Renal Hyperfiltration and Systemic Blood Pressure in Patients with Uncomplicated Type 1 Diabetes Mellitus

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Abstract

Background: Patients with type 1 diabetes mellitus (DM) and renal hyperfiltration also exhibit systemic microvascular abnormalities, including endothelial dysfunction. The effect of renal hyperfiltration on systemic blood pressure (BP) is less clear. We therefore measured BP, renal hemodynamic function and circulating renin angiotensin aldosterone system (RAAS) mediators in type 1 DM patients with hyperfiltration (n = 36, DM-H, GFR ≥ 135 ml/min/1.73 m²) or normofiltration (n = 40, DM-N), and 56 healthy controls (HC). Since renal hyperfiltration represents a state of intrarenal RAAS activation, we hypothesized that hyperfiltration would be associated with higher BP and elevated levels of circulating RAAS mediators.

Methods: BP, glomerular filtration rate (GFR - inulin), effective renal plasma flow (paraaminohippurate) and circulating RAAS components were measured in DM-H, DM-N and HC during clamped hyperglycemia (4–6 mmol/L). Studies were repeated in DM-H and DM-N during clamped hyperglycemia (9–11 mmol/L).

Results: Baseline GFR was elevated in DM-H vs. DM-N and HC (167±6 vs. 115±2 and 115±2 ml/min/1.73 m², p<0.0001). Baseline systolic BP (SBP, 117±2 vs. 111±2 vs. 109±1, p = 0.004) and heart rate (76±1 vs. 67±1 vs. 61±1, p<0.0001) were higher in DM-H vs. DM-N and HC. Despite higher SBP in DM-H, plasma aldosterone was lower in DM-H vs. DM-N and HC (42±5 vs. 86±14 vs. 276±41 ng/dl, p = 0.01). GFR (p<0.0001) and SBP (p<0.0001) increased during hyperglycemia in DM-N but not in DM-H.

Conclusions: DM-H was associated with higher heart rate and SBP values and an exaggerated suppression of systemic aldosterone. Future work should focus on the mechanisms that explain this paradox in diabetes of renal hyperfiltration coupled with systemic RAAS suppression.

Introduction

Diabetes mellitus (DM) is the leading cause of end-stage renal disease, which ultimately requires dialysis or transplantation. Although the physiological factors that cause early diabetic renal injury remain incompletely understood, renal hyperfiltration has been associated with microalbuminuria and a decline in glomerular filtration rate (GFR) in some but not all studies [1,2,3]. Inconsistencies around the role of hyperfiltration in the pathogenesis of diabetic nephropathy may relate to differences in GFR measurement methods, variable definitions of hyperfiltration and patient-related factors such as diet and ambient hyperglycemia [4,5,6]. Nevertheless, hyperfiltration may contribute to progression of kidney disease and has been attributed to alterations in renal hemodynamic function and tubuloglomerular feedback [4]. As such, a better understanding of the factors that contribute to the development of diabetic nephropathy, including hyperfiltration, is clearly warranted.

For hemodynamic factors that contribute to renal hyperfiltration, the renin angiotensin aldosterone system (RAAS) has been the most widely studied because of the availability of medications that block the RAAS [7,8]. RAAS activation is associated with high intraglomerular pressure in animals and humans with type 1 DM, and the use of RAAS inhibitors reduces intraglomerular pressure in animals and hyperfiltration in humans [8,9]. The etiology of the intrarenal RAAS characteristic of DM is incompletely understood but has been commonly attributed to the effect of ambient hyperglycemia on angiotensinogen generation [10]. Hyperglycemia does not, however, explain why the intrarenal RAAS is preferentially activated in some patients and not others, including those with renal hyperfiltration [4].

