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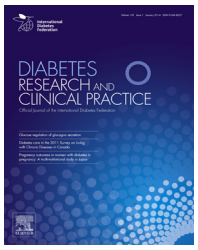

Non-diabetic renal disease in Croatian patients with type 2 diabetes mellitus

Ivica Horvatic[a,*], *Miroslav Tisljar*[a], *Patricia Kacinari*[a], *Ivana Matesic*[a], *Stela Bulimbasic*[a], *Danica Galesic Ljubanovic*[b,c], *Tina Katic*[a], *Darko Kristovic*[a], *Kresimir Galesic*[a,c]

[a] *Dubrava University Hospital, Zagreb, Croatia*
[b] *University Hospital, Zagreb, Croatia*
[c] *University of Zagreb Medical School, Croatia*

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ABSTRACT

Aim: Our study aimed to examine the prevalence of non-diabetic renal disease in selected patients with type 2 diabetes mellitus and to determine important risk factors for non-diabetic renal disease.

Methods: We conducted retrospective analysis of clinical, laboratory and pathohistological data of type 2 diabetes mellitus patients in whom renal biopsies were performed from January 2004 to February 2013 at Dubrava University Hospital Zagreb Croatia ($n = 80$).

Results: According to renal biopsy findings, isolated diabetic nephropathy was found in 46.25%, non-diabetic renal disease superimposed on diabetic nephropathy in 17.5% and isolated non-diabetic renal disease in 36.25% of the patients. The most common non-diabetic renal diseases found were: membranous nephropathy, followed by IgA nephropathy and focal segmental glomerulosclerosis. In univariate analysis shorter duration of diabetes, independence of insulin therapy, lower levels of HbA1c and absence of diabetic retinopathy were found to be significant clinical predictors of non-diabetic renal disease. In multivariate analysis only independence of insulin therapy (OR 4.418, 95%CI = 1.477–13.216) and absence of diabetic retinopathy (OR 5.579, 95%CI = 1.788–17.404) were independent predictors of non-diabetic renal disease.

Conclusions: This study confirmed usefulness of renal biopsy in patients with type 2 diabetes mellitus, due to the high prevalence of non-diabetic renal disease found. Since non-diabetic renal disease are potentially curable, we should consider renal biopsy in selected type 2 diabetes mellitus patients with renal involvement, especially in those with absence of diabetic retinopathy and independence of insulin therapy.

* *Corresponding author at*: Dubrava University Hospital, G. Susak Avenue 6, HR-10000 Zagreb, Croatia. Tel.: +385 12903434; fax: +385 12863652.
E-mail address: ivica.horvatic@yahoo.com (I. Horvatic).

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1. Introduction

The incidence and prevalence of type 2 diabetes mellitus (T2DM) are increasing and becoming one of the major health care problems in the world [1,2]. Diabetic nephropathy (DN) is one of the major complications of diabetes mellitus and is reported as the leading cause of the end-stage renal disease (ESRD) worldwide [1,3]. The diagnosis of DN is mostly clinical, based on duration of T2DM and the presence of retinopathy, neuropathy and other chronic complications, proteinuria and slowly progressing azothemia. This kind of diagnostic approach has been constantly challenged, due to the fact that other non-diabetic renal diseases (NDRD) have been found in T2DM patients. The prevalence of other biopsy-proven glomerular, tubulointerstitial and/or vascular diseases in T2DM in reported studies [4–27] varies considerably, ranging from 8% [4] to 93.5% [5]. This depends on the selection criteria, indications and availability of renal biopsy as well as on the population investigated. Despite the fact that NDRD in selected T2DM patients is not uncommon and renal biopsy is the only tool to absolutely identify DN or NDRD, the role of renal biopsy in T2DM patients with signs and symptoms of renal disease remains controversial. The findings of NDRD could have major therapeutic and prognostic implications, since the majority of glomerular and tubulointerstitial diseases are treatable, even remittable, which is quite different from DN. This is supported by the results of a recent study, which showed that the patients with NDRD have significantly better renal outcomes compared to patients with DN only [7]. The results of previous studies on discriminatory factors between DN and NDRD are not uniform, and there are differences in study populations and selection criteria [4–27]. The purpose of this study was to evaluate the indications of renal biopsy and to determine predictors of NDRD and DN in Croatian patients with T2DM referred to our center. In our center the majority of adult native renal biopsies in Croatia are performed, and our results were recently published [28].

