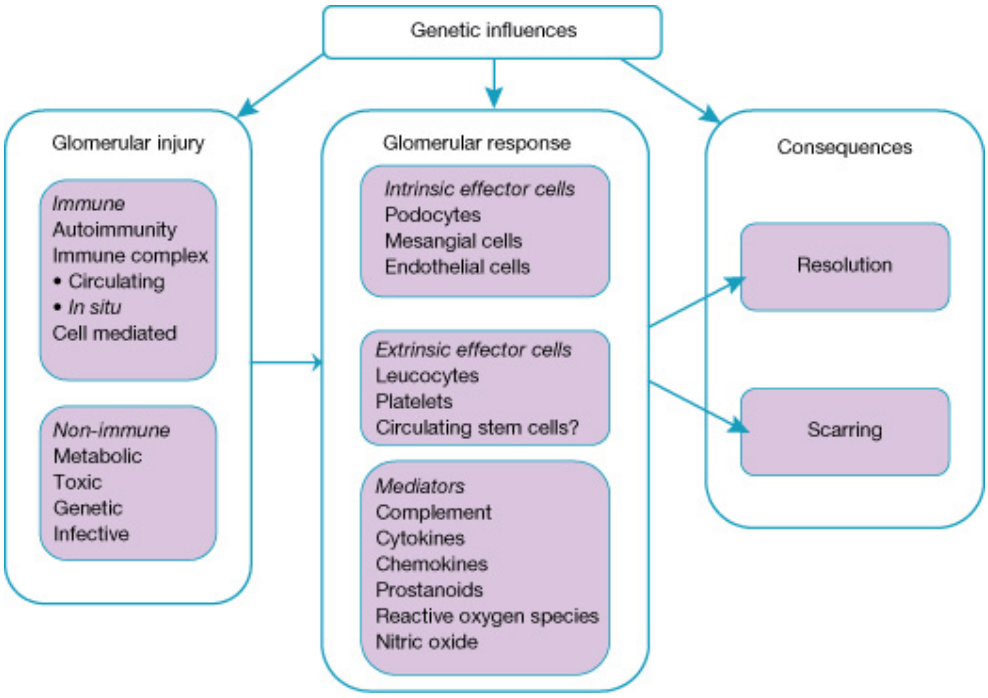
Most glomerular diseases are immune-mediated, and described by the generic term glomerulonephritis (GN). Although the glomerulus is the primary site of damage, subsequent injury to the tubulointerstitium plays a major role in the overall outcome of glomerular disease.

Many forms of GN are characterized by the deposition of immune reactants, particularly immunoglobulin and complements, in the glomerulus which is accompanied by varying degrees of glomerular inflammation and injury. However, both cellular and humoral immune mechanisms may provoke glomerular injury in the absence of such deposits [2].

The underlying cause of most glomerular diseases remains an enigma. Infectious agents, autoimmunity, drugs, inherited disorders, and environmental agents have been implicated as causes of certain glomerular diseases. Until the precise etiology and pathogenesis of glomerular disorders is unraveled, we continue in the tradition of Richard Bright—studying the relationship of clinical, pathological, and laboratory signs and symptoms of disease, and basing our diagnostic categorization on these features rather than on etiology [3].

Glomerular diseases may be categorized into those that primarily involve the kidney (primary glomerular diseases), and those in which kidney involvement is part of a systemic disorder (secondary glomerular diseases) [4-5].

Overview of mechanisms of glomerular injury



Minimal Change Disease

MCD, sometimes known as nil lesion, causes 70–90% of nephrotic syndrome in childhood but only 10–15% of nephrotic syndrome in adults [6, 8].

MCD usually presents as a primary renal disease but can be associated with several other conditions, including Hodgkin's disease, allergies, or use of nonsteroidal anti-inflammatory agents; significant interstitial nephritis often accompanies cases associated with use of nonsteroidal anti-inflammatory drugs.

MCD on renal biopsy shows no obvious glomerular lesion by light microscopy and is negative for deposits by immunofluorescent microscopy, or occasionally shows small amounts of IgM in the mesangium .

Electron microscopy, however, consistently demonstrates an effacement of the foot process supporting the epithelial podocytes with weakening of slit-pore membranes.

The pathophysiology of this lesion is uncertain. Most agree there is a circulating cytokine, perhaps related to a T cell response that alters capillary charge and podocyte integrity. The evidence for cytokine-related immune injury is circumstantial and is suggested by the presence of preceding allergies, altered cell-mediated immunity during viral infections, and the high frequency of remissions with steroids.

MCD presents clinically with the abrupt onset of edema and nephrotic syndrome accompanied by acellular urinary sediment.

In children, the abnormal urine principally contains albumin with minimal amounts of higher molecular weight proteins, and is sometimes called selective proteinuria.

Although up to 30% of children have a spontaneous remission, all children today are treated with steroids; only children who are non responders are biopsied in this setting [5].

Ninety to 95% of children will develop a complete remission after 8 weeks of steroid therapy, and 80–85% of adults will achieve complete remission, but only after a longer course of 20–24 weeks

Relapses occur in 70–75% of children after the first remission, and early relapse predicts multiple subsequent relapses. The frequency of relapses decreases after puberty. Relapses are less common in adults but are more resistant to subsequent therapy.

Predinisolone is first-line therapy, and other immunosuppressive drugs, such as Cyclophosphamide, Chlorambucil, and Mycophenolate Mofetil, Cyclosporine are saved for frequent relapses, steroid-dependent, or steroid-resistant patients.

Focal Segmental Glomerulosclerosis

FSGS refers to a pattern of renal injury characterized by segmental glomerular scars that involve some but not all glomeruli; the

clinical findings of FSGS largely manifest as proteinuria. The incidence of this disease is increasing, and it now represents up to one-third of cases of nephrotic syndrome in adults and one-half of cases of nephrotic syndrome in African Americans, in whom it is seen more commonly [7, 9].

The pathogenesis of FSGS is probably multifactorial. Possible mechanisms include a T cell–mediated circulating permeability factor, TGF-–mediated cellular proliferation and matrix synthesis, and podocyte abnormalities associated with genetic mutations.

The pathologic changes of FSGS are most prominent in glomeruli located at the corticomedullary junction, so if the renal biopsy specimen is from superficial tissue, the lesions can be missed, which sometimes leads to a misdiagnosis of MCD.

In addition to focal and segmental scarring, other variants have been described, including cellular lesions with endocapillary hypercellularity and heavy proteinuria; collapsing glomerulopathy with segmental or global glomerular collapse and a rapid decline in renal function; or the glomerular tip lesion, which seems to have a better prognosis [8].

Table 1. Columbia Classification of the Morphologic Variants of FSGS

Variant	Positive Criteria	Negative Criteria
FSGS, Not otherwise specified	• At least one glomerulus with segmental increase • There may be segmental GBM collapse without podocyte hyperplasia	Exclude other defined variants below
Perihilar variant	• At lease one glomerulus with perihilar hyalinosis, with or without with hyalinosis • Perihilar sclerosis and hyalinosis involving >50% of segmental sclerotic glomerulous	Exclude cellular, tip, and collapsing variants
Cellular variant	• At least one glomerulus with segmental endocapillary hypercellularity occluding Lumina, with or without foam cells and karyorrhexis	Exclude tip and collapsing variants
Tip variant	• At least one segmental lesion involving the tip domain (outer 25% of the tuft next to the origin of the proximal tubule) • The tubular pole must be identified in the defining lesion • The lesion must have either an adhesion or confluence of podocytes with parietal or tubular cells at the tubular lumen or neck	Exclude collapsing variant exclude if any glomeruli show perihilar sclerosis
Collapsing variant	• The tip lesion may be sclerosing or cellular • At least one glomerulus with segmental or global collapse and podocyte hypertrophy	No exclusions

Secondary FSGS

With IV drug abuse

With HIV disease

With other drugs (e.g., pamidronate, interferon)

With identified genetic abnormalities (e.g., in podocin, alpha-actinin-4, TRPC6)

With glomerulomegaly

Morbid obesity

Sickle cell disease

Cyanotic congenital heart disease

Hypoxic pulmonary disease

With reduced nephron numbers

Unilateral renal agenesis

Oligomeganephronemia

Reflux-interstitial nephritis

Post-focal cortical necrosis

Post nephrectomy

FSGS can present with any level of proteinuria, hematuria, hypertension, or renal insufficiency.

FSGS rarely remits spontaneously, but treatment-induced remission of proteinuria significantly improves prognosis.

Treatment of patients with primary FSGS should include inhibitors of the renin-angiotensin system. Based on retrospective studies, patients with nephrotic range proteinuria can be treated with steroids but respond far less often than patients with MCD. Proteinuria remits in only 20–45% of patients receiving a course of steroids over 6–9 months. Use of cyclosporine in steroid-responsive patients helps ensure remissions, while other cytotoxic agents confer little added benefit over steroid therapy.

Primary FSGS recurs in 25–40% of patients given allografts at end-stage disease, leading to graft loss in half of those cases. The treatment of secondary FSGS typically involves treating the underlying cause and controlling proteinuria. There is no role for steroids or other immunosuppressive agents in secondary FSGS.

Membranous Glomerulonephritis

MGN, or membranous nephropathy as it is sometimes called, accounts for approximately 30% of cases of nephrotic syndrome in

adults, with a peak incidence between the ages of 30–50 years and a male to female ratio of 2:1. It is rare in childhood and by far the most common cause of nephrotic syndrome in the elderly [9].

In 25–30% of cases, MGN is secondary to malignancy (solid tumors of the breast, lung, colon), infection (Hepatitis B, Malaria, Schistosomiasis), or Rheumatologic disorders like lupus or rarely rheumatoid arthritis.

It is rare in childhood and by far the most common cause of nephrotic syndrome in the elderly.

Primary/idiopathic membranous glomerulonephritis

Secondary membranous glomerulonephritis

Infection: Hepatitis B and C, Syphilis, Malaria, Schistosomiasis, Leprosy, Filariasis.

Cancer: Breast, colon, lung, stomach, kidney, esophagus, neuroblastoma.

Drugs: gold, mercury, penicillamine, nonsteroidal anti-inflammatory agents, probenecid.

Autoimmune diseases: Systemic lupus erythematosus, Rheumatoid arthritis, Hashimoto's thyroiditis.

Uniform thickening of the basement membrane along the peripheral capillary loops is seen by light microscopy on renal biopsy; this thickening needs to be distinguished from that seen in diabetes and amyloidosis.

Immunofluorescence demonstrates diffuse granular deposits of IgG and C_3, and electron microscopy typically reveals electron-dense subepithelial deposits. The presence of subendothelial deposits or the presence of tubuloreticular inclusions strongly points to a diagnosis of membranous lupus nephritis, which may precede the extrarenal manifestations of lupus.

