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NEPHROLOGY - ORIGINAL PAPER

Trends of primary glomerular disease in Turkey: TSN-GOLD registry report

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Abstract

Background Although several renal biopsy registry reports have been published worldwide, there are no data on primary glomerular disease trends in Turkey.

Methods Three thousand eight-hundred fifty-eight native kidney biopsy records were assessed in the Turkish Society of Nephrology Primary Glomerulopathy Working Group (TSN-GOLD) Registry. Secondary disease and transplant biopsies were not recorded in the registry. These records were divided into four periods, before 2009, 2009 to 2013, 2013–2017, and 2017–current.

Results A total of 3858 patients (43.6% female, 6.8% elderly) were examined. Nephrotic syndrome was the most common biopsy indication in all periods (58.6%, 53%, 44.1%, 51.6%, respectively). In the whole cohort, IgA nephropathy (IgAN) (25.7%) was the most common PGN with male predominance (62.7%), and IgAN frequency steadily increased through the periods ($\times 2 = 198$, $p < 0.001$). MGN was the most common nephropathy in the elderly (> 65 years), and there was no trend in this age group. An increasing trend was seen in the frequency of overweight patients ($\times 2 = 37$, $p < 0.0001$). Although the biopsy rate performed with interventional radiology gradually increased, the mean glomeruli count in the samples did not change over the periods.

Conclusions In Turkey, IgAN is the most common primary glomerulonephritis, and the frequency of this is increasing.

Keywords IgA nephropathy · FSGS · Kidney biopsy registry · Primary glomerulopathy

Introduction

Primary glomerulonephritis (PGN) is among the important causes of end-stage renal disease (ESRD) worldwide. The reasons remain unclear, but a temporary change in glomerular disease frequency has occurred over the past 30 years [1]. Environmental exposure or behavioral reasons are often held responsible. In recent years, non-invasive techniques have been proposed, and with the use of -omics-based biomarkers in particular such as genomics, proteomics, and metabolomics, it has been attempted to determine kidney tissue damage and disease types. However, these techniques cannot replace the gold standard technique of kidney biopsy for the determination of kidney disease and the estimation of its prognosis [2].

There are many regional registration systems around the world that record kidney biopsies, with variations seen in kidney biopsy rates, indications, and histological glomerulonephritis from center to center and country to country. Some of the reasons for the variations are known to be socioeconomic status, access to health services, lack of biopsy data, and variations in the time frame of published data [2]. Of

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PGNs, the prevalence of focal segmental glomerulosclerosis (FSGS) and IgA nephropathy (IgAN) is increasing in most parts of the world [2]. IgAN is the most common PGD in Australia and Asian regions [1, 3–5], while FSGS and membranous glomerulonephritis (MGN) is most common in African Americans, and IgA and MGN more common in Caucasians and Native Americans in the USA [6–8]. In some regions of the Middle East and South America, FSGS is the most common type of PGN [9, 10]. In Europe, IgA nephropathy is the most common PGN, followed by FSGS, according to numerous registry reports [11–17].

Data on biopsy-proven renal diseases in Turkey are scarce, and there are no published data on temporal trends in PGD. The aim of this study was to report PGD trends in Turkey from 2009 to 2017. A total of 3858 native kidney biopsy records were evaluated in the Turkish Society of Nephrology Primary Glomerulopathy Working Group (TSN-GOLD) Registry.

Material and method

Patient selection

All biopsy data used in this study were extracted from the TSN-GOLD database created by the Turkish Society of Nephrology in 2008. The data of 4399 patients from 47 centers across the country were analyzed, and the study included the data of 3858 patients with complete records. The oldest date of kidney biopsy was in 1994, and the most recent was in 2019. Only primary GN were assessed; kidney transplants and secondary GN were excluded. IgAN, membranous glomerulonephritis (MGN), FSGS, minimal change disease (MCD), membranoproliferative GN types 1 and 2, non-IgA mesangioproliferative nephropathy, and crescentic GN with or without ANCA positivity were assessed as primary GN and were included in the study. Amyloidosis, diabetic nephropathy, secondary FSGS, cholesterol embolism, light-chain deposition disease, tubulointerstitial nephritis, hypertensive nephrosclerosis, thrombotic microangiopathy, anti-GBM disease, hemolytic uremic syndrome and other secondary glomerulonephritides, hereditary diseases such as Alport's disease and Fabry disease, and renal transplants recipients were excluded.

