

Evolution of Renal Hyperfiltration and Arterial Stiffness From Adolescence Into Early Adulthood in Type 1 Diabetes

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OBJECTIVE—To determine, in a small but carefully physiologically characterized cohort of subjects with uncomplicated type 1 diabetes, the changes in renal hemodynamic function and arterial stiffness that occur over time as the participants transitioned from adolescence into early adulthood. The classical paradigm for type 1 diabetes suggests that glomerular filtration rate (GFR) declines in patients with renal hyperfiltration, but the natural history of peripheral vascular function abnormalities in uncomplicated type 1 diabetes is less well understood, particularly as patients transition from adolescence to early adulthood.

RESEARCH DESIGN AND METHODS—Renal hemodynamic function (inulin and *p*-aminohippuric acid clearance), blood pressure, arterial stiffness (radial augmentation index), albumin excretion, and circulating renin-angiotensin system measures were obtained during clamped euglycemia at baseline and at follow-up 6.8 ± 2.5 years later in 10 patients with hyperfiltration ($\text{GFR} \geq 135 \text{ mL/min/1.73 m}^2$) and in 8 with normofiltration.

RESULTS—Compared with baseline values, GFR (171 ± 20 to $120 \pm 15 \text{ mL/min/1.73 m}^2$) and filtration fraction (FF, 0.24 ± 0.06 to 0.18 ± 0.03) declined in hyperfilterers (ANOVA $P \leq 0.033$), and renal vascular resistance increased (0.0678 ± 0.0135 to $0.0783 \pm 0.0121 \text{ mmHg/L/min}$, $P = 0.017$). GFR and FF did not change in normofiltering subjects. In contrast, the radial augmentation index decreased in hyperfiltering (1.2 ± 11.7 to $-11.0 \pm 7.8\%$) and normofiltering (14.3 ± 14.0 to $2.5 \pm 14.6\%$) subjects (within-group changes, ANOVA $P \leq 0.030$). The decline in circulating aldosterone levels was similar in both groups.

CONCLUSIONS—During the transition from adolescence to early adulthood, hyperfiltration is not sustained in subjects with type 1 diabetes, whereas GFR remains stable in normofiltering subjects. Our findings suggest early normofiltration may predict stable renal function. In contrast, arterial stiffness decreased in all patients regardless of filtration status, suggesting that age-related increases in arterial stiffness occur at older ages.

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Hyperfiltration is associated with the development of diabetic nephropathy, possibly because of high intraglomerular pressure that results in glomerular injury (1). A variety of hormonal factors influence hyperfiltration, including the renin-angiotensin system (RAS), cyclooxygenase 2, protein kinase C- β , and changes in hormones related to puberty (2–5). Blockade of these hormonal pathways partially reduces the glomerular filtration rate (GFR) in hyperfiltering subjects but has no effect in

normofilterers, suggesting that individuals with hyperfiltration are physiologically distinct (2–4). More recently, hyperfiltration has been associated with peripheral vascular alterations, including low arterial stiffness and endothelial dysfunction (6,7). It has therefore been suggested that the hyperfiltration state reflects generalized microvascular and macrovascular functional changes (6–8).

Although it is generally accepted that hyperfiltration represents a renal risk factor in diabetes, the natural history for

changes in renal function in normofiltering subjects remains poorly defined. For example, normofilterers may represent a group of former hyperfiltering individuals who have had a decline in kidney function and were simply studied at a time when GFR was within the normal range. Alternatively, normofiltration may represent a subgroup that is protected against renal and vascular injury.

Peripheral vascular function testing has suggested that normofiltration is associated with preserved endothelial function, which is important for two reasons (6). First, this observation suggests that normofiltration represents a “protective” vascular phenotype. Second, measures of peripheral vascular function, such as arterial stiffness, may offer additional, non-invasive insight into renal and vascular risk, before the onset of clinical end points such as declining renal function, hypertension, or microalbuminuria (9).

Although renal hyperfiltration and changes in macrovascular function, such as low arterial stiffness, appear to be linked in cross-sectional studies of early type 1 diabetes, the interaction between these preclinical abnormalities over time, in the same individuals, is not known (7). This association is important, because hyperfiltration is associated with declining renal function (1). For example, if declining GFR in hyperfiltering subjects is also associated with a deleterious rise in arterial stiffness, this could yield important pathophysiologic insights into mechanisms of disease progression and clinical prognostic information (1,7). A more complete understanding of preclinical factors that may increase future renal risk is of particular importance during the transition from adolescence to early adulthood, which may represent a crucial period when renal injury is initiated (10).

