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Impaired glucose metabolism – A potential risk factor for idiopathic nodular glomerulosclerosis: A single center study

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ABSTRACT

Nodular glomerulosclerosis is a characteristic histological finding of diabetic nephropathy (DN) with thickened glomerular basement membrane and hyalinized arterioles. Idiopathic nodular glomerulosclerosis (ING), a distinct clinicopathologic entity, is the term used to denote classic DN confirmed by light microscopy, immunofluorescence, and electron microscopy but in the absence of diabetes mellitus (DM). ING has been linked to heavy tobacco smoking, chronic hypertension, and obesity. We report the result of a retrospective study identifying seventeen subjects from Thomas Jefferson University (1999–2014) with biopsy-proven nodular glomerulosclerosis but no pre-existing history of DM. The main indications for percutaneous kidney biopsy (PKB) were either reduced renal function or the presence of proteinuria. The subjects' mean (± SD) age was 60.2 (14.4) years, their highest documented random glucose level was 104.4 (23.5) mg/dL, serum creatinine measured 2.35 (1.03) mg/dL, and body mass index calculated 29.4 (6.2) kg/m^2. None of the patients fulfilled criteria for diabetes at the time of PKB. However, review of medical records revealed history of intermittently elevated blood glucose or borderline-high HgbA1c levels. The role of impaired glucose metabolism or insulin resistance, as a possible etiology for ING is potentially underestimated and needs additional studies.

Introduction

Diabetic nephropathy (DN), the most common cause of end-stage renal disease, has a multifactorial and complex pathophysiology [1]. Its most specific lesion is nodular glomerulosclerosis, a histologic pattern of nodular mesangial sclerosis with glomerular lobularity. The differential diagnosis for nodular glomerulosclerosis is broad and includes membranoproliferative glomerulonephritis, amyloidosis, monoclonal immunoglobulin deposition disease, fibrillary or immunotactoid glomerulonephropathy, glomerulopathy associated with a chronic hypoxic state such as Takayasu's arteritis, and idiopathic nodular glomerulosclerosis (ING). ING remains a diagnosis of exclusion [2]. The defining pathological features of ING are diffuse and nodular mesangial sclerosis accompanied by glomerular basement membrane (GBM) thickening, glomerulomegaly, and arteriolosclerosis, and it is strongly associated with hypertension and heavy smoking. The aim of this study was to identify clinicopathologic correlates of ING in non-diabetic patients with evidence of DN features by histology.

Methods

We conducted a single-center, retrospective chart review study at our institution, Thomas Jefferson University, to investigate patients who underwent native kidney biopsy between 1999 and 2014 and had been diagnosed with nodular glomerulosclerosis. The Thomas Jefferson University Institutional Review Board approved the study, approval #14D.460. The clinical data of individuals with biopsy-proven diagnosis of nodular glomerulosclerosis was collected retrospectively from clinic and hospital records. The collected data included age, gender, race, body mass index, creatinine level, degree of proteinuria, history of diabetes mellitus (DM), highest random glucose level, presence of glucosuria, glycosylated hemoglobin (Hgb A1c) level, history of hypertension, and history of tobacco use. Select patients underwent an additional phone interview to specifically inquire about their past or

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Table 1
Patients' Clinical Data.

Patients' Clinical Data												
Patient	Age at Biopsy	Gender	Race	BMI (kg/m^2)	Cr (mg/dL)	P/Cr (g/g)	Highest A1c Recorded	Highest Random Glucose (mg/dL)	Glucosuria	Prednisone use	HTN	Tobacco use
1	54	M	U	33	2.5	2+	U	125	No	Yes	Yes	Former
2	61	M	W	27	2	3+	U	160	No	U	Yes	Former
3	52	M	B	37	1.6	0.8	5.5	79	No	No	Yes	No
4	53	M	W	26	4	U	4.9	112	No	U	Yes	Yes
5	69	M	B	U	1.9	12.3	5.8	106	Yes	U	Yes	No
6*	76	F	B	21	1.7	3.1	U	87	No	U	Yes	No
7	72	M	W	28.5	1.3	1.1	5.4	111	No	U	Yes	Former
8	73	M	W	26	2.2	8.6	5.7	105	Yes	Yes	Yes	Former
9*	27	F	B	31	0.6	1+	U	99	No	No	Yes	No
10	81	M	W	25	2.5	0.3	5.6	146	No	No	Yes	Former
11	57	M	B	27.5	4.4	5	5.4	73	No	No	Yes	yes
12*	73	F	B	U	1.8	2+	U	82	No	No	Yes	Former
13	78	F	W	32	1.8	1.4	6.1	100	No	U	Yes	Former
14	47	M	A	38	3	1.7	6	120	No	U	Yes	No
15*	56	M	W	43	1.6	1+	U	92	U	U	Yes	No
16	48	M	B	22	3.7	1.5	U	79	U	U	Yes	Yes
17	47	M	H	24	3.4	U	U	99	U	U	Yes	Former