Table 2. Pathological Staging of Membranous Nephropathy

Stage	Electron Microscopy
I	Sub epithelial electron–dense deposits
II	Sub-epithelial electron – dense deposits with intervening basement membrane (“spikes”)
III	Incorporation of sub-epithelial electron – dense deposits into the basement membrane
IV	1. Reabsorption of deposits with loss of electron – dense deposits and development of lucent area in the basement membrane. 2. Remodeling of basement membrane and loss of electron – dense deposits.

Heyman’s nephritis, an animal model of MGN, suggests that glomerular lesions result from in situ formation of immune complexes with megalin receptor–associated protein as the putative antigen. This antigen is not found in human podocytes, but human antibodies have been described against neutral endopeptidase expressed by podocytes, hepatitis antigens B/C, tumor antigens, and thyroglobulin.

Eighty percent of patients with MGN present with nephrotic syndrome and nonselective proteinuria. Microscopic hematuria is seen in up to 50% of patients. Spontaneous remissions occur in 20–33% of patients and often occur late in the course after years of nephrotic syndrome. One-third of patients continue to have relapsing nephrotic syndrome but maintain normal renal function, and approximately another third of patients develop renal failure or die from the complications of nephrotic syndrome [10, 11].

Male gender, older age, hypertension, and the persistence of proteinuria are associated with worse prognosis. Although thrombotic complications are a feature of all nephrotic syndrome.

MGN has the highest reported incidences of renal vein thrombosis, pulmonary embolism, and deep vein thrombosis. Prophylactic anticoagulation is controversial but has been recommended

for patients with severe or prolonged proteinuria in the absence of risk factors for bleeding.

In addition to the treatment of edema, dyslipidemia, and hypertension, inhibition of the renin-angiotensin system is recommended. Therapy with immunosuppressive drugs is also recommended for patients with primary MGN and persistent proteinuria (>4.0 g/24 h) and in renal failure.

IgA Nephropathy

Berger first described the glomerulonephritis termed IgA nephropathy. It is classically characterized by episodic hematuria associated with the deposition of IgA in the mesangium. IgA nephropathy is one of the most common forms of glomerulonephritis worldwide. There is a male preponderance, a peak incidence in the second and third decades of life, and rare familial clustering [12].

Henoch-Schönlein purpura is distinguished clinically from IgA nephropathy by prominent systemic symptoms, a younger age (<20 years old), preceding infection, and abdominal complaints. Deposits of IgA are also found in the glomerular mesangium in a variety of systemic diseases, including chronic liver disease, Crohn's disease, gastrointestinal adenocarcinoma, chronic obstructive bronchiectasis, idiopathic interstitial pneumonia, dermatitis herpetiformis, mycosis

fungiodes, leprosy, ankylosing spondylitis, relapsing polychondritis, and Sjögren's syndrome. IgA deposition in these entities is not usually associated with clinically significant glomerular inflammation or renal dysfunction and thus is not called IgA nephropathy.

IgA nephropathy is an immune complex-mediated glomerulonephritis defined by the presence of diffuse mesangial IgA deposits often associated with mesangial hypercellularity. IgM, IgG, C_3, or immunoglobulin light chains may be co-distributed with IgA. IgA deposited in the mesangium is typically polymeric and of the IgA_1 subclass, the pathogenic significance of which is not clear.

Abnormalities have been described in IgA production by plasma cells, particularly secretory IgA; in IgA O-glycosylation; in IgA clearance, predominately by the liver; in mesangial IgA clearance and receptors for IgA; and in growth factor and cytokine-mediated events. Despite the presence of elevated serum IgA levels in 20–50% of patients, IgA deposition in skin biopsies in 15–55% of patients, or elevated levels of secretory IgA and IgA-fibronectin complexes

Although the immunofluorescent pattern of IgA on renal biopsy defines IgA nephropathy in the proper clinical context, a variety of histologic lesions may be seen on light microscopy, including DPGN;

segmental sclerosis; and, rarely, segmental necrosis with cellular crescent formation, which typically presents as RPGN.

The two most common presentations of IgA nephropathy are recurrent episodes of macroscopic hematuria during or immediately following an upper respiratory infection in children (Henoch-Schönlein purpura) or asymptomatic microscopic hematuria most often seen in adults. Between episodes, the urinalysis is normal. When the hematuria persists, one finds increasing amounts of proteinuria; nephrotic syndrome, however, is uncommon.. Rarely, patients can present with acute renal failure and a rapidly progressive clinical picture.

IgA nephropathy is a benign disease for the majority of patients, with progression to renal failure seen in only 25–30% over 20–25 years; in fact, 5–30% of patients go into complete remission. Risk factors for the loss of renal function include the presence of hypertension or proteinuria, the absence of episodes of macroscopic hematuria, male age, older age of onset, and more severe changes on renal biopsy [13].

There is no agreement on optimal treatment. Both large studies that include patients with multiple glomerular diseases or small studies of patients with IgA nephropathy support the use of angiotensin-converting enzyme (ACE) inhibitors in patients with proteinuria or declining renal function. Tonsillectomy, steroid therapy, and fish oil

have all been suggested in small studies to benefit select patients with IgA nephropathy. When presenting as RPGN, patients typically receive steroids, cytotoxic agents, and plasmapheresis.

Post streptococcal Glomerulonephritis

Post streptococcal glomerulonephritis is prototypical for acute endocapillary proliferative glomerulonephritis. Acute post streptococcal glomerulonephritis typically affects children between the ages of 2 and 14 years, but 10% of cases are patients older than 40. It is more common in males, and the familial or cohabitant incidence is as high as 40%.

Skin and throat infections with particular M types of streptococci (nephritogenic strains) antedate glomerular disease; M types 47, 49, 55, 2, 60, and 57 are seen following impetigo and M types 1, 2, 4, 3, 25, 49, and 12 with pharyngitis. Post streptococcal glomerulonephritis due to impetigo develops 2–6 weeks after skin infection and 1–3 weeks after streptococcal pharyngitis.

The renal biopsy in post streptococcal glomerulonephritis demonstrates hypercellularity of mesangial and endothelial cells, glomerular infiltrates of polymorphonuclear leukocytes, granular subendothelial immune deposits of IgG, IgM, C_3, and subepithelial deposits (which appear as "humps").

Post streptococcal glomerulonephritis is an immune-mediated disease involving putative streptococcal antigens, circulating immune complexes, and activation of complement in association with cell-mediated injury. Many candidate antigens have been proposed over the years; three such candidates from nephritogenic streptococci are zymogen, a precursor of exotoxin B; glyceraldehyde phosphate dehydrogenase, also known as prescribing antigen (PA-Ag); and streptokinase. All have a biochemical affinity for GBMs, and in this location they may act as a target for antibodies.

The classic presentation is an acute nephritic picture with hematuria, pyuria, red blood cell casts, edema, hypertension, and oliguric renal failure, which may be severe enough to appear as RPGN. Systemic symptoms of headache, malaise, anorexia, and flank pain (due to swelling of the renal capsule) are reported in as many as 50% of cases.

Five percent of children and 20% of adults have proteinuria in the nephrotic range. In the first week of symptoms, 90% of patients will have a depressed CH_{50} and decreased levels of C_3 with normal levels of C_4.

Positive cultures for streptococcal infection are inconsistently present (10–70%), but increased titers of ASO (30%), anti-DNAase

(70%) or antihyaluronidase antibodies (40%) can help confirm the diagnosis.

Treatment is supportive, with control of hypertension, edema, and dialysis as needed. Antibiotic treatment for streptococcal infection should be given to all patients and their cohabitants. There is no role for immunosuppressive therapy, even in the setting of crescents. Recurrent post streptococcal glomerulonephritis is rare despite repeated streptococcal infections.

Overall, the prognosis is good, with permanent renal failure being very uncommon (1–3%), and even less so in children. Complete resolution of the hematuria and proteinuria in children occurs within 3–6 weeks of the onset of nephritis.

Membranoproliferative Glomerulonephritis

MPGN is sometimes called mesangiocapillary glomerulonephritis or lobar glomerulonephritis. It is an immune-mediated glomerulonephritis characterized by thickening of the GBM with mesangioproliferative changes; 70% of patients have hypocomplementemia. MPGN is rare in African Americans, and idiopathic disease usually presents in childhood or young adulthood. MPGN is subdivided pathologically into Type I, Type II, and Type III disease. Type I MPGN is commonly associated with persistent

hepatitis C infections, autoimmune diseases like lupus or cryoglobulinemia, or neoplastic diseases. Types II and III MPGN are usually idiopathic, except in the presence of C_3 nephritic factor and/or in partial lipodystrophy producing Type II disease or complement receptor deficiency in Type III disease.

Type I Disease (Most Common)

- Idiopathic
- Subacute bacterial endocarditis
- Systemic lupus erythematosus
- Hepatitis C ± cryoglobulinemia
- Mixed cryoglobulinemia
- Hepatitis B
- Cancer: Lung, breast, and ovary (germinal)

Type II Disease (Dense Deposit Disease)

- Idiopathic
- C_3 nephritic factor-associated
- Partial lipodystrophy

Type III Disease

- Idiopathic
- Complement receptor deficiency

Type I MPGN, the most proliferative of the three types, shows mesangial proliferation with lobular segmentation on renal biopsy and mesangial interposition between the capillary basement membrane and endothelial cells, producing a double contour sometimes called tram-tracking. Subendothelial deposits with low serum levels of C_3 are typical, although 50% of patients have normal levels of C_3 and occasional intra-mesangial deposits.

Low serum C_3 and a dense thickening of the GBM containing ribbons of dense deposits and C_3 characterize Type II MPGN, sometimes called dense deposit disease. Classically, the glomerular tuft has a lobular appearance; intramesangial deposits are rarely present and subendothelial deposits are generally absent.

Proliferation in Type III MPGN is less common than the other two types and is often focal; mesangial interposition is rare, and subepithelial deposits can occur along widened segments of the GBM that appear laminated and disrupted.

Type I MPGN is secondary to glomerular deposition of circulating immune complexes or their in situ formation. Types II and III MPGN may be related to "nephritic factors," which are autoantibodies that stabilize C_3 convertase and allow it to activate serum C_3.

Patients with MPGN present with proteinuria, hematuria, and pyuria (30%), systemic symptoms of fatigue and malaise that are most common in children with Type I disease, or an acute nephritic picture with RPGN and a speedy deterioration in renal function in up to 25% of patients. Low serum C_3 levels are common. Fifty percent of patients with MPGN develop end-stage disease 10 years after diagnosis, and 90% have renal insufficiency after 20 years. Nephrotic syndrome, hypertension, and renal insufficiency all predict poor outcome.

Although all primary renal diseases can recur over time in transplanted renal allografts, patients with MPGN are well known to be at risk for this adverse event.

Diabetic Nephropathy

Diabetic nephropathy is the single most common cause of chronic renal failure in the United States, accounting for 45% of patients receiving renal replacement therapy, and is a rapidly growing problem worldwide.

