Acta Clin Croat (Suppl. 1) 2021; 60:133-141
doi: 10.20471/acc.2021.60.s1.20

Original Scientific Paper

CLINICAL SIGNIFICANCE OF ZERO-TIME RENAL TRANSPLANT BIOPSIES AND THIN GLOMERULAR BASEMENT MEMBRANES IN ZERO-TIME RENAL TRANSPLANT BIOPSIES

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SUMMARY – *Aim.* To investigate morphological findings of zero-time biopsies analyzed at the Department of Nephropathology and Electron Microscopy, Dubrava University Hospital, Zagreb.

Materials and methods. The retrospective search of data was performed for the period from 2006 to 2018. A total of 316 zero-time renal biopsies were analyzed. Glomerular basement membrane (GBM) thickness was remeasured in 84 zero-time biopsies and 80 protocol biopsies of the same patients 12 months after transplantation.

Results and conclusion. The acute tubular injury was present in 90% and glomerular pathology in 17% of zero-time biopsies, with thin basement membranes (TBM) being the most common entity (13%). Chronic graft changes were evaluated according to Banff classification. Most cases showed Banff scores ci0 (82.6%) and ct0 (65.1%). Banff scores cv2 and cv3 were present in 13% and ah2 and ah3 in 36.4% of specimens. Among 84 remeasured zero-time samples, TBM was present in 26 patients (31%). There were no differences between Banff scores and clinical parameters 12 months after transplantation between recipients with TBM and recipients with normal GBM thickness.

Zero-time renal biopsy is of great importance for allograft assessment and comparison with consecutive biopsies. Further investigation is needed to determine the long-term significance of TBM on graft survival.

Key words: *Zero-time renal biopsies, Glomerular basement membrane, Thin basement membrane*

Introduction

Zero-time kidney biopsies are performed at the time of kidney transplantation, either before or after perfusion of the allograft, with the purpose of assessing the overall condition of the allograft so that consecutive biopsies can be compared to the condition of the allograft at the time of transplantation.[1] They can also be used to predict the long-term function of the allograft, although such predictions are limited by factors such as immunosuppression toxicity or the occurrence of glomerular diseases.[2,3]

Thin glomerular basement membrane nephropathy (TBMN) is the most common cause of persistent hematuria in children and adults, with a 1% prevalence in

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the general population. TBMN, Alport syndrome (AS) and IgA nephropathy together account for almost all causes of persistent hematuria.[4-6] Even though the main feature of TBMN is persistent microscopic hematuria,[4,7] occasionally it can be associated with proteinuria.[6] There are no pathological findings on light microscopy, while electron microscopy (EM) shows diffuse thinning of the GBM.[8] World Health Organization (WHO) recommends a threshold for TBMN of 250 nm for adults and 180 nm for children up to 11 years of age.[9] However, the referential span differs among laboratories, also depending on the gender and the age of patients, the methodology of the sample preparation, and the method of measurement of GBM thickness. Many authors state the importance of the standardization of GBM measurement and setup of the normal GBM thickness reference span for every single EM laboratory.[10,11]

Usually, TBMN represents carriers of autosomal recessive Alport syndrome. Given that Alport spectrum disorders can cause renal failure, the question of the suitability of patients with TBMN as a kidney donor arises. Literature data in this area are quite scarce. Cases of transplantation where donors were diagnosed with TBMN have been described.[12] To our knowledge, there are no specific studies, and expert opinions vary and range from a complete rejection of TBMN patients as donors to allowing TBMN patients as donors with a low risk of disease progression.[13] In 2018, Choi et al. published a study showing 11 recipients who received allografts from donors diagnosed with TBMN whose clinical data were analyzed retrospectively. The study involved living donors who were diagnosed with TBMN on a pre-transplant biopsy. Recipients were monitored after transplant for 57.4 ± 28.6 months. Seven recipients had acute rejection with a median of 9.7 months after transplantation and the renal function of all recipients recovered after treatment. One kidney failed due to arterial occlusion of the allograft and other allografts were preserved during the follow-up period. Donors were monitored for 41.0 ± 39.1 months and subsequently contacted by telephone (56.8 ± 32 months in total). All donors maintained normal renal function during the follow-up period without significant complications and did not report any symptoms during the telephone conversation. The authors concluded that kidney donors with TBMN and their recipients have maintained renal function during the follow-up period and were without significant complications and that kidney donors with TBMN could be a safe option for kidney transplantation.[14]