Abbreviations: A: Asian, B: Black, BMI: Body Mass Index, Cr: Creatinine, F: Female, H: Hispanic, HTN: Hypertension M: Male, P: Protein, U: Unknown, W: White.
* Patients denied having DM during phone interview.

current diagnoses of DM, when contact phone number was available. After excluding subjects receiving antidiabetic medication and cases with insufficient data, 17 subjects were included in the final tally. Reason for renal biopsy was proteinuria (1+ on urinalysis to 12.3 g/day on spot urine protein to creatinine ratio), with or without renal insufficiency (creatinine 0.6–4.4 mg/dL). The diagnosis of ING was made based on histologic findings on light microscopy (LM), immunofluorescence (IF), and electron microscopy (EM) in the absence of a diagnosis or clinical picture of DM. Other possible differential diagnoses were excluded by special stains on LM, negative IF, and EM. Group results are reported with means ± standard deviation (SD) for continuous variables and percentage values (%) for categorical variables.

Results

Full clinical data for the study's 17 subjects are shown in Table 1. Mean age at the time of biopsy was 60.2 (14.4) years. The cohort's mean body mass index (BMI) was 29.4 (6.2) kg/m^2, serum creatinine measured 2.35 (1.03) mg/dL, and the highest documented random glucose level was 104.4 (23.5) mg/dL. The group included 7 patients who identified themselves as African Americans, 7 as non-Hispanic whites, 1 as Hispanic, and 1 as Asian; the ethnicity of 1 patient was not documented. Thirteen of the 17 patients (76.4%) included in the study were male. No patient had diagnosis of DM prior to the renal biopsy despite some having intermittently elevated blood glucose and borderline-high HgbA1c levels. Nine patients had HgbA1c in the range of 4.9–6.1%. Another 4 patients who were reached by phone denied having DM. All patients were treated for hypertension. Eight patients were former smokers and another 3 were active tobacco users. One patient was post-liver transplant.

Renal biopsy findings

A representative renal biopsy finding from our study subject number 4 is shown below (Fig. 1). On light microscopy, the glomeruli showed development of nodular glomerulosclerosis. There were no mesangial immune complex deposits. Immunofluorescence was only positive for segmental IgM in the glomeruli, but otherwise negative for human IgG, IgA, kappa light chain, lambda light chain, C1q, C3, C4, albumin, and fibrinogen. Electron microscopy showed a widening of the mesangial areas by mesangial matrix and areas of nodular glomerulosclerosis. There was no visible immune-complex deposition or deposits compatible with light chain. There was no fibrillary material compatible with amyloid or fibrillary glomerulonephritis.

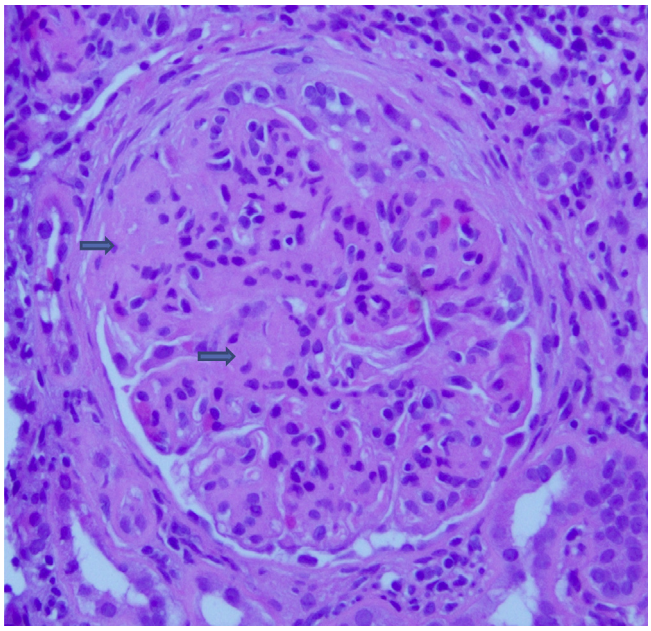

Fig. 1. LM (H&E original magnification ×200): The arrows show developing nodular glomerulosclerosis.

Discussion

Diabetes mellitus (DM) is a serious metabolic disease associated with an increased risk of cardiovascular morbidity and mortality that is further increased with development of kidney dysfunction. The onset of impaired glucose metabolism is associated with the development of hyperinsulinemia or insulin resistance (IR), which is central to the development of type 2 DM [3]. IR or compensatory chronic hyperinsulinemia is a paradoxical pathophysiologic state that increases the chances of developing several closely-related abnormalities and