Glomerular Capillary Hypertrophy in the Diabetic Rat Normalizes Wall Shear Stress: A Modeling Study

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Introduction: Diabetes mellitus (DM) reduces renal hemodynamic autoregulation, leading to increased glomerular pressure (ΔP) and afferent plasma flow (Qₐ) which is assumed to increase glomerular capillary wall shear stress (SS). However, glomerular capillaries undergo hypertrophy in DM, causing an increase in capillary diameter that would assumedly reduce capillary wall SS. The actual magnitudes of SS in the glomerular capillaries have not been estimated in DM and are of significance because in response to increased SS, endothelial cells increase expression of adhesion molecules and growth factors associated with glomerulopathy. While hypertrophy of the glomerular capillaries may reduce SS, this may lead to an increased hoop stress in the glomerular capillaries. This information is crucial not only for the understanding of the etiology of nephropathy in DM, but also for the accurate development of a “glomerulus-on-a-chip” microphysiological system. Mechanical forces are known to crucially affect the efficacy of these systems as models of disease and drug testing platforms (Musah, 2017) however it is unclear whether these mechanical forces are altered in diseases such as DM.

Materials and Methods: We developed a mathematical model of blood flow through an anatomically-accurate rat glomerular capillary network to estimate the magnitudes of SS on the glomerular capillary walls in DM and control. Individual filtration rates and wall SS were calculated for each capillary segment of the network based on values of Qₐ, ΔP and single nephron GFR (SNGFR) obtained from micropuncture studies. To validate mechanical predictions of our model, we compared our calculated SS magnitudes to results from intravital imaging studies of blood flow in rat glomeruli (Ferrell, 2015). To calculate SS magnitudes in the rat glomerulus in control and DM, we performed simulations with parameters obtained from micropuncture studies using normal rats and rats with streptozotocin induced Type I diabetes. In this study, DM increased Qₐ and ΔP by 74.6% and 33.3%, respectively but reduced the filtration coefficient (K₁) such that filtration fraction (FF) was maintained (Zatz, 1986). To simulate glomerular capillary hypertrophy in DM, the capillary diameters were all increased by 14% (Seyer-Hansen, 1983). The Young-Laplace equation was used to calculate hoop stress in each capillary.

Results and Discussion: The model was calibrated using an algorithm previously described (Remuzzi, 1992). Our model's calculated mean glomerular capillary wall SS was within 10% of the mean SS predicted using intravital imaging, validating our model for use in predicting mechanical aspects of blood flow in the glomerulus. Using parameters from micropuncture experiments and taking into account hypertrophy of the glomerular capillaries, the model predicted mean SS values of 42.1 dynes/cm² in control and 42.3 dynes/cm² in DM. In other words, the hypertrophy of the glomerular capillaries normalized SS in DM, indicating that the hypertrophy may act as a protective mechanism to reduce injury of the glomerular capillaries by increased SS. Our simulations also demonstrated a wide variance in SS throughout the glomerular capillary network, with standard deviations over 100 dynes/cm². Assuming a 10% increase in glomerular basement membrane thickness in DM (Yagihashi, 1978), glomerular capillary hoop stress was found to be increased by 38%.

Translational Impact: The results of this study demonstrate that in DM, glomerular capillary hypertrophy appears to normalize SS on glomerular endothelial cells. This will prove impactful in development of a “glomerulus-on-a-chip” microfluidic device, as it appears that flow conditions will not have to be altered to simulate DM on the chip. However, the wide variance of shear stresses experienced in different segments of the capillary network raise an important challenge of accurately recapitulating the heterogeneous mechanical microenvironment that is the glomerular capillary network on a chip. On the other hand, it is apparent that strategies must be developed to accurately simulate the increased hoop stress found in DM in such a device.

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