Methods

In the first part of this study, we have conducted a retrospective analysis of the data registry at the Unit of Nephropathology and Electron Microscopy, Dubrava University Hospital, Zagreb, Croatia. Data registry was searched by term zero-time renal transplant biopsy for the period from 2006 to 2018. Data about diagnosis and chronic graft changes according to Banff classification were also collected.[15]

In the second part of the study, 90 patients were selected for additional investigation. The GBM thickness measurement was performed using a modification of the GBM direct measurement method described by Haas.[10,16] The calculation of the arithmetic mean of these measurements at 30 sites in the glomerulus was made. iTEM software, Olympus Soft Imagin Solutions GmbH, was used. Measurements were performed on x4000 - x8000 magnification digital photographs (Fig. 1), using a 150 - 400% digital magnification for more accurate positioning and measurement of the GBM using the distance from endothelial to the podocyte cell membrane. For capillary loops with the full range represented in digital EM photography, direct GBM thickness measurements were made at 3 points of some GBM cross-section so that, assuming that the mesangial area is located at 12 hours, measurements were made at positions closest to 3, 6 and 9 hours, as shown in the Figure 1A. For other capillaries, GBM measurement sites were two points of nonoblique cross-section of the GBM closest to the edges of the photograph or transition to the mesangial area (not including the actual mesangial portion of the GBM). The third measurement was determined as the point of a nonoblique GBM section as close as possible to the midpoint (with respect to the length of the GBM) between the above two points (Figure 1B).

The normal GBM thickness range for each gender was defined as the range within the previously published referential span of normal GBM thickness for our laboratory (men at 268 - 412 nm and women at 213 - 389 nm).[17] The remeasured GBM thicknesses of 84 biopsy specimens (in 6 cases there were no glom-