We initially measured GFR and arterial stiffness in a well-characterized adolescent cohort with uncomplicated type 1 diabetes (3,4). The same measures were repeated 6.8 ± 2.5 years later in a subgroup during the transition from adolescence to early adulthood. The goals of the present analysis were to 1) describe the

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relationship between changes in GFR and arterial compliance and 2) elucidate the natural history of arterial stiffness in patients with early type 1 diabetes renal hyperfiltration or normofiltration. Our hypotheses were that 1) renal hyperfiltration would decrease, in association with renal vasoconstriction and a concordant rise in arterial stiffness, as study participants transitioned from adolescence into early adulthood, and 2) normofiltration represents a state of preserved kidney function and stable macrovascular function that does not change significantly in early type 1 diabetes.

RESEARCH DESIGN AND METHODS

Subjects

Inclusion criteria included duration of type 1 diabetes ≥ 5 years; blood pressure $< 140/90$ mmHg; and no history of renal disease, microalbuminuria, or macrovascular disease. Subjects were divided on the basis of the presence of absence of renal hyperfiltration (GFR ≥ 135 mL/min/ 1.73 m²) (2,3). To be eligible at baseline, young adult subjects were required to be at a minimum of Tanner stage 4–5 of puberty. No subjects were taking angiotensin receptor blockers; ACE inhibitors; or medications that could affect renal hemodynamic function or arterial stiffness, including statins or antihypertensives. Subjects taking oral contraceptive and hormone replacement medications were excluded. Female subjects were studied during the follicular phase of the menstrual cycle, determined by counting days and measuring 17 β -estradiol levels.

The local Research Ethics Board at the University Health Network and Hospital for Sick Children (Toronto, Canada) approved the protocol, and all patients gave informed consent. Subjects younger than 18 years provided assent, and parents signed informed consent documents in compliance with Hospital for Sick Children Research Ethics Board policies and procedures.

Experimental design

Subjects adhered to a sodium-replete (> 140 mmol/day) and moderate protein (< 1.5 g/kg/day) diet during the 7-day period before each experiment (Table 1) (2–4). Dietary adherence was assessed using the mean of two timed urine collections obtained in the 7-day prestudy period, and no subjects were excluded because of dietary nonadherence. A sodium-replete diet was used to avoid effective circulating volume contraction and RAS activation (2–4). After admission to the Renal Physiology Laboratory, euglycemic (4–6 mmol/L) conditions were maintained by a modified glucose clamp technique for approximately 6 h preceding and during all investigations, as described previously (2–4). In the left arm, a 16-gauge peripheral venous cannula was inserted into the antecubital vein for infusion of glucose and insulin, and a second cannula was inserted for blood sampling more distally. Blood glucose was measured every 10 to 15 min, and the insulin infusion was adjusted to maintain the desired glycemic level.

After the glucose clamp, right radial artery waveforms were recorded with a high-fidelity SPC-301 micromanometer

(Millar Instruments, Houston, TX). The validated transfer function was used to generate corresponding central aortic pressure waveform data (SphygmoCor, AtCor Medical Systems Inc., Sydney, NSW, Australia). The augmentation index, an estimate of systemic arterial stiffness, was calculated as the difference between the second systolic peak and inflection point, expressed as a percentage of the central pulse pressure corrected to an average heart rate of 75 bpm. The interoperator variability and reproducibility of the augmentation index have been validated to be $0.4 \pm 6.4\%$. Our group has published and validated the use of the SphygmoCor device (7).

Renal hemodynamic function tests were performed immediately after arterial stiffness data were collected. A third intravenous catheter was inserted into the arm contralateral to the insulin infusion and was connected to a syringe infusion pump for infusions of inulin and *p*-aminohippuric (PAH) acid. Peripheral blood pressure was measured in the right brachial artery with an automated DINAMAP sphygmomanometer (Critikon, Tampa, FL) before each blood sample throughout the study. After blood was collected for inulin and PAH blank, a priming infusion containing 25% inulin (60 mg/kg) and 20% PAH (8 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/dL. Subjects remained supine at all times.