In addition to abnormalities in the kidney, renal hyperfiltration is associated with changes in systemic vascular function, including endothelial dysfunction and low levels of circulating nitric oxide bioavailability [11,12]. These subclinical abnormalities in endothelial function may be of particular importance in hyperfiltration...
individuals, who may also exhibit modest elevations in blood pressure within the normal range, including impaired nocturnal blood pressure dipping patterns [13,14]. Elevations in systemic blood pressure within the “normal range” may in turn be important because of the increased risk of microalbuminuria and retinopathy associated with these changes [15,16,17]. Despite what is known about the RAAS in the kidney in hypertensive patients, less is known about the interaction between blood pressure, levels of circulating RAAS mediators and renal hyperfiltration, as well as the effect of ambient glycemia on these factors.

Accordingly, we examined a cohort of young patients with type 1 DM with either renal hyperfiltration (DM-H, GFR $\geq$135 ml/min/1.73 m²) or normofiltration during clamped euglycemia (DM-N, GFR <135 ml/min/1.73 m²) [12,18], and compared them to a similar cohort of healthy control (HC) participants. Participants were studied under these controlled baseline glycemic conditions to avoid the confounding effects of different ambient glucose levels on GFR [18,19]. Since DM-H exhibit intrarenal RAAS activation in previous work [8], we hypothesized that DM-H would exhibit higher blood pressure values compared with DM-N and HC, and that higher blood pressure values would be associated with elevated levels of circulating RAAS mediators. We also studied diabetic participants under clamped hyperglycemic conditions because of the activating effect of hyperglycemia on the RAAS. We hypothesized that hyperglycemia would result in blunted hemodynamic effects in DM-H due to baseline activation of the RAAS.

Methods

A total of 56 healthy control (HC) and 76 participants with uncomplicated type 1 DM (36 normofiltering – “DM-N”) and 40 hyperfiltering – “DM-H”) were included in this study. Hyperfiltration was defined using the usual definition of a GFR $\geq$135 ml/min/1.73 m² [2]. Inclusion criteria were: duration of type 1 DM >1 year, ages 18–30 years, blood pressure <140/90 mmHg, normoalbuminuria on a 24-hour urine collection, no history of renal disease or macrovascular disease or regular medications other than insulin, including oral contraceptives. Patients taking RAAS blocking agents were excluded. Visits for female subjects were scheduled to coincide with the follicular phase of the menstrual cycle, determined by cycle day and measurement of 17ß-estradiol levels. DM participants were studied under both clamped euglycemic (Day 1, 4–6 mmol/L) and hyperglycemic (Day 2, 9–11 mmol/L) conditions and HC were studied under normoglycemic conditions. The Research Ethics Board at the University Health Network approved the protocol and all subjects gave written informed consent.

In order to maintain suppression of endogenous RAS activity and to standardize study conditions, subjects adhered to a high sodium (>140 mmol/day) and moderate protein (<1.5 g/kg/day) diet during the 7-day period before each experiment, as described previously [20]. On two consecutive days, brachial artery blood pressure (Critikon, Tampa, Florida, USA) and renal hemodynamic parameters were obtained after a 6-hour modified clamp, during clamped euglycemia (and hyperglycemia) [20]. On the euglycemic day, renal hemodynamic functions (GFR and effective renal plasma flow - ERPF) were estimated using inulin and paraaminohippurate (PAH) clearance techniques, respectively. In brief, a 16-gauge peripheral venous cannula was inserted into the left antecubital vein for infusion of glucose and insulin and a second cannula was inserted for blood sampling more distally. Blood glucose was measured every 3–10 minutes and the insulin infusion was adjusted to maintain euglycemia. After the desired level of ambient glycemia was maintained for 6 hours, a third intravenous line was inserted into the right arm and was connected to a syringe infusion pump for administration of inulin and PAH. After collecting blood for inulin and PAH blanks, a priming infusion containing 25% inulin (60 mg/kg) and 20% PAH (80 mg/kg) was administered. Thereafter, inulin and PAH were infused continuously at a rate calculated to maintain their respective plasma concentrations constant at 20 and 1.5 mg/ml. After a 90 minute equilibration period, blood was collected for inulin, PAH and hematocrit (HCT) measurements. Blood was further collected at 30 minutes and 60 minutes for inulin and PAH measurements. GFR and ERPF were estimated by steady state infusion of inulin and PAH, respectively [21].

