In-Depth Topic Review

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Renal Biopsy in 2015 – From Epidemiology to Evidence-Based Indications

Marco Fiorentino[a] Davide Bolignano[b, c] Vladimir Tesar[d] Anna Pisano[b]
Wim Van Biesen[c] Graziella D'Arrigo[b] Giovanni Tripepi[b] Loreto Gesualdo[a]
On behalf of the ERA-EDTA Immunonephrology Working Group

[a]Department of Emergency and Organ Transplantation, Nephrology, Dialysis and Transplantation Unit, University of Bari, Bari, and [b]CNR-Institute of Clinical Physiology, Reggio Calabria, Italy; [c]European Renal Best Practice, University Hospital Ghent, Ghent, Belgium; [d]Department of Nephrology, 1st School of Medicine, Charles University, Prague, Czech Republic

Key Words
Renal biopsy · Epidemiology · Glomerulonephritides · Indications · Nephrotic syndrome · Proteinuria · Hematuria · Acute kidney injury · Chronic kidney disease · Diabetes · Elderly

Abstract
Background: Although the number of patients reaching end-stage kidney disease without a biopsy-proven diagnosis is increasing, the utility of renal biopsy is still an object of debate. We analyzed epidemiological data and the main indications for renal biopsy with a systematic, evidence-based review at current literature. ***Summary:*** There is a high discrepancy observed in biopsy rates and in the epidemiology of glomerular diseases worldwide, related to the different time frame of the analyzed reports, lack of data collection, the different reference source population and the heterogeneity of indications. The evidence-based analysis of indications showed that renal biopsy should be crucial in adults with nephrotic syndrome or urinary abnormalities as coexistent hematuria and proteinuria and in corticosteroid resistant-children with severe proteinuria. The knowledge of renal histology can change the clinical management in patients with acute kidney injury significantly, after the exclusion of pre-renal or obstructive causes of kidney damage. Scarce evidence indicates that renal biopsy can be useful in patients with advanced chronic kidney disease and its use should always be considered after weighing the benefits and potential risks. Renal biopsy should be crucial in patients with renal involvement due to systemic disease. In patients with diabetes with atypical features, renal biopsy may be fundamental to diagnose an unexpected parenchymal disease mislabeled as diabetic nephropathy. Finally, in elderly patients, the indications and the risks are not different from those in the general population. ***Key Message:*** Renal biopsy still remains a concrete approach for managing a substantial percentage of renal diseases.

Introduction

The prevalence and incidence of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) are steadily increasing. There are more than one million ESKD patients worldwide [1, 2]. By 2030, the number of patients needing chronic replacement therapy is expected to increase by 60% [3]. Even though diabetes and hypertension are the most frequent causes of CKD, recent evi-

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Prof. Loreto Gesualdo
Division of Nephrology, Dialysis and Transplantation
'Aldo Moro' University of Bari
Piazza Giulio Cesare 11, IT–70124 Bari (Italy)
E-Mail loreto.gesualdo@uniba.it

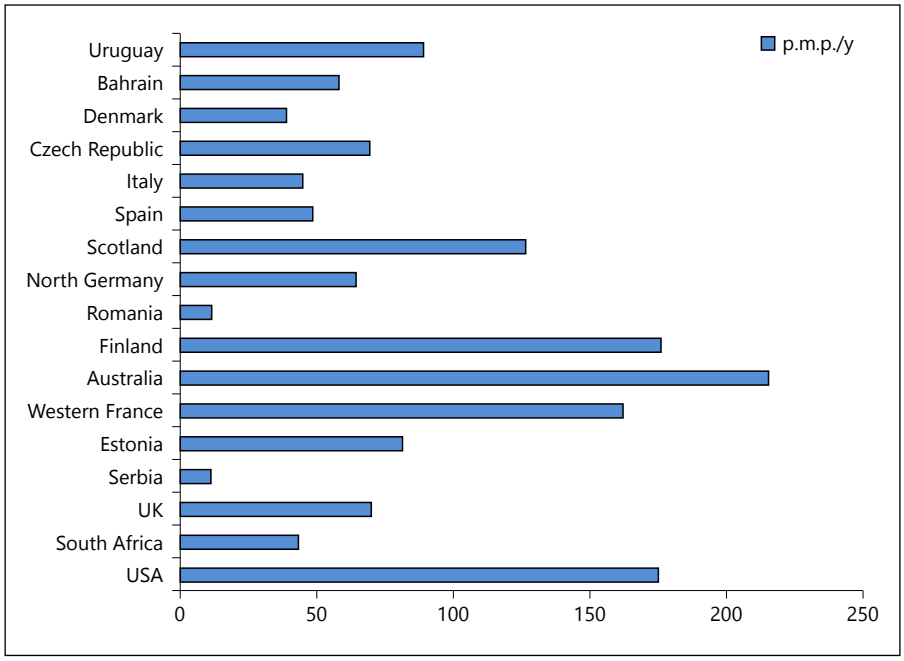

Fig. 1. Annual renal biopsy rate as reported in national and macro-regional registries (data are obtained from table 2).

dence indicates that the number of patients starting chronic renal replacement therapy due to glomerular diseases is on the rise, currently ranging from 6.5 to 27 persons/million person/year (p.m.p./year) [1, 4].

In the past years, several noninvasive approaches for identifying early renal damage have been proposed, mostly based on 'omics' techniques (genomics, proteomics, metabolomics) for the evaluation of urine or plasma biomarkers [5]. However, the impact of these biomarkers on patient-management and long-term outcomes still awaits concrete validation in everyday clinical practice.

Although renal biopsy remains the gold standard for diagnosis [6], therapeutic management and outcome prediction in patients with renal parenchymal diseases, there is currently poor consensus about proper indications and clinical usefulness of this procedure [7]. As a result, the decision on performing renal biopsy is usually based on personal opinion and/or single-center policies.

A vast majority of studies agree that renal biopsy can improve clinical management of patients [8–12]. In a 3-year prospective study of 80 patients with various renal parenchymal diseases, the predicted diagnosis, prognosis and therapeutic approach were modified in 44, 57 and 31% of the cases, respectively, based on histological findings [13]. In another observational study of 100 patients, renal biopsy led to therapeutic changes (particularly, introduction of immunosuppressive drugs) in 54% of cases [14]. Conversely, in a survey conducted on 24 board-certified nephrologists, the knowledge of the renal histology did not significantly change the prognosis, therapy management or follow-up strategy [15].

Lack of clear guidelines on indications for renal biopsy may hamper the epidemiological classification of renal diseases, as well as the future of biomarkers validation. In the last report of the ERA-EDTA registry [4], the average percentage of prevalent and incident dialysis patients without a specific renal diagnosis stood at 15 and 16% respectively (ranging from 1.5% in Croatia to 38% in Romania), values very similar to those reported in UK [16] and US registries [1].

With this background in mind, we aim to review the role of renal biopsy in current practice (1) by analyzing epidemiology data on the clinical application of this technique at the global level and (2) by appraising the currently applied main indications for this procedure with a systematic, evidence-based approach to the available literature.

Renal Biopsy: A Global Epidemiology Overview

Based on registry and single-center data, there is a high variability in the rate of renal biopsies performed worldwide (fig. 1). In 9 national renal biopsy registries (Scotland, Italy, Spain, Czech Republic, Japan, Brazil, Bahrain, Uruguay, Denmark) [17–28], the median total

Table 1. Factors influencing the variability of biopsy practice worldwide

1	Different time frame of reports
2	Lack of renal biopsy data collection
3	Reference source population
4	Social and economic status
5	Heterogeneity of indications of renal biopsy

number of biopsies performed was 1,818, ranging from 498 [20] to 14,607 [24]. In data from 6 macro-regional databases (France, Finland, Romania, Australia, North Germany, West Saudi Arabia) [29–35] and 12 single-center reports [36–47], the overall number of biopsies ranged from 251 [29] to 3,310 [34].

