Renal affection in patients with diabetes mellitus is not always caused by diabetic nephropathy

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Abstract

Accumulated clinical data suggest that non-diabetic nephropathy complicating type 1 diabetes mellitus is rare, accounting for 2-3% of unselected diabetic patients with proteinuria. In contrast, non-diabetic kidney disease is a common finding in patients with type 2 diabetes mellitus. Joint analysis of available data on prevalence of non-diabetic kidney disease among type 2 diabetic patients revealed that non-diabetic nephropathy was evident on kidney biopsy approximately in 22% of European and 26.7% of Asian patients with type 2 diabetes mellitus. Therefore, kidney biopsy may become a useful diagnostic option among proteinuric patients with type 2 diabetes mellitus. However, it is generally agreed that renal biopsy cannot be used as a routine diagnostic test in all type 2 diabetic patients with proteinuria. Diabetic subjects that may benefit form kidney biopsy should be rather identified on a case-by-case basis. Absence of diabetic retinopathy, particularly used in combination with acanthocyturia, may come useful in decisions about kidney biopsy in type 2 diabetic patients.

Key words: diabetes mellitus, diabetic nephropathy, non-diabetic nephropathy, kidney biopsy.

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Kidney biopsy in diabetic patients with proteinuria – potential therapeutic implications

Proteinuria in diabetic patients is usually interpreted as a clinical manifestation of diabetic nephropathy [1]. Although kidney biopsy is the most unbiased method of evaluation in proteinuric patients, it is rarely used in subjects with diabetes mellitus. Theoretically, in each proteinuric patient with diabetes mellitus kidney biopsy may reveal different renal pathologies including:

a) diabetic nephropathy,
b) non-diabetic kidney disease superimposed on diabetic nephropathy,
c) non-diabetic nephropathy,
d) normal renal structure.

Consequently, therapeutic decisions based on the results of the biopsy may differ – treatment of diabetic patients with non-diabetic nephropathy (i.e. primary glomerulonephritis) may be adjusted to eliminate the primary trigger causing the renal pathology with a potential to halt or reverse the decline in renal function. Paradoxically, therapy in subjects whose renal structure was normal on kidney biopsy will not differ significantly from patients with biopsy-confirmed diabetic nephropathy – in both cases prevention of diabetic kidney disease is warranted. Thus, the primary aim of kidney biopsy in proteinuric patients with diabetes mellitus is to confirm/exclude non-diabetic renal disease.

Non-diabetic kidney disease in patients with type 1 diabetes mellitus

A routine kidney biopsy in proteinuric patients with type 1 diabetes mellitus, although postulated by several authors [2], is not supported by both prospective as well as [3,4] cross-sectional studies [5]. A long-term prospective observation of a large cohort of Caucasians have provided evidence for uncommon

occurrence of non-diabetic kidney disease among patients with type 1 diabetes mellitus – only 2.5% of subjects developed non-diabetic proteinuria [3]. A slightly higher rate (9%) of non-diabetic renal disease in patients with type 1 diabetes mellitus reported in a cross-sectional observation may be caused by a selection bias (inclusion of patients with atypical clinical manifestation of renal disease) [5]. It is generally agreed that non-diabetic nephropathy complicating type 1 diabetes mellitus is relatively rare, accounting for 2-3% in unselected proteinuric patients with diabetes longer then 10 years [6]. Although guidelines with precise indications for kidney biopsy in subjects with diabetes mellitus are lacking, accumulating clinical data suggest that renal biopsy should not be a routine diagnostic test in proteinuric patients with type 1 diabetes mellitus.

Non-diabetic kidney disease in patients with type 2 diabetes mellitus

Due to significantly higher prevalence of type 2 diabetes mellitus (when compared to type 1) as well as its increasing rates of incidence in many populations [7] chronic kidney disease in type 2 diabetic patients is common in clinical setting. In contrast to data on type 1 diabetes mellitus, there is no general agreement on prevalence of non-diabetic kidney disease among patients with type 2 diabetic mellitus. Consequently, it is not clear whether kidney biopsy should become a part of the standard evaluation of proteinuric patients with this type of diabetes mellitus.