The dramatic increase in the number of patients with diabetic nephropathy reflects the epidemic increase in obesity, metabolic syndrome, and Type 2 diabetes mellitus. Approximately 40% of patients with Types 1 or Type 2 diabetes develop nephropathy, but due to the

higher prevalence of Type 2 diabetes (90%) compared to Type 1 (10%), the majority of patients with diabetic nephropathy have Type 2 disease.

Risk factors for the development of diabetic nephropathy include hyperglycemia, hypertension, dyslipidemia, smoking, a family history of diabetic nephropathy, and gene polymorphisms affecting the activity of the renin-angiotensin-aldosterone axis.

Within 1–2 years after the onset of clinical diabetes, morphologic changes appear in the kidney. Thickening of the GBM is a sensitive indicator for the presence of diabetes but correlates poorly with the presence or absence of clinically significant nephropathy. The composition of the GBM is altered notably with a loss of heparan sulfate moieties that form the negatively charged filtration barrier. This change results in increased filtration of serum proteins into the urine, predominately negatively charged albumin. The expansion of the mesangium due to the accumulation of extracellular matrix correlates with the clinical manifestations of diabetic nephropathy. This expansion in mesangial matrix can be associated with the development of mesangial sclerosis. Some patients also develop eosinophilic, PAS^{+} nodules called nodular glomerulosclerosis or Kimmelstiel-Wilson nodules. Immunofluorescence microscopy often reveals the nonspecific deposition of IgG (at times in a linear pattern) or complement staining without immune deposits on electron microscopy. Prominent vascular

changes are frequently seen with hyaline and hypertensive arteriosclerosis. This is associated with varying degrees of chronic glomerulosclerosis and tubulointerstitial changes. Renal biopsies from patients with Types 1 and Type 2 diabetes are largely indistinguishable.

Since the onset of Type 1 diabetes is readily identifiable and the onset of Type 2 diabetes is not, a patient newly diagnosed with Type 2 diabetes may have renal disease for many years before nephropathy is discovered and presents as advanced diabetic nephropathy. At the onset of diabetes, renal hypertrophy and glomerular hyperfiltration are present. The degree of glomerular hyperfiltration correlates with the subsequent risk of clinically significant nephropathy.

In the approximately 40% of patients with diabetes who develop diabetic nephropathy, the earliest manifestation is an increase in albuminuria detected by sensitive radioimmunoassay. Albuminuria in the range of 30–300 mg/24 h is called microalbuminuria. In patients with Types 1 or Type 2 diabetes, microalbuminuria appears 5–10 years after the onset of diabetes. It is currently recommended to test patients with Type1 disease for microalbuminuria 5 years after diagnosis of diabetes and yearly thereafter, and, because the time of onset of Type 2 diabetes is often unknown, to test Type 2 patients at the time of diagnosis of diabetes and yearly thereafter [14].

Microalbuminuria is a potent risk factor for cardiovascular events and death in patients with Type2 diabetes. Many patients with Type2 diabetes and microalbuminuria succumb to cardiovascular events before they progress to proteinuria or renal failure. Proteinuria in frank diabetic nephropathy can be variable, ranging from 500 mg to 25 g/24 h, and is often associated with nephrotic syndrome.

More than 90% of patients with Type1 diabetes and nephropathy have diabetic retinopathy, so the absence of retinopathy in Type 1 patients with proteinuria should prompt consideration of a diagnosis other than diabetic nephropathy; only 60% of patients with Type 2 diabetes with nephropathy have diabetic retinopathy. There is a highly significant correlation between the presence of retinopathy and the presence of Kimmelstiel-Wilson nodules [15].

Also, characteristically, patients with advanced diabetic nephropathy have normal to enlarged kidneys, in contrast to other glomerular diseases where kidney size is usually decreased. Using the above epidemiologic and clinical data, and in the absence of other clinical or serologic data suggesting another disease, diabetic nephropathy is usually diagnosed without a renal biopsy [16].

After the onset of proteinuria >500 mg/24 h, renal function inexorably declines, with 50% of patients reaching renal failure in

5–10 years; thus, from the earliest stages of microalbuminuria, it usually takes 10–20 years to reach end-stage renal disease.

Hypertension may predict which patients develop diabetic nephropathy, as the presence of hypertension accelerates the rate of decline in renal function.

Good evidence supports the benefits of blood sugar and blood pressure control as well as inhibition of the renin-angiotensin system in retarding the progression of diabetic nephropathy. In patients with Type1 diabetes, intensive control of blood sugar clearly prevents the development or progression of diabetic nephropathy. The evidence in patients with Type 2 disease, although less compelling, also supports intensive control of blood sugar. Controlling systemic blood pressure to levels of 130/80 mmHg or less decreases renal and cardiovascular adverse events in this high-risk population. The vast majority of patients with diabetic nephropathy require three or more antihypertensive drugs to achieve this goal. Drugs that inhibit the renin-angiotensin system, independent of their effects on systemic blood pressure, have been repeatedly shown to slow the progression of diabetic nephropathy at early (microalbuminuria) and late (proteinuria with reduced glomerular filtration) stages, independent of any effect they may have on systemic blood pressure.

Since angiotensin II increases efferent arteriolar resistance and, hence, glomerular capillary pressure, one key mechanism for the efficacy of ACE inhibitors or angiotensin receptor blockers (ARBs) is reducing glomerular hypertension. Patients with Type1 diabetes for 5 years who develop albuminuria or declining renal function should be treated with ACE inhibitors. Patients with Type2 diabetes and microalbuminuria or proteinuria may be treated with ACE inhibitors or ARBs [17].

Renal Amyloidosis

Most renal amyloidosis is either the result of primary fibrillar deposits of immunoglobulin light chains [amyloid L (AL)], or secondary to fibrillar deposits of serum amyloid A (AA) protein fragments. Even though both occur for different reasons, their clinicopathophysiology is quite similar and will be discussed together. Amyloid infiltrates the liver, heart, peripheral nerves, carpal tunnel, upper pharynx, and kidney, producing restrictive cardiomyopathy, hepatomegaly, macroglossia, and heavy proteinuria sometimes associated with renal vein thrombosis.

In systemic AL amyloidosis, also called primary amyloidosis, light chains produced in excess by clonal plasma cell dyscrasias are made into fragments by macrophages so they can self-aggregate at acid pH. A disproportionate number of these light chains (75%) are of the

lambda class. About 10% of these patients have overt myeloma with lytic bone lesions and infiltration of the bone marrow with >30% plasma cells; nephrotic syndrome is common, and about 20% of patients progress to dialysis.

AA amyloidosis is sometimes called secondary amyloidosis and also affects the kidney with nephrotic syndrome. It is due to deposition of -pleated sheets of serum amyloid A protein, an acute phase reactant whose physiologic function is unknown. Forty percent of patients with AA amyloid have rheumatoid arthritis, and another 10% have ankylosing spondylitis or psoriatic arthritis; the rest derive from other lesser causes.

Fragments of serum amyloid A protein increase and self-aggregate by attaching to receptors for advanced glycation end products in the extracellular environment; nephrotic syndrome is common, and about 40–60% of patients progress to dialysis.

AA and AL amyloid fibrils are detectable with Congo red or in more detail with electron microscopy. Biopsy of involved liver or kidney is diagnostic 90% of the time when the pretest probability is high; abdominal fat pad aspirates are positive about 70% of the time, but apparently less so when looking for AA amyloid. Amyloid deposits are

distributed along blood vessels and in the mesangial regions of the kidney.

The treatment for primary amyloidosis is not particularly effective; Melphalan and autologous hematopoietic stem cell transplantation can delay the course of disease in about 30% of patients. Secondary amyloidosis is also relentless unless the primary disease can be controlled. Some new drugs in development that disrupt the formation of fibrils may be available in the future [18].

Lupus Nephritis

Lupus nephritis is a common and serious complication of systemic lupus erythematosus (SLE) and most severe in African-American female adolescents. Thirty to fifty percent of patients will have clinical manifestations of renal disease at the time of diagnosis, and 60% of adults and 80% of children develop renal abnormalities at some point in the course of their disease. Lupus nephritis results from the deposition of circulating immune complexes, which activate the complement cascade leading to complement-mediated damage, leukocyte infiltration, activation of procoagulant factors, and release of various cytokines. In situ immune complex formation following glomerular binding of nuclear antigens may also play a role in renal

injury. The presence of antiphospholipid antibodies may trigger a thrombotic microangiopathy in a minority of patients.

Table 3. Pathological Indices of Activity and Tonicity in Lupus Nephritis

Chronicity Index	Activity Index
Glomerular sclerosis	Cellular proliferation
Fibrous crescents	Fibrinoid necrosis, Karyorrhexis
Tubular Atrophy	Cellular Atrophy
Interstitial Fibrosis	1. Hyaline thrombi , wire loop lesions 2. Leukocyte infiltration in glomerulus 3. Mononuclear –cell infiltration in interstitium

Importance of biopsy in Lupus

Border Suggested > 6 RBC / HPF and urine protein > 200mg / 24hrs. Abnormal serum creatinine [18]. Mahajan et al. described 12 patients with diffused proliferative lupus nephritis but without clinical or laboratory evidence of renal involvement so biopsy recommended in patients with SLE even in the absence of overt clinical renal involvement [19].

Histological scoring system for lupus nephritis is an effort to accurately predict the renal outcome and to help to determine which patients are likely to benefit from aggressive therapy.

The clinical manifestations, course of disease, and treatment of lupus nephritis are closely linked to the renal pathology. The most common clinical sign of renal disease is proteinuria, but hematuria, hypertension, varying degrees of renal failure, and active urine sediment with red blood cell casts can all be present.

The extrarenal manifestations of lupus are important in establishing a firm diagnosis of systemic lupus because, while serologic abnormalities are common in lupus nephritis, they are not diagnostic. Anti-dsDNA antibodies that fix complement correlate best with the presence of renal disease. Hypocomplementemia is common in patients with acute lupus nephritis (70–90%) and declining complement levels may herald a flare. Renal biopsy, however, is the only reliable method of identifying the morphologic variants of lupus nephritis.

The World Health Organization (WHO) workshop in 1974 first outlined several distinct patterns of lupus-related glomerular injury; these were modified in 1982. In 2004 the International Society of Nephrology in conjunction with the Renal Pathology Society again updated the classification. This latest version of lesions seen on biopsy

best defines clinicopathologic correlations, provides valuable prognostic information, and forms the basis for modern treatment recommendations.

Class I nephritis describes normal glomerular histology by any technique or normal light microscopy with minimal mesangial deposits on immunofluorescent or electron microscopy. **Class II** designates mesangial immune complexes with mesangial proliferation. Both Class I and II lesions are typically associated with minimal renal manifestation and normal renal function; nephrotic syndrome is rare. Patients with lesions limited to the renal mesangium have an excellent prognosis and generally do not need therapy for their lupus nephritis.

Table 4. Revised in 2004 by the International Society of Nephrology-Renal Pathology Society Study Group.