Higher biopsy rates were reported in the Australian database (215 p.m.p./year) [32] and in single-center experiences of the University Hospital of Helsinki, Finland (176 p.m.p./year) [34] and the Olmsted County, USA (up to 175 p.m.p./year) [42]. Conversely, very low rates were reported in 2 regional databases in Romania (11.3 p.m.p./year) [33] and in a Serbian single-center biopsy registry (10.8 p.m.p./year) [38]. The high variability can be explained by different factors (table 1). First, the time frame considered by each report was different. For instance, the Olmsted county renal biopsy study [42] encompassed a 30-year-observation (1974–2003), while the Victoria registry (Australia) [32] was limited to 3 years (1995–1997). Furthermore, only 9 reports [17, 19, 20, 35–38, 40, 48] covered up to the first decade of the 21st century, while the remainder were mostly focused on the nineties. Lack of temporal overlap among these different registries limits the possibility to compare data; moreover, different trends in the diagnosis of different glomerular diseases might exist according to the time period and the time frame considered [42]. Moreover, the actual registry may miss renal biopsy registration due to the voluntary data collection. Therefore, cumulative data provided by most registries may not properly reflect the current situation in a given country. Moreover, a majority of cases analyzed were strictly dependent on the reference source population, which may affect the generalizability of the reported annual rate. Finally, since there are different opinions on the indications for renal biopsy, this may have had a significant impact on the single-specialist decision about the choice of performing this procedure. Moreover, the social and economic status and the financial resources allocated to nephrology services are profoundly different among countries. For instance, in 2 registries [34, 38], the lower biopsy rate was motivated by the economic recession in certain historical periods.

The mean age of subjects undergoing renal biopsy was also very homogeneous, being on average 40.6 ± 5.5 (range 33–56). With respect to gender, a majority of patients analyzed were male (percentage ranging from 50.5 to 60%), but reports from South Africa, Brazil and Hong-Kong were an exception [18, 37, 47]. The most frequent indication for performing renal biopsy was the presence of nephrotic syndrome (NS, mean 40.35%, range 20–70%).

Table 2 summarizes main data on the epidemiology of renal biopsy worldwide.

The incidence rate of patients who have been diagnosed with any glomerulonephritis (GN) within Europe has increased over the last 4 decades, peaking at 15.3% of the overall renal diagnoses made in 2010–2012 [4]. However, in about 21% of cases, the presence of GNs was only based on clinical signs and not histologically classified. The epidemiology of GNs is strongly influenced by the biopsy rate. In fact, renal registries with lower biopsy rates can be more likely to have a low incidence of biopsy-proven glomerular disease and vice-versa. Geography, race, age and indications for renal biopsy are other well-recognized factors that may impact the epidemiology of primary GN. Furthermore, poor socio-economic conditions may affect the epidemiology of GNs in at least 2 possible ways. First, according to the 'hygiene hypothesis' [49], the increased exposure to bacterial antigens in developing countries may reflect a different pattern of response of the immune system, which translates in a different exacerbation of particular glomerular diseases (higher prevalence of membrano-proliferative GN (MPGN), in developing areas, higher prevalence of IgA-nephropathy (IgAN), and minimal change disease (MCD), in more developed countries). Accordingly, in the Romanian database [33], the improvement of the national health system, as well as the economic status and resources allocated to preventive medicine, were followed by a reduction of MPGN and infection-related GNs. In addition, although light microscopy and immunofluorescence techniques were almost widely performed, poor economic resources may also limit the overall accessibility to appropriate techniques for making clear-cut diagnoses, such as electronic microscopy (table 2).

As shown in table 3 and figures 2–4, IgAN represents the most frequent primary, biopsy-proven GN in 6 out of 8 national registries (Italy, Spain, Czech Republic, Denmark, Scotland, Japan) [17, 19, 22–28], in 3 macro-regional (Western France, Finland, Victoria-Australia)

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Table 2. Main epidemiology of renal biopsy from national and macro-regional registry data

Registry	Registry source	Time-frame	Number of RBs performed	RB rate, p.m.p./year	Microscopy	Patients' age	Patients' gender, M/F, %	Indications for RB
Scotland [19]	National	2002–2006	2,480	126	LM, IF, EM	55.6±1.3	56.9/43.1	CKD (45 p.m.p./year), AUA (40 p.m.p./year)
Spain [23, 25]	National	1994–2001	9,378	48	LM, IF, EM	–	60/40	NS (35.5%), AUA (25.9%), AKI (12.9%), CKD (12.1%)
Italy [27]	National	1987–1993	13,835	45	LM, IF, EM	–	–	AUA (30.8%), NS (27.1%), AKI (9.2%)
Italy [24]	National	1996–2000	14,607	–	LM, IF, EM	–	–	AUA, NS
Czech Republic [28]	National	1994–2011	10,472	44–61.6	LM, IF, EM (not systematically)	44.5	57.8/42.2	NS (39.3%), AUA (36.2%), CKD (19.4%)
Japan [17]	National	2007–2010	7,034	–	–	47.9±20.9	52.7/47.3	Chronic nephritic syndrome (52.5%), NS (24.2%)
Brazil [18]	National	1993–2007	9,062	–	LM, IF, EM (not systematically)	35.1±18.7	49/51	NS (39%), AUA (20.7%), AKI (16.8%)
Denmark [26]	National	1985–1997	2,380	39	LM, IF (78%)	43	57.7/42.3	–
Bahrain [20]	National	1990–2006	643	54	LM, IF, EM (wherever necessary)	–	56.9/43.1	Proteinuria, macro/microscopic hematuria, NS, impaired renal function
Uruguay [21]	National	1980–2003	2,058	40–138	–	39.1±19.6	52/48	NS (30%), AUA (18%)
France [30, 31]	Regional	1976–2002	1,742	162	LM, IF, EM (not systematically)	41	–	AUA (39.1%), NS (23.2%), AKI (19.8%), CKD (17.7%)
Finland [34]	Regional	1980–2000	3,310	176	LM, IF, EM	44	58.6/41.4	AUA (19.5%), NS (16.4%), renal failure (17.6%)
Romania [33]	Regional	1995–2004	635	11.3	LM, IF (not always)	38.5±15.2	51.5/48.5	NS (52.%), AKI (12.4%), CKD (10.2%)
North Germany [48]	Regional	2001–2008	251	64	–	–	–	–
Western Saudi Arabia [35]	Regional	1989–2007	568	–	LM, IF, EM	17–76	55/45	–
Australia [32]	Regional	1995–1997	2,030	215	LM, IF, EM (the majority)	–	–	–
China [45]	Single-center	1979–2002	13,519	–	LM, IF, EM	32.7±12.2	57.3/42.7	–
Serbia [38]	Single-center	1987–2006	1,626	10.8	LM, IF (16.1%), EM (5%)	39.1±13.8	51.2/48.8	NS (53.6%), AUA (24.3%), CKD (8.6%)
USA [42]	Single-center	1974–2003	375	82–175	LM, IF, EM	44±20	–	–
South Africa [37]	Single-center	2000–2009	1,284	39–43	LM, IF, EM	36.8±14	45.2/54.8	NS (52.5%), AKI (21.3%), AUA (13.6%)
Korea [40]	Single-center	1987–2006	1,818	–	LM, IF, EM (selected cases)	36 (16–82)	50.5/49.5	–

Table 2. (continued)

Registry	Registry source	Time-frame	Number of RBs performed	RB rate, p.m.p./year	Microscopy	Patients' age	Patients' gender, M/F, %	Indications for RB
India [43]	Single-center	1986–2002	5,415	–	LM, IF, EM (selected cases)	–	–	NS (65%), nephritic syndrome (13%), CKD (10.2%)
Iran [41]	Single-center	1998–2001	407	–	LM, IF	33.6±15.7	57.8/42.2	NS (70%), AKI (4%), AUA (5%)
Macedonia [46]	Single-center	1975–2001	1,304	–	LM, IF	–	–	–
UK [39]	Single-center	1976–2005	1,844	20–70	LM, IF (97%), EM (43%)	47±17	61/39	–
The Netherlands [44]	Single-center	1977–2003	1,348	–	LM, IF, EM	–	55.4/44.6	–
Hong Kong [47]	Single-center	1993–1997	1,629	–	LM, IF, EM	38.7	42.5/57.5	NS (27.3%), AUA
Estonia [36]	Single-center	2001–2010	578	81	LM, IF, EM (selected cases)	39.9±17.9	58.8/41.2	–

Patients' age is indicated in mean, mean ± SD, mean (range) or range as provided in the original report.
EM = Electronic microscopy; IF = immunofluorescence; LM = light microscopy; RB = renal biopsy; AUA = asymptomatic urinary abnormalities; – = data not available.