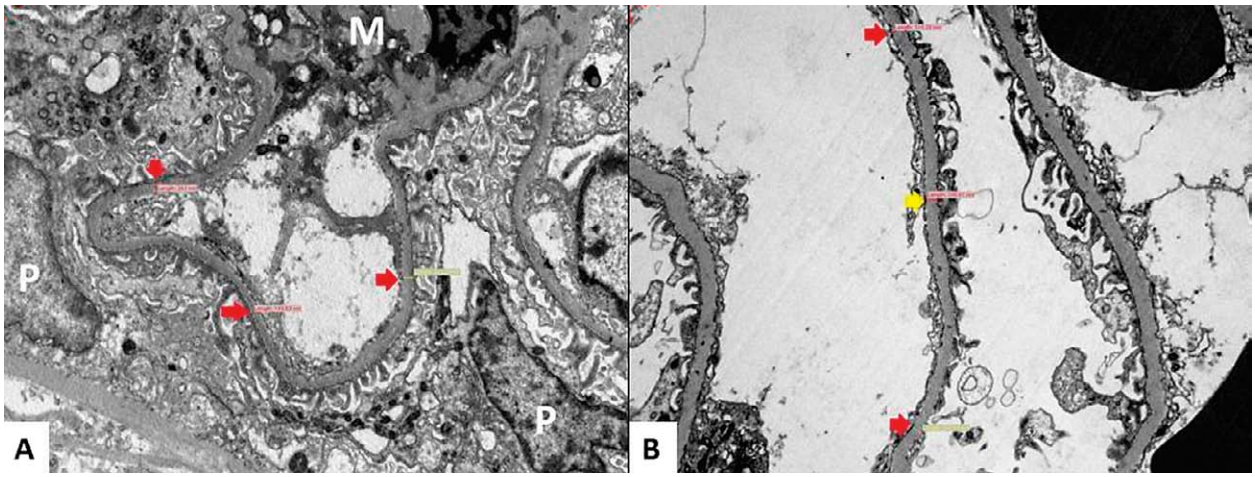

Figure 1. Measurements of glomerular basement membranes (GBM) on digital photographs. A) For capillary loops with the full range represented in digital EM photography, direct GBM thickness measurements were made at 3 points of the same GBM cross-section so that, assuming that the mesangial area is located at 12 hours, measurements were made at positions closest to 3, 6 and 9 hours (red arrows). Original magnification x8000. B) For other capillaries, GBM measurement sites were two points of nonoblique cross-section of the GBM closest to the edges of the photograph or transition to the mesangial area (not including the actual mesangial portion of the GBM) (red arrows). The third measurement was determined as the point of a nonoblique GBM section as close as possible to the midpoint between the above two points (yellow arrow). Original magnification x8000.

eruli available for EM analysis) zero-time biopsies were compared to previously described reference values for the normal thickness of GBM and the frequency of exact thin glomerular basement membranes (TBM) in the group of zero-time biopsies was determined. We have compared the difference in the GBM thickness in transplanted subjects between zero-time biopsy and protocol biopsy performed in the same subject 12 months after the transplantation. Clinical data were collected at the Department of Nephrology, Merkur University Hospital, Zagreb, Croatia and also data about chronic graft changes according to the Banff classification[15].

The data are presented textually and graphically. Categorical data are presented in absolute and relative frequencies. Differences in category variables were tested by the $\chi 2$-square test and, if necessary, by Fisher's exact test. The normality of the distribution of numerical variables was tested by the Shapiro - Wilk test. Numerical data are described by the arithmetic mean and standard deviation and median with interquartile range. Differences of normally distributed numerical variables between two independent groups were tested by Student's t-test. For comparison of dependent continuous variables (on zero-time biopsy and 12 months post transplantation) the t-test of paired samples was used for normally distributed variables. For each analysis, the significance level was set to $\alpha = 0.05$. All P

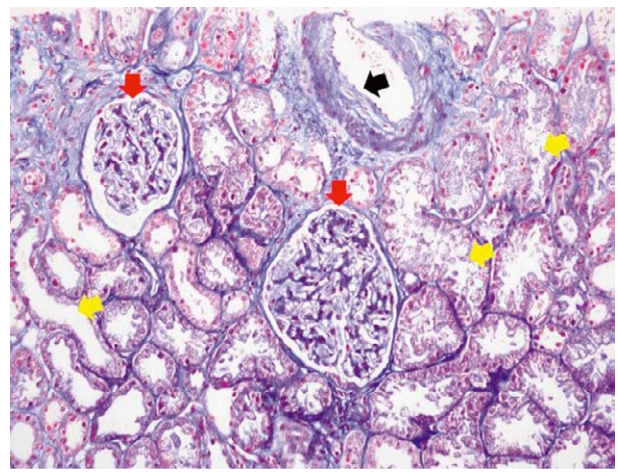

Figure 2 Zero-time kidney biopsy specimen. Renal cortex with normal glomeruli (red arrows), artery showing mild fibrointimal thickening (black arrow), and tubules showing signs of moderate acute tubular injury (the loss of the brush borders and thinning of the tubular epithelial cells) (yellow arrows). Masson trichrome stain, original magnification x200.

