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Sub-Nephrotic Proteinuria as the Indication for a Kidney Biopsy: Review

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Abstract

Sub-nephrotic proteinuria as a clinical syndrome and an indication to renal biopsy has not much attention. In this systematic review, series from 24 studies have been researched. IgA nephropathy, MesPGN and MGN were respectively defined as the most likely diagnoses for patients undergoing renal biopsies due to sub-nephrotic proteinuria. Profound disparities were also detected with regard to the patients' region of origin as well as their age subgroup. Due to the limitation of the number of series reporting data on sub-nephrotic proteinuria and associated pathological diagnoses, further data coming with the prospective reports are necessary to make more precise estimations.

Keywords: IgA nephropathy; MesPGN; MGN; Sub-nephrotic Proteinuria; Pathological Diagnoses

Abbreviations: MesPGN: Mesangial Proliferative Glomerulonephritis; MGN: Membranous Glomerulonephritis; FSGS: Focal & Segmental Glomerulosclerosis; CI: Confidence Interval; DN: Diabetic Nephropathy.

Introduction

Proteinuria is a major indicator of kidney disease and also a main indication for renal biopsy worldwide.

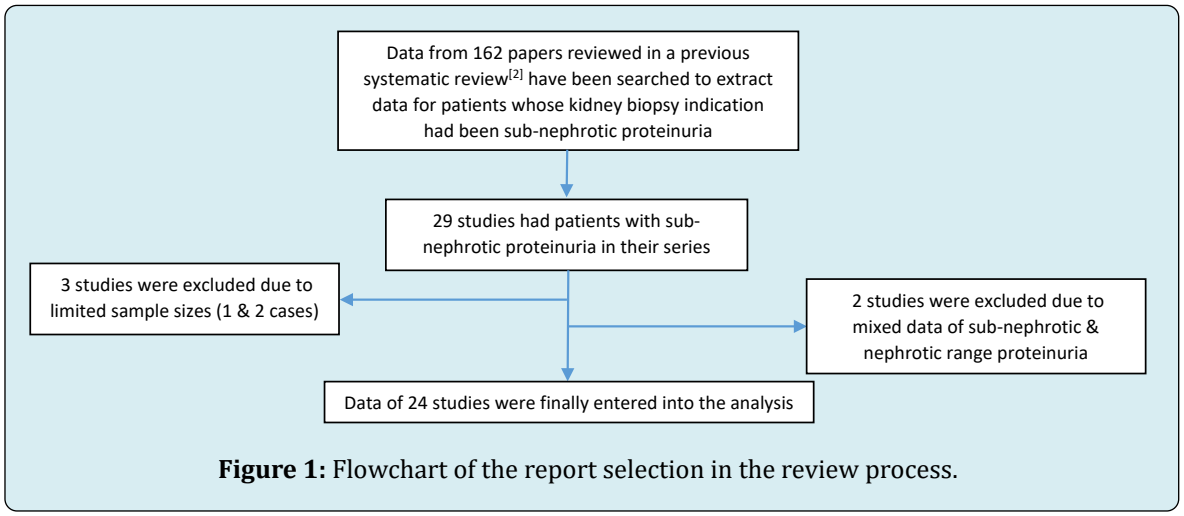

Figure 1: Flowchart of the report selection in the review process.

Despite the high prevalence of proteinuria in the nephrology setting [1] our knowledge on the diagnoses made upon evaluation of renal biopsies in this context mainly comes from individual series, and there is scarcity of systematic reviews properly handling different aspects of the problem. In a previous systematic review [2] the current author investigated the diagnosis rates of different nephropathy entities reported by a large number of studies worldwide, and subsequently, the epidemiology of this diagnosis have been documented among patients with nephrotic syndrome [3]. In this study however, the respective epidemiology has been sought among the subpopulation of patients whose proteinuria had been reportedly below the nephrotic range.