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Table 3. Epidemiology spectrum of renal biopsy diagnosis from registry data

Registry	Registry source	IgAN	MsPGN	MCD	FSGS	MN	MPGN	CrescGN	Diabetes	SLE	Vasculitides	Other secondary GN	Vascular disease	AIN	Others
Spain [25]	National	15.20	–	7.80	10	9.70	4.30	–	–	8.8	7.3	4	5.4	–	23
Italy [24]	National	35.20	13.90	7.80	11.80	20.70	–	4.60	–	–	–	–	4.7	5.3	–
Czech Republic [28]	National	37.4	6	11.1	12.6	13	5.8	2.1	2.6	0.6	0.4	6.8	3.4	4.4	2.4
Japan [17]	National	31	38.80	12.10	5.30	10.70	2.60	6.30	5.3	5.1	4.8	4.4	4.2	2.2	15.4
Brazil [18]	National	20.10	5.10	15.50	24.60	20.70	4.20	1.70	1.9	9.8	1.1	4.3	2.8	2.2	–
Bahrain [20]	National	4.8	–	2.75	5.5	4.1	6.9	0.7	8.9	15.7	–	8.2	2	7.5	25.5
Uruguay [21]	National	12.40	7.30	19.60	29.30	11.70	5.20	–	–	–	–	–	–	–	–
Western Saudi Arabia [35]	Regional	17.60	4.70	5.40	21.30	25.70	11.50	–	–	–	–	25.7	–	1.6	21.7
Australia [32]	Regional	34.10%	–	4.40	16.90	10.60	20.20	–	–	13.9	12.3	–	–	–	–
France [30]	Regional	33.40	5.80	11.40	10.60	17.70	6.60	5.20	–	–	–	–	–	–	–
Finland [34]	Regional	34.90	–	5	3.90	11.60	14	5.70	–	–	–	–	–	–	–
Romania [33]	Regional	28.90	–	8.50	12	11.20	29.40	7.90	–	7.4	6.5	7.5	2.3	1.5	3.6
South Africa [37]	Single-center	5.80	39.60	6	10.50	18.50	–	11.40	6.3	19	–	–	–	11	–
Korea [40]	Single-center	28.30	–	15.50	5.60	12.30	4	–	2	8.7	1	–	–	–	–
India [43]	Single-center	8.60	20.20	11.60	17	9.80	3.70	–	2.5	6.5	1	–	3.8	2.5	–
Iran [41]	Single-center	13.50	2.20	9.80	10.30	23.60	11.50	5.20	–	10.6	–	–	0.7	–	–
Macedonia [46]	Single-center	11.80	4.40	7.20	9.90	17.90	8.40	7.40	–	–	–	–	–	–	–

Table 3. (continued)

Registry	Registry source	IgAN	MsPGN	MCD	FSGS	MN	MPGN	CrescGN	Diabetes	SLE	Vasculitides	Other secondary GN	Vascular disease	AIN	Others
UK [39]	Single-center	39	–	10	6	29	11	–	–	–	–	–	3.5	5.9	10
The Netherlands [44]	Single-center	12.60	1	4	4	9	2	2.50	–	4.1	10.6	2.5	4.5	5.5	6.1
Hong Kong [47]	Single-center	23.90	9.50	8.80	4.70	8.30	–	0.60	5.7	20.5	0.7	5	6.2	–	1.3
Estonia [36]	Single-center	16.10	2.60	6.40	7.30	2	3.50	1.50	1.5	7.5	3.7	8	–	8.2	24
China [45]	Single-center	45.20	25.60	0.93	6	9.89	3.38	1.90	1.6	13.4	5	1.4	0.8	3.4	2.1
Serbia [38]	Single-center	12.20	25.10	7.80	18.90	18.90	10	5.10	–	–	–	–	–	–	–
USA* [42]	Single-center	14	–	3	11	7	4	4	–	0.8	–	1.1	–	–	–
Denmark* [26]	National	10.8	–	7.3	5.7	4.8	2.1	5	–	5.5	3.6	0.9	2.8	–	–
Scotland* [19]	Single-center	14–27	–	–	9.8–12	13	–	–	7–14	–	–	–	5–12	–	–
North Germany* [48]	Regional	–	20.9	3.2	11.2	5.2	–	4.9	–	2.9	5.4	–	–	–	–

Data are expressed in percentage, with the exclusion of* where data have been provided in cases p.m.p./year.
MsPGN = Mesangioproliferative GN; AIN = Acute tubule-interstitial nephritis; – = data not available.

[30, 32, 34] and 7 single-center databases [36, 39, 40, 42, 44, 45, 47] with a percentage of total diagnoses ranging from 12.6% [44] to 45% [45]. Focal segmental glomerulosclerosis (FSGS) was the most frequent primary GN in Brazil (24.6%) [18], in the Uruguayan registry of glomerulopathies [21] (29.3%) and in Bahrain (23.8%) [20, 35]. Conversely, MPGN appeared to be the most frequent glomerular disease diagnosed in Romania (29.4%) [33]. Membranous nephropathy (MN) predominated in 2 single-center retrospective reports in Macedonia (17.9%) [46] and Iran (23.6%) [41]. Non-IgA mesangioproliferative GN was the most frequent primary GN in Serbia (25.1%) [38]. The most frequent secondary GN was lupus nephritis in Spain (8.8%) [25], Italy (2.6 p.m.p./year) [24, 27], Brazil (9.8%) [18], Bahrain (15.7%) [20], Australia (13.9%) [32], Romania (7.4%) [33], Korea (8.7%) [40], China [45] and Hong Kong (20.5%) [47]; diabetic nephropathy (DN) predominated in Czech Republic (2.6%) [22], Japan (5.3%) [17] and Scotland (7–14 p.m.p./year) [19]. Acute tubulo-interstitial nephritis (AIN) diagnosis was reported in 13 registries, with a percentage ranging across 1.5% [33] to 11% [37] of overall diagnosis.

Renal Biopsy: Indications

Table 2 and figure 5 highlight the high variability in the main indications for renal biopsy among national and macro-regional registries. Indeed, there are a few indications for which the need for renal biopsy is almost universally recognized (e.g. NS in adults). Conversely, in a majority of conditions including urinary abnormalities, diabetes, acute kidney injury (AKI) or CKD of unknown origin, the usefulness and timing of this procedure still remain a subject of debate. We adopted a systematic approach to identify any evidence available supporting or contradicting the main known clinical indications for renal biopsy. PubMed and Ovid MEDLINE were searched for articles without time and language restriction through a focused search strategy (table 4). References from relevant studies and reviews published on the same topic were screened for supplementary articles. The search was designed and performed by 3 authors (D.B., M.F. and A.P.).