Each patient was screened for malignancy according to the clinical practice of each center. Routine physical examination was performed to detect lymphadenopathy, organomegaly, breast mass, skin lesion, or urological abnormality. Eligible patients had lung imaging for lung cancer [(chest X-ray or computed tomography (CT)]). Abdominal imaging (ultrasound or magnetic resonance imaging or CT) and endoscopic scans were made for abdominal origin cancers. Breast and gynecological cancers were screened by cervical smear, mammography, and breast ultrasonography for eligible female patients as well. Also, standard laboratory testing was performed to exclude secondary forms of glomerulopathy, including protein electrophoresis, serum light chains, viral serology, complement level, and soluble rheumatologic markers such as ANCA profile, anti-nuclear antibody. Patients with suspected genetic disease; eye examination, audiogram, and also genetic screening in some centers.

Approval for the study was obtained from the Ethics Committee of Istanbul University, Istanbul Medical Faculty.

Patient characteristics and definitions

Demographic parameters and chronic diseases before renal biopsy (hypertension, tuberculosis, diabetes mellitus, and cardiac disease), indication for renal biopsy, the date of biopsy, the clinic at which the biopsy was performed, clinical diagnosis, pathological diagnosis, the medications that the patients were taking before renal biopsy and detailed description of pathological findings were recorded for all patients to the database [18, 19].

The patients' data collected include age, gender, body mass index (BMI), blood pressure, and laboratory parameters including hemogram, lipid profile, renal function tests, albumin, total protein, 24-h proteinuria, glucose, uric acid, calcium, alanine aminotransferase (ALT), erythrocyte sedimentation rate (ESR) and light microscopic findings including tubular atrophy, interstitial fibrosis, number of total glomeruli, number of crescentic glomeruli, and number of sclerotic glomeruli, immunofluorescence findings such as immunoglobulin (Ig)G, IgA, IgM, kappa, lambda, fibrinogen, C3 and C1q, serology for human immunodeficiency virus and hepatitis C virus and hepatitis B surface antigen, and an autoimmune panel including complement levels (C3 and C4 levels), anti-nuclear antibody (ANA), anti-double-stranded DNA antibody (anti-dsDNA Ab), ANCA [as anti-myeloperoxidase (anti-MPO) and anti-proteinase 3 (anti-PR3)], and anti-GBM antibody. No limitation was applied to the methods of laboratory investigations, and all parameters were measured with the locally available techniques [18, 19].

Indications for biopsy were grouped as nephrotic syndrome, nephritic syndrome including RPGN, nephrotic syndrome with hematuria, and asymptomatic urinary abnormalities (AUA). Nephrotic syndrome was defined as proteinuria of > 3.5 g/day associated with edema, hypoalbuminemia, and hyperlipidemia. Nephritic syndrome was defined as proteinuria < 3.5 g/day associated with hematuria, hypertension, and slowly progressive renal failure. Nephrotic syndrome with hematuria was defined as nephrotic syndrome together with findings of nephritic syndrome. Proteinuria of < 3.5 g/ day and/or isolated microscopic hematuria were recorded as asymptomatic urinary abnormalities (AUA). RPGN was defined as an acute/subacute

decrease in renal functions within hours or days associated with proteinuria, microscopic hematuria, and positive autoantibodies. "Active urinary sediment" was defined by the presence of dysmorphic red blood cells (40% of the erythrocytes) or erythrocyte casts (one or more red blood cell casts/HPF) or hematuria (presence of at least five red blood cells/HPF) in urine microscopy [18, 19].

Bodyweight changes were evaluated according to the BMI thresholds defined by the World Health Organization. BMI was calculated as weight in kilograms divided by height in meters squared, and evaluated as overweight at BMI of 25–29.9 kg/m^2, and obese at BMI ≥ of 30 kg/m^2.

Histological assessment

The kidney biopsies were performed percutaneously using an automated gun guided by ultrasound. The biopsy samples were processed using LM and IF examination. Overall, 3% of biopsy samples in this series were examined by electron microscopy.