Ref.	First author	Country	Region/ Town	Nephrology centers	Study duration	Publication year	Age range/ Mean	Total patients (n)	Sub-nephrotic proteinuria population (n)
4	Shahrzad Ossareh	Iran	Tehran	Hasheminejad Kidney Center	1998 - 2007	2010	12–84	1,407	142
5	M. Saberafsharian	Iran	Mashhad	Ghaem & Emam Reza hospitals,	2016 - 2018	2020	41.40 ± 16.02	860	171
6	Talal AlFaadhel	Kingdom of Saudi Arabia	Riyadh & Jeddah	King Faisal Specialist Hospital and Research Centre, Riyadh; King Abdulaziz University Hospital, Jeddah; Security Forces Hospital, Riyadh; College of Medicine, King Saud University, Riyadh	1998-2017	2019	18-65	1070	95
7	Mohamed Shawarby	Kingdom of Saudi Arabia	Al-Khobar	King Fahd Hospital	1986–2008	2010	7--70	233	33
8	Mabrouk I. Ismail	Egypt	Zagazig	Zagazig University	Jun 2012-Nov 2014	2016	16 to 70	150	12
9	Ayham Haddad	Jordan	Amman	Princess Iman Research and Laboratory Center, King Hussein Medical Center	Jan 2005 - Dec 2008	2010	14-75	273	38
10	LK Yuen	China	Laichikok, Hong Kong	Princess Margaret Hospital	Apr 1997–Mar 2007	2008	Feb-24	161	8
11	Xiu Xu	China (Central)	Hubei	Huazhong University	Sep 1994-Dec 2014	2016	10–76	4931	385
12	Bo Jin	China	Nanjing	Jinling Hospital	Jan 2003 - Dec 2012	2014	65–81	851	93

13	Sheng Nie	China	Guangzhou, Hefei, Shanghai, Wuhan, Sichuan, Chengdu, Beijing	Nanfang Hosp., Anhui Hosp., Ruijin Hosp., Togji, Sichuan People's Hosp., Shijitan Hosp.	Jan 2004 - Dec 2014	2018	0 - 18	7962	772
14	D.A. Moutzouris	United States	New York	Columbia University Medical Center	Jan 2005- Aug 2008	2009	80 to 99	235	12
15	C.W. Devadass	India (South)	Bangalore	M.S. Ramaiah Medical College and Hospitals	2008 - 2013	2014	8 mo - 78 yr	680	66
16	Pallav Gupta	India	New Delhi	Sir Ganga Ram Hospital	Jan 2011 - Dec 2014	2018	60–85	109	13
17	Anjali Mohapatra	India	Vellore	Christian Medical College and Hospital	Jan 1996- Dec 2015	.	12.8 ± 4.9	1740	66
18	Viktória Fisi	Hungary	Siklós	Hospital of Siklós	Jan 2006- Dec 2009	2012	49 +/- 14	353	61
19	F. Iglesias Marujo	Brazil	Sao Paulo	Federal University of Sao Paulo	2000 - 2005	2012	>= 65	222	24
20	Suhail Iqbal Malik	Pakistan	Bahawalpur	Bahawal Victoria Hospital	Jan 2012- Apr 2018	2019	aged >= 14	195	17
21	Salman Imtiaz	Pakistan	Karachi	The Kidney Center Post Graduate Training Institute	Jan 1996- Dec 2013	2017	18–88	1521	8
22	M. Mubarak	Pakistan	Karachi	Sindh Institute of Urology and Transplantation	Jul 1995- Dec 2008	2011	19–85	1793	22
23	J J Khoo, MPath	Malaysia	Johor Bahru	Sultanah Aminah Hospital	Jan 1994- Dec 2001	2004	1 - 15.8 yr	113	5
24	Manish Subedi	Nepal	Dharan	B.P. Koirala Institute of Health Sciences	Sep 2014- Aug2016	2016	35.37	175	15
25	Anas AlYousef	Kuwait	Sabah Al Nasser	Farwaniya Hospital	Jan 2013- Dec 2018	2020	Dec-90	545	247
26	D. Jegatheesan	Australia	Queensland	11 hospitals	Jan 2002- Dec 2011	2016	48 ± 17	2048	229
27	Mayerly Prada Rico	Colombia	Bogot´a, Cundi namarca	Fundaci´on Cardioinfantil, Bogot´	2007-2017	2013	11+/- 4.3	241	24

Table 1: Characteristics of the reviewed studies & their patient populations.

