Renal Hyperfiltration and Arterial Stiffness in Humans with Uncomplicated Type 1 Diabetes Mellitus

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Running Title: Hyperfiltration and arterial stiffness in diabetes

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Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org

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**Objective:** We have reported that renal hyperfiltration is associated with endothelial dysfunction in early type 1 DM. However the relationship between renal hyperfiltration and arterial stiffness is unknown. Accordingly, we measured arterial stiffness in type 1 DM subjects with hyperfiltering (n=20) or normofiltering (n=18).

**Methods:** Augmentation index (AIx), aortic pulse wave velocity (PWV), renal hemodynamic function (inulin and paraaminohippurate clearances), urinary and circulating plasma cGMP were measured in normoalbuminuric subjects with type 1 DM during clamped euglycemia (glucose 4-6 mmol/L) and hyperglycemia (glucose 9-11 mmol/L).

**Results:** During clamped euglycemia, hyperfiltering subjects (glomerular filtration rate [GFR] ≥135 ml/min/1.73m²) exhibited lower AIx values (-6.1±2.9% vs. 13.9±2.7%, p=0.001) and higher cGMP levels in urine and plasma compared with normofiltering subjects. These differences were maintained during clamped hyperglycemia. As expected, renal hemodynamic responses to clamped hyperglycemia were exaggerated in normofilterers, but values for AIx remained unchanged.

**Conclusions:** Renal hyperfiltration is associated with reduced arterial stiffness in subjects with uncomplicated type 1 DM.

Early type 1 diabetes mellitus (DM) is associated with renal hemodynamic function changes characterized by arteriolar vasodilatation and hyperfiltration (1). In addition to renal microvascular vasodilatation, previous work has suggested the presence of macrovascular arterial dysfunction in DM subjects with renal hyperfiltration, which may reflect generalized endothelial dysfunction (2). In addition to effects on endothelial function, DM is associated with increased arterial stiffness, which is correlated with progression of diabetic nephropathy and increased systemic vascular risk (3-7). The relationship between arterial stiffness and renal hyperfiltration, which is the earliest pre-clinical manifestation of diabetic renal microvascular dysfunction, is currently unknown.

Accordingly, we studied arterial stiffness in subjects based on renal filtration status to further elucidate the relationship between early renal and systemic abnormalities in DM (8; 9). We hypothesized that arterial stiffness would be lower in hyperfiltering subjects (glomerular filtration rate [GFR] ≥135 ml/min/1.73 m²) compared to those with normofiltration (GFR <135 ml/min/1.73 m²). Furthermore, we hypothesized that hyperfiltering subjects would exhibit higher levels of vasodilators.

**RESEARCH DESIGN AND METHODS**

Augmentation index (AIx), pulse wave velocity (PWV) and renal hemodynamic parameters were measured during euglycemia (4-6 mmol/L) and hyperglycemia (9-11 mmol/L) on two consecutive days for 6 hours by a modified clamp technique (8-10). In the left arm, a peripheral venous cannula was inserted for infusion of glucose and insulin and a second cannula was inserted for blood sampling more distally.

Peripheral blood pressure was first measured in the brachial artery with an automated DINAMAP® sphygmomanometer (Critikon, Tampa, Florida, USA). Right radial artery waveforms were recorded with a
high-fidelity micromanometer (SPC-301, Millar Instruments) and using the validated transfer function, corresponding central aortic pressure waveforms were generated (SphygmoCor, Sydney, Australia). Alx and aortic PWV were measured as described previously (11). Data were analyzed by a single observer (D.Z.I.C.) who was blinded to the glycemic day, renal hemodynamic measurements and filtration status.

After the arterial stiffness studies, a third intravenous line was then inserted into the right arm and connected to a syringe infusion pump to measure renal hemodynamic function (8-10; 12). Inulin and paraaminohippurate (PAH)-derived measures of GFR and effective renal plasma flow (ERPF) were taken. Circulating RAS mediators, urine and plasma cGMP, and insulin levels were also measured (8; 9; 12).

Data were analyzed on the basis of renal filtration status (Online Appendix A available at http://care.diabetesjournals.org) (8; 9). Based on previous work examining the effect of clamped hyperglycemia on arterial stiffness and a 10% standard deviation (13), our study had a >80% power to detect 10% differences in arterial stiffness at the 0.05 level of significance. Between group baseline comparisons were made using parametric methods (unpaired t-test). Between group and within group differences in all hemodynamic parameters were determined by repeated measures ANOVA (SPSS, version 14.0).

The University Health Network and Hospital for Sick Children (Toronto, Canada) Research Ethics Boards approved the protocols and patients gave informed consent.

RESULTS

Clinical parameters in the two groups were similar at baseline (Online Appendix B). Alx was lower in hyperfiltering versus normofiltering subjects during clamped euglycemia; values for PWV were similar in the two groups (Table 1). Urinary and plasma cGMP, GFR and FF were higher in hyperfiltering subjects; plasma aldosterone, angiotensin II, insulin levels, ERPF, RBF and RVR were similar in the two groups.

During clamped hyperglycemia, between-group differences in cGMP and Alx remained significant (Table 1). There were no observed within-group differences in Alx or PWV, but as expected, clamped hyperglycemia was associated with increases in GFR and FF in normofiltering subjects.

