**Review Article** 

# **Renal Biopsy for Research: An Overview of Russian Experience**

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#### Abstract

Renal biopsy is a relatively safe procedure with a well-defined risk profile. A biopsy for research is one that is carried out without clinical indications purely for research purposes. Research biopsies often have a parallel clinical purpose, therefore requiring more tissue to be sampled. Research as a purpose of a renal biopsy presupposes informed consent. This review is discussing several publications from the past, but the problem is still with us: invasive procedures performed primarily for research sometimes of questionable reliability. In the author's opinion, renal biopsy should always be performed according to clinical indications. If the patient gives consent to research on the renal tissue obtained for the diagnostic purposes, it can be done, provided that enough tissue remains for the diagnostics, and that Institutional Review Committee approves of the research project.

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Renal biopsy (RB) is a relatively safe procedure with a well-defined risk profile enabling patients to make shared decisions about the merits of having one [1]. RB forms a valuable part of the diagnostic process. Research as a purpose of RB obviously presupposes informed consent i.e. the patient must clearly understand that the main purpose of RB is research. A person involved should have legal capacity to give consent; should be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching; and should have sufficient knowledge and comprehension of the subject matter involved, as to enable him or her to make an understanding and enlightened decision [2]. RB was broadly used in the former Soviet Union (SU): for example, an overview comprising the years 1970-1999, performed at the I.M. Sechenov Medical Academy in Moscow, included 4400 RB [3]. The number of RB has decreased since the 1980s. Today, medical research is receiving a fresh impetus; and it might be helpful to overview some studies from the past to prevent the use of RB for research without sufficient clinical indications.

To start with, the studies [4, 5] were based on the wedge RBs sampled during the kidney-preserving operations such as lithotomy from patients with chronic

or acute (including purulent) pyelonephritis (Pn). Pn is not listed among conditions where RB is indicated, while acute inflammation is generally perceived as a contraindication [6-8]. In the study [9], RBs were sampled from patients with chronic Pn and hydronephrosis, while conclusions were based on the linear correlations between clinical and ultrastructural parameters. morphometric However. statistical significance of the correlation coefficients in this and similar studies were overstated. It is known that the level of significance (P) of a linear correlation coefficient (r) is defined by its own value and the number of correlation pairs (n). Confrontation with the reference tables [10] demonstrated that many claimed P-values were exceedingly high for the given r- and nvalues e.g. in the articles [9, 11-13]. Furthermore, the layer of renal parenchyma tends to be thinner in hydronephrosis, the risk of a calyx perforation being correspondingly higher. In a more recent study, "cytomembranes of the interstitial tissue of renal medullary layer" were studied in core RBs taken during lithotomies from patients with urolithiasis and secondary Pn [14]; more details are in [15]. Fine-needle RB in acute pyelonephritis was performed and recommended in a recent study [16]. RBs were taken for research from patients with amyloidosis [17, 18], renovascular hypertension, from both kidneys in some

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studies [19-23], chronic alcoholism [24-31], diabetes mellitus [32]; from children with congenital hydronephrosis [33] and with urinary tract anomalies including those combined with hydronephrosis [34] or pyelonephritis [35]. When RB was performed according to clinical indications, a part of the tissue cylinder was often consumed for scientific purposes: for biochemical tests, cell cultures etc. [14, 30, 31] The electron microscopy was infrequently used for diagnostics [36]. Nevertheless, about one third of the biopsy cylinder was routinely embedded in epoxy resin. The semithin resin sections, which can provide significant information, were made for scientific purposes but not used for diagnostics, the latter being performed mainly on the basis of paraffin sections and immunofluorescence [36]. In certain cohorts, for example, with insulin-dependent diabetes mellitus [32] or clinically manifest renal amyloidosis [17, 18], RBs were taken from all patients, even in those cases when the diagnosis was clinically evident (e.g. in familial Mediterranean fever) or could have been confirmed by invasive methods. Considering potentially less important information provided by RB and the low complication rate of the ultrasound- or CT-guided RB in modern institutions [1], it is a normal practice to perform RB in all patients of certain cohorts (excluding patients with contraindications), for example, in ALamyloidosis [38], but only in the presence of informed consent.