After the desired level of clamped euglycemia or hyperglycemia was achieved, baseline blood samples were also collected for the measurement of angiotensinogen, plasma renin concentration (PRC), plasma renin activity (PRA), angiotensin II and aldosterone. All measurements and samples were taken in the same warm (25°C) temperature-controlled rooms after 10 min of rest in the supine position.

Sample Collection and Analytical Methods

Blood samples collected for inulin and PAH determinations were immediately centrifuged at 3000 rpm for 10 minutes at 4°C. Plasma was separated, placed on ice, and then stored at −70°C before the assay. Inulin and PAH were measured in serum by colorimetric assays using anthrone and N-(1-naphthyl) ethylenediamine respectively [22,23,24]. The mean of two baseline clearance periods represents GFR and ERPF, expressed as per 1.73 m². Renal blood flow (RBF) was derived using ERPF/(1-hematocrit) and renal vascular resistance (RVR) was derived by dividing the MAP by the RBF, as described previously by our group and by others [20,25]. All renal hemodynamic measurements were adjusted for body surface area [22,24].

Ang II was measured by radioimmunoassay. Blood was collected into pre-chilled tubes containing EDTA and angiotensinase inhibitor (0.1 ml Bestatin Solution, Buhlmann Laboratories, Switzerland). After centrifugation, plasma samples were stored at −70°C until analysis. On the day of analysis plasma samples were extracted on phenylsilysilica columns. A competitive radioimmunoassay kit supplied by Buhlmann Laboratories AG (Switzerland) was used to measure the extracted Ang II. Aldosterone was measured by radioimmunoassay, using the Coat-A-Count system. Active plasma renin was measured by 2-site immunoradiometric assay where two monoclonal antibodies to human active renin are used. One antibody was coupled to biotin while the second was radiolabeled for detection. The sample containing active renin was incubated simultaneously with both antibodies to form a complex. The radioactivity of this complex was directly proportional to the amount of immunoreactive renin present in the sample. PRA was measured with a radioimmunoassay kit (GammaCoat® Plasma Renin Activity 125I RIA Kit, CA-1533, Diasorin, Stillwater, Minnesota 55082-0285, USA). PRA determination involves an initial incubation of plasma to generate angiotensin I, followed by quantitation of angiotensin I by radioimmunoassay. In the GammaCoat® Plasma Renin Activity 125I RIA Kit, the antibody is immobilized onto the lower inner wall of the GammaCoat tube. After incubation of standards, unknown samples and 125I angiotensin I in the GammaCoat tube, the reaction mixture is removed by aspiration and the bound tracer counted in a gamma counter. A standard curve is constructed and the concentration of angiotensin I of the unknown sample obtained by interpolation. Angiotensinogen was measured indirectly by converting endoge-
nous angiotensinogen to angiotensin I, then quantitating the amount of angiotensin I by radioimmunoassay. Plasma noradrenaline and adrenaline were measured using standard techniques [26].

Urinary albumin excretion rate was determined from three timed overnight urine collections. Urinary albumin concentration was determined by immunoturbidimetry to determine normoalbuminuria. Hemoglobin A1C was measured by high-performance liquid chromatography, and plasma insulin levels were measured using standard techniques [11].

Statistical Analysis

Data are presented as mean±SD. We based the sample size calculation on known effects of clamped hyperglycemia on renal hemodynamic function, since these effects are thought to be due to RAAS activation [27]. Under the assumption that the standard deviation of the AGFR in response to clamped hyperglycemia will approximate that in our previous work, we anticipated a standard deviation of 16 ml/min/1.73 m² [19]. To detect an approximately 80% power, the sample size should equal a minimum of 24 participants for a two-sided test with alpha 0.05 and a standard deviation of 16 ml/min/1.73 m². We based the sample size either group.