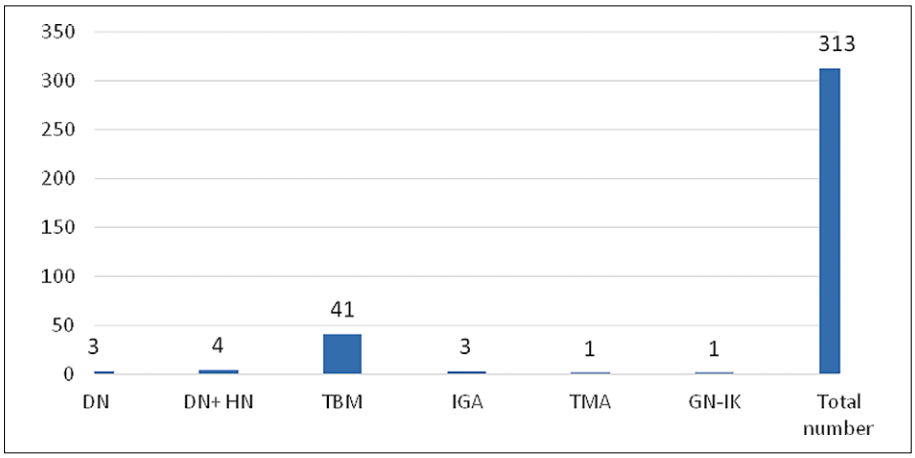

Figure 3 – Glomerular pathology in the zero-time kidney biopsies shown as an absolute number. (DN – diabetic nephropathy, DN+HN – diabetic and hypertensive nephropathy, TBM – thin glomerular basement membrane; IGA – IgA nephropathy, TMA – thrombotic microangiopathy, GN-IK- immune complex mediated glomerulonephritis).

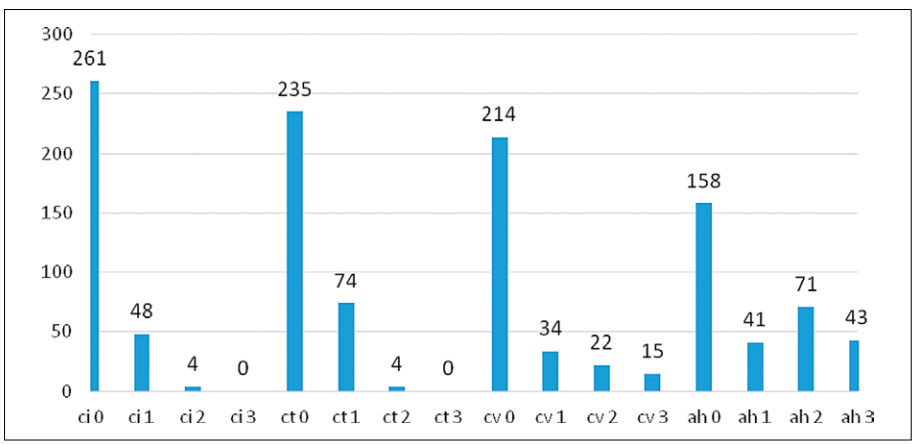

Figure 4 – Chronic changes of tubulointerstitium and blood vessels in the zero-time kidney biopsies shown as an absolute number. Banff classification scores: ci - interstitial fibrosis; ct - tubular atrophy; cv - arterial fibrointimal thickening; ah - arteriolar hyalinosis.

values are two-sided. The analysis was performed using computer programs SPSS 19.0 for Windows (SPSS Inc., Chicago, IL, USA) and MedCalc 11.4.2.0. (MedCalc Software bvba).

All procedures in this research were in accordance with the Helsinki Declaration of 1975, as revised in 1983. This research was approved by the ethical committee of Dubrava University Hospital and Merkur University Hospital.

Results

There were 316 zero-time renal biopsies. Three biopsy specimens (0.9%) were inadequate for pathohistological examination. Median recipient age was 51 years (range from 16 to 84 years), 204 (65%) male and 112 (35%) female.

The most common histological diagnosis was acute tubular injury (Figure 2), which was present in 90% of

Table 1. Kidney donors' characteristics.

