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## Title

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## Patient with Impaired Glucose Tolerance and Hypertension Shown to Have Moderately Advanced Diabetic Nephropathy on Renal Biopsy

Why the Hemoglobin A1c May Not Reveal the Whole Story

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### Introduction

Type 2 diabetes mellitus is present in epidemic proportions in the United States (US) and in developed nations, though its prevalence is rapidly increasing in the developing world as well. It is currently the most common cause of end stage renal disease in the US and industrialized nations. This is due to the increasing prevalence of diabetes and metabolic syndrome due to obesity, a sedentary life, and excess caloric intake.<sup>1</sup>

The development of overt Diabetic Nephropathy (DN) is dependent on many factors, time from initial diagnosis, blood glucose control, blood pressure control, and other genetic and environmental factors.<sup>2</sup> In general it takes 5 years for appearance of microalbuminuria, and 10-15 years for overt nephropathy.<sup>2</sup> It is generally accepted that DN, Diabetic Retinopathy (DR), and diabetic neuropathy occur on roughly the same time line. Published reports show 70-80 % concurrency between patients with diabetic retinopathy and diabetic nephropathy.<sup>3,4</sup>

Though new techniques like Ocular Coherence Tomography Angiography (OCTA) that detect early diabetic retinopathy may allow for increased sensitivity in detecting patients with diabetic eye changes than the standard dilated eye exam. These eye changes could provide clues about microvascular damage in renal arteries earlier than even microalbumin/creatinine ratio measurement allows.<sup>5</sup>

We present a case that highlights this issue, a 36 year old Chinese male presented to clinic with chronic kidney disease and no diagnosis of diabetes mellitus, but with a known history of hypertension. After an exhaustive laboratory workup was negative, a renal biopsy unexpectedly showed moderately advanced diabetic nephropathy along with the expected lesion of hypertensive nephro-sclerosis.

### Case Report

A 36-year-old Chinese male presented to establish care. He has not had an annual physical for 3 to 4 years. Two weeks ago, he was hospitalized for one day for hypertension, with systolic blood pressure in the 200's. He was discharged on amlodipine 10 mg daily and his blood pressures improved in the range of 130's to 150's over 80's to 90's since starting amlodipine. During the hospitalization, his creatinine was elevated at 2 mg/dL. Renal ultrasound showed no hydro-nephrosis but showed mildly increased renal cortical echogenicity suggestive of medical renal disease. He was thought to have a component of chronic kidney disease, likely due to hypertension.

Initial work up for elevated creatinine included nonreactive HIV and RPR, unremarkable complete blood count, calcium of 9.4 mg/dL, Urea Nitrogen of 24 mg/dL, potassium of 4.4 mmol/L, sodium of 141 mmol/L, chloride of 101 mmol/L, total CO2 of 22 mmol/L, phosphorus of 3.5 mg/dL, magnesium of 1.8 mEq/L, normal liver functions, normal thyroid stimulating hormone, normal serum aldosterone level (24.5 ng/dL), normal renin activity (1.2 ng/mL/hr), normal cortisol (13 mcg/dL), elevated parathyroid hormone (76 pg/mL), normal vitamin D, 25-Hydroxy of 26 ng/mL, fasting glucose in the 100's mg/dL and hemoglobin A1c of 6.2% indicating prediabetes, LDL of 103 mg/dL, total cholesterol of 168 mg/dL, HDL of 45 mg/dL, triglycerides of 99 mg/dL.

His urinalysis showed 1+ blood and 2+ protein, with total protein/creatinine ratio of 0.5 (500 mg/day). Patient was referred to nephrology. Additional work up included elevated cystatin C at 1.3 mg/L confirming chronic kidney disease, negative cyclic citrulline antibody IgG (4 units), negative DNase-B Antibody (< 86 U/mL), negative glomerular basement membrane IgG (0 AU/mL), negative histone antibody IgG (0.5 units), normal free Kappa/Lambda light chains ratio of 1.40, negative scleroderma (Scl-70) antibody IgG (14 AU/mL), nonreactive hepatitis panel, normal ANA (< 1:40), normal C3 (112 mg/dL), normal C4 (30 mg/dL), negative cardiolipin antibodies, negative DRVVT, negative dsDNA Antibody EIA (<=200 IU/mL), negative MTB-Quantiferon ELISA, negative neutrophil cytoplasmic antibody, normal UPEP, negative rheumatoid factor (< 10 IU/mL), negative Sm/RNP antibodies, negative SSA/SSB antibodies, CK borderline elevated at 659 U/L.

Renal biopsy was obtained and showed mild to moderate mesangial widening and arteriolar nephrosclerosis and mild to

moderate tubulointerstitial scarring suggestive of mild to moderate diabetic nephropathy and hypertensive nephronsclerosis. No immune complex deposits were seen. Renal artery stenosis was ruled out by doppler ultrasound. Echocardiogram showed no coarctation. MRI abdomen showed no adrenal masses. His hypertension regimen was changed to amlodipine, labetalol and losartan. He lost 7% of his body weight with hemoglobin A1c improving to 5%. See Figure 1 for lab trends in this patient and Figure 2 for biopsy slide results.

### Discussion

Given the increasing incidence and prevalence of Diabetes mellitus of both types it is expected that the rate of diabetic nephropathy will rise accordingly. This is especially worrisome given the rising number of younger patients who develop diabetic disease from increased caloric consumption, a sedentary lifestyle, and resultant metabolic syndrome. In this case we see a patient who presented for care after years of not being followed by a physician. The initial hemoglobin A1c was not in the diabetic range and it appeared that hypertension was predominantly responsible for his renal injury. The history that the patient lost 20-30 lbs prior to seeking care, however, provided a clue that can explain the pathological findings on biopsy-namely was that his diabetes was far worse at one point and improved with weight loss. It known even eating less in attempting to lose weight, and overt weight loss can help in controlling hemoglobin A1c and glycemic control.<sup>6</sup>

The importance of detecting diabetic retinopathy in predicting risk of diabetic nephropathy progression also highlights the need for more sensitive methods to detect diabetic retinopathy. The OCTA technique is promising and currently in study. Given the concurrency of DR and DN it is likely that any method used for early detection of one condition could help identify patients at risk for developing the other condition. In addition to increasing detection of DR there is a need for more sensitive markers to evaluate presence of diabetic nephropathy. The use of intra renal resistive indices,<sup>7</sup> and biomarkers such as TNF-alpha (tumor necrosis factor-alpha) FGF 23 (fibroblast growth factor 23), PEDF-1 (pigment epithelium-derived factor), and FGF 21 (fibroblast growth factor 21) in urine among other represents exciting developments in the quest for earlier diagnosis of diabetic nephropathy.<sup>8</sup>

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### Figures



**Figure 1.** Biopsy photo showing diabetic nephropathy and hypertensive nephrosclerosis. Diabetic nephropathy (DN) noted with findings of mesangial widening and nephrosclerosis noted in light microscopy with Periodic acid Schiff stain (PAS) 40x magnification. Classified as DN class IIb lesion per Tervaert et al JASN 2010.<sup>9</sup>



**Figure 2.** Plot of blood pressure (systolic and diastolic), fasting glucose, serum creatinine, and proteinuria in patient with IGT clinically and DN on biopsy. IGT= Impaired glucose tolerance, DN=Diabetic nephropathy

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