Heart Rate, Blood Pressure, Renal Hemodynamic Function and Circulating RAAS Mediators during Clamped Euglycemia

During clamped euglycemia, heart rate and systolic blood pressure (SBP) were higher in DM-H versus DM-N and HC, whereas only heart rate was higher in DM-N versus HC (Table 1). Diastolic blood pressure (DBP) was also higher in DM-H compared with HC. For renal hemodynamic function, GFR, ERPF and RBF were higher and RVR resistance lower in DM-H compared with the other 2 groups. Despite elevated blood pressure values in DM-H, serum aldosterone levels were lowest in DM-H versus DM-N and HC (42±5 vs. 86±14 vs. 276±41 ng/dl, p = 0.01). PRA, PRC, angiotensin II and angiotensinogen were also markedly suppressed in DM-H and DM-N compared with HC, but differences between DM-H and DM-N did not reach significance (Table 1). There were no significant between-group differences in circulating noradrenaline levels (Table 1).

Heart Rate, Blood Pressure, Renal Hemodynamic Function and Circulating RAAS Mediators during Clamped Hyperglycemia

During clamped hyperglycemia, heart rate remained unchanged in the three groups, while SBP increased significantly in DM-N compared with values during clamped euglycemia, (Table 2, between-group effect, p = 0.002). Weight remained unchanged compared to values during clamped euglycemia in both groups (Table 1).

For renal hemodynamic function, GFR, ERPF and RBF remained higher and RVR resistance lower in DM-H compared with DM-N (Table 2). In response to clamped hyperglycemia, however, the change in GFR was exaggerated in DM-N versus DM-H (Δ+25±6 vs. Δ+3±7 ml/min/1.73 m², between-group effect, p = 0.02).

During clamped hyperglycemia, levels of circulating RAS mediators were numerically lower in DM-H versus DM-N, but these differences were not significant (Table 2). In response to clamped hyperglycemia, PRA and PRC decreased significantly in both groups, and these changes were not significantly different in DM-H versus DM-N. Changes in angiotensin II, angiotensinogen and noradrenaline in response to hyperglycemia were not significant in either group.

Discussion

Renal hyperfiltration in patients with type 1 and type 2 DM is associated with the development of diabetic nephropathy in some studies and has been attributed to activation of neurohormonal factors such as the RAAS and to the influence of tubuloglomerular feedback [4,28]. In addition to effects in the kidney, renal hyperfiltration is associated with changes in systemic vascular function including endothelial dysfunction and abnormal patterns in nocturnal blood pressure dipping [11,12,13]. Whether this systemic macrovascular dysfunction in patients with renal hyperfiltration is dependent on systemic activation of the RAAS has previously been unknown. Furthermore, the effect of clamped hyperglycemia on blood pressure and circulating RAAS mediators in patients with renal hyperfiltration due to type 1 DM has not been clearly detailed. We hypothesized that DM-H would have higher BP and levels of circulating RAAS mediators, and that DM-H would exhibit blunted hemodynamic responses to clamped hyperglycemia. Our main findings were: (1) Heart rate and blood pressure values were higher in DM-H compared to DM-N and HC; (2) Despite higher blood pressures, circulating RAAS mediators were suppressed in DM-H versus DM-N; (3) Systemic blood pressure and renal hemodynamic responses to clamped hyperglycemia were exaggerated in DM-N versus DM-H.