Age (years)	N	90
	Min	8
	Max	75
	Median	50
Gender	N	90
	Male	44 (48.9%)
	Female	46 (51.1%)
Type of transplantation	N	90
	Cadaveric	82 (91.1%)
	Living donor	8 (8.9%)
Cold ischemia time (minutes)	N	71
	Min	28
	Max	1458
	Median	577
Presence of comorbidities in donor	N	90
	Yes	50 (55.6%)
	No	40 (44.4%)
Comorbidities in donors*	Nicotinism	24
	Hypertension	22
	Alcoholism	10
	Coronary heart disease	3
	Epilepsy	2
	Diabetes	2
	Depression	1
	Asthma	1
	Pancreatic fibrosis	1
	Sinusitis	1
	Obesity	1
	Hepatitis B	1

*N – number, *In some donors multiple comorbidities were present*

biopsies and was mainly moderate (51%), followed by mild (32%) and severe (17%).

In 53 (17%) biopsies, glomerular pathology was present. The most common entity was TBM (41, 13%), followed by diabetic nephropathy (7.2%) with or without signs of hypertensive nephropathy, IgA nephropathy (3, 1%), thrombotic microangiopathy (1, 0.3%), and immune-complex mediated glomerulonephritis (1, 0.3%) as shown in Figure 3.

Chronic changes of tubulointerstitium and blood vessels were evaluated according to Banff criteria for chronic changes (Figure 4)[15]. There was no interstitial fibrosis and tubular atrophy (ci0 and ct0) in 261 (83.4%) and 235 (75.1%) biopsies, respectively. There were no arteries in 28 (8.9%) biopsy specimens. Arteries showed mild fibrointimal thickening (cv1) in 34 (11.9%), moderate (cv2) in 22 (7.7%), and severe (cv3) in 15 (5.3%) out of 285 specimens with arteries. Mild arteriolar hyalinosis (ah1) was present in 41 (13.1%), moderate (ah2) in 71 (22.7%) and severe (ah3) in 43 (13.7 %) of cases.

Additional analyses (remeasurement of GBM thickness at the zero-time biopsy and at the protocol biopsy 12 months post transplantation in the same patient and correlation with histological and clinical data) included 90 patients, median age 49 years (17 to 73 years), 62 (68.9%) male and 28 (31.1%) female. Donors' characteristics are presented in Table 1. There were no chronic changes at zero-time biopsies in most patients. Scores for chronic changes according to Banff classification[15] for these 90 patients in zero-time biopsies are shown in Table 2.

The EM was performed in 84 zero-time biopsies. The mean value of patients' GBM thickness in zero-time biopsies was 268 nm, standard deviation 57 nm, median 266 nm with interquartile range 221 - 306 nm. If the measured values applied to the established reference span for our Department[17], TBM was present in 26 (31%) subjects. If the WHO criterion (GBM thinner than 250 nm regardless of gender) is applied, TBM was present in 35 (41.7%) subjects. There were no statistically significant differences ($\chi 2$ test and Fisher's exact test) in Banff scores (ci, ct, cv, ah) on zero-time biopsies between patients with TBM and no TBM according to criteria set up for our laboratory.

Table 3 shows chronic changes according to Banff classification[15] in protocol biopsies 12 months after transplantation.

The values of GBM thickness measured on protocol biopsies 12 months post transplantation was available for 80 out of 90 patients. The mean value was 256.5 nm, standard deviation 44.8 nm, median 258 nm, interquartile range 229 - 286 nm. If the measured values applied to the established reference span for our Department[17], TBM was present in 25 (31.3%) subjects. If the WHO criterion (GBM thinner than 250 nm regardless of gender) is applied, TBM was present in 34 (42.5%) subjects.

Table 2. Chronic changes scores according to Banff classification[15] in zero-time biopsies for 90 reanalyzed patients.