Nephrotic Syndrome

NS is the most frequent indication for renal biopsy in adults [50, 51], as shown by 3 national registries [18, 21, 25], one macro-regional database [33] and 3 single-center reports [37, 41, 43].

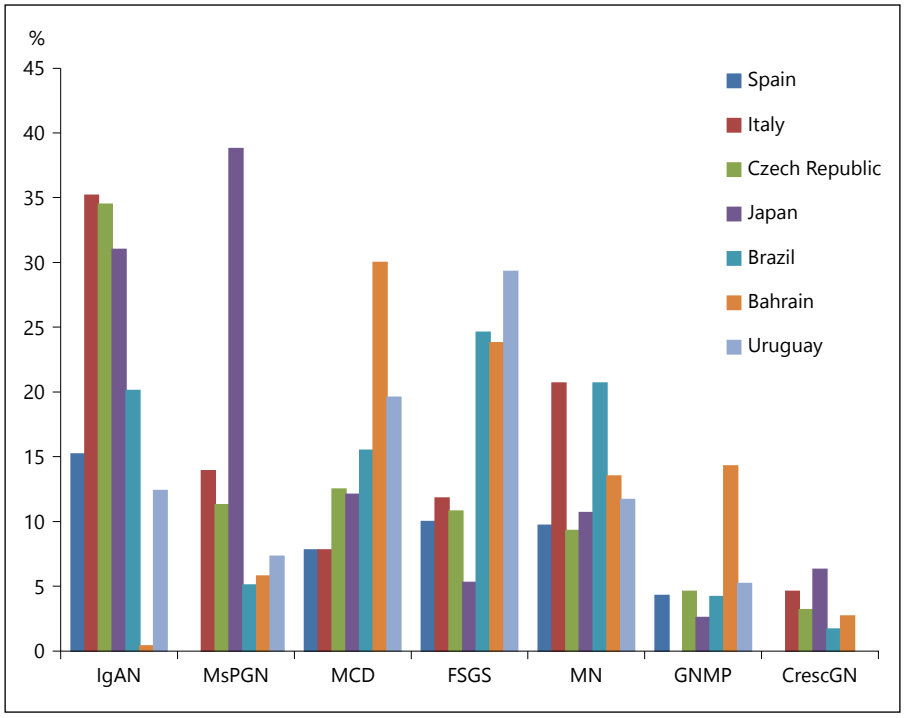

Fig. 2. Different incidence of primary glomerulonephritides as reported in national registries (data are obtained from table 2). MsPGN = Mesangioproliferative GN.

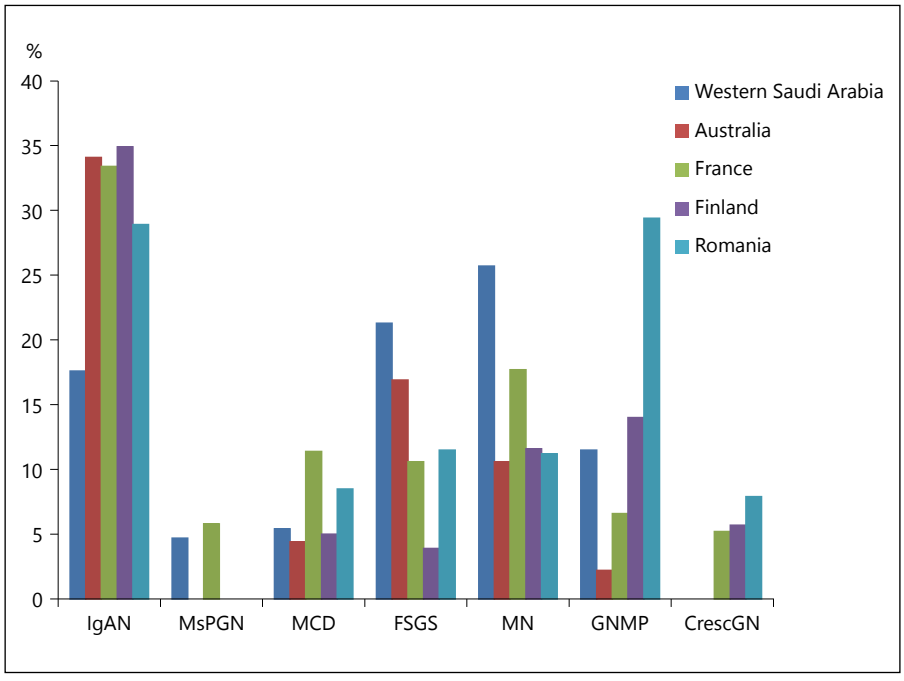

Fig. 3. Different incidence of primary glomerulonephritides as reported in macroregional registries (data are obtained from table 2). MsPGN = Mesangioproliferative GN.

The most frequent histological patterns related to primary NS in adults are MN, FSGS and MCD [52, 53]. However, cases of NS were also found to be due to diabetes, systemic lupus erythematosus (SLE), infections, multiple myeloma, amyloidosis or neoplasias [54].

Renal biopsy is fundamental to assess not only the type but also the degree of disease activity. The overall prognosis and response to treatment often depend on the severity of histological lesions and their reversibility [8]. For instance, the presence of glomerulosclerosis, arterioscle-

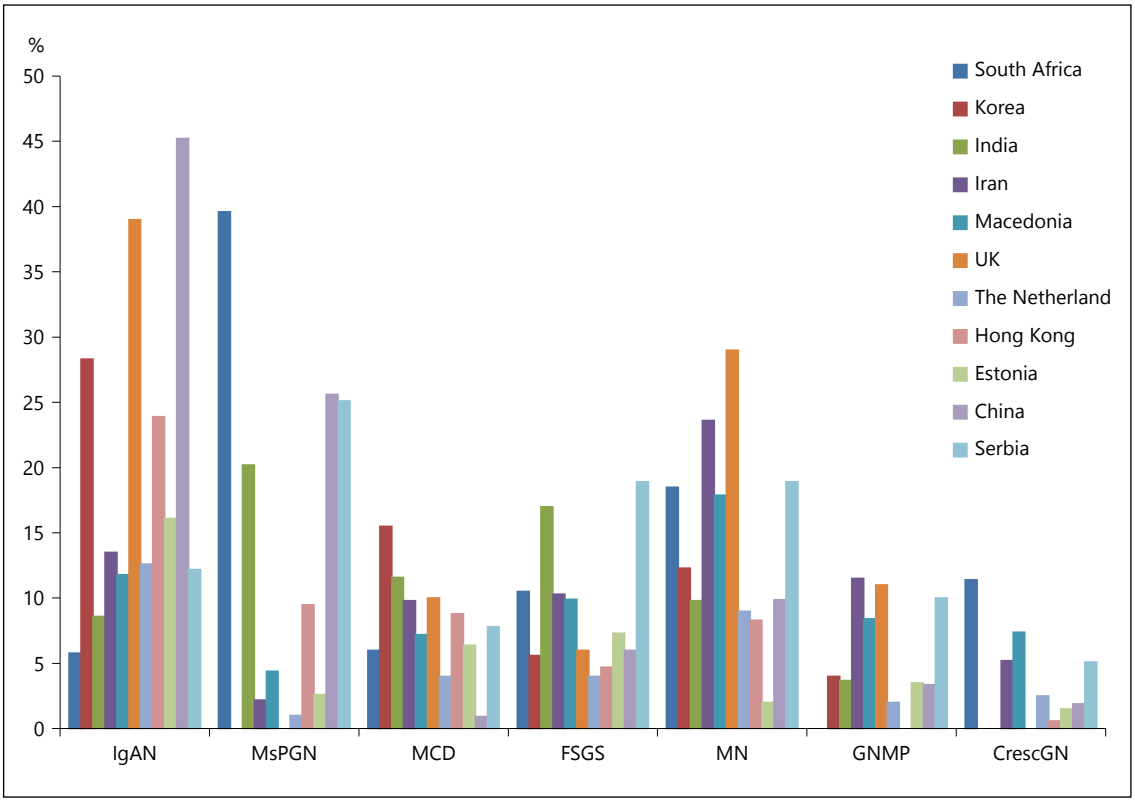

Fig. 4. Different incidence of primary glomerulonephritides in single-center reports (the data are obtained from table 2). MsPGN = Mesangioproliferative GN.