In chronic alcoholism, biopsies were taken from kidneys, pancreas, liver, lung, salivary glands, stomach and skin, repeatedly in some cases [27, 28]. It was concluded on the basis of a series of RB studies that a generalized cytoskeleton abnormality with accumulation of intermediary filaments in macrophages, epithelial and other cells, is typical for the cell damage by ethanol or the "alcoholic disease" [24, 27, 28]. It is known that Mallory bodies, typical for alcoholic hepatitis and some other liver conditions, are composed of filaments of intermediate diameter containing cytokeratins, being probably identical in structure regardless of initiating factors [39]. However, generalizations as in [24, 27, 28] have never been confirmed. In any case, the cytoskeleton could have been studied in experiments [40] or post mortem. Another example: RB were performed in a group of 40 patients with chronic alcoholism combined with nephritic symptoms; while in all cases the histopathological picture of "intracapillary proliferative glomerulonephritis" [30] was found, which is surprising because this morphological pattern is known post-infectious associated to be with glomerulonephritis (Gn), whereas alcoholism was associated with IgA nephropathy [41]. In a later study by the same researchers, the histopathological findings in 40 of 43 patients with alcoholism and nephritic

symptoms were classified as membranoproliferative or mesangiocapillary Gn; while in 29 of 31 patients with nephritic symptoms without alcoholism were diagnosed with "fibroplastic" Gn [31]. The drastic difference between the two groups appears unrealistic, questioning reliability of the histopathological examination and therefore indications for RB in the studies [30, 31]. There is not enough information in the articles [24-31] for a definite conclusion whether the patients who abused alcohol were treated in line with established ethical principles or not. However, repeated biopsies from different organs [27, 28], doubtful morphological descriptions and interpretations, information being obtainable by other means with less risk, give enough ground to question potential benefits from RB at least in a part of the patients. In regard to the research based on RB from both kidneys in renovascular hypertension (from the side of the renal artery stenosis and the contralateral kidney), indications for the RB have been questioned previously [15].

RBs were taken without sufficient indications also from patients with supposed Gn, which is less obvious because in the Russian literature RB has been regarded as indicated if Gn was suspected [42,43]. In the internationally used handbooks, however, the benefit from RB in nephritic syndrome in adults [6], isolated proteinuria and microhematuria [7], has been questioned. In the former SU, RB were sometimes taken from patients with the clinically diagnosed "inactive nephritic" or latent type of Gn, isolated proteinuria and/or hematuria [44-47]. At the same time, the clinically applied classification of Gn has been different from that used internationally, which could have hampered implementation of practical recommendations from the foreign literature. For example, the Gn classification applied in the former SU did not consider IgA nephropathy as a separate entity [48-50]. IgA-nephropathy was not mentioned even in the article from a leading institution dedicated to the "hematuric form" of chronic Gn [51]. IgA nephropathy was usually diagnosed on RB as mesangioproliferative Gn (MG). At the same time, special variants of Gn, absent in the international literature, were proposed [52-55]. Methods of glomerular morphometry, used earlier in [56-58] and criticized in [15, 59], were applied by other scientists [53, 55, 60] without references given to the sources, in spite of the personal consultation that had taken place regarding the use of the morphometric methods. Moreover, the same authors [54] stated that Maruyama et al. "attribute minimal changes to the group of primary Gn." [61] There are no such or similar statements in [61]. Another example: it was claimed with reference to [62] that enhanced expression of TGFbeta1 leads to a derangement of nephrogenesis, and postnatal is a cause

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of appearance of dysplastic tubules [34]. There are no such or similar statements in [62].

The diagnosis of MG was used broadly, encompassing 49-60.8 % of all Gn cases diagnosed with the help of RB [3, 50, 63]. Semithin sections and silver impregnation were not used for the diagnostics, while electron microscopy was applied only occasionally. By means of these methods, the "collecting-box" of MG could have been partly sorted out, excluding the cases morphologically bordering on (or indistinguishable from) the norm i.e. isolated proteinuria and/or hematuria without renal or systemic disease. In such cases, histologically are often found only minor glomerular abnormalities: mild mesangial widening and hypercellularity, scarce deposits of immunoglobulins and complement [64]. In conditions of insufficient quality of specimens, use of special stains and immunohistochemistry, these changes can be overdiagnosed as MG and accordingly overtreated.