Type 1 DM is associated with an increased risk of hypertension, which contributes to the progression of diabetic nephropathy [29,30]. Less is known about early, subclinical changes in blood pressure within the normal range in patients with uncomplicated type 1 DM. Because of our study design which used a careful pre-study preparation phase and control of ambient glycemia, we were able to demonstrate relatively small differences in BP between the three groups. In our previous work we demonstrated that brachial artery flow-mediated vasodilatation is impaired in young DM-H patients, suggesting the presence of more generalized abnormalities in vascular function [11,12,13]. Consistent with this work was the observation by Pecis et al that nocturnal blood pressure dipping is abnormal and SBP higher on ambulatory blood pressure monitoring in DM-H compared to DM-N and HC [13]. The mechanisms responsible for these BP differences, including the role of the RAAS and ambient hyperglycemia, were not known. In the present study during clamped euglycemia, DM-H also exhibited higher SBP compared with DM-N and HC, and DBP was higher in DM-H versus HC. These differences were no longer observed during clamped hyperglycemia due to a significant increase in SBP in the DM-N group only. Importantly, weight did not change in either group in response to hypergly-
groups. Plasma levels of sympathetic nervous system mediators are levels which were measured and tended to be similar in the three examine autonomic function, aside from circulating noradrenaline sympathetic tone [33]. The present study was not designed to hypothesized that these changes reflect an increase in systemic filtration status. For example, Christiansen et al. demonstrated however, analyze study participants on the basis of glomerular changes, which have also linked higher heart rate values within knowledge, higher heart rate values in diabetic patients have only been previously described in ambulatory blood pressure monitor-ing studies, which have also linked higher heart rate values within the normal range to greater risks of developing microalbuminuria and retinopathy [15,16,31,32]. These previous studies did not, however, analyze study participants on the basis of glomerular filtration rate. In addition to blood pressure differences, DM-H exhibited higher heart rate values compared with the other groups. To our knowledge, higher heart rate values in diabetic patients have only been previously described in ambulatory blood pressure monitoring studies, which have also linked higher heart rate values within the normal range to greater risks of developing microalbuminuria and retinopathy [15,16,31,32]. These previous studies did not, however, analyze study participants on the basis of glomerular filtration rate.

Table 1. Baseline characteristics, biochemistry and hemodynamic function in healthy control and type 1 diabetes patients during clamped euglycemia (mean±SD).

| Baseline parameters | HC (n = 56) | DM-N (n = 36) | DM-H (n = 40) |
|--------------------|-----------|--------------|--------------|
| Males              | 26 (46%)  | 17 (46%)     | 19 (48%)     |
| Age (years)        | 23.3±0.3  | 22.8±0.9     | 22.3±0.6     |
| Diabetes Duration (years) | N/A       | 16±1         | 15±1         |
| Weight (kg) – euglycemia | 70.0±2.1  | 74.7±1.9     | 71.1±1.8     |
| Height (meters)    | 1.70±0.01 | 1.72±0.01    | 1.70±0.01    |
| Body mass index (kg/m²) | 24±1       | 24±1         | 23±1         |
| HbA1C - % (mmol/mol) | N/A       | 8.6±0.3      | 8.4±0.2      |
| Estrogen (pmol/L - in women) | 170±56    | 135±53       | 168±29       |
| Albumin excretion (mg/day) | 9.0±1.0   | 8.3±1.4      | 9.8±1.6      |
| Sodium excretion (mmol/24 hr) | 175±8     | 178±14       | 164±7        |
| Protein intake (gram/kg/day) | 1.08±0.02 | 0.98±0.04    | 0.99±0.04    |
| Heart rate (beats per minute) | 61±1      | 67±1        | 76±1        |
| Systolic blood pressure (mmHg) | 109±1     | 111±2       | 117±2        |
| Diastolic blood pressure (mmHg) | 63±1      | 64±1        | 67±1        |
| Effective renal plasma flow (ml/minute/1.73 m²) | 629±12    | 662±14      | 891±45     |
| Glomerular filtration rate (ml/minute/1.73 m²) | 115±2     | 115±2       | 167±6     |
| Filtration fraction | 0.18±0.005 | 0.17±0.01  | 0.21±0.02   |
| Renal blood flow (ml/minute/1.73 m²) | 1057±25   | 1013±23     | 1419±73    |
| Renal vascular resistance (mmHg/L/minute) | 0.078±0.002 | 0.081±0.002 | 0.064±0.004 |
| GFR Range (ml/minute/1.73 m²) | 91–138    | 91–134      | 135–330    |
| Circulating neurohormonal factors |
| Aldosterone (ng/dl) | 276.1±41.0 | 85.9±13.5 | 41.8±5.2    |
| ANG II (pg/ml)     | 12.5±1.2  | 3.2±0.6     | 3.5±0.8    |
| Renin (pg/ml)      | 20.0±2.6  | 5.7±0.7     | 5.3±0.5    |
| Plasma renin activity (ng/mL/h) | 1.44±0.16 | 0.55±0.09 | 0.42±0.06 |
| Angiotensinogen (ng/ml) | 2072±290 | 1211±155 | 1280±198 |
| Norepinephrine (pmol/L) | 0.60±0.09 | 0.70±0.14 | 0.77±0.08 |