Time periods

Biopsies conducted between January 1, 1994 and May 31, 2019 were analyzed. To understand the trends and make a better comparison, these records were divided into four periods; before 2009, 2009–2013, 2013–2017, and 2017 to current.

Data analysis

Data were stored on a standard Microsoft Excel® database. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26 software (IBM Corp., Armonk, N.Y., USA). Descriptive statistics were used to present the distribution of the types of glomerulopathies and their relative frequencies. Normally distributed variables were presented as a percentage or mean ± standard deviation value and non-normally distributed variables as median and interquartile range values. The distribution of primary glomerular diseases was compared between the 5-year intervals using Pearson's chi-square analysis. One-way ANOVA with multiple comparisons was used to compare the mean values of continuous variables for two or more categories. Bonferroni correction was applied to multiple comparisons among groups. All statistical tests were two-sided, with a value of $p < 0.05$ defined as statistically significant.

Results

Demographics

The 3858 patients comprised 2168 (56.4%) males and 1690 (43.6%) females. Each time period included 965 ± 5 patients and no significant difference was determined between the four periods regarding the number of patients and gender distribution. The mean age of patients increased progressively from the first period to the 3rd period ($p < 0.001$), but there was no significant difference between the 3rd and last periods. The proportion of elderly patients of the total increased significantly from 4% in the first period to 9.5% in the last period ($p < 0.01$). The demographic data of the patients are shown in Table 1.

Trends in kidney biopsy indications

Nephrotic syndrome was seen to be the most common indication in all periods. The rate of biopsies performed with asymptomatic urine findings increased progressively from 11.8% in the first period, to 14.3% in the second period, 24.7% in the third period, and 22.2% in the last period ($\chi^2 = 112$, $p < 0{,}001$) (Fig. 1). In those patients, IgAN was the most common PGN, followed by FSGS at 39.8% and 21.5%, respectively.

Trends in kidney biopsy practice in nephrology clinics

The biopsy rates of nephrology clinics decreased over the time periods. Interventional radiology clinics performed 8.8% of kidney biopsies in the first period and this rate increased to 50.5% in the last period (Fig. 2). The glomeruli numbers obtained from the samples in the periods were 15 ± 10, 17 ± 11, 18 ± 11, and 18 ± 11, respectively (Fig. 3). There was a significant difference between the first period and the others ($p < 0.001$) and no significant difference between the other periods. Particularly, while interventional radiology performed most of the biopsies in the last period, there was no statistically significant increase in glomeruli numbers in the samples (4th vs. 2nd period $p > 0.05$ and 4th vs. 3rd period $p > 0.05$).

Primary glomerular disease diagnosis

In the whole cohort, IgAN (25.7%) was the most common PGN with male predominance (62.7%). When evaluated according to the periods, MN (29.9%, $n = 290$) was the most frequent PGN in the first period, followed by IgAN (17.7%, $n = 172$). IgAN (28.5%, $n = 274$) was the most

Table 1 Demographics

	–2009 *n* = 968	2009–2013 *n* = 960	2013–2017 *n* = 968	2017– *n* = 962
Age (years)	36.9 (14.8)	40 (14)	44 (14.7)	44 (15)
Gender (m/f)	542/426 (44%)	538/422 (43%)	545/423 (44%)	548/414 (43%)
Elderly (> 65)	40 (4%)	45 (5%)	86 (8.9%)	91 (9.5%)
Systolic BP (mmHg)	130 (22)	130 (21)	130 (19)	130 (17)
Diastolic BP (mmHg)	82 (13)	81(12)	80 (12)	80 (10)
BMI (kg/m^2)	26 (4.8)	28 (9)	28 (23)	28 (20)
Cr (mg/dL)*	1.0 (0.8–1.4)	1.0 (0.7–1.6)	1.0 (0.7–1.6)	1.0 (0.7–1.6)
eGFR (mL/Min/1.73m^2)*	76 (47–107)	74 (41–74)	70 (42–107)	74 (43–108)
LDL (mg/dL)	156 (81)	162 (86)	165 (88)	169 (80)
Serum Alb (g/dL)	3.2 (0.9)	3.2 (1)	3.3 (0.9)	3.2 (0.9)
Proteinuria (mg/day)*	3000 (1110–5500)	3400 (1382–6365)	3067 (1400–6262)	3726 (1800–6800)