Class I	Minimal mesangial	Normal histology with mesangial deposits
Class II	Mesangial proliferation	Mesangial hypercellularity with expansion of the mesangial matrix
Class III	Focal nephritis	Focal endocapillary ± extracapillary proliferation with focal subendothelial immune deposits and mild mesangial expansion
Class IV	Diffuse nephritis	Diffuse endocapillary ± extracapillary proliferation with diffuse subendothelial immune deposits and mesangial alterations.

Class V	Membranous nephritis	Thickened basement membranes with diffuse subepithelial immune deposits; may occur with Class III or IV lesions and is sometimes called mixed membranous and proliferative nephritis
Class VI	Sclerotic nephritis	Global sclerosis of nearly all glomerular capillaries

The subject of lupus nephritis is presented under acute nephritic syndromes because of the aggressive and important proliferative lesions seen in Class III–V renal disease.

Class III describes focal lesions with proliferation or scarring, often involving only a segment of the glomerulus Class III lesions have the most varied course. Hypertension, an active urinary sediment, and proteinuria are common with nephrotic-range proteinuria in 25–33% of patients. Elevated serum creatinine is present in 25% of patients. Patients with mild proliferation involving a small percentage of glomeruli respond well to therapy with steroids alone, and fewer than 5% progress to renal failure over 5 years. Patients with more severe proliferation involving a greater percentage of glomeruli have a far worse prognosis and may have lower remission rates. Treatment of those patients is the same as that for Class IV lesions, as some nephrologists believe that Class III lesions are simply an early presentation of Class IV disease.

Class IV describes global, diffuse proliferative lesions involving the vast majority of glomeruli. Patients with Class IV lesions commonly have high anti-DNA antibody titers, low serum complement, hematuria, red blood cell casts, proteinuria, hypertension, and decreased renal function; 50% of patients have nephrotic-range proteinuria. Patients with crescents on biopsy may have a rapidly progressive decline in renal function. Without treatment, this aggressive lesion has the worst renal prognosis. However, if a remission is achieved with treatment, renal outcomes are excellent. Treatment must combine high-dose steroids with either Cyclophosphamide or Mycophenolate Mofetil. Current evidence suggests that inducing a remission with administration of steroids and either Cyclophosphamide or Mycophenolate Mofetil for 2–6 months, followed by maintenance therapy with lower doses of steroids and Mycophenolate Mofetil, may best balance the likelihood of successful remission with the side effects of therapy.

The **Class V** lesion describes subepithelial immune deposits producing a membranous pattern; a subcategory of Class V lesions is associated with proliferative lesions and is sometimes called mixed membranous and proliferative disease. Sixty percent of patients present with nephrotic syndrome or lesser amounts of proteinuria. Patients with lupus nephritis Class V, like patients with idiopathic membranous nephropathy, are predisposed to renal-vein thrombosis and other

thrombolic complications. A minority of patients with Class V will present with hypertension and renal dysfunction.. Patients with severe nephrotic syndrome, elevated serum creatinine, and a progressive course will probably benefit from therapy with steroids in combination with other immunosuppressive agents. Therapy with inhibitors of the renin-angiotensin system also may attenuate the proteinuria.

Patients with any of the above lesions also can transform to another lesion; hence patients often require reevaluation, including repeat renal biopsy. Lupus patients with **Class VI** lesions have greater than 90% sclerotic glomeruli and end-stage renal disease with interstitial fibrosis. As a group, approximately 20% of patients with lupus nephritis will reach end-stage disease, requiring dialysis or transplantation. Systemic lupus tends to become quiescent once there is renal failure, perhaps due to the immunosuppressant effects of uremia. Renal transplantation in renal failure from lupus, usually performed after approximately 6 months of inactive disease, results in allograft survival rates comparable to patients transplanted for other reasons.

Antiglomerular Basement Membrane Disease

Patients who develop autoantibodies directed against glomerular basement antigens frequently develop a glomerulonephritis termed antiglomerular basement membrane (anti-GBM) disease. When they

present with lung hemorrhage and glomerulonephritis, they have a pulmonary-renal syndrome called Good pasture's syndrome.

The target epitopes for this autoimmune disease lie in the quaternary structure of 3 NC1 domain of collagen IV. MHC-restricted T cells initiate the autoantibody response because humans are not tolerant to the epitopes created by this quaternary structure. The epitopes are normally sequestered in the collagen IV hexamer and can be exposed by infection, smoking, oxidants, or solvents. Good pasture's syndrome appears in two age groups: in young men in their late 20s and in men and women in their 60–70s.

Disease in the younger age group is usually explosive, with hemoptysis, a sudden fall in hemoglobin, fever, dyspnoea, and hematuria. Hemoptysis is largely confined to smokers, and those who present with lung hemorrhage as a group do better than older populations who have prolonged, asymptomatic renal injury; presentation with oliguria is often associated with a particularly bad outcome [20].

The performance of an urgent kidney biopsy is important in suspected cases of Good pasture's syndrome to confirm the diagnosis and assess prognosis. Renal biopsies typically show focal or segmental necrosis that later, with aggressive destruction of the capillaries by

cellular proliferation, leads to crescent formation in Bowman's space. As these lesions progress, there is concomitant interstitial nephritis with fibrosis and tubular atrophy. The presence of anti-GBM antibodies and complement is recognized on biopsy by linear immunofluorescent staining for IgG .

Between 10–15% of sera from patients with Good pasture's syndrome also contain ANCA antibodies against myeloperoxidase. This subset of patients has a vasculitis-associated variant, which has a surprisingly good prognosis with treatment.

Prognosis at presentation is worse if there are >50% crescents on renal biopsy with advanced fibrosis, if serum creatinine is >5–6 mg/dL, if oliguria is present, or if there is a need for acute dialysis. Patients with advanced renal failure who present with hemoptysis should still be treated for their lung hemorrhage, as it responds to plasmapheresis and can be lifesaving. Treated patients with less severe disease typically respond to 8–10 treatments of plasmapheresis accompanied by oral prednisone and Cyclophosphamide in the first 2 weeks.

Kidney transplantation is possible, but because there is risk of recurrence, patients should wait for 6 months and until serum antibodies are undetectable.

ANCA Small Vessel Vasculitis

A group of patients with small-vessel vasculitis (arterioles, capillaries, and venules; rarely small arteries) and glomerulonephritis have serum ANCA; the antibodies are of two types, anti-proteinase 3 (PR3) or anti-myeloperoxidase (MPO). ANCA are produced with the help of T cells and activate leukocytes and monocytes, which together damage the walls of small vessels. Endothelial injury also attracts more leukocytes and extends the inflammation. Wegener's granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome belong to this group because they are ANCA-positive and have a pauci-immune glomerulonephritis with few immune complexes in small vessels and glomerular capillaries. Patients with any of these three diseases can have any combination of the above serum antibodies, but anti-PR3 antibodies are more common in Wegener's and anti-MPO antibodies are more common in microscopic polyangiitis or Churg-Strauss. While each of these diseases have some unique clinical features, most features do not predict relapse or progression, and as a group they are generally treated in the same way. Only the presence of upper-airway involvement, persistent pulmonary injury, and anti-PR3 antibodies suggests that the course of disease will be more difficult. Induction therapy usually includes some combination of Plasmapheresis, Methylprednisolone, and

Cyclophosphamide. The benefit of Plasmapheresis in this setting is uncertain.

The steroids are tapered soon after acute inflammation subsides, and patients are maintained on Cyclophosphamide or Azathioprine for up to a year to minimize the risk of relapse.

Wegener's Granulomatosis

Patients with this disease classically present with fever, purulent rhinorrhea, nasal ulcers, sinus pain, polyarthralgias/arthritis, cough, hemoptysis, shortness of breath, microscopic hematuria, and 0.5–1 g / 24 h of proteinuria; occasionally there may be cutaneous purpura and mononeuritis multiplex. Presentation without renal involvement is termed limited Wegener's granulomatosis, although some of these patients will show signs of renal injury later. Chest x-ray often reveals nodules and persistent infiltrates, sometimes with cavities. Biopsy of involved tissue will show a small-vessel vasculitis and adjacent noncaseating granulomas. Renal biopsies during active disease demonstrate segmental necrotizing glomerulonephritis without immune deposits. The cause of Wegner's granulomatosis is unknown.

Microscopic Polyangiitis

Clinically, these patients look somewhat similar to those with Wegener's granulomatosis, except they rarely have significant lung disease or destructive sinusitis. The distinction is made on biopsy where the vasculitis in microscopic polyangiitis is without granulomas. Some patients will also have injury limited to the capillaries and venules.

Churg-Strauss Syndrome

When small-vessel vasculitis is associated with peripheral eosinophilia, cutaneous purpura, mononeuritis, asthma, and allergic rhinitis, a diagnosis of Churg-Strauss syndrome is considered.

Hypergammaglobulinemia, elevated levels of serum IgE, or the presence of rheumatoid factor sometimes accompanies the allergic state. Lung inflammation, including fleeting cough and pulmonary infiltrates, often precedes the systemic manifestations of disease by years; lung manifestations are rarely absent. A third of patients may have exudative pleural effusions associated with eosinophils. Small-vessel vasculitis and focal segmental necrotizing glomerulonephritis can be seen on renal biopsy, usually absent eosinophils or granuloma. The cause of Churg-Strauss syndrome is autoimmune, but the inciting factors are unknown. Interestingly, some asthma patients treated with leukotriene receptor antagonists will develop this vasculitis.

OBJECTIVES OF THE STUDY

1. To study and analyse the clinical pattern of Glomerulonephritis and to observe the changing pattern of Glomerulonephritis in our centre during two study periods, i.e. 2000-2006 and 2007-2008.

2. To compare our data with the data of other centre.

MATERIALS AND METHODS

- The study was done as prospectively from Jan 2007- Dec 2008. Retrospective data from Jan 2000-Dec 2006 were retrieved from case record.

- Study centre : Department of Nephrology , Government General Hospital , Madras Medical College , Chennai – 600 003

- Plan of study: All patients who had clinical, laboratory and histopathological features of Glomerular disease were analysed.

- Detailed history and Clinical examination were done to find out evidence of volume status, BP measurements and Funduscopic examination followed by basic laboratory investigation like urine analysis complete blood count, coagulation profile, renal function test, liver function test, Chest X–Ray, Ultrasonographic examination of the Abdomen with done and basic serelogical and immunological workup like HBsAg, anti HCV, HIV, ASO Titre and ANA were done.

- After informed consent Ultrasound guided Renal Biopsy was done with spring loaded semi-automatic gun.

- All biopsies were evaluated by Light microscopy and immunoflorescence.

- Patients were grouped according to age, gender, presence of Hypertension, renal function and their results were analysed.

STATISTICAL ANALYSIS

Demographic variables like age, sex and histology categories were given in frequencies with their percentages.

Sex-wise and year wise difference on histological categories was analysed using Two Sample Binomial Proportion Test.

Sex-wise, renal biopsy in diabetes was analyzed using Pearson Chi Square Test.