	Chronic changes according to Banff classification[15]			
Banff score	ci	ct	cv	ah
0	68 (75.6%)	62 (68.9%)	66 (73.3%)	44 (48.9%)
1	20 (22.2%)	27 (30%)	9 (10%)	14 (15.5 %)
2	2 (2.2%)	1 (1.1%)	7 (7.8%)	16 (17.8%)
3	0 (0%)	0 (0%)	7 (7.8%)	16 (17.8%)
X	0 (0%)	0 (0%)	1 (1.1%)	0 (0%)

X- analysis not possible – no arteries, ci - interstitial fibrosis score, ct - tubular atrophy score, cv – arterial fibrous intimal thickening score, ah - arteriolar hyalinosis score

Table 3. Chronic changes scores according to Banff classification[15] in biopsies 12 months after transplantation for 90 reanalyzed patients.

Chronic changes according to Banff classification[15]				
Banff score	ci	ct	cv	ah
0	31 (34.4%)	21 (23.3%)	65 (72.2%)	40 (44.4%)
1	41 (45.6%)	51 (56.7%)	11 (12.2%)	12 (13.3%)
2	14 (15.6%)	14 (15.6%)	6 (6.7%)	24 (26.7%)
3	4 (4.4%)	4 (4.4%)	8 (8.9%)	14 (15.6%)

ci - interstitial fibrosis score, ct - tubular atrophy score, cv – arterial fibrous intimal thickening score, ah - arteriolar hyalinosis score

We compared GBM thickness on zero-time biopsy with values measured on protocol biopsy in the same patients 12 months post transplantation. No statistically significant difference ($p>0.05$) in GBM thickness was found (paired sample t-test).

Mean value of the estimated glomerular filtration rate for patients 12 months after transplantation was 55.76 ml/min/1.73m^2, standard deviation 17.09 ml/min/1.73m^2, median 55.76 ml/min/1.73m^2 with interquartile range 44.90 – 65.85 ml/min/1.73m^2. Clinical data about proteinuria was available for 78 patients and hematuria for 77 patients. Proteinuria was present in 10 (12.8%) patients and hematuria in 7 (9.1%). There was no statistically significant difference between subjects with and without TBM on their protocol biopsies 12 months post transplantation in proteinuria, hematuria, estimated glomerular filtration rate ($\chi 2$ test, Student t-test), and Banff chronic scores: ci, ct, cv, ah (Fisher's exact test).

Discussion

Zero-time kidney biopsies are performed at the time of kidney transplantation, either before or after the perfusion of the allograft, with the purpose of assessing the overall condition of the allograft so that consecutive biopsies can be compared to the condition of the allograft at the time of transplantation.[1] Certain abnormalities are often found during the pathohistological assessment of zero-time kidney biopsies. A very common finding is nephroangiosclerosis due to hypertension. Nickleit et al.[1] reported nephroangiosclerosis to be present in 68% of allograft, 19% of which were moderate or severe. In our study, arteries showed mild fibrointimal thickening (cv1) in 34 (11.9%) and moderate (cv2) or severe (cv3) in 37 (13%) zero-time biopsies. Mild arteriolar hyalinosis (ah1) was present in 41 (13.1%) and moderate (ah2) or severe (ah3) in 114 (36.4%) zero-time biopsies.

There are also other subclinical disorders in donor kidneys. IgA deposition was present in 9 - 11% of living donor biopsies.[18,19] Prevalence of IgA nephropathy in our study was low and was present in 1% of zero-time biopsy specimens. This kind of lower percentage could be explained by the fact that zero-time specimens were received fixed in formalin and the immunofluorescent analysis on paraffin embedded tissue was

performed only if glomerular abnormalities on light microscopy and/or EM were found.