In order to evaluate genuine rates of non-diabetic nephropathies in patients with type 2 diabetes, we analysed available English publications on kidney biopsy in proteinuric patients with this type of diabetes mellitus [8-18]. Altogether, 665 cases of renal biopsies were included in the analysis that was performed separately for Caucasian and Asian populations. Prevalence of biopsy-proven diabetic nephropathy, non-diabetic kidney disease superimposed on diabetic nephropathy, non-diabetic nephropathy and normal renal structure were reported for each study and the final average percentage of each kidney biopsy finding was calculated. The results of this analysis are presented in *Tab. 1*.

Prevalence of non-diabetic kidney disease among European patients with type 2 diabetes mellitus varied from 3% among Danish [8] to 32% in Italian subjects [12]. Coexistence of both non-diabetic nephropathy and diabetic nephropathy was the most infrequent result of kidney biopsies. On average, diabetic nephropathy was the most common pathology in proteinuric patients with type 2 diabetes mellitus (64.8%), followed by non-diabetic kidney diseases (18.7%), normal renal structure (13.2%) and non-diabetic nephropathy superimposed on diabetic nephropathy (3.3%). Altogether, non-diabetic kidney disease was present in approximately 22% of patients with type 2 diabetes mellitus.

Analysis of kidney biopsy results from Asian patients with type 2 diabetes mellitus (subjects from Japan, China and India) provided consistent findings. A significant variation in prevalence of diabetic nephropathy (from 87.7% in subjects from India [13] to 35.3% in Chinese patients [18]) was evident across the studies. Non-diabetic nephropathy without coexistent diabetic nephropathy was found in 16.8% cases and superimposition of chronic non-diabetic renal pathology on diabetic nephropathy accounted for 9.9% cases. Altogether, non-diabetic renal disease affected 26.7% of Asian subjects with type 2 diabetes mellitus.

Significant differences in prevalence of non-diabetic renal diseases among the studies are caused, at least in part, by discrepancies in methodology. First, in several studies [18] only diabetic patients with atypical clinical manifestation of renal disease were included in the study group. This may lead to overrepresentation of cases with non-diabetic kidney disease among proteinuric subjects with type 2 diabetes mellitus. Second, different pathologic criteria of diabetic nephropathy were used in several studies and this may result both in overestimation and underestimation of non-diabetic renal disease in diabetic patients. Finally, a confounding influence caused by interobserver variability cannot be excluded in several studies [19].

Taken together, the results of this analysis indicate that, even after adjusting for differences in methodology among the studies, non-diabetic renal disease may affect a significant percentage of patients with type 2 diabetes mellitus. Therefore, kidney biopsy may become a useful diagnostic option among proteinuric patients with this type of diabetes mellitus.

Types of non-diabetic kidney disease among type 2 diabetic patients undergoing kidney biopsy

Primary glomerulonephritis was the most common renal pathology among all types of non-diabetic kidney disease in patients with type 2 diabetes mellitus. Almost all types of glomerulonephritis including IgA nephropathy [11,15,19-20] membranous nephropathy [18], mesangiocapillary glomerulonephritis [18,20], rapidly progressive glomerulonephritis [14] and minimal change disease [15] were represented in these patients. In fact, coexistence of more then one type of glomerulonephritis, superimposed on diabetic nephropathy, although not common, was reported in diabetic subjects [21].

IgA nephropathy was consistently the most common type of glomerulonephritis in both Caucasian [11,19] and non-Caucasian [15] populations accounting for approximately 6-19% of kidney biopsies. Several observations suggest that common occurrence of IgA nephropathy in diabetic patients is not coincidental [22-24]. Diabetes itself, by affecting either glomerular structure and function [24] and/or non-enzymatic glycation of immunoglobulins may facilitate [16] the development of immunopathological alterations [24]. In support of this notion, circulating levels of IgA fraction of immunoglobulins were higher in type 2 diabetic patients than age- and sex-matched controls [15] and superimposition of IgA nephropathy on diabetic nephropathy was associated with higher IgA levels when compared to diabetic nephropathy alone [16]. Nevertheless, IgA nephropathy remains the most common type of glomerulonephritis in the general population [24] and its high prevalence among type 2 diabetic patients may simply reflect general epidemiological trends.