Overdiagnosis of MG is evident from the figures given e.g. in [50], where percentages of different glomerular diseases diagnosed by RB were compared between Moscow and Rostock in Germany: MG in Moscow -55.5 %, in Rostock - 40.2 %; minor glomerular abnormalities in Moscow - 7.1 %, and in Rostock from 20.8 % [50] to 30 % in a later study [65]. Insufficient stability of the hematoxylin-eosin, van Gieson and PAS stains, used for the diagnostics, together with uneven and relatively high thickness of histological sections, can mimic a glomerular capillary wall thickening. Accordingly, membranous Gn was diagnosed in Moscow in 9.2 % and in Rostock in 4.1 % of all glomerulopathies detected by RB [50]. Outdated equipment, e.g. sledge microtomes from the 1930s, was used in many institutions. The author of this review participated in research [15] during 1983-89 using semithin epoxy resin sections cut by a pyramitome with glass knives; after that he found it difficult to evaluate the diagnostic paraffin sections, less clearly visualizing mesangial matrix and glomerular basement membranes. As mentioned above, RB were sometimes taken from patients with the "inactive nephritic" or latent type of Gn [44-47] that is with minimal symptoms. It is therefore not surprising that 83.5 % of MG cases were classified clinically as inactive nephritic type of Gn [46]. The 18-year survival rate of patients with the inactive nephritic Gn type was reportedly as high as 100 % [46]. In another paper by the same researchers the "actuarial survival" up to 18 years approached 100 % [63]. Elsewhere it was stated that active therapy of Gn including that with urinary symptoms (proteinuria/hematuria) allowed increasing the 10-year renal survival from 30 % to 100 % [44]. The difference in meaning between these statements appears to be minor in view of the relatively low availability of renal

replacement therapy in Russia [66]. Considering the renal survival figures for different morphologic types of Gn given e.g. in [67], the reported survival rates up to 100 % provides additional evidence in favor of overdiagnosis of Gn. In some studies, patients with the inactive nephritic or latent types of Gn, isolated proteinuria or hematuria, were treated with corticosteroids and/or cytotoxic drugs such as azathioprin, cyclophosphamide and chlorambucil [68-73]. In a recent study, RB was taken from patients with supposed Gn including cases with low (< 1 g/day) proteinuria; while immunosuppressive therapy was applied in this group of patients [74]. However, further details are not given in the article [74], which makes an evaluation of indications for RB and the treatment hardly possible.

Furthermore, a questionable concept of hypoplastic renal dysplasia was developed by means of RB. It was described as follows: "Racemosely arranged glomeruli with single capillary loops, abundant rounded cells freely lying in the cavity of a capsule; single mesangial cells; irregular enlargement, loosening, and thinning of the basement membrane", narrow extracapillary space [75], glomeruli having irregular form and singular capillary loops [54] or total absence of capillaries [75], which has no analogues in the international literature, where the terms renal dysplasia and hypoplasia are used with a different meaning [76-78]. In the author's opinion, the descriptions as in [54, 75] were based on artifacts or tangential sections of glomeruli, which appears probable looking at the illustrations e.g. in [75]. The author has advised at that time, that the concept can be verified on nephrectomy or autopsy material counting percentages of glomeruli "with single capillary loops" [75]; but it has not been done, and the concept has been persisting. Hypoplastic dysplasia was diagnosed as a main renal condition e.g. in 8 from 34 patients aged 9-54 years with nephrotic syndrome and histologically minimal glomerular changes [52]. At the same time, there was no one case of Alport syndrome among 4440 RB including 2770 cases of glomerular disease overviewed in [3]. Apparently, the concept of hypoplastic dysplasia [52, 75] has hampered diagnostics of Alport syndrome and thin basement membrane nephropathy. For comparison, the two latter conditions together constituted more than 1 % of all renal conditions diagnosed by RB in Rostock, Germany [65]. Note that the diagnosis of Alport syndrome is important because of genetic implications [79]. Today, the same authors apply the term hypoplastic dysplasia to the glomerular changes in congenital hydronephrosis and other congenital renal conditions in children (where intra-operative wedge renal biopsies have been collected), interpreting them as inborn nephropathy reportedly affecting a majority of glomeruli [33, 34, 80]. It should be commented that a coincidence of two