A diffuse thinning of GBM on EM should be present for TBMN diagnosis. However, determining the presence of diffuse thinning of GBM could be problematic. Primarily, there are no standard criteria for defining the normal span of GBM thickness or lower threshold below which GBM can be considered thin, and there is also a significant variability among those values determined at different centers. A potential problem in diagnosing TBMN is the methodology for measuring GBM on EM images. GBM thickness varies depending on gender and age. Also, the methodology of preparation of samples for the analysis greatly influences the thickness of GBM. The normal span of GBM thickness varies in centers of excellence and literature citations. Given the variability of GBM thicknesses among laboratories, several authors emphasized the necessity of defining their own normal span of GBM thickness.[10,11] Variability is also related to the methodology of GBM thickness measurement. Dische,[20] using the orthogonal intersection method/mean harmonic thickness of GBM measurements,[21] established a normal span of GBM thickness in adults from 330 to 460 nm, with the definition of TBMN as an average GBM thickness of less than 330 nm. Using a similar methodology, Tiebosch et al.[22] established the lower threshold of the normal GBM thickness at 264 nm. Apart from the random sampling of the GBM cross-section, the advantages of this method are that it gives a normal distribution of GBM thickness and that the results are reproducible when the same glomerulus is re-photographed.[20] The main disadvantage is that it is extremely time-consuming to be used in most laboratories for diagnostic pathology.[10] An alternative is the method of direct measurement of GBM thickness (distance from endothelial to podocyte cell membrane) and assessing the arithmetic mean of these measurements. This method is easily applied in diagnostic laboratories without a specialized camera or software, although it excludes obliquely truncated areas of the GBM and shows a tendency to give lower normal GBM thickness spans than the orthogonal intersection/mean harmonic thickness method.[16,23-25] Das et al.[24] found that if 16 measurements from each of the two glomeruli were performed by this method, results could be reproduced on the same results obtained using the orthogonal intersection/mean harmonic thickness method, although values were approximately 40% higher if the latter method was performed.[24]

In our Department's routine clinical work, we have noticed the appearance of thin GBM in EM findings of zero-time kidney biopsies.[26] Routinely EM is performed on zero-time kidney biopsy specimens and GBM thickness is measured on at least 10 random places using EM JEOL 1400 and iTEM software, Olympus Soft Imagin Solutions GmBH using direct measurement/arithmetic mean measurement method. The number and place of measurement were not standardized until recently. Thus, the aim of the second part of our study with an examination of 84 zero-time kidney biopsies was to determine the frequency of TBM when GBM thickness was measured with a standardized method and to examine clinical characteristics of such subjects. According to the reference span for our Department (normal GBM thickness range set for men at 268-412 nm and women at 213-389 nm)[17], TBM was present in 26 (31%) subjects in a zero-time biopsy, while according to the WHO reference span (GBM thinner than 250 nm regardless of gender), thin GBM was present in 35 (41,7 %) subjects.

Literature data on potential kidney donors with TBMN is quite scarce. Cases of transplant where donors were diagnosed with TBMN have been described.[12] Dische et al. described in newly transplanted allograft kidneys five out of 76 donor kidneys who had TBM, and in two additional cases, the measurements of GBM were in the range between thin and normal.[7]

Hassan et al.[27] described TBMN in 13 of 45 (28.9%) subjects. It is important to note that these were kidney biopsies of potential living kidney donors who had isolated microscopic hematuria. Choi et al.[28] reported the presence of TBMN in 7 of 15 patients undergoing kidney biopsy for donation suitability assessment. This data from the literature and the data from our study in which the TBM was found in 31% zero-time kidney biopsies are surprisingly high, given that the literature often cites the prevalence of TBMN in the general population of 1%, and our study consisted of zero-time biopsies of kidney allografts rather than selected cohort with asymptomatic patients with disorders in urine analysis.[16,29]

Interestingly, a study by Choi et al.[14] from 2018 showed that only 2 allografts of 11 kidneys analyzed before transplantation and diagnosed with TBMN showed TBMN in protocol biopsy 10 days after transplantation. In recipients of two allografts who had

TBMN on protocol biopsy 10 days after transplantation, one recipient had normal GBM thickness on protocol biopsy one year after transplantation while the other showed type IIA acute cellular rejection with irregular thickening of the GBM 6 years after transplantation. The other 9 recipients had normal GBM thickness in the protocol or indication biopsies averaging 11,0 ± 11,4 months after transplantation. There was no statistically significant difference in GBM thickness between zero-time biopsies and protocol biopsies 12 months after transplantation in the same patients in our study.