Data are given mean (± SD) or *n* (%)

BMI body mass index, *Cr* serum creatinine, *eGFR* estimated glomerular filtration rate calculated by CKD-EPI equation, *LDL* low density lipoprotein

*Median (interquartile range)

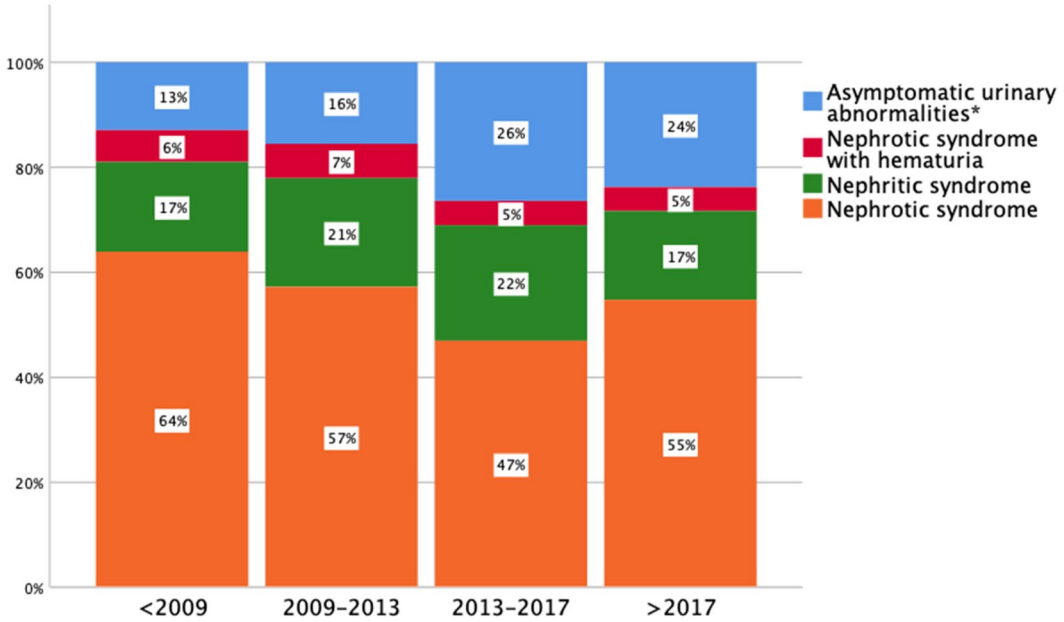

Fig. 1 Biopsy indications. Figure legend: *The rate of biopsies was performed with asymptomatic urine findings was increased over the periods ($\chi^2 = 112$, $p < 0.001$)

common glomerulopathy in the second period, followed by MN (25.5%, *n* = 245). IgAN (29.9%, *n* = 285) was the most common glomerulopathy in the third period, followed by FSGS (22.9%, *n* = 222) and MN. In the last period, FSGS (26.8, *n* = 258) was the most common glomerulopathy, followed by IgAN (26.7%, *n* = 257) and MN (24.5%, *n* = 236.) (Fig. 4).

Primary glomerular disease type and trends in patients aged > 65 years

MN was the most frequent PGN in all periods (40.2%). Crescentic GN was the second, and FSGS was the third in the first three periods (23%, and 15.2%, respectively). In the last period, FSGS was the second, and crescentic GN was