Tubulointerstitial renal disease was a relatively rare finding on renal biopsy in patients with type 2 diabetes mellitus [13,17]. In particular, pathology indicating chronic pyelonephritis was not common among diabetic patients undergoing kidney biopsy [13]. This under-representation of chronic pyelonephritis among type 2 diabetic patients is surprising in light of the well-known tendency to asymptomatic bacteriuria among diabetic subjects [25].

Clinical markers of non-diabetic kidney disease among patients with type 2 diabetes mellitus and renal affection

In light of relatively high prevalence of non-diabetic kidney disease among patients with type 2 diabetes mellitus indication for routine kidney biopsy was postulated by several authors [19]. However, it is generally agreed, that kidney biopsy cannot be applied as a standard diagnostic test in all type 2 diabetic patients with proteinuria and identification of subjects that may benefit from kidney biopsy should be made on a case-by-case basis. Several clinical and laboratory features including absence of diabetic neuropathy [26], absence of diabetic retinopathy [10], hematuria [15], short duration of diabetes [27], sudden progression of renal failure [11] and acanthocyturia [28] were proposed as markers of non-diabetic renal disease in diabetic patients. None of the proposed markers has either absolute sensitivity or 100% specificity for non-diabetic renal disease. Therefore, they cannot be used as sole indicators of non-diabetic renal disease in patients with type 2 diabetes mellitus. Nevertheless, some of these markers, particularly used in combination, may come useful when decisions about kidney biopsy in type 2 diabetic patients are made.

Absence of diabetic retinopathy as a marker of non-diabetic renal disease in patients with type 2 diabetes mellitus and renal affection

It is not clear to what extent absence of diabetic retinopathy in type 2 diabetic patients with renal affection may serve as an indicator of non-diabetic renal disease. To address this issue we performed a joint analysis of 4 available publications (*Tab. 1*) [11,19,27,29] evaluating prevalence of non-diabetic renal disease in type 2 diabetic patients without diabetic retinopathy. Altogether, 154 Caucasian diabetic patients undergoing kidney biopsy were included in this analysis. Consistent with the previous joint examination, there were substantial differences in prevalence of non-diabetic renal disease among the studies. As discussed before, these discrepancies are probably related to the lack of methodological consistency among these investigations. Overall, the prevalence of diabetic nephropathy, non-diabetic renal disease superimposed on diabetic nephropathy, non-diabetic renal disease and normal renal structure were 45.5%, 13.6%, 35.1% and 5.8%, respectively. Subjects with apparent non-diabetic renal disease accounted for 48.7% of type 2 diabetic patients without diabetic retinopathy. This number is almost twice higher when confronted with the percentage of cases of non-diabetic renal disease among type 2 diabetic patients with renal affection.

These results are supported by the data on prevalence of diabetic retinopathy among type 2 diabetic patients with diabetic nephropathy when compared to type 2 diabetic subjects with non-diabetic renal disease. Coexistence of diabetic retinopathy with biopsy-proven diabetic nephropathy was documented in 41.4-75% patients [11-20]. In contrast, diabetic retinopathy was consistently absent [10-11,30] or present in a small (9.7%) number of patients [18].

Altogether, these data suggest that diabetic retinopathy occurs significantly less frequently in type 2 diabetic patients with non-diabetic renal disease when compared to subjects with diabetic nephropathy. Therefore, absence of diabetic retinopathy in proteinuric patients with type 2 diabetes mellitus may suggest that non-diabetic renal disease may be responsible for renal affection.