Decade-wise clinical syndrome was analyzed using Two Sample Binomial Proportion Test.

Comparison with other studies was analysed using Pearson Chi Square Test.

P value less than 0.05 was taken as significant.

RESULTS

Distribution of Patients

- Total number of biopsies done from 2000-2008 is 893 are included in this study.

- Datas were collected from the case records for the years 2000-2006 and between 2007-2008 were studied prospectively.

- Total number of biopsies done from 2000-2006 was 454 out of which 350(77%) was due to primary glomeluar disease and 104(23%) was due to secondary gomerular disease.

- Number of biopsies in 2007-2008 was 439 out of which 342 (78%) was primary glomeluar disease and 97 (22%) was contributed secondary glomeluar disease.

Table 5. Distribution of patients

Histology	2000-06	2007-08	TOTAL
Primary GN	350 (77%)	342 (78%)	692
Secondary GN	104 (23%)	97 (22%)	201
TOTAL	**454**	**439**	**893**

The distribution of various primary glomerular diseases are given below:

Table 6. Distribution of Primary Glomerular Disease

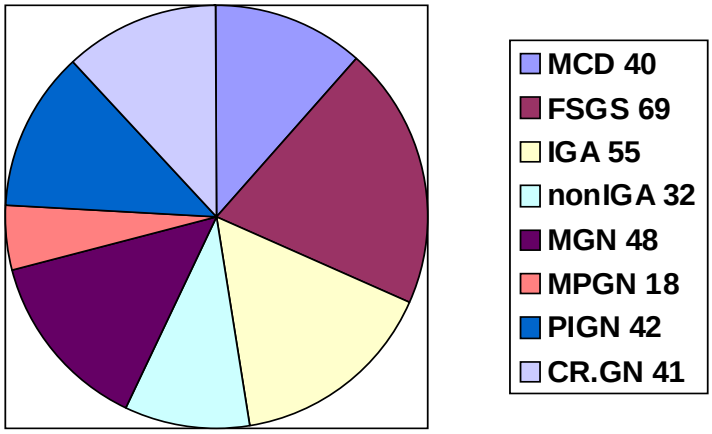
Histology	2000-06	2007-08	Total	p value
MCD	40 (11.4%)	48 (14%)	88 (12.7%)	0.30
FSGS	69 (19.70)	92 (26.9%)	161(23.2%)	0.03
IGA	55 (15.7%)	31 (9%)	86 (12.4%)	0.008
NonIGA mpgn	32 (9.1%)	24 (7%)	56 (8.09%)	0.30
MGN	48 (13.7%)	35(10.2%)	83(11.9%)	0.16
MPGN	18(5.1%)	11(3.2%)	29(4.1%)	0.20
PIGN	42(12%)	59(17.2%)	111(16%)	0.01
CR.GN	41(11.7%)	37(10.8%)	78(11.2%)	0.10
TOTAL	**350**	**342**	**692**	**-**

P=0.05 significant

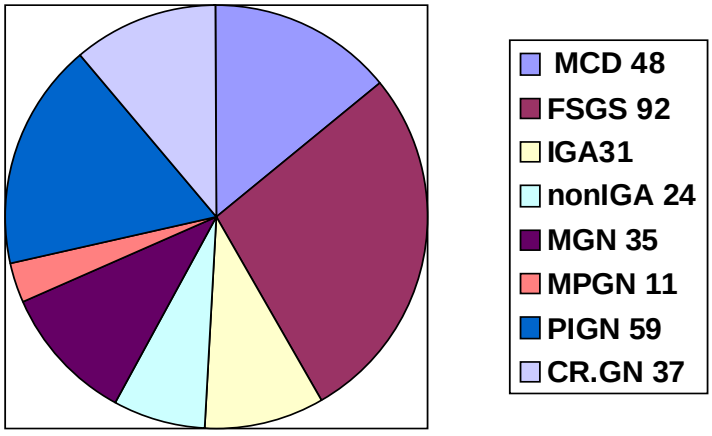
Incidence of FSGS and PIGN has increased significantly from 2000-06 to 2007-08.

Incidence of IgA nephropathy has decreased significantly from 2000-06 to 2007-08.

Distribution of Primary Glomerular Disease 2000-2006



Distribution of Primary Glomerular Disease 2007-2008



Distribution of Secondary Glomerular Disease

Number of biopsies done between 2000 and 2006 was 104 whereas the number of biopsies done between 2007 and 2008 was 97.The incidence of secondary Glomerular disease –Lupus Nephritis was 59(56%), Diabetic nephropathy(Where non diabetic kidney disease was suspected) was 31(29%) and Amyloidosis 14(11.4%) respectively .In second group between 2007-2008 the number of biopsies done was 201, Lupus Nephritis was 74(76%), Diabetic nephropathy was 12(12.3%) and Amyloidosis 11(145%) respectively.

Table 7. Distribution of Secondary Glomerular Disease

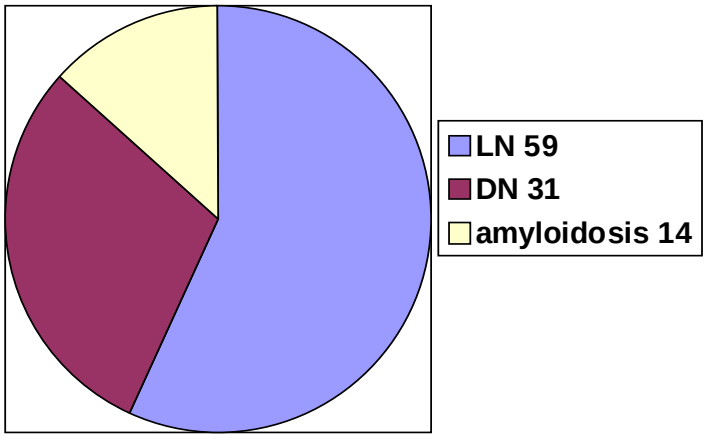
Histology	2000-06	2007-08	Total	P Value
LN	59(56%)	74(76%)	133(66%)	0.01
DN	31(29 %)	12(12.3%)	43(21.4%)	0.002
Amyloidosis	14(13%)	11(11.4%)	25(12.4%)	0.65
Total	**104**	**97**	**201**	

P= 0.05 significant

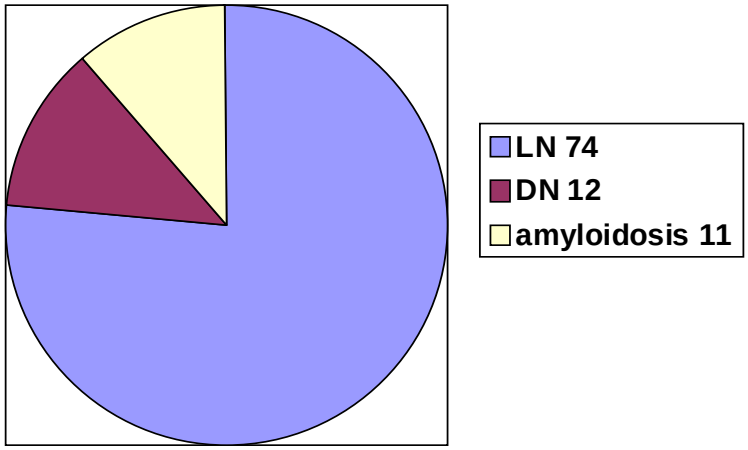
Incidence of diabetic nephropathy has decreased in our study because of our biopsy protocol.

This is probably of change in biopsy policy in patients with diabetic mellitus with proteinuria. We do biopsy only if patient had active urine sediment, micro hematuria, rapidly progressive renal failure, absence of retinopathy.

Distribution of Secondary Glomerular Disease 2000-2006



Distribution of Secondary Glomerular Disease 2007-2008



The Distribution of Age in various Primary Glomerular Disease are given below

Table 8. Distribution of Age in Primary Glomerular Disease

Histology	No	No	No	M.age	M.age	M.age	Age range	Age range	Age range
	00-06	07-08	Total	00-06	07-08	Total	00-06	07-08	Total
MCD	40	48	88	19.3	20.3	19.6	14-40	15-35	14-40
FSGS	69	92	161	27	25.3	26.4	14-65	15-63	14-65
IGA	55	31	86	31.3	35.4	32.8	20-55	18-61	18-61
NonIGA mp	37	29	66	21.1	23.2	22.1	15-62	18-63	15-63
MGN	48	35	83	45.3	40.1	43.2	30-73	33-68	30-73
MPGN	18	11	29	19.2	23.5	21.6	14-30	18-23	14-30
PIGN	42	59	111	23.4	28.1	25.1	16-55	18-61	16-61
CR.GN	41	37	78	28.3	35.5	30.3	20-58	23-61	20-61

Mean age is higher in PIGN & Cr.GN .As for FSGS & MGN are concerned mean age is lower.

Table 9. Distribution of Age in Secondary Glomerular Disease

Histology	No	No	No	M.age	M.age	M.age	Age range	Age range	Age range
	00-06	07-08	Total	00-06	07-08	Total	00-06	07-08	Total
LN	59	74	113	24.3	26.3	25	18-62	20-58	18-62
DN	31	12	43	43	39	41.8	33-58	30-49	30-58
Anyloidosis	11	14	25	46	42	45.6	39-63	36-65	36-65

The increasing trend observed for mean age in Lupus Nephritis.

The decreasing trend was observed for Diabetic Nephropathy.

The Distribution of Gender in various Primary Glomerluar Diseases is given below:

Table 10. Distribution of Gender in Primary Glomerluar Disease

Histology	M/F Ratio		Total
	00-06	07-08	
MCD	1.4	1.4	1.4
FSGS	2.2	2.4	2.3
IGA	2.2	2.5	2.3
nonIGA mp	1.3	1.6	1.4
MGN	1.6	1.8	1.7
MPGN	1.4	1	1.3
PIGN	2.1	2.6	2.3
CR.GN	0.8	0.9	0.8

Male predominance was observed in FSGS, IgAN, MGN and PIGN, whereas same status was observed for MCD, MPGN and CrGN.

The Distribution of Gender in various secondary Glomerluar Diseases is given below.

Table 11. Distribution of Gender in Secondary Glomerular Disease

Histology	M/F Ratio		Total
	00-06	07-08	
LN	0.32	0.20	0.29
DN	2.3	2.2	2.3
Anyloidosis	1.3	1.5	1.4

Female predominance was observed in Lupus nephritis whereas male dominance was observed in Diabetic nephropathy.

The distribution of various glomerular diseases with age group is given below.

Table 12. Distribution of Glomerular Disease with Age Group

Histology	**<30**	**30-60**	**>60**	**Total**
Primary GN	327	308	57	692
Secondary GN	124	71	6	201
Total	**451**	**379**	**63**	**893**

Incidence of primary glomerular disease was similar between 30 to 60 years and less than 30 years, whereas incidence of secondary glomerular disease was higher in less than 30 years of age group.