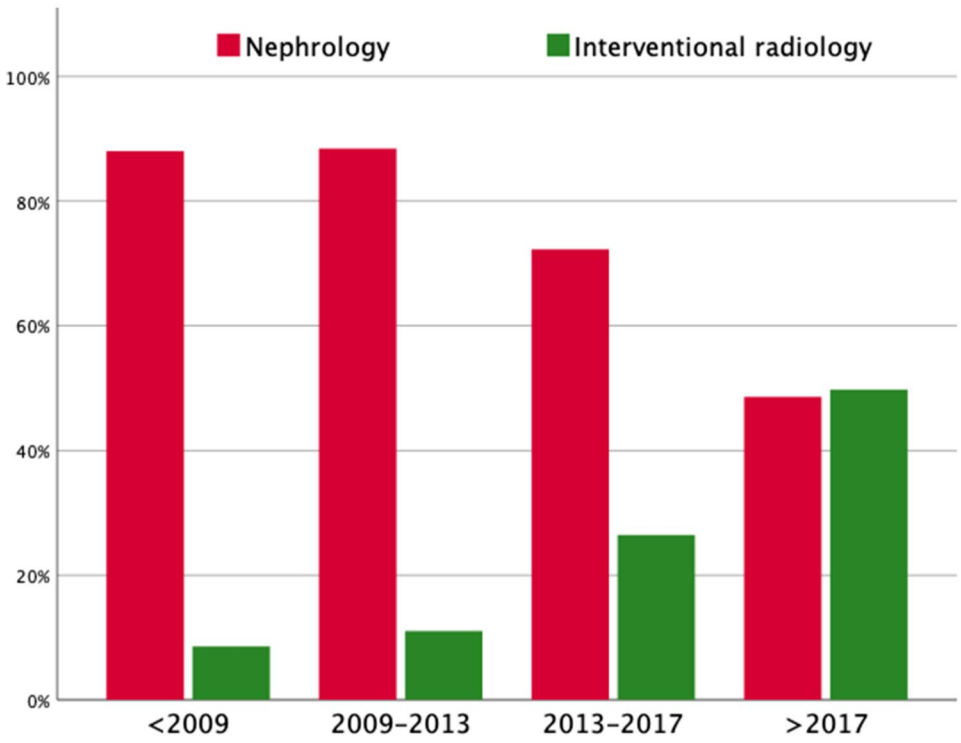

Fig. 2 Clinics where biopsies were performed

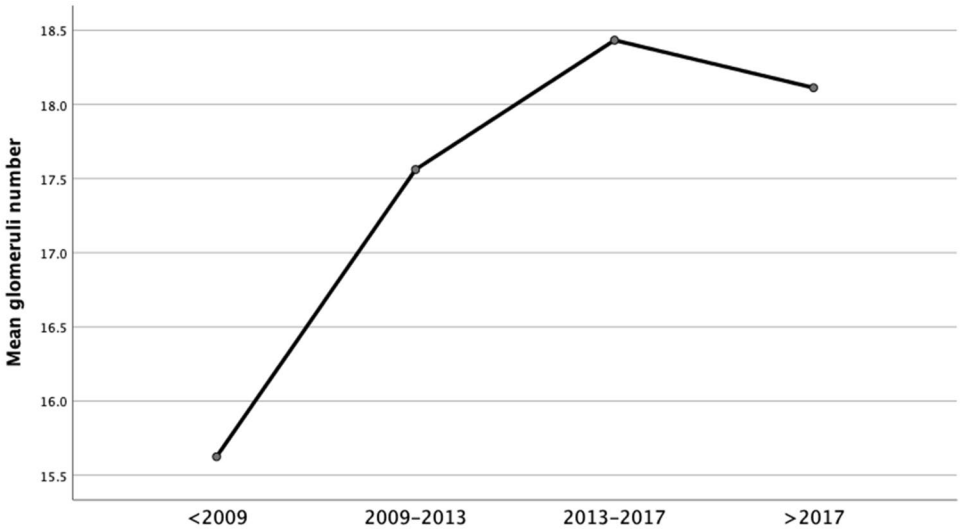

Fig. 3 Mean glomeruli number in the kidney biopsy sample

the third (17.4%, and 15.1%, respectively) (Fig. 5). Another important finding was that compared to the first two periods, there was an increase in the biopsy rate performed on elderly patients in the last two periods; 4.6% ($n=85$), 10.75% ($n=177$) respectively ($p<0.01$).

Bodyweight trends

In all periods, the proportion of patients in the overweight group increased from the first period at the rates of 7.22%, 9.39%, 10.48%, and 14.17%, respectively ($\chi^2=37$, $p<0.0001$) (Fig. 6). This trend was not observed in other BMI categories.