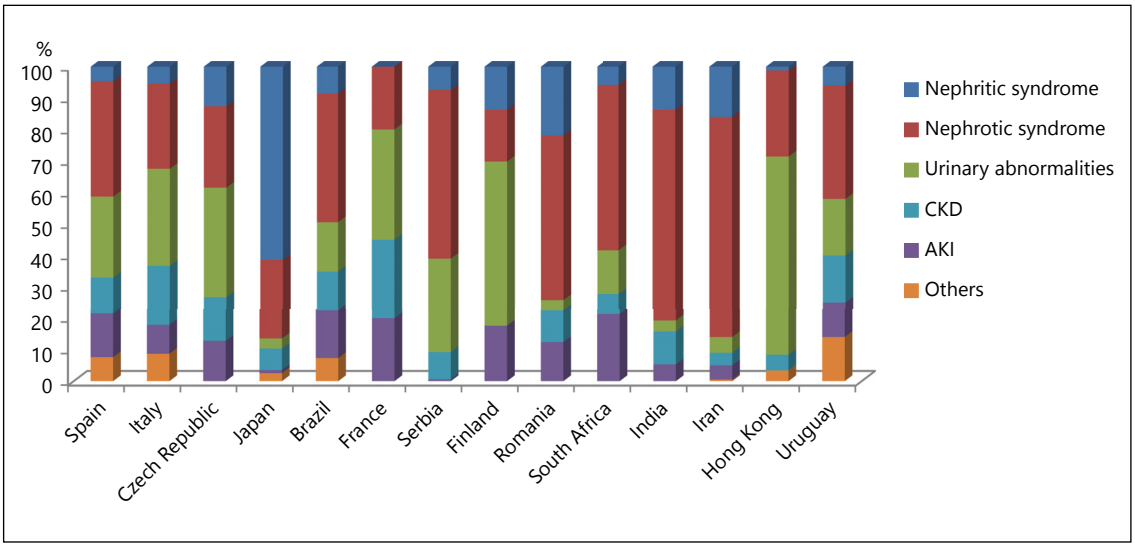

Fig. 5. Main indications for renal biopsy as reported in national and macro-regional registries. Data are obtained from the national and macro-regional registries reported in the text.

rosis, and interstitial fibrosis are all suggestive of an irreversible process that is less likely to respond to treatment; conversely, the presence of active lesions potentially indicates good responsiveness to corticosteroid treatment. Therapeutic effectiveness is also strongly influenced by the histological diagnosis per se. MCD is usually controlled by corticosteroid treatment alone, while MN and FSGS often require the addition of other immunosuppressive agents [55]. SLE patients with more aggressive and acute lesions (class IV nephritis) may benefit from treatment with corticosteroids and other cytotoxic drugs, whereas those with less severe or chronic lesions may have less to gain. Renal biopsy in these patients is thus mandatory not only for diagnosis but also for the early identification of renal flares [56, 57]. NS in multiple myeloma may reflect the presence of amyloidosis or light-chain deposition. Since the presence of active renal lesions predicts poor prognosis, renal biopsy may be helpful to plan early countermeasures [58].

Histological diagnosis is therefore helpful in driving therapeutic management of patients with NS [9, 55, 59]. Indeed, in an old prospective study [9], renal biopsy was useful to change clinical approaches in 24 of 28 patients presenting with NS. In another study [60] of 276 native renal biopsies performed on 266 patients, histological information produced significant changes in clinical management in 42% of cases, particularly in patients with nephrotic range proteinuria (86%). Finally, in another prospective analysis of 108 biopsy specimens, clinical and pathological diagnoses differed in 63% and therapeutic approach was altered in 34% of cases, particularly in subjects with NS of rapid onset [61]. Moreover, the knowledge of renal histology may be crucial, particularly when patients are transplant candidates, considering the risk of recurrent disease after kidney transplantation.

The indications for renal biopsy in NS are more restrictive in pediatric subjects. It is widely accepted that NS in children does not require any histological evaluation as first-line approach [55, 62]. Indeed, in this population about 90% of idiopathic NS are related to minimal glomerular lesions with very high response-rate to corticosteroid treatment and a very low risk of progression to ESKD [63, 64]. In a study of 30 children, the response to cyclophosphamide therapy correlated better with the initial corticosteroid response than to renal histopathology [65]. Similar findings were reported in a retrospective analysis of 85 patients with steroid-sensitive NS [66]. Conversely, renal biopsy in children should be considered if NS is not responsive to standard corticosteroid treatment or is associated to frank renal impairment [55, 67].

Table 4. Literature search criteria adopted

Ovid-MEDLINE

1	((Kidney or renal) and biopsy adj1 indicat*).mp,kw,tw.
2	Hematuria.mp,kw,tw.
3	(Microhematuriaormicro-hematuria).mp,kw,tw.
4	(Macrohematuria or macro-hematuria).mp,kw,tw.
5	Nephroticsyndrome.mp,tw,kw.
6	Nephrosis.mp,tw,kw.
7	Proteinur*.mp,tw,kw.
8	(Macroproteinur* or macro-proteinur*).mp,kw,tw.
9	Nephritic syndrome.mp,kw,tw.
10	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	Renal insufficiency (including related terms)
12	Kidney failure (including related terms)
13	Kidney diseases (including related terms)
14	(Chronic kidney or chronic renal).tw.
15	(CKF or CKD or CRF or CRD).tw.
16	(Acute kidney or acute renal).tw.
17	(AKI or ARF).tw.
18	11 or 12 or 13 or 14 or 15 or 16 or 17
19	Diabetes mellitus (including related terms)
20	Exp diabetes mellitus, type 1/
21	Exp diabetes mellitus, type 2/
22	Diabetic nephropathies (including related terms)
23	Diabet*.tw.
24	(NIDDM or IDDM).tw.
25	Exp hyperglycemia/
26	19 or 20 or 21 or 22 or 23 or 24 or 25
27	10 or 18 or 26
28	1 and 27
29	Limit 28 to human

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((Chronic kidney disease) OR (renal impairment) OR (impaired kidney function) OR (acute renal failure) OR (acute kidney injury) OR (diabetes) OR (diabetic nephropathy) OR (proteinuria) OR (hematuria) OR (nephrotic syndrome) OR (nephrotic syndrome) OR (nephrosis) OR (diagnosis)) AND (kidney biopsy indications)

Urinary Abnormalities

Urinary abnormalities (such as microhematuria or non-nephrotic proteinuria) emerged as the most common reasons for performing renal biopsy in 2 national registries [22, 24, 28], in 2 macro-regional reports [31, 34] and in a single-center database [47].