After a 90-min equilibration period, blood was collected for inulin, PAH, and hematocrit (HCT); GFR and effective

Table 1—Baseline characteristics by GFR at baseline and at follow-up

Parameter	Hyperfiltering group (n = 10)		Normofiltering group (n = 8)	
	Baseline	Follow-up	Baseline	Follow-up
Male	70	N/A	63	N/A
Age (years)	16.3 \pm 3.2	23.4 \pm 2.7	17.4 \pm 3.3	24.0 \pm 1.9
Weight (kg)	74.2 \pm 12.8	75.7 \pm 10.1	71.4 \pm 13.7	69.1 \pm 13.6
Height (cm)	170.6 \pm 5.9	174.9 \pm 8.7	162.4 \pm 3.7	165.0 \pm 9.3
BMI (kg/m ²)	24.3 \pm 2.6	24.8 \pm 3.1	26.4 \pm 2.6	25.4 \pm 3.8
HbA _{1c} (%)	7.89 \pm 0.70	9.2 \pm 1.2	7.86 \pm 0.69	8.6 \pm 1.59
24-h albumin excretion (mg/min)	4.4 \pm 2.8	5.0 \pm 2.8	5.2 \pm 2.3	3.1 \pm 2.4
Sodium (mmol/day)	186 \pm 35	191 \pm 36	219 \pm 56	214 \pm 55
Protein (g/kg/day)	0.90 \pm 0.36	0.99 \pm 0.43	0.94 \pm 0.45	0.97 \pm 0.39
Plasma insulin (pmol/L)	41 \pm 24	32 \pm 27	46 \pm 28	29 \pm 20
Total insulin dose (units/kg/day)	1.2 \pm 0.4	0.9 \pm 0.4	1.1 \pm 0.2	0.7 \pm 0.1
Estrogen (pmol/L)	127 \pm 60	267 \pm 99	147 \pm 113	159 \pm 37

Data are presented as percentage or mean \pm SD. N/A, not available.

renal plasma flow (ERPF) were estimated by the steady-state infusion method for inulin and PAH, respectively, as described previously (2–4). All experiments were performed in the same warm (25°C), temperature-controlled room and in a dark, quiet environment.

Sample collection and analytic methods

Blood samples collected for inulin and PAH determinations were immediately centrifuged at 3000 rpm for 10 min at 4°C. Plasma was separated, placed on ice, and 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. The blank subtraction (preinfusate sample) method was used to correct for the effect of hyperglycemia on anthrone (2–4). The filtration fraction (FF) was determined as the ratio of GFR/ERPF. Renal blood flow (RBF) was calculated by dividing the ERPF by (1 – HCT). Renal vascular resistance (RVR) was derived by dividing the mean arterial pressure by the RBF. All renal hemodynamic measurements were adjusted for body surface area (BSA), expressed per 1.73 m².

Angiotensin II was measured by radioimmunoassay. Blood was collected into prechilled tubes containing EDTA and angiotensinase inhibitor (0.1 mL Bestatin Solution, Bühlmann Laboratories AG, Schönenbuch, Switzerland). After centrifugation, plasma samples were stored at –70°C until analysis. On the day of analysis, plasma samples were extracted on phenylsilylica columns. A competitive radioimmunoassay kit (Bühlmann Laboratories AG) was used to measure the extracted angiotensin II. Aldosterone was measured by radioimmunoassay, using the Coat-A-Count system (Siemens Healthcare Diagnostics, Deerfield, IL). The urinary albumin excretion rate was determined using a 24-h urine collection by immunoturbidimetry, and HbA_{1c} was measured by high-performance liquid chromatography. As in our previous work, plasma insulin was also measured on the morning of each study day to account for the influence of insulin levels on vascular function (3,6,7).

Statistical analysis

Descriptive statistics were used to compare baseline clinical and demographic characteristics. Between-group comparisons in baseline parameters in the hyperfiltering and normofiltering groups were

made using parametric methods (unpaired *t* test). Between-group changes in hemodynamic parameters over time were determined by repeated measures ANOVA. All statistical analyses were performed using SAS 9.2 software (SAS Institute, Cary, NC). The vascular data were obtained and analyzed by a single observer (D.Z.I.C.), who was blinded to renal hemodynamic measurements.