Methods

A search of data from the 162 reports reviewed in a previously published systematic review [2] on the epidemiology of nephropathy diagnoses has been conducted to find cases whose indication for renal biopsy was sub-nephrotic proteinuria. Figure 1 summarizes the selection process. Finally a total of 24 studies [4-27]. Containing series of such patients were selected for the review. The total number of patients undergoing renal biopsy evaluations due

to sub-nephrotic proteinuria reported by these studies were ~2,550 (since some of the numbers have been calculated from the presented proportions, minor deviations from the actual numbers should be reasonably considered) reported from 15 different countries. The methodology of the systematic review could be found in full details in a previous publish [2]. Table 1 summarizes characteristics of the selected studies as well as their patients.

Histopathological report classification

The classifications of the nephropathy diagnoses are fully explained previously [2]. Here the principles of the classifications are provided: Data of mesangial proliferative glomerulonephritis have been pooled with the unspecific proliferative glomerulonephritis. Proliferative endocapillary glomerulonephritis as well as C3 glomerulonephritis has been reported as membranoproliferative glomerulonephritis. Data of Henoch-Schönlein purpura has been pooled with IgA nephropathy (Berger's disease) and finally necrotizing glomerulonephritis has been reported as crescentric glomerulonephritis. All vascular causes of nephropathy including the vasculitis were subclassified as vascular nephropathy. Amyloidosis has been particularly reported and other types of paraproteinemia were thus coined as unspecific paraproteinemia, after exclusion of tubulointerstitial diseases.

Age categorizations

Overall patients younger than 20 years of age were considered 'pediatric'. 'Elderly' subgroup was defined as patients older than 60 years of age (Some studies defined the age of 65 years as the cut off). The Adults subgroup were assigned to the patients whose age were beyond the pediatric subgroup. The General subgroup alludes to the patients whose age specifications were overlapping between the pediatrics and others.

Methodology of pooling data & meta-analyses

The estimated incidence for each of the nephropathy diagnosis entities and 95% confidence interval (CI) of the estimate has been entered into meta-analyses. Lower CI values were set zero whenever it was negative. Notably, since different reports were employing very inconsistent organization of the diagnosis, an estimated zero incidence reported for any of the diagnoses (could be found in the forest plots) doesn't essentially mean that in the respective series there were no such a patient, but they might be simply reported as e.g. miscellaneous diagnosis by the respective report. So, zero incidences were all censored from calculation of the cumulative incidence (95%CI) rates.

In order to conduct meta-analysis, for each report, incidence (95% (CI)) of nephropathy diagnoses have been calculated for either the pooled study population data or the age-subgroups as defined below. Then meta-analyses have then been conducted to determine the incidence (95%CI) of any nephropathy diagnoses, for the whole global reports and for the subgroups including the global regions as well as for the age categories (as defined above). Software STATA version 9 (Stata Corp.©, College Station, Tex, United States) was used for the meta-analyses.

Results

Sub-nephrotic proteinuria was the indication for renal biopsies in %4.1(%3.9-%4.3) throughout the reviewed series, with the lowest rate for adults subpopulation and the highest for the elderly and general subgroups. In the world regions, the highest rate of sub-nephrotic proteinuria (as the clinical indication for a kidney biopsy) had been observed in the Europe (%15.1(%11.6-%18.7)) and lowest in the South Asia (%1.3(%1-%1.6)). Table 2 summarizes the meta-analysis results, and the forest plots are illustrated by the supplementary figures 1-42. As could be acquired from the table 2, IgA nephropathy is the most frequent diagnosis made upon analysis of renal biopsies obtained from the patients with sub-nephrotic proteinuria, followed by mesangial proliferative glomerulonephritis (MesPGN) and membranous glomerulonephritis (MGN).

Age subcategories: For the pediatric patients, sub-nephrotic proteinuria had been most frequently associated with the diagnosis of IgA nephropathy and Henoch-Schönlein purpura followed by MesPGN. For the adults however, vascular reasons were the most likely diagnosis followed by IgA nephropathy and focal & segmental glomerulosclerosis (FSGS). Elderly patients with sub-nephrotic proteinuria were most frequently diagnosed with diabetic nephropathy followed by MGN and membranoproliferative glomerulonephritis (MPGN).