Discussion

This study presents the results of the TSN-GOLD registry, which collects kidney biopsy data from 47 centers nationwide in Turkey. This is the first report of analysis of PGN trends in Turkey. Many regional or macroregional registry reports have been published in Europe and other parts of the

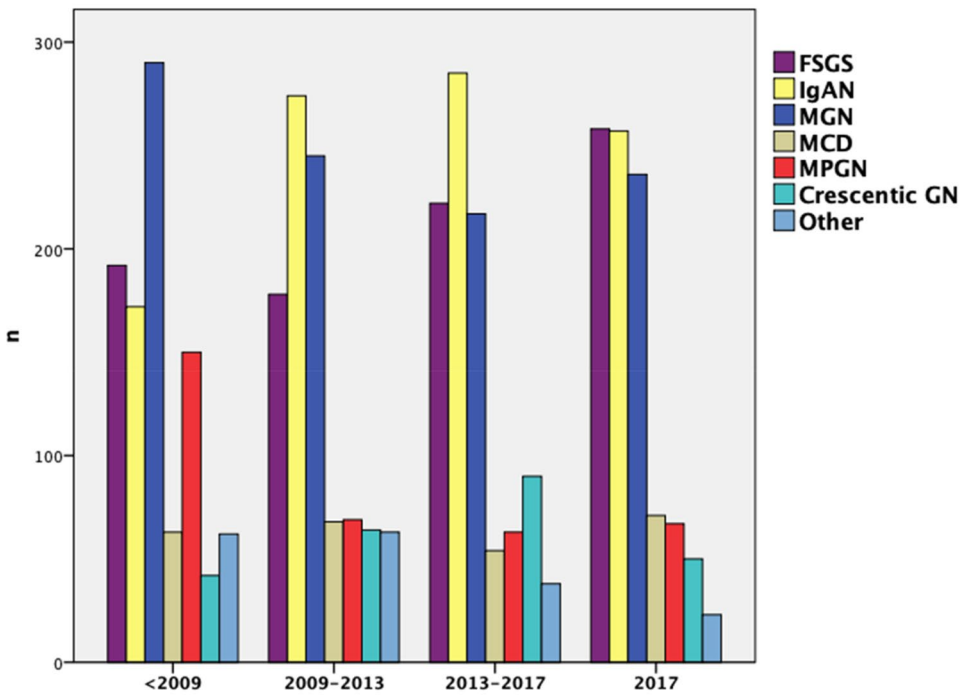

Fig. 4 Trends in primary glomerulonephritis over the periods ($n = 3858$). *FSGS* focal segmental glomerulosclerosis, *IgAN* IgA nephropathy, *MGN* membranous glomerulonephritis, *MCD* minimal change disease, *MPGN* membranoproliferative glomerulonephritis, *GN* glomerulonephritis