The Distribution of various Primary Glomerular Diseases with Age group is given below.

Table 13. Distribution of Primary Glomerular Disease with Age Group

Histology	<30	30-60	>60	Total	P Value
MCD	66(21.2%)	22(7.1%)	0	88	0.001
FSGS	84(25.6%)	70(22.7%)	7(17.3%)	161	0.01
IGA	20(7.9%)	53(17.2%)	13(22.8%)	86	0.001
NonIgA mp gn	34(10.4%)	18(5.8%)	4(7%)	56	0.101
MGN	7(2.1%)	60(19.4%)	16(20%)	83	0.01
MPGN	22(6.7%)	7(2.2%)	0	29	0.01
PIGN	75(22.9%)	27(8.7%)	9(15.8%)	111	0.101
CR.GN	19(5.8%)	51(16.5%)	8(14%)	78	0.001

P=0.05 significant

Incidence of MCD, PIGN and FSGS was higher < 30 years of age group. Incidence of IgA, CrGN & MGN nephropathy was more in the age group between 30 to 60 years.

The Distribution of various Secondary glomerular diseases with Age Group is given below.

Table 14. Distribution of Secondary glomerular disease with Age Group

Histology	<30	30-60	>60	Total	P Value
LN	117(94.3%)	14(19.7%)	2(33.3%)	133	0.10
DN	4(3.2%)	38(53.5%)	1(16.6%)	43	0.10
Amyloidosis	3(2.4%)	19(26.7%)	3(50%)	25	0.001
Total	**124**	**71**	**6**	**201**	

P=0.05

Incidence of lupus nephritis was higher in less than 30 years of age group. Incidence of diabetic nephropathy was seen in 30 to 60 years.

The Clinical Presentation of various Glomerular Diseases at initial presentations is given below.

Table 15. Clinical Presentation of Glomerular Disease on Presentation

Histology	Edema	Oliguria	Macrohe-maturia	Fever	Anorexia	Dyspnoea	Total
MCD	80	6	0	12	6	6	88
FSGS	98	26	3	18	23	31	161
IGA	21	23	25	8	21	19	86
nonIGA mp	15	13	2	7	3	7	56
MGN	40	7	3	3	7	8	83
MPGN	12	2	3	7	4	3	29
PIGN	60	71	24	25	19	23	111
CR.GN	60	55	21	23	33	35	78
LN	31	23	17	43	23	20	133
DN	36	21	1	7	8	10	43
Amyloidosis	12	4	0	3	3	3	25

MCD (90.9%), FSGS (60.8%) & MGN (48.1%) are most commonly presented with edema.

In IgA nephropathy, 29% had Macrohaematuria.

In PIGN 63.96 % had Oliguria 18% had Marohaematuria.

In CrGN 76.92% had edema, 70.5% had oliguria 26.92% had macrohaematuria.

In Lupus nephritis 32.3% had fever 17.29 had oliguria.

In diabetic nephropathy, 83.72% had edema.

The Examination Findings of various Glomerular Diseases at initial presentations are given below.

Table 16. Examination Findings of Glomerular Disease on Presentation

Histology	Edema	Ht	Retinopathy	Pleural effusion	Ascitis	Total
MCD	84	10	0	32	33	88
FSGS	106	41	31	31	32	161
IGA	25	34	12	9	8	86
nonIGA mp	18	16	3	2	3	56
MGN	45	27	13	5	4	83
MPGN	15	12	5	3	2	29
PIGN	73	65	4	12	11	111
CR.GN	66	53	8	19	7	78
LN	36	70	23	33	21	133

Incidence of hypertension in MCD (11.36%), FSGS (25.46%), MGN (32.53%).

Incidence of hypertension in IgA nephropathy (39.53%), PIGN (28.55%).

Incidence of hypertension in CrGN (67.94%).

Incidence of hypertension in lupus nephritis (52.63%)

The lab features of various primary and secondary diseases are given below:

Table 17. Lab Features of Glomerular Disease

Histology	Microhe-maturia	Blood urea >7 Mmol	Sr.creat >130 micromo	Chol >200 mg/dl	Avg. Urine pcr	Avg.sr. Albumin <3g/dl	Total
MCD	12	3	2	52	6.2	43	88
FSGS	36	53	48	73	2.8	73	161
IGA	41	34	31	10	2.1	2.2	86
nonIGA mp	11	13	11	8	1.3	7	56
MGN	37	13	10	12	5.8	22	83
MPGN	8	7	6	7	3.1	8	29
PIGN	73	73	69	9	3.1	9	111
CR.GN	69	61	63	5	3.3	13	78
LN	101	33	30	8	2.1	12	133
DN	13	29	20	21	4.3	16	43
Amyloidosis	2	6	4	7	3.6	10	25

In MCD 2 of them presented with renal failure. One had sepsis (22 yrs) due to spontaneous bacterial peritonitis and recovered with antibiotics. Another person (41 yrs) presented with renal vein thrombosis recovered with anticoagulant and 52 of them had cholesterol

more than 200 mg/dl with average urine PCR 6.2 and 43 of them presented with hypo Albuminemia.

In FSGS 48 of them presented with renal failure and 73 of them presented with hyper lipidemia.

In IgA nephropathy 41 of them presented with micro hematuria and 31 of them presented with renal failure.

In PIGN 69 of them presented with renal failure.

In CrGN 69 of them presented with micro hematuria and 63 of them presented with renal failure.

In lupus nephritis 30 of them presented with renal failure and 8 of them had hyper lipidemia.

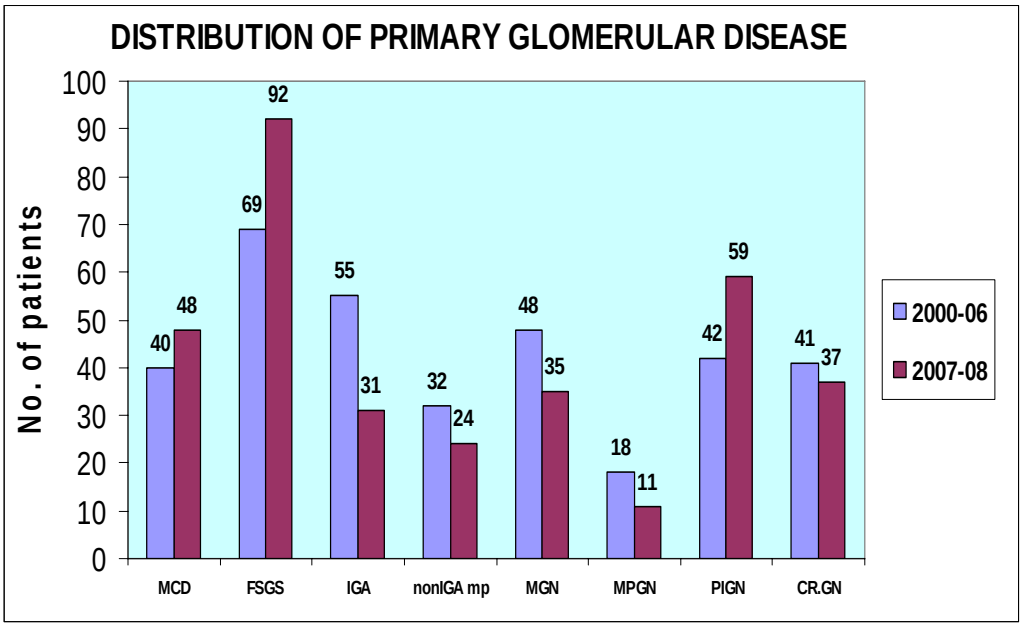
In diabetic nephropathy 20 of them presented with renal failure.