Regional disparities: Profound regional disparities also exist regarding the diagnosis rates. While about 35% of patients with sub-nephrotic proteinuria in the United States & Australia were finally diagnosed with FSGS, this rate among the South Asian counterparts was only about 3%; on the other hand, the South Asians were extremely more likely to get a diagnosis of diabetic nephropathy (~43%) or hereditary nephropathy (~7%), substantially higher than that from the other world regions (figures S.5, S.11, S.15). The predominant diagnoses in the Middle East & North Africa were lupus nephritis and MGN, for the Latin America was MPGN, and for the European patients was vascular nephropathies (Table 2).

Nephropathy	Highest rate	Lowest rate	Pediatric	Adults	Elderly	General	Total
MGN	MENA, .118(.095-.141)	EA, .060(.047-.073)	.041(.027-.056)	.090(.054-.127)	.188(.126-.251)	0.13	.075(.064-.086)
IgA nephropathy	EA, .228(.205-.251)	LA, .042(0-.106)	.278(.248-.308)	.138(.101-.176)	.063(.023-.103)	.159(.138-.180)	.172(.157-.186)
*Henoch Schönlein purpura**	EA, .036(.026-.045)	-	.251(.221-.282)	-	.011(0-.027)	.016(.005-.026)	.033(.024-.041)
FSGS	USCA, .348(.288-.409)	SA, .027(.006-.048)	.032(.020-.043)	.218(.181-.254)	.013(0-.029)	.075(.059-.090)	.047(.039-.054)
Lupus nephropathy	MENA, .140(.111-.168)	SA, .023(.004-.042)	.117(.096-.138)	.046(.008-.084)	.013(0-.028)	.047(.035-.060)	.048(.040-.057)
MCD	Eu, .098(.021-.175)	EA, .020(.012-.027)	.084(.066-.105)	.017(.002-.032)	.024(0-.049)	.017(.009-.025)	.024(.018-.030)
Crescentric GN	MENA, .029(.016-.043)	-	-	-	-	.029(.016-.043)	.029(.016-.043)
MPGN	LA, .167(.006-.327)	EA, .005(0-.011)	.061(.002-.120)	.054(.019-.090)	.167(.006-.327)	.010(.004-.015)	.011(.006-.017)
*PEGN**	SA, .030(0-.073)	-	.030(0-.073)	-	-	-	.030(0-.073)
Amyloidosis	USCA, .083(0-.217)	-	-	.061(.014-.108)	.082(.038-.126)	.009(.002-.017)	.013(.005-.020)
Diabetic nephropathy	SA, .427(.324-.530)	EA, .010(.002-.018)	-	.089(.060-.118)	.316(.234-.398)	.016(.008-.023)	.022(.015-.029)
TID	SA, .123(.056-.190)	EA, .011(0-.027)	.042(0-.106)	.043(.010-.077)	.011(0-.027)	.043(.025-.062)	.028(.016-.039)
Vascular nephropathy	Eu, .361(.237-.485)	EA, .028(.014-.043)	-	.257(.170-.344)	.026(0-.051)	.035(.021-.048)	.037(.025-.049)
*Nephroangiosclerosis**	Eu, .344(.222-.467)	EA, .017(.006-.028)	-	.344(.222-.467)	.024(0-.049)	.014(.005-.023)	.017(.008-.025)
Hereditary nephropathy	SA, .071(.016-.126)	EA, .004(.001-.008)	.010(.003-.017)	.040(.002-.078)	-	.003(0-.006)	.005(.001-.008)
HBV nephropathy	EA, .013(.006-.019)	-	.012(.004-.019)	-	-	.016(.003-.028)	.013(.006-.019)
Unspecific Proliferative GN	EA, .176(.155-.197)	MENA, .019(.005-.034)	.228(.200-.257)	.039(.003-.075)	.056(.016-.095)	.040(.025-.054)	.072(.060-.083)

*MesPGN**	EA, .171(.150-.191)	SA, .112(.047-.177)	.228(.200-.257)	.059(0-.151)	.054(.007-.101)	.146(.012-.170)	.164(.145-.183)
*IgM nephropathy**	SA, .072(.001-.143)	-	-	.072(.001-.143)	-	-	.072(.001-.143)
Unspecific Paraproteinemia	USCA, .083(0-.217)	-	-	-	.049(.008-.107)	-	.049(.008-.107)