DISCUSSION

Early type 1 DM is commonly accompanied by renal hyperfiltration. Although renal hyperfiltration is related to the eventual development of clinical diabetic nephropathy in some individuals, the risk of nephropathy is also impacted upon by a number of other factors including differences in blood pressure or glycemic control, and age at diagnosis (9; 14). Previous work has described differences in the regulation of the renal and, more recently, the systemic circulation in hyperfiltering vs. normofiltering subjects (2; 8). To our knowledge, this is the first time that arterial stiffness has been measured in type 1 DM subjects who were analyzed on the basis of renal filtration status. Our first major observation was that Alx was lower in hyperfiltering subjects, while aortic PWV was similar. This suggests that Alx reflecting smaller peripheral resistance artery stiffness segregates based on filtration status, whereas aortic PWV reflecting larger central conduit artery stiffness does not. Higher urinary and plasma cGMP levels support the concept of increased nitric oxide bioactivity in hyperfiltering subjects with uncomplicated type 1 DM, leading to generalized vasodilatation, decreased peripheral and renal vascular resistance with an elevated GFR.

We used a hyperglycemic clamp target of 9-11 mmol/L to avoid an osmotic diuresis and renin angiotensin system activation and
have previously observed exaggerated renal responses to hyperglycemia in normofiltering subjects (8). In the current study, the renal response to hyperglycemia was not accompanied by changes in AIx. In contrast, Gordin et al reported that under higher 15 mmol/L hyperglycemic conditions, AIx increases (13). Taken together, this suggests that renal hemodynamic function may be more sensitive to acute changes in blood glucose levels compared with arterial stiffness, where changes may depend on longer-term glycemic control (15).

This study has important limitations. We attempted to limit the effect of sample size by studying a homogeneous cohort. Given the narrow age of subjects, the findings cannot be generalized to older individuals with DM.

In conclusion, renal hyperfiltration in uncomplicated type 1 DM is associated with lower values for arterial stiffness, suggesting that hyperfiltration identifies a group of subjects with generalized changes in vascular function.

Author Contributions: D.Z.I.C researched data, wrote the manuscript. E.B.S. wrote the manuscript. V.L., M.G.D. and C.S researched data. J.W.S. contributed to discussion, reviewed/edited manuscript. T.J.B. researched data and wrote manuscript.

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Conflict of interest: The results presented in this paper have not been published previously in whole or in part.

REFERENCES:
Table 1: Arterial stiffness, blood pressure and renal hemodynamic function responses during clamped euglycemia and hyperglycemia in hyperfiltering and normofiltering subjects with uncomplicated type 1 DM (mean±SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hyperfiltering group (n=20)</th>
<th>Normofiltering group (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Euglycemia</td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td><strong>Circulating factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine cGMP (pmol/L)</td>
<td>957±326</td>
<td>426±101</td>
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<tr>
<td>Plasma cGMP (pmol/L)</td>
<td>4.8±0.7</td>
<td>4.9±0.5</td>
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<tr>
<td>Angiotensin II (pg/ml)</td>
<td>5.4±2.0</td>
<td>3.3±0.8</td>
</tr>
<tr>
<td>Aldosterone (pmol/L)</td>
<td>167±45</td>
<td>166±33</td>
</tr>
<tr>
<td>Plasma insulin (pmol/L)</td>
<td>129±40</td>
<td>125±42</td>
</tr>
<tr>
<td><strong>Systemic hemodynamic function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIx (%)</td>
<td>-6.1±2.9</td>
<td>-5.3±3.5</td>
</tr>
<tr>
<td>Aortic PWV (m/s)</td>
<td>6.85±0.22</td>
<td>6.87±0.19</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>117±10</td>
<td>115±10</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>65±8</td>
<td>63±5</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>80±9</td>
<td>79±6</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>71±12</td>
<td>71±13</td>
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<tr>
<td><strong>Renal hemodynamic function</strong></td>
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<tr>
<td>ERPF (ml/min/1.73 m²)</td>
<td>693±70</td>
<td>733±94</td>
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<tr>
<td>GFR (ml/min/1.73 m²)</td>
<td>144±3</td>
<td>149±7</td>
</tr>
<tr>
<td>FF</td>
<td>0.20±0.03</td>
<td>0.20±0.03</td>
</tr>
<tr>
<td>RBF (ml/min/1.73 m²)</td>
<td>1147±28</td>
<td>1210±39</td>
</tr>
<tr>
<td>RVR (mmHg/L/min)</td>
<td>0.068±0.004</td>
<td>0.066±0.003</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; AIx = radial augmentation index corrected to an average heart rate of 75 bpm; Aortic PWV = carotid-femoral pulse wave velocity ERPF = effective renal plasma flow; GFR = glomerular filtration rate; FF = filtration fraction, determined by dividing the GFR by the ERPF; RBF = renal blood flow (ERPF / [1-HCT]); RVR = renal vascular resistance, derived by dividing the MAP by RBF.

* p≤0.001 in hyperfiltering vs. normofiltering subjects during clamped euglycemia
† p≤0.048 in hyperfiltering vs. normofiltering subjects during clamped hyperglycemia
‡ p≤0.025 for the within-group effect of clamped hyperglycemia