We found a surprisingly high prevalence of TBM in zero-time and protocol biopsies 12 months after transplantation in the same patients, but with no difference in proteinuria, hematuria, and estimated glomerular filtration rate between subjects with and without TBM 12 months after transplantation.

Hematuria in transplant subjects is most frequently caused by urinary tract infections, followed by renal neoplasms, graft rejection, recurrence of the underlying disease, and urolithiasis.[30] Dische et al. stated that there were factors that could affect GBM measurement results, such as cerebrovascular accident, which might be suspected of having a pathogenetic association with thin GBM, technical factors such as warm and cold ischemia of the graft and tissue fixation.[7] In the process of measurement standardization, a normal GBM thickness reference span was created at our Department.[17] Considering our reference span of normal GBM thickness similar to one described by Haas[10,16], we believe our morphometric method should be satisfactory.

Further research on a larger number of zero-time biopsies with the gathering of additional follow up data are planned to confirm our results on a larger specimen. We plan to additionally investigate whether the GBM thickness of zero-time biopsies influences long term graft survival.

Acknowledgment

This research was done as a part of a project entitled "Genotype-Phenotype correlation in Alport's syndrome and Thin Glomerular Basement Membrane Nephropathy" (IP-2014-09-2151) funded by the Croatian Science Foundation.

We would like to thank all our transplant colleagues for long-standing collaboration.

The authors have no conflict of interest to declare.

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Sažetak

KLINIČKO ZNAČENJE NULTIH BIOPSIJA TRANSPLANTIRANIH BUBREGA I TANKIH GLOMERULARNIH BAZALNIH MEMBRANA U NULTIM BIOPSIJAMA TRANSPLANTIRANIH BUBREGA

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Cilj. Ispitati morfološke karakteristike nultih biopsija bubrega analiziranih na Odjelu za nefropatologiju i elektronsku mikroskopiju Kliničke bolnice Dubrava, Zagreb.

Materijali i metode. Retrospektivno pretraživanje podataka provedeno je za razdoblje od 2006. do 2018. godine. Analizirano je ukupno 316 nultih biopsija bubrega. Debljina glomerularne bazalne membrane (GBM) ponovno je izmjerena u 84 nulte i 80 protokolarnih biopsija istih pacijenata 12 mjeseci nakon transplantacije.

Rezultati i zaključak. Akutno tubularno oštećenje bilo je prisutno u 90% nultih biopsija, a u 17% biopsija pronađena je glomerularna patologija, od toga je najčešći entitet bio tanke bazalne mebrane (TBM) (13%). Kronične promjene presatka procijenjene su prema Banff klasifikaciji. Većina slučajeva pokazala je Banff skorove ci0 (82,6%) i ct0 (65,1%). Banff skorovi cv2 i cv3 bili su prisutni u 13%, a ah2 i ah3 u 36,4% uzoraka. Među 84 ponovno izmjerenih nultih biopsija TBM su bile prisutne u 26 pacijenata (31%). Nije bilo razlika između Banff skorova i kliničkih parametara 12 mjeseci nakon transplantacije između primatelja s TBM i primatelja s normalnom debljinom GBM.

Nulte biopsije bubrega su iznimno važne za procjenu presatka i usporedbu s kasnijim protokolarnim biopsijama. Kako bi se utvrdio dugoročni značaj TBM-a na preživljavanje presatka potrebna su dodatna istraživanja.

Ključne riječi: *nulte biopsije bubrega, glomerularna bazalna membrana, tanka bazalna membrana*