*p<0.0001 for HR, SBP, DBP, renin, aldosterone, ANG II, PRA, angiotensinogen in DM-N vs. HC. p=0.027 for angiotensinogen in DM-H vs. HC.

p<0.05 for HR, renin, aldosterone, ANG II, PRA, angiotensinogen in DM-N vs. HC.

p=0.009 for between group differences in DM-H vs. DM-N.

doi:10.1371/journal.pone.0068908.t001

In addition to blood pressure differences, DM-H exhibited higher heart rate values compared with the other groups. To our knowledge, higher heart rate values in diabetic patients have only been previously described in ambulatory blood pressure monitoring studies, which have also linked higher heart rate values within the normal range to greater risks of developing microalbuminuria and retinopathy [15,16,31,32]. These previous studies did not, however, analyze study participants on the basis of glomerular filtration rate. For example, Christiansen et al. demonstrated that young, normoalbuminuric type 1 DM patients have increased heart rate and contractility measures compared with HC, and hypothesized that these changes reflect an increase in systemic sympathetic tone [33]. The present study was not designed to examine autonomic function, aside from circulating noradrenaline levels which were measured and tended to be similar in the three groups. Plasma levels of sympathetic nervous system mediators are...
Table 2. Biochemistry and hemodynamic function in type 1 diabetes patients during clamped hyperglycemia (mean±SD).

|                              | DM-N (n = 36) | DM-H (n = 40) |
|------------------------------|--------------|--------------|
| **Systemic hemodynamic function** |              |              |
| Heart rate (beats per minute) | 68±2         | 74±2         |
| Systolic blood pressure (mmHg) | 116±2*       | 117±2        |
| Diastolic blood pressure (mmHg) | 65±1         | 64±1         |
| **Renal hemodynamic function** |              |              |
| Effective renal plasma flow (ml/minute/1.73 m²) | 725±24* | 925±41       |
| Glomerular filtration rate (ml/minute/1.73 m²) | 143±5*       | 175±6        |
| Filtration fraction | 0.19±0.01    | 0.20±0.01    |
| Renal blood flow (ml/minute/1.73 m²) | 1132±36*    | 1477±65      |
| Renal vascular resistance (mmHg/L/minute) | 0.074±0.001* | 0.058±0.002 |
| **Circulating neurohormonal factors** |              |              |
| Aldosterone (ng/dl) | 77±19        | 47±10        |
| ANG II (pg/ml) | 3.1±0.5      | 2.7±0.5      |
| Renin (pg/ml) | 3.9±0.6*     | 3.2±0.4*     |
| Plasma renin activity (ng/ml/h) | 0.35±0.06*  | 0.26±0.03*   |
| Angiotensinogen (ng/ml) | 1170±150     | 1154±182     |
| Norepinephrine (pmol/L) | 0.53±0.05    | 0.82±0.25    |

*p<0.004 for level during clamped euglycemia.  
*p=0.01 for level during clamped euglycemia.  
*p=0.026 vs. level during clamped euglycemia.  
*p=0.02 for effect of hyperglycemia on GFR in DM-N vs. DM-H.  
p=0.002 for effect of hyperglycemia on blood pressure in DM-N vs. DM-H.

*p<0.001 compared to value during clamped hyperglycemia.

*p<0.001 for effect of hyperglycemia on GFR in DM-N vs. DM-H.

*p=0.002 for effect of hyperglycemia on blood pressure in DM-N vs. DM-H.

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