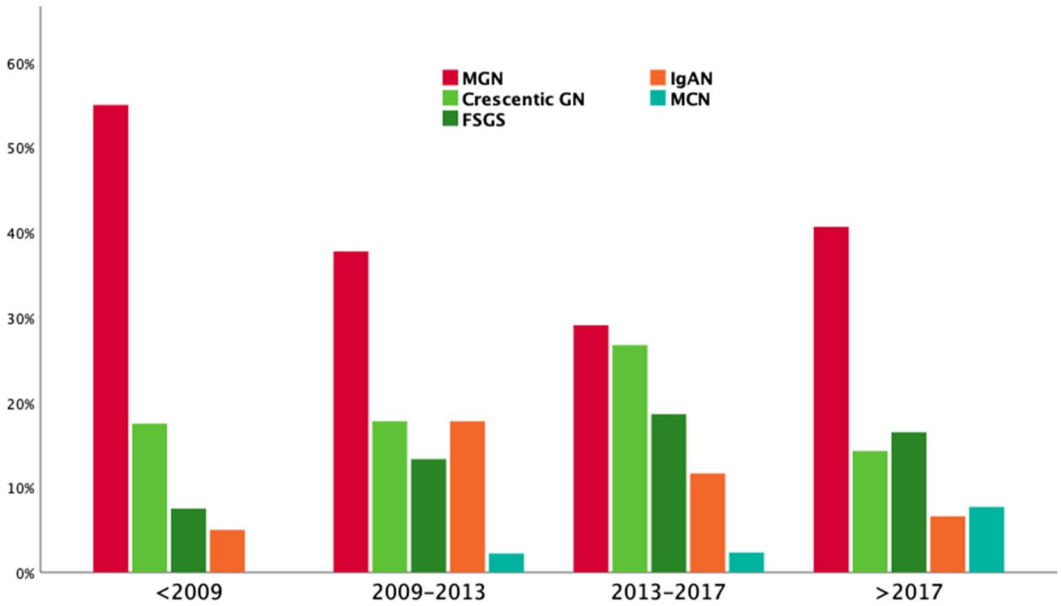

Fig. 5 Histological diagnosis types of older (> 65 years old) patients. *MGN* membranous glomerulonephritis, *FSGS* focal segmental glomerulosclerosis, *IgAN* IgA nephropathy, *MCD* minimal change disease, *GN* glomerulonephritis

world, and there can be seen to be temporal and geographical variations in the glomerular disease pattern. The major finding of this study was that although IgAN was the most common PGN in the whole cohort, the frequency of IgAN and FSGS increased constantly throughout all the periods.

The most notable finding was a steady increase in the frequency of IgAN over the four study periods (17.7%, 28.5%, 29.4 and 26.7%, respectively; $p < 0.001$). This finding is consistent with other studies presented in Europe and Asia [6, 8, 11, 12, 20–22] and some regions of the United States [6–8]. IgAN is associated with socioeconomic status and environmental factors. Since the onset of this cohort in Turkey, without any significant improvement in environmental conditions, there has been an increase in the number

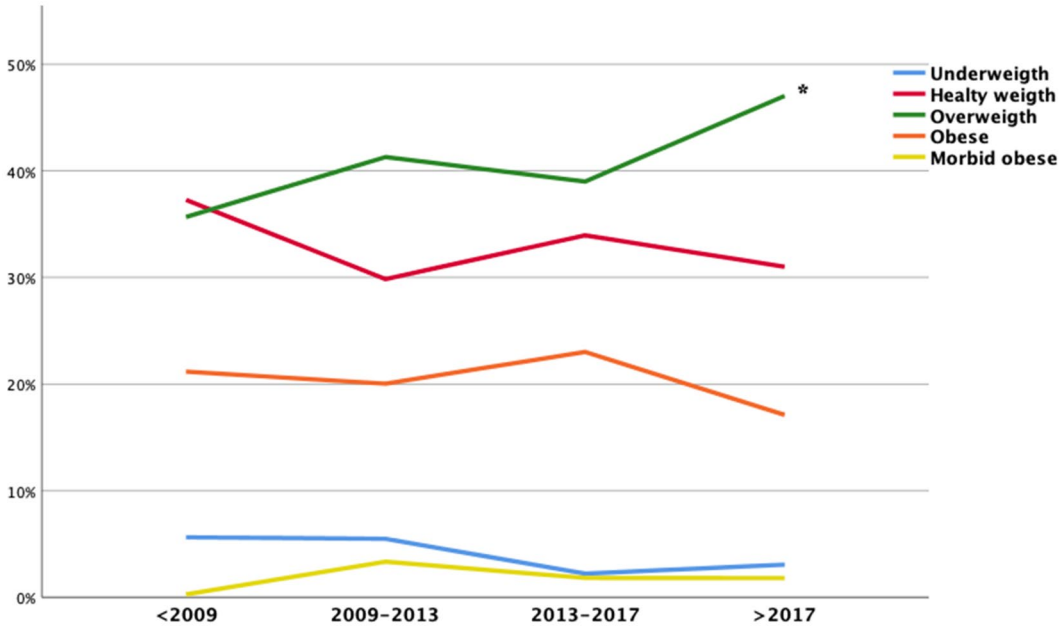

Fig. 6 Bodyweight trends over the years. Figure 5 legend: *There was a significant increasing trend only in the overweight category ($\chi^2 = 37$, $p < 0.0001$)

of biopsies performed in patients with asymptomatic urine findings from the first period to the last period. Therefore, the increasing willingness of nephrologists to perform biopsy on patients with isolated hematuria may be a reason for the increase in IgAN incidence over all the time periods. High IgAN frequency has been reported in countries with routine urine screening, such as Japan and South Korea [23, 24]. In parallel with the current study, Hanko et al. reported an increase in the incidence of IgAN in the Northern Ireland population, with a 4.7-fold increase in the biopsy rate [21]. However, socioeconomic deprivation can cause an increasing IgAN incidence [25]. In the current study, data related to socioeconomic status were not collected. However, the World Bank [26] and Turkey Statistical Agency data did not indicate a sudden deterioration in socioeconomic status, so it can only be speculated that a change in socioeconomic status cannot explain this increase.