There is no consensus on the use of renal biopsy in patients with isolated non-nephrotic proteinuria. Hama et al. [68] suggested that urinary protein/creatinine ratio ≥0.5 g/g may represent an optimal cut-off to distinguish between minor glomerular lesions and significant glomerular disease in children with asymptomatic proteinuria. In a survey made among Italian nephrologists [69], isolated proteinuria <1 g/day was not considered as a suf-

Table 5. Main characteristics of the reviewed studies on diabetic patients undergoing renal biopsy

Study/year	Country	n	Histological finding			NDRD diagnosis
			DN, %	NDRD, %	mixed, %	
Hironaka et al. [119], 1991	Japan	35	71.4	14.3	14.3	–
Richards et al. [139], 1992	United Kingdom	68	62	34	4	MN (7%), IgAN (2%), PICGN (2%), MPGN (2%)
Parving et al. [135], 1992	Denmark	35	77.1	20	2.9	Mesangio-proliferative GN
Kleinknecht et al. [125], 1992	France	53	64	36	–	MN (14%), FSGS (14%), AIN (3%)
Gambara et al. [114], 1993	Italy	52	36.5	33	30.5	IgAN, MN, FSGS, MCD, PICGN (4%)
John et al. [123], 1994	India	80	18.7	60	21.3	MCD (16%), IgAN (8%), MN (8%), AIN (6%), FSGS (6%)
Olsen and Mogensen [134], 1996	Denmark	33	88	3	9	IgAN (3%), mesangio-proliferative GN (3%), CrioGN (3%)
Fioretto et al. [104], 1996	Italy	34	29.4	41.2	–	–
Mak et al. [128], 1997	China	51	67	16	17	IgAN (59%), hypertensive nephrosclerosis (24%)
Schwartz et al. [140], 1998	United States	36	94	6	–	IgAN (3%), MN (3%)
Lee et al. [126], 1999	South Korea	22	36.4	50	13.6	IgAN (22%), MN (21%), MCD (21%), AIN (5%)
Cordonnier et al. [113], 1999	United Kingdom	26	85	15	–	–
Nzerue et al. [132], 2000	United States	31	41.9	19.4	38.7	FSGS (18%), nephrosclerosis (17%), MN (6%), PICGN (6%)
Christensen et al. [112], 2000	Denmark	51	69	13	–	IgAN (8%), MPGN (4%)
Izzedine et al. [122], 2001	France	21	62	38	–	FSGS, IgAN, vascularnephropathy
Suzuki et al. [144], 2001	Japan	109	73.3	–	26.7	IgAN (44.8%), proliferative GN (37.9%), MN (6.9%), AIN (6.9%), FSGS (3.4%)
Serra et al. [141], 2002	Spain	35	74.3	17.1	8.6	IgAN (8%), FSGS (3%)
Castellano et al. [109], 2002	Spain	20	45	55	–	MN (35%), renal vasculitis (15%), IgAN (5%)
Mazzucco et al. [129], 2002	Italy	393	39.7	43	17.3	MN (23.1%), IgAN (20.3%), post-infectious GN (20.9%), MCD (12.4%), FSGS (12.4%), extracapillary GN (9.6%)
Wong et al. [146], 2002	China	68	35	46	19	IgAN (19%), nephrosclerosis (13%), MN (12%), MCD (6%)
Premalatha et al. [138], 2002	India	18	50	50	–	MN (33.3%), AIN (12.5%), MCD (12.5%)
Rychlik et al. [22], 2004	Czech Republic	163	42.4	47.5	10.1	IgAN (15%), MN (12%), PICGN (12%)
Tone et al. [145], 2005	Japan	97	36	47.5	16.5	IgAN (16%), MN (13%), MCD (8%), FSGS (5%)
Moger et al. [130], 2005	India	26	34.6	23.1	42.3	Proliferative GN (27%), AIN (15.3%), PICGN (11.5%)
Soni et al. [143], 2006	India	160	27.5	42.5	30	AIN (18.1%), post-infectious GN (17.2%), MN (11.2%), FSGS (7.7%)
Pham et al. [136], 2007	United States	232	27.5	53.2	19.3	FSGS (21%), MCD (15.3%), IgAN (15.3%), MN (13.3%)
Huang et al. [120], 2007	China	52	55.7	38.5	5.8	Mesangial proliferative GN (9.6%), MCD (7.7%)
Kharrat et al. [124], 2007	Tunisia	72	34.1	69.5	–	–
Prakash et al. [137], 2007	India	23	56.5	30.5	13	MN (8.7%), FSGS (8.7%)

Table 5. (continued)

Study/year	Country	n	Histological finding			NDRD diagnosis
			DN, %	NDRD, %	mixed, %	
Zhou et al. [150], 2008	China	110	54.5	45.5	–	IgAN (34%), MN (22%), MPGN (14%)
Akimoto et al. [105], 2008	Japan	50	68	26	6	MN (8%), IgAN (6%), MPGN (6%)
Lin et al. [127], 2009	Taiwan	50	48	22	30	AIN (46%), MN (19.2%), IgAN (11.5%)
Ghani et al. [115], 2009	Kuwait	31	54.8	–	45.2	PICGN (21.4%), AIN (14.4%), IgAN (7.1%)
Arif et al. [106], 2009	Pakistan	73	27.3	31.7	41	FSGS/MCD (30.56%), MN (8.3%), IgAN (5.5%)
Hashim Al-Saedi [118], 2009	Iraq	80	–	100	–	MPGN (40%), FSGS (25%), MN (20%), MCD (10%), amyloidosis (5%)
Mou et al. [131], 2010	China	69	47.8	52.2	–	FSGS (37.7%), IgAN (15.9%), MCD (15.9%), MN (8.7%)
Biesenbach [108], 2011	Austria	84	78.5	21.5	–	–
Haider et al. [116], 2011	Austria	567	46.6	32	31.4	FSGS (17%), AIN (13%), IgAN (9%), MN (3%)
Chang et al. [110], 2011	South Korea	119	36.2	53.8	10	MN (32.9%), MCD (15.8%), FSGS (11.8%), IgAN (11.8%)
Bi et al. [107], 2011	China	220	54.5	–	45.5	IgAN (34%), MN (22%), mesangial proliferative GN (14%)
Zhang et al. [149], 2011	China	130	73.9	26.1	–	IgAN (16.9%), MN (6.15%)
Y et al. [148], 2012	Marocco	16	62.5	37.5	–	IgAN (19%), myeloma (6%)
Yaqub et al. [147], 2012	Pakistan	68	31	52	17	AIN (26.4%), post-infectious GN (10.3%), MN (5.9%), PICGN (5.9%)
Oh et al. [133], 2012	South Korea	126	39.7	51.6	8.7	IgAN (16%), MN (11.9%), FSGS (7.6%), MPGN (4.7%)
Chong et al. [111], 2012	Malaysia	110	62.7	18.2	19.1	AIN (48.8%), hypertensivenephrosclerosis (24.4%), MCD (7.3%)
Zhuo et al. [103], 2013	China	216	6.5	82.9	10.7	In patients aged 17–59 years, IgAN (29–34%), MN (11–15%), FSGS (8.8–5.4%) In patients aged >60 years, MN (25.7%), AIN (17%), MPGN (11%)
Sharma et al. [102], 2013	United States	620	37	36	27	ATN (17–43%), FSGS (13–22%), hypertensive nephrosclerosis (19%), IgAN (7–11%)
Harada et al. [117], 2013	Japan	55	54.5	34.5	10.9	IgAN (23.6%), FSGS (5.4%), MN (1.8%)

ATN = Acute tubular necrosis; Crio-GN = crioglobulinemic GN; PICGN = pauci-immune crescentic GN; – = data not available.

ficient indication for renal biopsy in the absence of other serum and urinary abnormalities. Conversely, patients with proteinuria ≥1 g/day would deserve renal biopsy for clarifying the nature of the underlying nephropathy [69] and should periodically be followed if such levels persist over time [70].

