Supplementary Methods

Clinical assessment/population. The study has been approved by The Joslin Committee on Human Subjects. All Medalists are characterized at the Joslin Diabetes Center (JDC) through: (1) Extensive patient questionnaire and review of medical records. (2) Collection of DNA for genetic studies. (3) Collection of biological specimens including plasma, serum, circulating mononuclear cells and urine for measurements by registered nurses. Urine ACR, serum creatinine and eGFR (Cr CKD-EPI) determined renal function All Medalist visits took place at the Clinical Research Center at the JDC under the supervision of George L. King, MD. Post-mortem specimens will be obtained from Medalists who have given consent for kidney donation.

Data management. All questionnaire data are kept in the Research Electronic Data Capture (REDCap) system (Vanderbilt University), an electronic database stored on a secure server, and linked to the anonymized study ID number which has been assigned by the study staff. Standard verification processes were followed. Assay results are either manually entered with verification or electronically uploaded when possible. A master list corresponding to participants' personal health identifiers (PHI) will be kept by study staff member(s) in order to retain the ability to look up missing information or contact the individual in the future. After processing, specimens will be stored in designated freezers on site at JDC. Additionally, samples will be tracked using FreezerWorks.

Human kidney pathology assessment. Briefly, Class I =Mild or non-specific changes by light microscopy, with glomerular basement membrane thickening seen by EM only; Class IIA = Mild mesangial expansion, seen in >25% of observed mesangium; Class IIB = Severe mesangial expansion, seen in >25% of observed mesangium, with no nodule formation; Class III = Nodular sclerosis (Kimmelstiel-Wilson lesions), seen in at least one glomerulus; Class IV = advanced diabetic glomerulosclerosis, with >50% global glomerulosclerosis. Mesangial expansion was defined as an increase in mesangium that exceeds two mesangial cell nuclei in at least two glomerular lobules. Mesangial expansion was defined as severe when the mesangial area was larger than the mean area of a capillary lumen; otherwise it was classified as IIA. Percentage of globally sclerotic glomeruli was obtained based on evaluation of all glomeruli present on the section (mean number of glomeruli evaluated = 226). Additional grading according to the Renal Pathology Society (RPS) classification was also performed**.** Interstitial fibrosis and tubular atrophy (IFTA) was graded on the Trichrome sections as follows: None = 0, <25% = 1, 25-50% = 2 and >50% = 3. Interstitial inflammation was graded as follows: absent = 0, in relation to IFTA only = 1, inflammation in areas without IFTA = 3. Arteriolar hyalinosis was graded as follows: absent = 0, involving only one vessel = 1, involving >1 vessel = 2. Arteriosclerosis was graded as follows: absent = 0, intimal thickening less than medial thickness = 1, intimal thickening greater than medial thickness = 2. In addition, arteriolar hyalinosis, GBM and glomerular cross sectional area were evaluated more comprehensively using a quantitative technique as described below.

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Immunofluorescence Microscopy: frozen sections of unfixed renal tissue (cut at 5 microns) were stained for IgG, IgA, kappa, lambda, and albumin, with FITC-conjugated anti-human antibodies (MP Biomedicals) using standard clinical protocols.

Electron Microscopy: Tissue blocks of approximately 5 mm3 were collected from each kidney, including a portion of the renal cortex and outer medulla and fixed in 2.5% glutaraldehyde in 0.1 M Na-Cacodylate buffer (Tousimis Research Corp., Rockville, Maryland); then processed for EPON embedding by standard protocols. Sections were examined with JEOL 1011 Transmission Electron Microscope, with a Hamamatsu Orca-HR Digital Camera, and AMT (Advanced Microscopy Techniques Corp.) image capture system. GBM measurements were generated from transmission electron microscopy images at a magnification of ×15,000. 2-3 cross-sectional measurements per capillary loop were achieved using the point-to point measurement function. 20 perpendicular measurements of the GBM were taken for each kidney. Statistical analysis was done to generate mean GBM values for each kidney.

Glomerular Cross Sectional Area: Evaluation was performed on PAS stained 2 micron sections. Ten randomly selected glomeruli were digitally imaged at 40 X (original magnification) with a 50-micron scale bar embedded in the image. ImageJ (version 1.48v) software was used to measure cross-sectional glomerular area in microns. Briefly, a global scale was set in ImageJ, based on the scale bar. Then, the freehand selection tool was used to outline each glomerular tuft profile. The “Measure” tool was then used to measure the cross sectional area of each outlined profile. A mean glomerular profile area for each sample was calculated from the ten glomeruli measured.

Index of Arteriolar Hyalinosis: The index of arteriolar hyalinosis (IAH) was obtained by evaluating every arteriole present on the PAS stained section (Mean number of arterioles evaluated = 99, range = 27-382) using a previously described method, weighted towards arterioles with greater arteriolar wall replacement by hyaline.

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