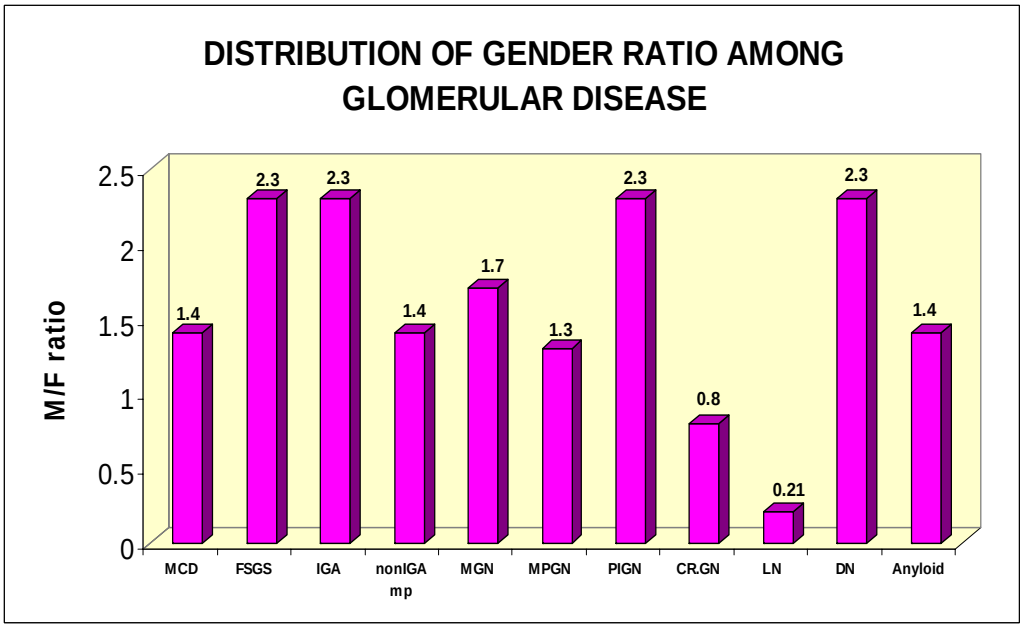
Table 18. Comparison with Other Studies

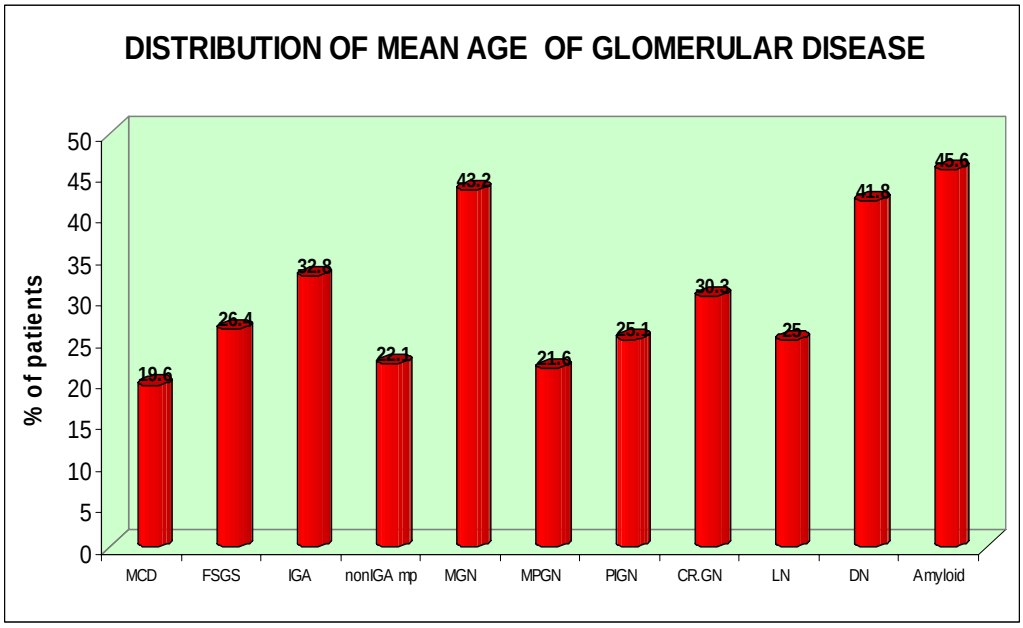
Histological Categories	MMC Study (n=893)		CMC, Vellore (n=4035)		Minnesota (n=195)		Italian Study (n=13835)		Pearson Chi Square Test	Comparison between Studies
	n	%	n	%	n	%	n	%		
FSGS	161	11.79	677	16.8	33	21.5	1730	12.5	χ^2 =181.6 P=0.001	1 Vs 2,3
PIGN	111	7.70	543	13.5	7	3.6	360	2.6	χ^2 =760.1 P=0.001	1 Vs 2,3,4
MCD	88	6.48	433	10.8	8	4.1	1065	7.7	χ^2 =162.2 P=0.001	1 Vs 2
Mesangial PGN	56	5.09	293	7.3			1231	8.9	χ^2 =36.75 P=0.001	1 Vs 2,4
MN	83	5.92	384	9.5	20	10.2	3127	22.6.	χ^2 =572 P=0.001	1 Vs 2,3,4
IgAN	86	6.04	338	8.4	42	21.5	5188	37.5	χ^2 =173.1 P=0.001	1 Vs 2,3,4
Lupus Nephritis	133	8.97	279	6.9	25	12.8			χ^2 =14.71 P=0.001	1 Vs 2
Crescentic GN	78	4.21	140	3.5	10	5.1	941	6.8	χ^2 =72.64 P=0.001	1 Vs 2,4
Diabetic Nephropathy	43	3.77	111	2.8					χ^2 =4.32 P=0.04	1 Vs 2
Amyloidosis	75	4.15	41	1.0	5	2.6			χ^2 =62.8 P=0.001	1 Vs 2

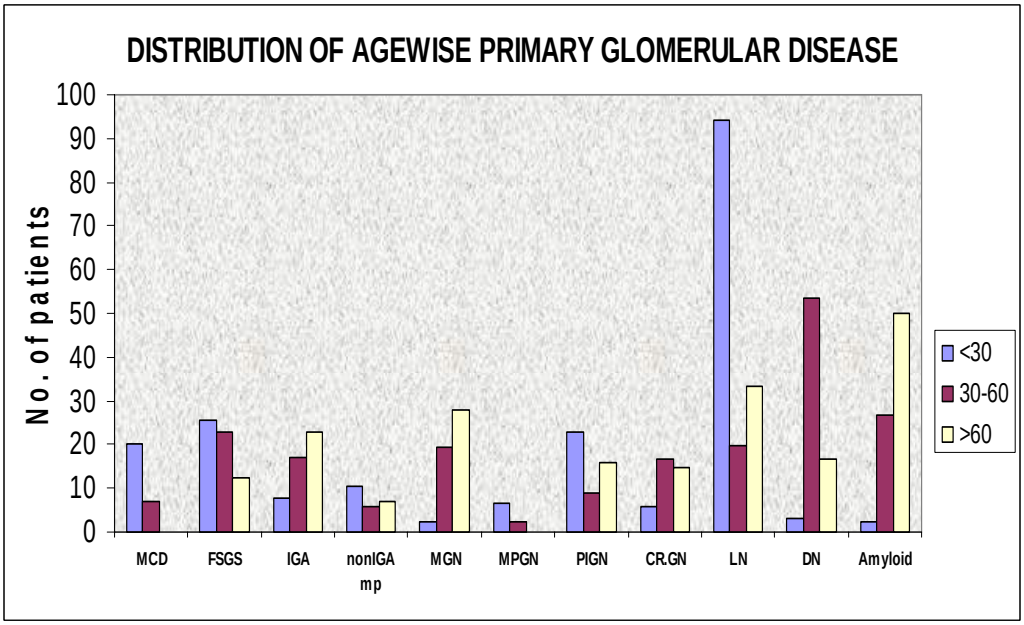
The results of this study correlate significantly with south Indian study (CMC, Vellore) for FSGS, MCD, MN, IgAN and Lupus Nephritis.

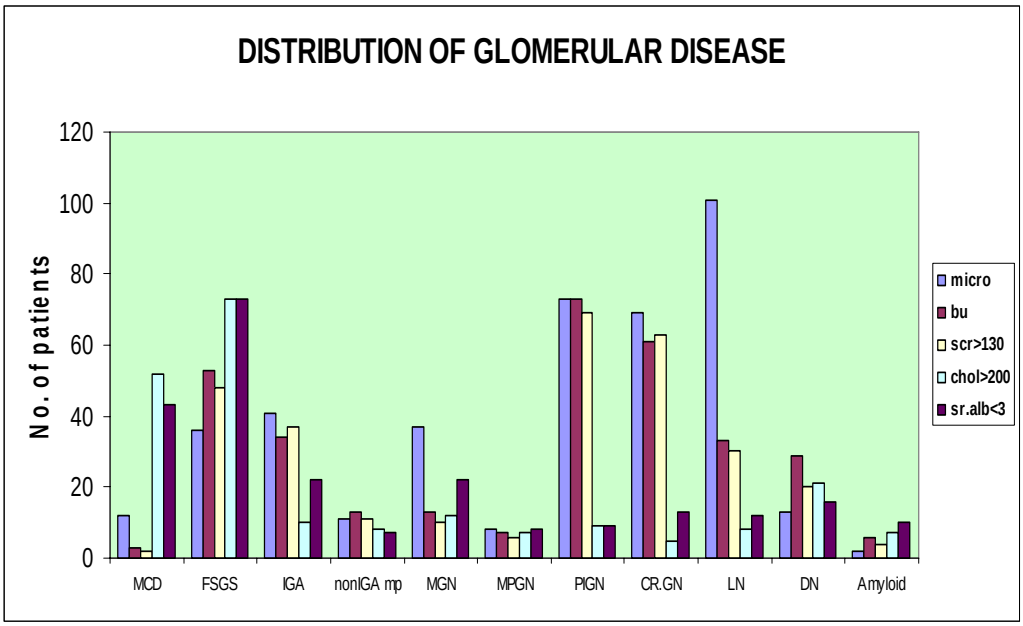
The results of this study significantly correlate with Italian study and US study for the following IgAN, MGN and PIGN.

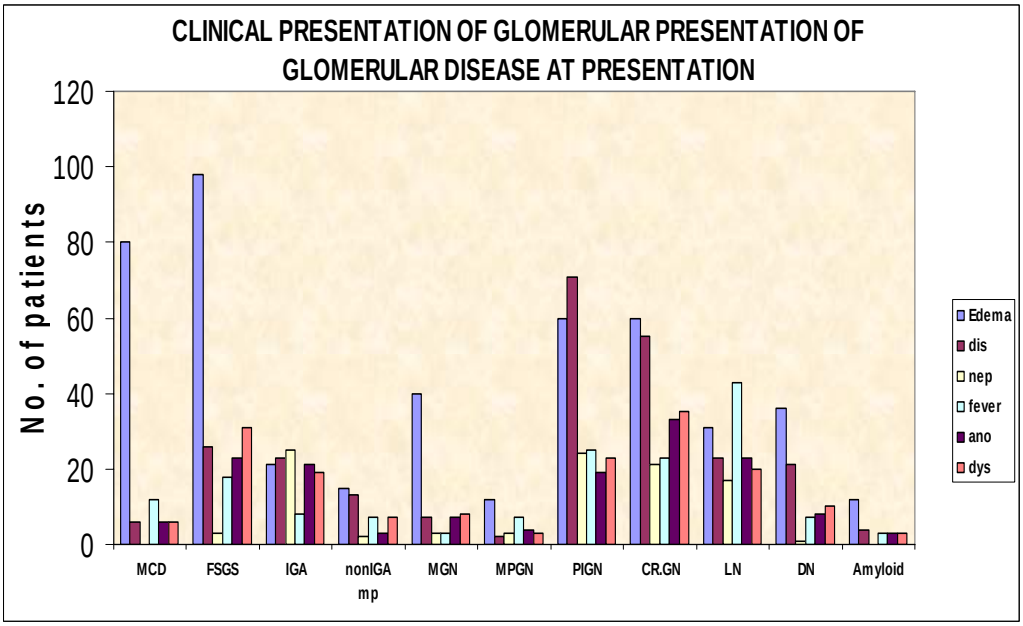

DISTRIBUTION OF PRIMARY GLOMERULAR DISEASE
No. of patients
100
90
80
70
60
50
40
30
20
10
0
40
48
69
92
55
31
32
24
48
35
18
11
42
59
41
37
MCD
FSGS
IGA
nonIGA mp
MGN
MPGN
PIGN
CR.GN
2000-06
2007-08

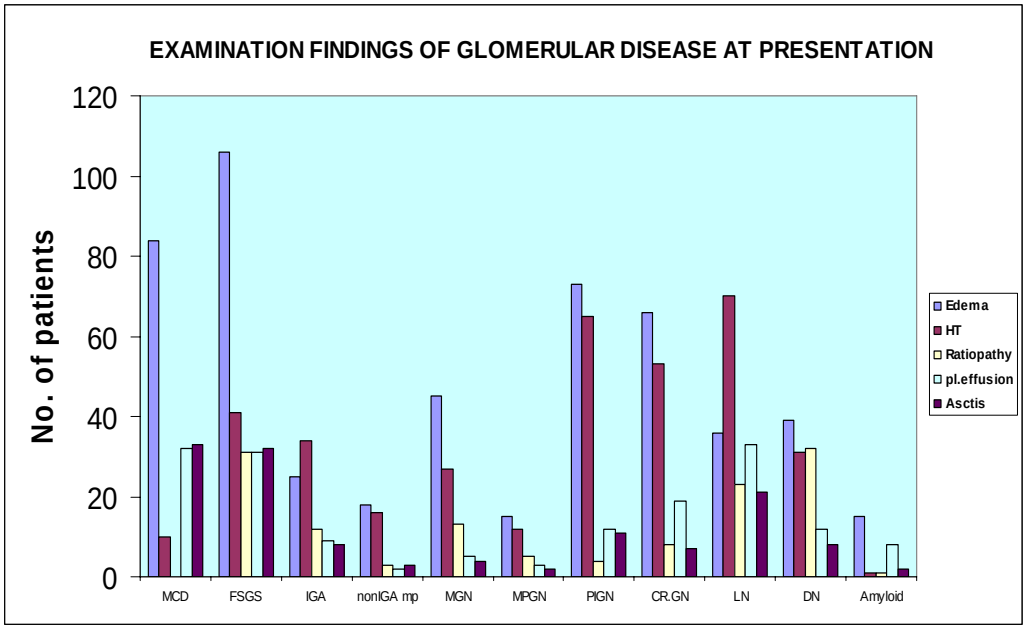

DISTRIBUTION OF GENDER RATIO AMONG GLOMERULAR DISEASE
M/F ratio
2.5
2
1.5
1
0.5
0
1.4
2.3
2.3
1.4
1.7
1.3
2.3
0.8
0.21
2.3
1.4
MCD
FSGS
IGA
nonIGA mp
MGN
MPGN
PIGN
CR.GN
LN
DN
Anyloid