Zero incidence rates have been omitted to report*: Subsections of their abovementioned entity as described previously; [2] FSGS, focal & segmental glomerulosclerosis; HBV, hepatitis B virus; MGN, membranous glomerulonephritis; MCD, minimal change disease; MPGN, membranoproliferative glomerulonephritis; MesPGN, mesangial proliferative glomerulonephritis; TID, tubulointerstitial diseases; E.A, East Asia; S.A, South Asia; USCA, USA-Canada-Australia; L.A, Latin America; SS.A, sub-Saharan Africa (only included S. Africa); Eu, Europe; MENA, Middle East & North Africa

Table 2: Estimated incidence (95% confidence interval) of nephropathy entities diagnoses according to meta-analysis conducted on studies reporting renal biopsy evaluation from patients with sub-nephrotic proteinuria worldwide.

Discussion

In this systematic review, the rates of nephropathy diagnoses in patients undergoing renal biopsy due to sub-nephrotic proteinuria were found to be profoundly different regarding the subjects' global region of report as well as age subcategories. These offer ethnical specifications, environmental factors - including life styles more frequent in specific world regions - and age of the patients as the main determining factors in the probability of reaching a particular diagnoses in these patients. In a recent systematic review, the same author has reported similar epidemiological data for patients with nephrotic range proteinuria, [3] and since clinical syndromes studied in the two reports could be considered two spectrums of the same entity (proteinuria), comparing reported rates in the two studies could be interesting. Although it was possible to directly compare the rates of diagnoses between the nephrotic versus sub-nephrotic range proteinuria by meta-analyses, since achieving significance levels or not for potential disparities between the two clinical syndromes were of no clinical implications, analyses were not conducted.

MGN is particularly interesting for this comparison. While East Asia which had been reported as the predominant global region for the diagnosis of MGN in patients with nephrotic syndrome [3] it represented the lowest rate of diagnosis of the same entity among patients with sub-nephrotic proteinuria, compared to the other world regions (Table 2). This concludes that MGN in the East Asian population is most likely to present as nephrotic syndrome than sub-nephrotic proteinuria. Another interesting diagnosis regarding the regional disparities is the MCD; while nephrotic syndrome patients from the Europe were the most likely to be diagnosed with MCD [3] however for the sub-nephrotic proteinuria, this region represented the lowest rate of MCD diagnosis. Again, there was a similar disparity regarding the diagnosis of diabetic nephropathy (DN) for which, South Asia was the least likely region to get the diagnosis among the nephrotic syndrome patients [3] while DN represented the predominant diagnosis in the same region when evaluating patients with sub-nephrotic proteinuria. For the case of amyloidosis however, United States was the predominant region of diagnosis for either clinical syndromes (both nephrotic range & sub-nephrotic proteinuria).

There were similar profound disparities regarding the age-specific subgroups; almost half of the pediatric patients who had undergone renal biopsies due to nephrotic syndrome were finally getting diagnosed with MCD [3] while this rate was less than 10% for sub-nephrotic proteinuria. Moreover, while compared to the other age-specific populations, the pediatric patients with nephrotic syndrome were the most likely one to be diagnosed for MPGN [3] for sub-nephrotic proteinuria, the highest rate went to the elderly population. An unexpected finding was the predominance of adult age group in the diagnosis of hereditary nephritis for patients expressing either nephrotic or sub-nephrotic proteinuria (as well as the high rates of vascular reasons among the adult subgroup versus the elderly, which could potentially be explained by the limited number of studies and sample sizes).

As mentioned above, besides the overall limited number of studies reporting their series with sub-nephrotic proteinuria, a major limitation to the current study is the limited population sizes reported in each of the series getting into the meta-analysis. As is evident in the forest plots, for some of the analyses the number of studies with any reported rate was very limited, and this would, in part, explain some of the unexpectedly high or low diagnosis rates found by regional or age specific categorizations. In conclusion, this study was an attempt to define epidemiology of nephropathy

diagnoses in patients undergoing renal biopsies due to sub-nephrotic proteinuria with IgA nephropathy, MesPGN and MGN defined as the most likely diagnoses for this clinical syndrome, respectively. Further data coming with the prospective reports would enable us to make more precise estimations.

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