The diagnostic approach to isolated microscopic hematuria (IMH) changes according to the patient's age [71]. In children, IMH is usually associated with hypercalciuria (30–35%), hyperuricemia (5–20%) and glomerular disease, such as IgAN and thin basement membrane nephropathy [72]. Zhai et al. [73] described the histological patterns of 112 renal biopsies in children with asymptomatic urinary abnormalities. Mild glomerular lesions predominated in patients with IMH while chronic GNs (particularly, IgAN) were more

prevalent in patients where proteinuria and hematuria co-existed. The utility of renal biopsy in these patients is highly debated since the overall prognosis in the mid-long term is excellent. In a study of 251 children with IMH [74], no patients developed hypertension or any other sign of renal impairment over a 7-year follow-up. Similar observations were reported by Lee et al. [75] in a study on 289 children undergoing renal biopsy for the same indication.

Conversely, the use of renal biopsy might be very important to predict the disease course if IMH is associated with proteinuria or impaired renal function or in the presence of a history of macroscopic hematuria [71, 76, 77]. In a retrospective study of 169 young patients undergoing renal biopsy for microscopic hematuria [78], the severity of the glomerular findings and the progression of renal disease were strictly correlated to urinary protein excretion.

In a study of 351 children with various urinary abnormalities, normal histology was more frequent in subjects with IMH than in those with both microhematuria and proteinuria. Moreover, in these latter, the worsening of proteinuria or the impairment in renal function occurred more significantly over a 10-year follow-up [79].

In adults presenting with IMH, non-glomerular causes (such as nut-cracker syndrome, infectious diseases, lithiasis or neoplastic disease) should firstly be excluded [71, 80]; the contribution of finding dysmorphic erythrocytes and acanthocytes should be important for the diagnostic decision [81]. Glomerular causes of IMH are miscellaneous and mostly represented by IgAN, Alport syndrome, thin basement membrane nephropathy and FSGS [82].

Renal biopsy in IMH may be more useful to assess the individual risk of progressive renal disease or inspire the screening of relatives (e.g. in case of Alport syndrome), than to guide clinical management [83]. Conversely, the presence of pathological albuminuria or other altered serum parameters might be a stronger indication for renal biopsy [69, 84], as this may reflect a more prominent histopathological damage [85] and higher risk of renal disease progression [86, 87].

Acute Kidney Injury

Although AKI patients are notoriously at high risk for post-biopsy bleeding [88, 89], in subjects with no evidence of pre-renal or obstructive diseases, the benefits of renal biopsy may outweigh the risks as the histological diagnosis might be useful to guide therapy and to predict outcomes.

Many, non-evidence-based biopsy policies have been proposed so far for approaching AKI patients such as an unknown origin of AKI, AKI duration of more than 3 or 4 weeks [69] or the presence of extra-renal manifestations, suggestive of a systemic disease.

In an old report of 84 patients presenting with AKI and evidence of intrinsic renal disease, renal biopsy was useful in establishing the diagnosis, in indicating the reversibility of the lesion and in guiding treatment [90]. In another study conducted in the nineties, renal biopsy altered the management of 71% of patients with AKI [9].

In another milestone paper of 250 AKI patients, one half of which had parenchymal diseases, the etiology of AKI could be determined only by renal biopsy and this procedure was also useful to drive diagnosis and treatment [91]. In a series of 259 patients with AKI undergoing renal biopsy [92], glomerular disease (particularly pauci-immune crescentic GN (crescGN) and post-infectious GN, anti-GBM nephritis, IgAN) was the most frequent histological pattern, while tubulo-interstitial disease (AIN and acute tubular necrosis) and vascular injury (atheroembolic disease) accounted for about 40 and 12% respectively of the remaining diagnoses. The clinical diagnosis corresponded with histological findings in two third of cases and patients with tubulo-interstitial disease had a better renal prognosis as compared with those with GNs and renal vasculitis [92]. AIN and rapidly progressive GN were the most frequent histological findings in another study of 109 patients with unexplained acute renal impairment and normal-size kidney [93]. Of note, 52% of patients with AIN and 60% with rapidly progressive glomerular damage improved or remained stable after the establishment of appropriate treatment.

Chronic Kidney Disease

The utility of renal biopsy in patients with CKD is even more controversial. These subjects may have a higher risk of bleeding and have lower chances of diagnostic success, particularly when the kidneys are smaller and more scarred [94]. Nevertheless, renal biopsy in CKD patients is relatively a safe procedure as reported in several studies [94–99] and may represent a valid tool for clinical management. Renal tissue obtained by biopsy cannot give a great quantity of information if chronic damage (tubulo-interstitial fibrosis, glomerulosclerosis, arteriosclerosis) prevails [8] and there is usually an inverse relationship between the degree of renal function and the need for therapeutic changes [94]. Sparse evidence indicates that

the histological diagnosis made in CKD patients can differ from the expected, clinically made diagnosis in a significant percentage of cases [95–97]. In patients with NS and non-advanced CKD, renal biopsy is still a useful tool for managing immunosuppressive therapy, as well as for the knowledge of a specific renal diagnosis for transplant candidates [99]. Other studies confirmed that renal biopsy can lead to a change in therapeutic management in a significant percentage of patients with CKD of unknown origin [9, 100, 101], although the risk-benefit profile of such procedures in the CKD population is not yet well defined.

Diabetes Mellitus

The utility of renal biopsy in patients with diabetes is another timely and debated issue [102, 103]. A common opinion is that patients with diabetes with proteinuria and other micro-vascular complications, such as retinopathy, are very likely to have a typical DN so that renal biopsy cannot give additional information for their clinical management [2]. However, a significant percentage of patients with diabetes may instead have a non-diabetic renal disease (NDRD), which can be even superimposed on a typical DN (mixed forms). Since clinical parameters such as proteinuria or albuminuria may not parallel with the great variability of renal histology [104], renal biopsy remains the gold standard for the correct assessment of renal damage in this setting and would be crucial for planning an optimal therapeutic approach (e.g. immunosuppressive therapies) [2].

So far, a discrete number of studies have investigated this issue [22, 104–150] (table 5). In these studies, indications for biopsy included the following: (1) a nephrotic range proteinuria or renal impairment in the absence of diabetic retinopathy; (2) a nephrotic range proteinuria or renal impairment with diabetes vintage less than 5 years or normal kidney function; (3) an unexplained microscopic hematuria or AKI; (4) a rapidly worsening of renal function in patients with a previously stable renal function. Diagnosis of DN ranged from 6.5% [103] to 94% [140] of all the biopsies made. NDRD spanned from 3% [134] to 82.9% [103], while mixed forms accounted for 4% [139] to 45.5% [107] of all the histological pictures. Moreover, Mazzucco et al. [129] identified a subgroup of patients with diabetes (15.2%) characterized by the prevalence of severe vascular changes affecting glomeruli associated with marked arteriosclerosis and arteriolosclerosis in the absence of typical diabetic damage. IgAN was the most frequently observed NDRD [22, 103, 107, 112, 114, 117, 126, 128, 134, 140, 141, 144–146, 148, 150] with a prevalence ranging from 3% [134] to 59% [128]. MN was the predominant NDRD in 9 cohorts [105, 109, 110, 125, 129, 137–139] (7% [139] to 35% [109]); FSGS prevailed in 6% [106, 116, 122, 131, 132, 136] (17% [116] to 37.7% [131]), while AIN was the main NDRD in 4 studies [111, 127, 143, 147] (18% [143] to 48.8% [111]).