RESULTS

Baseline demographic parameters

At baseline, hyperfiltering and normofiltering subjects were similar in sex distribution, age, BMI, diabetes duration (15 ± 5 vs. 13 ± 3 years) and albumin excretion rate (Table 1). The *z* score for BMI at baseline was also similar in hyperfiltering versus normofiltering patients (1.12 ± 0.42 vs. 1.29 ± 0.39, *P* = 0.39). In addition, the values for baseline total cholesterol (3.9 ± 0.6 vs. 4.3 ± 0.8 mmol/L), HDL (1.3 ± 0.3 vs. 1.4 ± 0.3 mmol/L), LDL (2.3 ± 0.5 vs. 2.5 ± 0.6 mmol/L), and triglycerides (0.86 ± 0.16 vs. 0.99 ± 0.26 mmol/L) were similar in the hyperfiltering and normofiltering groups. Dietary parameters and circulating insulin, aldosterone, and angiotensin II were also similar in the two groups.

Follow-up was a mean of 7.4 ± 1.6 years in the hyperfiltering group and 6.5 ± 1.5 years in the normofiltering group. Differences in clinical and biochemical parameters did not reach statistical significance in either group at follow-up, and the between-group changes over time were not significant. Baseline insulin doses were similar in the two groups (Table 1), and at follow-up, both groups exhibited similar reductions in insulin dosing that would be expected at this age (*P* = 0.15) (11).

At baseline, systemic blood pressure and heart rate values were similar in the two groups, whereas renal hemodynamic function testing revealed expected higher ERPF, GFR, FF, and RBF values and lower RVR values in the hyperfiltering group (Table 2). Consistent with our previous observations in a similar cohort (7) was the observation that the radial augmentation index was lower in hyperfiltering subjects, although differences were not statistically significant.

Changes in arterial stiffness, renal hemodynamic function, and circulating RAS mediators over time

At follow up, GFR and FF decreased in the 10 members of the hyperfiltering group,

resulting in a mean decline in GFR from 171 ± 20 to 120 ± 15 mL/min/1.73 m² (Table 2, Fig. 1A and B). Between-group changes in GFR and FF were significant (ANOVA for between-group differences, *P* ≤ 0.033). Hyperfiltration was also associated with a rise in RVR (within-group change, *P* = 0.017; Fig. 1C) and numerical reductions in ERPF, RBF (*P* > 0.05). Renal hemodynamic function did not change significantly in the normofiltration group.

When analyzed as a single group (without accounting for filtration status), the radial augmentation index decreased from 6.1 ± 14.8 to –4.6 ± 13.1% (*P* = 0.0003). In contrast with discordant renal hemodynamic changes in hyperfiltering and normofiltering subjects, filtration status analysis showed the radial augmentation index declined from 1.2 ± 11.7 to –11.0 ± 7.8% (*P* = 0.014) in the hyperfiltering group and from 14.3 ± 14.0 to 2.5 ± 14.6% (*P* = 0.015) in the normofiltering group. The magnitude of change was similar in the two groups (Table 2, Fig. 1D). At baseline, circulating RAS mediators were similar. At follow-up, only the decline in aldosterone reached statistical significance (Table 2).

CONCLUSIONS—Renal hyperfiltration is associated with an increased risk for nephropathy in type 1 diabetes (1). Hyperfiltration is also associated with nocturnal blood pressure nondipping, lower arterial stiffness, and endothelial dysfunction, suggesting that hyperfiltration represents a distinct physiologic state of generalized vascular dysfunction (6–8). Our goal was to determine, in a small but carefully physiologically characterized cohort with uncomplicated type 1 diabetes, the changes in renal hemodynamic function and arterial stiffness that occur over time as the participants transitioned from adolescence into early adulthood. Our major findings were as follows: 1) in contrast with significant declines in GFR in the hyperfiltration group, early normofiltration was associated with stable renal function, and 2) arterial stiffness and circulating aldosterone decreased in all participants, regardless of filtration status.

Hyperfiltration is associated with the development of nephropathy when assessed using a variety of GFR determination techniques, including inulin, ⁵¹Cr-EDTA, and [¹²⁵I]iothalamate (1,12–14). In cross-sectional human physiology studies involving young subjects with type 1 diabetes, it is less clear if normofiltration represents a group with normal renal function or if

Table 2—Mean systemic and renal hemodynamic function in hyperfiltering and normofiltering participants