Microscopic hematuria and acanthocyturia as markers of non-diabetic renal disease in patients with type 2 diabetes mellitus

Although microscopic hematuria has been suggested as a rare clinical finding in diabetes mellitus [31], its prevalence in diabetic subjects in most of the available studies was relatively high (from 29% [15] to 72.7% [32]). In addition, comparison of rates of microscopic hematuria between patients with diabetic nephropathy and primary glomerulonephritis revealed no statistically significant differences [18]. Taken together, these data indicate that utility of microscopic hematuria as a marker of differentiation between diabetic and non-diabetic renal disease is limited.

Urinary excretion of acanthocytes (dysmorphic ring-formed erythrocytes with vesicle-shaped protrusions) has been long recognised as a marker of glomerular bleeding [33]. Unlike other dysmorphic red cells (echinocytes, anulocytes, ghost cells, schizocytes, stomatocytes, knizocytes) found on urinalysis, clinically significant acanthocyturia (>5% of excreted erythrocytes) was shown as a relatively sensitive (approximately 52%) and very specific (98%) marker of primary glomerulonephritis [33]. The recent clinical study on acanthocyturia supports its utility as a diagnostic tool to differentiate diabetic kidney disease and glomerulonephritis – acanthocytes were significantly less frequent in urinalysis from patients with diabetic nephropathy when compared with subjects with biopsy-proven primary glomerulonephritis [24].

Conclusions

Non-diabetic kidney disease is a relatively common finding in patients with type 2 but not type 1 diabetes mellitus. Reliable confirmation of non-diabetic kidney disease in a diabetic patient with renal affection requires renal biopsy. It is reasonable to postulate that although renal biopsy cannot be a routine diagnostic procedure, it should be taken into consideration in all

Table 1. **Prevalence of non-diabetic kidney disease in type 2 diabetic patients undergoing renal biopsy**

Study No	Total number of subjects	Subjects with diabetic nephropathy	Subjects with non-diabetic renal disease superimposed on diabetic nephropathy	Non-diabetic kidney disease	Normal renal structure	Reference
Caucasian populations						
1.	33-100%	87.9% (29)	9.1% (3)	3.0% (1)	0% (0)	8.
2.	26-100%	84.6% (22)	0% (0)	15.4% (4)	0% (0)	9.
3.	35-100%	77.1% (27)	0% (0)	22.9% (8)	0% (0)	10.
4.	35-100%	74.3% (26)	8.6% (3)	11.4% (4)	5.7% (0)	11.
5.	53-100%	26.4% (14)	0% (0)	32.1% (17)	41.5% (22)	12.
Altogether	182-100%	64.8% (118)	3.3% (6)	18.7% (34)	13.2% (24)	
Non-diabetic kidney disease – altogether			22.0% (40)			
Asian populations						
1.	260-100%	87.7% (228)	1.2% (3)	11.1% (29)	0% (0)	13.
2.	35-100%	71.4% (25)	14.3% (5)	14.3% (5)	0% (0)	14.
3.	51-100%	66.7% (34)	17.6% (9)	15.7% (8)	0% (0)	15.
4.	53-100%	66.0% (35)	44.0% (18)	0% (0)	0% (0)	16.
5.	16-100%	50.0% (8)	0% (0)	50.0% (8)	0% (0)	17.
6.	68-100%	35.3% (24)	20.0% (13)	45.6% (31)	0% (0)	18.
Altogether	483-100%	73.3% (354)	9.9% (48)	16.8% (81)	0% (0)	
Non-diabetic kidney disease – altogether			26.7% (129)			
Type 2 diabetic patients without diabetic retinopathy						
1.	23-100%	73.9% (17)	0% (0)	26.1% (6)	0% (0)	11.
2.	49-100%	69.4% (34)	0% (0)	12.2% (6)	18.4% (9)	19.
3.	75-100%	22.7% (17)	28.0% (21)	49.3% (37)	0% (0)	27.
4.	7-100%	28.6% (2)	0% ()	71.4% (5)	0% (0)	29.
Altogether	154-100%	45.5% (70)	13.6% (21)	35.1% (54)	5.8% (9)	
Non-diabetic kidney disease – altogether			48.7% (75)			

type 2 diabetic patients with renal affection, particularly in those without diabetic retinopathy and/or acanthocyturia.

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