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conditions with different pathogenesis: an inborn glomerulopathy and hydronephrosis with secondary pressure atrophy of renal parenchyma appears to be improbable. The same researchers collected 60 pancreatic excision biopsies 5x5 mm in size [81] during the surgical operations of "pancreatic blood shunting into the systemic blood flow in insulin-dependent diabetics." [82] From the same patients, 51 renal core biopsies were collected [81]. Apart from several reports from Russia and Ukraine [82-90], we have found in the literature no analogues of this surgical treatment modality of diabetes mellitus, which is beyond the scope of this review. Morphological descriptions of pancreatic and renal biopsies in type 1 diabetes included the following: islets of Langerhans "containing B-cells with destructive changes" [91], presence of endocrine-like cells in the acini and among the cells of the inter-acinar ducts [92, 93], glomerulonephritis and mesangiolysis as consecutive stages of diabetic glomerulosclerosis [94], frequent mesangial interposition with displacement of mesangial cells to the peripheral capillary loops and formation of double-contour glomerular basement membranes [94, 95], which is partly at variance with usual morphological descriptions [96-99]. In particular, glomerulonephritis, if detected in diabetic patients, has been interpreted as a superimposed condition or a complication [98, 99]. Collection of renal biopsies from diabetic patients for research was planned in advance [100]. It should be commented that in diabetes mellitus, RB is currently regarded to be indicated for patients under the suspicion of renal diseases other than diabetic nephropathy [101]. It is important to identify a nondiabetic renal disease, which can justify a more extensive use of RB in diabetics [1, 101]; however the aims and quality of the biopsy examination should be taken into account making decisions about extended indications for RB and other biopsies [102].

The RB material used in some studies discussed above was unique e.g. wedge and/or core biopsies in hydronephrosis [9, 33, 34], acute [4] or chronic [5, 9, 14, 35] Pn; but instructiveness of the results has been impaired due to instable quality of morphological examination and other reasons [15]. Apart from the papers discussed above, no other studies based on RB in hydronephrosis and acute Pn are known to us, while in chronic pyelonephritis no other studies performed abroad later than in the 1960s [103] have been found.

#### DISCUSSION

The Nuremberg Code and the Declaration of Human Rights have established the principles of free and informed consent and avoiding harm in scientific experiments involving human participants [104]. There is an opinion, shared by the author, that considering potential complications, "RB for research" should not exist as such; it should always be done with a clear clinical justification for a patient's diagnosis, prognosis and treatment. If the patient gives consent to research on the renal tissue obtained for the diagnostic purposes, it can be done, provided that enough tissue remains for the diagnostics (if non-morphological or otherwise suboptimal for the diagnosis research methods are applied), and that Institutional Review Committee approves of the research project. In any case, the research involving humans should yield fruitful results for the good of society, being unprocurable by other methods or means of study [2]. Furthermore, medical research involving human subjects must be conducted only by experts with the appropriate ethics and scientific education, training and qualifications [105].

Today, an upturn in Russian economy enables importation of modern equipment, ready-made kits, and professional literature, introducing new methods into research and practice; while the broadening international cooperation is facilitating the flow of foreign expertise into the country. Improved financing comes along with a growing endeavor to perform research. including that applying invasive manipulations. This review has discussed several studies from the past, but the problem is still with us: invasive procedures performed primarily for research of questionable quality, without sufficient clinical indications. In conclusion, international documents regulating research involving humans [2, 105, 106] should be better known and observed.

## **CONFLICTS OF INTEREST**

The author declares that there are no conflicts of interest.

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