Parameter	Hyperfilterers (n = 10)		Normofilterers (n = 8)	
	Baseline	Follow-up	Baseline	Follow-up
Peripheral vascular parameters				
Heart rate (bpm)	69 ± 8	65 ± 10	72 ± 11	71 ± 9
Blood pressure (mmHg)				
Systolic	112 ± 8	112 ± 7	114 ± 12	112 ± 12
Diastolic	61 ± 3	61 ± 4	64 ± 4	62 ± 5
Mean arterial pressure (mmHg)	78 ± 4	80 ± 4	78 ± 7	79 ± 6
Augmentation index (%)	1.2 ± 11.7	-11.0 ± 7.8*	14.3 ± 14.0	2.5 ± 14.6*
Renal hemodynamic function				
ERPF (mL/min/1.73 m ²)	713 ± 120	654 ± 111	664 ± 114	689 ± 124
GFR (mL/min/1.73 m ²)	171 ± 20	120 ± 15*†	120 ± 6‡	125 ± 13
FF	0.24 ± 0.06	0.18 ± 0.03*†	0.18 ± 0.03‡	0.19 ± 0.03
RBF (mL/min/1.73 m ²)	1,145 ± 86	1,063 ± 200	1,073 ± 159	1,072 ± 191
RVR (mmHg/L/min)	0.0678 ± 0.0135	0.0783 ± 0.0121*	0.0745 ± 0.0118	0.0780 ± 0.0159
Circulating RAS mediators				
Plasma renin activity (ng/L/s)	0.40 ± 0.31	0.24 ± 0.30	0.35 ± 0.40	0.63 ± 0.40
Angiotensin II (pmol/L)	4.3 ± 2.0	2.7 ± 2.5	2.8 ± 2.7	1.5 ± 2.6
Aldosterone (pmol/L)	155 ± 122	44 ± 43*	126 ± 50	34 ± 23*

Data are shown as the mean ± SD. * $P \leq 0.030$ for the within-group change in parameter vs. baseline. † $P \leq 0.033$ for the change in hemodynamic parameter in hyperfiltering vs. normofiltering subjects. ‡ $P \leq 0.010$ for the between-group difference in baseline parameter in normofiltering vs. hyperfiltering subjects.

these subjects were previous hyperfilterers in whom declining renal function developed over time. Our results suggest that normofiltration represents a physiologic state characterized by stable GFR and RBF. In conjunction with endothelial function data demonstrating higher flow-mediated vasodilatation in normofiltering individuals (6), our results support the concept that normofiltering individuals exhibit a more protective vascular phenotype compared with those with hyperfiltration. In hyperfiltering subjects, the observation that GFR declined, in the absence of microalbuminuria, is consistent with recent work suggesting that renal function can deteriorate in the absence of microalbuminuria or proteinuria and highlights the need to identify novel predictors for early declining renal function (15).

In contrast with normofilterers, hyperfiltering subjects exhibited declines in GFR and RBF and a rise in RVR. Our data are consistent with previous work by Mogensen et al. (13), who examined type 1 diabetic patients during a 7-year period. In this study, the group that progressed to nephropathy initially exhibited renal hyperfiltration. At follow-up, GFR and ERPF both declined, suggesting a rise in preglomerular arteriolar resistance. Our results are also consistent with previous work demonstrating a decline in ERPF in type 1 diabetic patients divided into increasing age-groups (9,16). Although

we could not determine the mechanism underlying these renal hemodynamic function changes, a variety of factors have been implicated, including diabetes-induced activation of the sympathetic

nervous system, reactive oxygen species, and reduced bioavailability of important vasodilators such as nitric oxide (17).