Another important finding of this study was the steadily increasing frequency of FSGS, which was consistent with the findings reported in several studies [7, 11, 12, 27, 28]. However, Hanko et al. reported no increase in the frequency of FSGS in their study on a relatively stable population in Northern Ireland [21]. It is known that FSGS shows racial differences, especially in black populations, but as the current study population was Caucasian, it does not seem possible to explain the increase in the frequency of FSGS by ethnicity. Advances in biopsy techniques, such as real-time ultrasound-guided biopsies, can improve sample quality. In the current study cohort, the number of glomeruli in biopsy specimens gradually increased, so FSGS diagnosis frequency may have increased. Another important finding of this study was the increase in the rate of overweight patients, and this may have increased the frequency of FSGS. As the electron microscopy rate was very low in the current cohort, primary and secondary FSGS have not been definitively differentiated. This constitutes an important limitation of this study. Familial FSGS and unidentified environmental conditions may be responsible for the increase in FSGS frequency. Consanguineous marriage, which may be responsible for this situation, is common, especially in some regions of Turkey, but genetic examinations and detailed marital status inquiries were not recorded in this study cohort.

In elderly patients, expectations of chronicity findings such as interstitial fibrosis, vascular changes, and atrophy may prevent the application of kidney biopsy. Theoretically, there are no significant differences in biopsy indications between the elderly and younger adults. Renal biopsy may guide successful treatment in 40% to 67% of cases or at least advise against potentially harmful approaches in elderly patients [2, 29, 30]. In the current cohort, the proportion of elderly (age > 65 years) patients gradually increased, with MN being the most common PGN, followed by crescentic GN. In line with these findings, some previous studies have shown that the most common glomerulonephritis in the elderly population is MN, followed by crescentic GN [31–33]. However, others have shown that crescentic GN is the most common glomerulonephritis [29, 30, 34]. These differences may have occurred because the age criterion is

variable in these studies. However, the frequency of crescentic GN increases in very elderly patients [30].

A remarkable finding in the current study was that the rate of kidney biopsy performed by interventional radiology has gradually increased, and in the last period, this rate exceeded the nephrology clinics. In a survey published in 1990, 95% of nephrologists stated that they performed renal biopsies [35]. Tøndel et al. assessed 9288 kidney biopsies performed in Norway in 1988–2010, and reported that nephrologists performed only 33.4% of the biopsies, and this number decreased during the study period, radiologists performed the biopsy in 53.5%, and in 13.1% of the cases, they handled the procedure together [36]. The current study finding is in line with the literature, but this finding prompts concern for nephrology education.

In conclusion, this is the first report to analyze the temporal trends of PGNs in Turkey. The data obtained from the TSN-GOLD registration system has provided important contributions to the knowledge of the frequency and temporal trends of PGNs in Turkey, thereby making it possible to compare Turkish data with other registration systems in the world.

The study does not have information about actual incidence or prevalence. It can only be highlighted that glomerular disease epidemiology cannot be generalized, and each nation should have its own database to assess the actual trend.

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Author contributions Dr. GUL and Dr. Ozturk wrote the manuscript, and all the other authors shared patient information at their center.

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Availability of data and material All data are stored in an Excel file in the Turkish Society of Nephrology GOLD registration database. The registry web site address is: https://gold.nefroloji.org.tr.

Code availability Not applicable.

Declarations

Conflict of interest All authors have no conflict of interests to declare.

Ethical approval Ethical clearance was obtained from The Ethics Committee of Istanbul University, Istanbul Medical Faculty.

Consent to participate Before kidney biopsy was performed, patient consent was obtained from the centers that entered data in the registry.

Consent for publication The informed consent form contained the following warning: "Your data will be used in a clinical trial without personal information."

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