DISTRIBUTION OF MEAN AGE OF GLOMERULAR DISEASE
% of patients
50
45
40
35
30
25
20
15
10
5
0
19.6
26.4
32.8
22.1
43.2
21.6
25.1
30.3
25
41.8
45.6
MCD
FSGS
IGA
nonIGA mp
MGN
MPGN
PIGN
CR.GN
LN
DN
Amyloid


DISTRIBUTION OF AGEWISE PRIMARY GLOMERULAR DISEASE
No. of patients
100
90
80
70
60
50
40
30
20
10
0
MCD
FSGS
IGA
nonIGA mp
MGN
MPGN
PIGN
CR.GN
LN
DN
Amyloid
<30
30-60
>60


DISTRIBUTION OF GLOMERULAR DISEASE
No. of patients
120
100
80
60
40
20
0
MCD
FSGS
IGA
nonIGA mp
MGN
MPGN
PIGN
CR.GN
LN
DN
Amyloid
micro
bu
scr>130
chol>200
sr.alb<3


CLINICAL PRESENTATION OF GLOMERULAR PRESENTATION OF GLOMERULAR DISEASE AT PRESENTATION
No. of patients
120
100
80
60
40
20
0
MCD
FSGS
IGA
nonIGA mp
MGN
MPGN
PIGN
CR.GN
LN
DN
Amyloid
Edema
dis
nep
fever
ano
dys


EXAMINATION FINDINGS OF GLOMERULAR DISEASE AT PRESENTATION
No. of patients
120
100
80
60
40
20
0
MCD
FSGS
IGA
nonIGA mp
MGN
MPGN
PIGN
CR.GN
LN
DN
Amyloid
Edema
HT
Ratiopathy
pl.effusion
Asctis

DISCUSSION

It has been widely accepted that MCNS is by far the most common cause of nephrotic syndrome in children in ISKDC. It was reported almost 30 years ago that MCD was present in 77% all renal biopsies performed in children with idiopathic nephrotic syndrome [6].

In our study 12.7% of them presented with MCD and two of them had renal failure and recovered. In this study, the relative decline in the frequency of minimal change nephropathy could be that fewer patients with such regions are actually being subjected to biopsy [25]. Studies from Siegel et al. and Trachtman et al. have shown a higher incidence of FSGS in pediatric patients with steroid sensitive nephrotic syndrome, but increased incidence of FSGS is reported in steroid dependent and frequent relapsers. According to D'Agati and has increased incidence of FSGS has been observed in recent years [26].

In this study results demonstrate a high incidence of FSGS which contributes to 23.2%. Ethnicity seems to play a critical role in the epidemiology of nephrotic syndrome [27] and observed, strong predominance of FSGS among African Americans. A potential explanation for this recent surge in FSGS could be a change in ethnic

composition of our population [28]. Another consideration for the risk in the incidence of FSGS is a potential increase in the age of patients who are resistance to corticosteroid (R).Unfortunately, because the etiology of FSGS in unknown, it is difficult to postulate a potential mechanism for this increasing incidence [29].

We cautiously excluded from this study patients with identified systemic disease are conditions known to be associated with FSGS like HIV, heroin abuse and drugs like lithium and palmidronate etc.

However, it is recognized that a wide variety of factors can trigger a response in nephron that would eventually lead to the development of the histological lesions of FSGS. FSGS also appears to be a rather heterogeneous condition. For example, circulating factors cause proteinuria in FSGS patients, particularly those who have recurrence of the disease following renal transplant.

We also observe a lower relative frequency of MPGN (inclusive of all subtypes) and also relatively higher frequency of IgAN (R).In this study as well as that of Korbete et al. suggested that IgAN should be considered in the differential diagnosis of adult nephortic syndrome of unknown etiology, particularly in young patients [30].

Korbete et al. (R) noted a decrease in the incidence of MGN in black individuals, compared with an increase of approximately 10%

over 10 years in the white individuals (R).In this study findings suggest increase in incidence of MGN significantly higher (11.9).

In this Study the incidence of lupus nephritis has increased significantly with Class 4 & Class 5 types. Increasing incidence of male lupus has also observed in this study.

The incidence of Diabetic Nephropathy was more common in age group of 30yrs and above as expected .In this study only limited number of Diabetic patients were subjected to Renal Biopsy if they had any indication like active urine sediment, significant proteinuria without Diabetic retinopathy, unusual or rapid decline in renal function, massive proteinuria unexplained renal failure with normal size kidney [31].

Total number of Biopsies done in this study was 43 out of which 23 were due to Diabetic Nephropathy and 13 were due to non diabetic renal disease and 10 of them due to had both Diabetic Nephropathy and non diabetic disease.

Table 19. Renal Biopsy in Diabetics

Sex	ND		NDRD		DN+NDRD		Total
	No. of Patients	Percentage (%)	No. of Patients	Percentage (%)	No. of Patients	Percentage (%)	
Male	16	37.29	8	18.06	7	16.27	31
Female	7	16.27	2	24.65	3	6.92	12
Total	23		10		10		43

Table 20. Non-Diabetic Renal Disease

Type of Renal lesion	Male (n=31)	Female (n=12)	Percentage, % (n=43)
Membranous Nephropathy	5	2	16.27
Post Infectious Glomerulonephritis	6	2	18.06
Acute Interstitial Nephritis	2	1	6.97
Acute Tubular Necrosis	2	-	4.65

For non-diabetic Renal disease membranous nephropathy contributes to 16.27%. Highest incidence of non-diabetic renal disease was PIGN which is about 18.06 %. AIN contributes 6.97% whereas ATN contributes only 4.65 %.

Finally we also found that in significant fractions of patients, at least more than 55years of age with unexplained nephrotic syndrome, had amyloid nephropathy although amyloid is not a primary renal disease. But we included in this study of patients with unexplained nephrotic syndrome if at the time of biopsy they had no known evidence of a systemic disease related to amyloid [32].

TRIALS DONE FOR CHANGING TREND OF GLOMERULAR DISEASE

Changing incidence of glomerular disease Olmsted County, Minnestoa: a 30 year renal biopsy study

Sundararaman swaminathan et al Clinical J Am Soc Nephrol 1: 483-487, 2006 [21].

Period of study: 1974-2003 Retrospective time trends in the annual age: and gender adjusted (2000 US population) incidence rate per 1,00,000 on Olmsted county residents estimated.

Total numbers of 195 biopsies were analysed.

IgN nephropathy -22 %, FSGS-17%, MGN-10%.

Between 1974-1983 and 1994-2003 incidence of any type of GN among Olmsted county residents increased more than 2-fold ($P<0.001$).

FSGS-13-fold($P<0.001$), IgAN – 3 fold($P=0.002$), MGN-2.5 fold ($P=0.13$).

1994 to 2003 IgAN 25% annual incidence rate 2.1 per 100000/ year, FSGS 20% annual incidence rate 1.8/100000 per year, MGN 11% annual incidence rate 1.0/100000 per year.

This study confirms that the incidence of GN is growing overall particularly FSGS which is the leading cause of nephrotic syndrome in white adults.

Spectrum of biopsy proven renal disease and changing trends at a tropical tertiary care center 1990-2001

N Balakrishnan, George T John *et al*. Indian J Nephrol 2003; 13:29-35 [22].

Period of study: 1994-2001

Total number of biopsy -4035

MCD-47.2%

FSGS-12.5%

PIGN-8.8%

Non IgA Misangial PGN-11.3%

Lupus nephritis -3.5%

MPGN-2.6%

Non diabetic renal disease-72%

Between 1970 and 1985, MCD-8.7%, FSGS – 22%, MGN-11%, MPGN-7.2%, PIGN-40.7%.

In this study MCD, FSGS, Misangial PGN and PIGN were significantly more common in the present study.

SURVEY OF THE ITALIAN REGISTRY OF RENAL BIOPSIES

Frequency of renal disease for 7 consecutive years

F.P.Schena et al Nephrol dial Transplant (1997)12:418-426 [23].

Period of study: 1987-1993

Total number of biopsies: 15461

Between 1987-1989 Primary glomerular disease -59.9%

IgAN - 36.9%

MGN-21.7%

FSGS-10.4%

Secondary glomerular disease – 25.4%

Lupus nephritis-51.6%

Amyloidosis-39.3%

In 1993 MGN-32.9%, FSGS-12.3%, MCD-12%,

PIGN-16.1%, IgAN-14%.

Primary glomerular disease (22.7 p.m.p)

Secondary glomerular disease (11.8 p.m.p)

The frequency of main groups of nephrotic syndrome and the distribution of different GN changes only slightly over a long period.

CONCLUSIONS

Our studies show that the most common primary glomerular disease is FSGS, followed by PIGN, IGAN, MCNS and MGN, in that order, respectively.

There is increased incidence of FSGS and PIGN during the year 2007-08.

The mean age of presentation for FSGS and MGN was lower during 2007-08.

The occurrence of FSGS, PIGN and MCN was seen more in younger age group, while in elderly patients, IgA nephropathy was common primary glomerular disease.

Our studies have shown decreased incidence of MCD, FSGS, IgA nephropathy and MGN, and increased incidence of lupus nephritis compared to CMC studies.

The incidence of Crescentic GN and diabetic nephropathy was similar in both the studies.

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WORK SHEET

Year	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**Total**
FSGS	13	10	14	4	20	8	32	28	32	161
PIGN	5	7	6	9	8	7	20	20	19	111
MCD	7	11	8	2	10	9	17	19	4	88
Mesangial PGN	5	8	5	2	5	6	9	14	6	56
MN	9	4	13	10	4	8	10	12	13	83
IgAN	6	10	9	12	9	9	15	9	7	86
Lupus Nephritis	13	5	8	18	8	17	24	28	22	133
Crescentic GN	7	10	9	9	8	8	6	8	14	78
Diabetic nephropathy	5	0	4	5	4	13	5	3	4	43
MPGN	2	8	2	5	7	1	4	3	4	29
Amyloidosis	1	1	0	5	2	5	3	4	4	25