Previous studies have demonstrated a consistent association between increasing

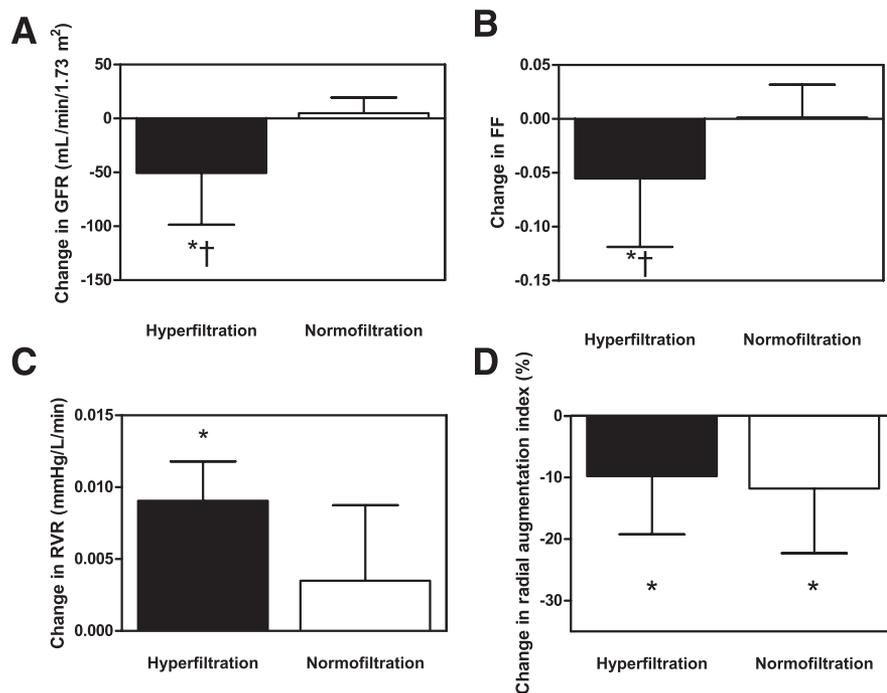


Figure 1—Changes in GFR (A), FF (B), RVR (C), and radial augmentation index (D) are shown in hyperfiltering and normofiltering participants (mean ± SD). * $P \leq 0.030$ for the within-group change in parameter vs. baseline. † $P \leq 0.033$ for the change in the hemodynamic parameter in hyperfiltering vs. normofiltering subjects.

age and a rise in arterial stiffness in type 1 diabetes in adults (18). For example, Schram et al. (19) demonstrated age-related increases in pulse pressure in cross-sectional and prospective observational studies in subjects in the 4th decade of life. Rönnback et al. (18) similarly demonstrated that pulse pressure is higher in type 1 diabetic individuals in the 5th compared with the 4th decade of life, and more recently, we demonstrated that arterial stiffness is higher in older (mean age, 45.0 ± 9.4 years) compared with younger (18.0 ± 2.7 years) patients with type 1 diabetes (9).

Our current results extend this previous work by examining changes in arterial stiffness over time in the same young individuals and at earlier ages. Contrary to our hypothesis, our findings suggest that in early type 1 diabetes, arterial stiffness declines as patients transition from adolescence into early adulthood, regardless of renal filtration status. The mechanistic basis for this decline is unclear but may have several explanations.

First, aldosterone levels declined over time in both groups, which may have lowered arterial stiffness. This observation is consistent with cross-sectional observational studies that have consistently demonstrated age-related declines in circulating RAS mediators in normal, hypertensive, and diabetic patients, in association with changes in baroreflex sensitivity (20–22). Our results extend this previous work by showing the same finding in a small group of carefully characterized study participants who were prospectively examined at two separate times. The decline in circulating RAS mediators may have been responsible for the reduction in arterial stiffness in our cohort because the RAS increases arterial stiffness (23). The decrease in circulating RAS mediators may also offer important insights into understanding the observed changes in the renal circulation in the hyperfiltering group. RAS activation is associated with renal hyperfiltration through postglomerular vasoconstriction. The reduction in GFR in hyperfiltering participants may therefore have been from a decline in aldosterone, leading to postglomerular vasodilatation (4).

A second possible explanation for the uniform decline in arterial stiffness relates to puberty-associated hormonal changes. Upregulation of the growth hormone axis, for example, is associated with renal hyperfiltration and hyperperfusion (24), and in nondiabetic individuals, elevated

circulating growth hormone levels are associated with low arterial stiffness (25). Whether growth hormone or other puberty-associated pathways influence longitudinal GFR and arterial stiffness measures in uncomplicated type 1 diabetes should be explored in future studies that are designed to address this question.

The study had important limitations. The sample size was small, which may have limited our ability to detect significant differences in some variables such as the baseline RVR and radial augmentation index. We minimized the effect of the small sample size by including a homogeneous study cohort and by careful prestudy preparation. We ensured that subjects were ingesting similar amounts of salt and protein to minimize RAS activation and studied subjects only during clamped euglycemic conditions for similar reasons. We also attempted to minimize the effect of variations in estrogen on renal hemodynamic and RAS function in female subjects by only studying those who were nonusers of oral contraceptive medications, and only during the follicular (low-estrogen) phase of the menstrual cycle. We used a study design that allowed each subject to act as his or her own control, thereby decreasing variability. Finally, future follow-up of this cohort is required to generate a third timepoint, which would help to confirm the GFR and arterial stiffness trends observed in this study.

In conclusion, our results in normofiltering individuals suggest these are not former hyperfilterers with declining kidney function; instead, the presence of early renal normofiltration may predict stable renal function. In contrast, arterial stiffness decreases uniformly as patients transition from adolescence to early adulthood, regardless of filtration status.

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D.Z.I.C. and E.B.S. researched data and wrote the manuscript.

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