2. Subjects, materials and methods

2.1. Patients and methods

The present study was conducted by reviewing the medical records of T2DM patients who underwent percutaneous renal biopsy in Dubrava University Hospital, Zagreb, Croatia from January 2004 to February 2013. All patients were diagnosed at the time of biopsy with T2DM as defined by the WHO, ADA and EDA [1,29,30]. Biopsy indications were uniform throughout the study period and were based on clinically strong suspicion of NDRD and included one or more of the following factors: heavy proteinuria or nephrotic syndrome, renal failure (acute, rapidly progressive or unexplained chronic), absence of diabetic retinopathy, findings of persistent glomerular hematuria, clinical or laboratory findings of systemic autoimmune disease or hematologic malignancy. The following clinical data were collected for each patient: age at the time of the biopsy, gender, duration of diabetes prior to biopsy, presence of hypertension (including systolic, diastolic and mean arterial pressure), presence of diabetic retinopathy, presence of glomerular hematuria, history of insulin therapy. Laboratory data collected at the time of the biopsy were as follows: urinalysis, serum creatinine, serum albumin and proteins, hemoglobin A1c (HbA1c), maximal 24-hour proteinuria, estimated glomerular filtration rate (EGFR, determined by the CKD-EPI formula). Ultrasound was used to determine kidney size and enlarged kidneys were defined as >12 cm on the longitudinal axis bilaterally. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or antihypertensive medications being taken by the patient. Diabetic retinopathy was diagnosed by direct ophthalmoscopy performed by an ophthalmologist. Hematuria was defined as >3 red blood cells per high power microscope field in a centrifuged urine sample. Percutaneous renal biopsy using kidney biopsy gun (16G) was performed after obtaining a signed informed consent from each patient. Renal tissue obtained was sent for light, immunofluorescence and electron microscopic examination routinely. All biopsies were reviewed by two experienced and independent pathologists.

Only biopsies suitable for definitive diagnosis were included in the study. DN was diagnosed based on the presence of mesangial expansion and diffuse intercapillary glomerulosclerosis with or without Kimmelstiel-Wilson nodules, basement membrane thickening and exudative lesions, such as fibrin caps, capsular drop or hyaline thrombi [31]. Based on the biopsy findings, patients were divided into three basic groups: patients with isolated DN, patients with NDRD superimposed on DN (mixed lesions) and patients with isolated NDRD. Because we planned to investigate predictors for DN and for NDRD, we furthermore created two more classification groups, which distinguished patients on the basis of having DN (DN vs. non DN patients) and on the basis of having NDRD (NDRD vs. non NDRD patients).

2.2. Statistical analysis

Statistical analyses were performed using PASW Statistics (version 18.0, SPSS Inc. Chicago, IL, USA). Normally distributed data were expressed as mean $\pm$ SD, skewed data as median with interquartile range and categorical data as frequency (%). Differences between groups were evaluated by Student t-test or ANOVA for normally distributed data, by Mann–Whitney U test or Kruskal–Wallis test for skewed data and by chi-square (χ^2)-test for categorical data. Multiple logistic regression using forward stepwise method was performed to determine independent predictors for DN and for NDRD, including all covariates with a p-value of <0.05 in univariate analysis. Receiver operating characteristics (ROC) curves were constructed for significant variables of NDRD and DN by plotting sensitivity vs. 1-specificity and the areas under the ROC curves (AUC) were calculated for determining sensitivity and specificity of predictors. Significance was evaluated using a two-sided p value of <0.05.

3. Results

80 patients with T2DM were included in this study. Mean age at biopsy was 59.5 $\pm$ 9.8 years, 70% of patients were male and