Renal Biopsy in the Elderly Setting

Kidney disease is highly prevalent among elderly persons [151]. The aging kidney is characterized by structural and functional changes due to age and systemic disease (diabetes, hypertension, obesity) such as glomerulosclerosis, tubulo-interstitial fibrosis, atrophy and, consequently, a reduction in the functional renal reserve, which makes the elderly prone to develop CKD, sooner or later [152–154]. Although in most cases renal biopsy cannot differentiate between chronic renal damage and age-related changes, some specific conditions may require histological details for a clear-cut diagnosis, etiological frame-working and therapeutic planning [155]. Theoretically, the indications for performing renal biopsy in the elderly should not diverge from those in an adult, non-elderly population [69]; however, since old patients are more likely to present with decreased renal function, cardiovascular, pulmonary or hematologic comorbidities and poorer general health, a prudent and complete evaluation of risk factors is mandatory for guiding decision to biopsy [151]. Nevertheless, preliminary evidence suggests that the rate and type of complications in the elderly patients do not differ from those observed in the general population [156]. Kohli et al. [156] analyzed the rate of complications in 210 patients with native renal biopsies, of which 26 were done in elderly patients. The incidence of gross hematuria was higher in the elderly than in younger individuals (15 vs. 3%), but the rate of more severe complications (hematuria with need of blood transfusions, perinephric hematoma, need of invasive interventions…) was not different between the 2 subgroups. In the study of Pincon et al. [157], only 5 old patients (3.3%) presented biopsy-related complications. In another report [158], the incidence of post-biopsy complications in the elderly was similar to that seen in the non-elderly adults (11.9 vs. 10%) and never required blood transfusion or invasive maneuvers.

As reported in table 6, data from 16 studies show that the 2 most common indications for RB in elderly populations are AKI (12% [159] to 73% [156]) and NS of rapid onset (13% [160] to 68% [159]). There is indeed great variability of histological pictures found in the elderly population, and even more in the very elderly (≥80

Table 6. Main studies on renal biopsy in elderly populations

References	Population	Age, years	Principal indications to RB	Main histological findings
Okpechi et al. [165]	111	>60	NS (48.6%)	MN (14.4%), DN (12.6%)
Yokoyama et al. [162]	2,802	>65	NS (36.2%)	MN (38.5%), IgAN (10%), ANCA-vasculitis (11.2%)
	276	>80	NS (50.7%), AKI (22.5%)	MN (28%), amyloidosis (11.9%), MCD (11.9%), FSGS (7.5%)
Verde et al. [164]	71	>85	AKI (47%), NS (32%)	Amyloidosis (16.9%), crescGN (14.1%)
Omokawa et al. [163]	73	>80	NS, AKI, UA	MN, MCD
Brown et al. [152]	236	>65	AKI (31.8%), NS (25%), proteinuria (7.6%)	PICGN (17.4%), AIN (11%), MN (8.9%)
Pincon et al. [157]	150	>70	AKI (31%), NS (30%), CKD (11%)	AIN (23%), PICGN (22.5%), vascula nephropathy (12%), MPGN (6.5%)
Heras et al. [167]	39	>65	AKI (46.2%), NS (38.5%), UA (10.3%)	PICGN (23.1%), AIN (15.5%), amyloidosis (10.3%)
Di Palma et al. [158]	110	>60	UA (57%), NS (36%), AKI (17%)	MN (26.4%), DN (18.2%), PICGN (9.1%)
de Oliveira et al. [153]	71	>60	NS (49.3%), AKI (6.8%), UA (16.9%)	MN (50%), amyloidosis (20%), FSGS (20%) ATN (35%), cast-nephropathy (15%), post-infectious GN, DN, hypertensive damage
Moutzouris et al. [160]	235	>80	AKI (46.4%), CKD (23.8%), NS (13.2%)	PICGN (19%), FSGS (7.6%), hypertensivenephrosclerosis (7.1%), IgAN (7.1%)
Kohli et al. [156]	26	>60	AKI (73%), NS (27%)	PICGN (15%), AIN (15%), cast nephropathy (11%)
Ferro et al. [166]	150	>65	NS, AKI, CKD	PICGN
Nair et al. [161]	100	>80	NS (33%), AKI (23%), nephriticsyndrome (20%)	PICGN (19%), FSGS (7%), MCD (6%)
Haas et al. [92]	1,065	>60	NS (25.7%), AKI (24.3%), CKD (23.1%)	PICGN (31.2%), AIN (18.6%), ATN (17%)
Moulin et al. [159]	32	>75	NS (68%), AKI (12.5%)	MCD (21%), MN (18%), amyloidosis (15%)
Mbakop et al. [168]	119	>60	NS (29%), AKI (29%)	MN (15%), SLE (5%), amyloidosis (6%)

ATN = Acute tubular necrosis; PICGN = pauci-immune crescentic glomerulonephritis; RB = renal biopsy; UA = urinary abnormalities.

years) [160, 161]. In a recent analysis of Japanese renal biopsy registry [162], primary glomerular diseases, such as MN, were the most common findings. In this registry amyloidosis, MN and ANCA-associated vasculitis prevailed in the elderly, while IgAN was more frequent in the non-elderly adults [163]. Amyloidosis was the most common diagnosis (16.9%) among 71 very elderly patients (>85 years) in the Spanish registry of GN [164]. In a retrospective analysis of 111 elderly patients in South Africa, MN predominated (14.4%) [165]. CrescGN is another common histologic finding among old persons [92, 152, 156, 160, 161, 166, 167], with a frequency of overall diagnoses ranging from 15% [156] to 31% [92]. AIN is exceedingly prevalent in the elderly [92, 152, 156, 167]; in one retrospective study in Western France [157], AIN was even the most frequent histological report (23%). Studies analyzing the clinical impact of renal biopsy on the management of the elderly patients show results that are in line with those reported in the general population. Histological diagnosis in the elderly patients may lead to targeted, successful treatment in 40% [161] to 67% of cases [160] or, at least, advise against potentially harmful approaches [160]. In the study of Pincon et al. [157], 64% of the elderly nephrotic patients receiving immunosuppressive therapy after renal diagnosis made by biopsy were more likely to have complete or partial remission of their disease as well as an improvement in survival.

Conclusions

Although renal biopsy can be considered a determinant factor for characterizing renal diseases and for collecting useful diagnostic and prognostic information, the clinical application of this technique and the correspondent histological findings are highly variable across the world. This is mostly a consequence of lack of consensus in national and single-center biopsy policies which, in turn, depends on the disagreement on the real indications for this procedure. The utility of renal biopsy is related to the possibility to assess the extent of renal damage for appropriate and timely intervention to delay the progression of ESKD in patients with NS, urinary abnormalities, acute or chronic kidney failure and in renal injuries related to systemic diseases such as SLE, diabetes, vasculitides or myeloma. Our evidence-based approach to the current literature indicates that renal biopsy should be mandatory to assess the type and degree of lesions and to guide the therapeutic management in adults with NS. Renal biopsy might be highly informative in patients with coexistence of unexplained hematuria and proteinuria or in children with severe proteinuria non-respondent to corticosteroid treatment. Furthermore, this procedure may give important diagnostic and prognostic information in non-pre-renal and non-obstructive AKI, as the histology awareness may lead to substantial change in therapeutic management. However, in AKI patients, potential benefits of renal biopsy should always be weighted to the risk of bleeding complications. In patients presenting with IMH, low proteinuria or early unexplained CKD, the choice of performing renal biopsy should be evaluated on a case-by-case basis, taking into account the possibility of improving the disease management. Indications for renal biopsy in the elderly should not differ from those in the general population, as there is no convincing evidence that an older age conveys a higher risk of complications. Conversely, renal biopsy appears to be of limited utility in patients with unexplained advanced CKD where risks outweigh possible improvements in clinical management. Finally, in patients with diabetes with short duration of disease (<5 years), severe proteinuria, rapid onset or worsening of renal impairment, particularly in the absence of diabetic retinopathy, renal biopsy should be advocated for excluding the presence of a NDRD. Considering the relative safety and the low risk of complications of this procedure, future improvement in renal biopsy practice due to widespread access to educational programs and renal biopsy courses may contribute to an increase in awareness of the need of renal biopsy in patient care.

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Disclosure Statement

All authors declare no conflicts of interest.

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