



Renal Function Is Associated With Peak Exercise Capacity in Adolescents With Type 1 Diabetes

Diabetes Care 2015;38:126–131 | DOI: 10.2337/dc14-1742

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OBJECTIVE

Diabetic nephropathy and cardiovascular disease are strongly related in adults with type 1 diabetes, yet little is known about this relationship in adolescents prior to the onset of detectable clinical disease. We hypothesized that cardiopulmonary fitness would be directly associated with albumin-to-creatinine ratio (ACR) and inversely related to estimated glomerular filtration rate (eGFR) in adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS

Sixty-nine adolescents with type 1 diabetes and 13 nondiabetic control subjects of similar pubertal stage and BMI had insulin sensitivity (glucose infusion rate [GIR]), measured by hyperinsulinemic-euglycemic clamp, and lean body mass, measured by DEXA. Cardiopulmonary fitness was measured by cycle ergometry to obtain peak volume of oxygen (VO₂peak), and renal function was measured by eGFR using the Bouvet equation (measuring creatinine and cystatin C levels) and ACR.

RESULTS

Adolescents (15.5 ± 2.2 years of age) with type 1 diabetes (6.3 ± 3.8 years diabetes duration) had reduced VO₂peak (31.5 ± 6.3 vs. 36.2 ± 7.9 mL/kg · min, *P* = 0.046) and VO₂peak/lean kg (43.7 ± 7.0 vs. 51.0 ± 8.6 mL/lean kg · min, *P* = 0.007) compared with nondiabetic control subjects. eGFR was inversely associated with VO₂peak and VO₂peak/lean kg after adjusting for sex, Tanner stage, GIR, HbA_{1c} level, systolic blood pressure, and LDL cholesterol level (β ± SE, VO₂peak: −0.19 ± 0.07, *P* = 0.02; VO₂peak/lean kg: −0.19 ± 0.09, *P* = 0.048). Moreover, participants in the highest tertile for eGFR had significantly lower sex- and Tanner-adjusted VO₂peak and VO₂peak/lean kg compared with participants in the lowest tertile.

CONCLUSIONS

Adolescents with type 1 diabetes had reduced exercise capacity, which was strongly associated with renal health, independent of insulin sensitivity. Future studies should examine the underlying interrelated pathophysiology in order to identify probable targets for treatment to reduce cardiovascular and renal complications.

Cardiovascular disease (CVD) and diabetic nephropathy (DN) are the major causes of mortality in individuals with type 1 diabetes (1–3), and a growing body of evidence from basic and clinical studies (4–7) supports the relationship between CVD and renal function in health and disease. CVD and DN have been proposed to be

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Received 19 July 2014 and accepted 26 September 2014.

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manifestations of the same underlying pathology and also exist as interrelated risk factors (8,9). The increased mesangial matrix associated with DN is similar to the pathophysiology of coronary atherosclerosis (8). While atherosclerosis tends to remain subclinical until adulthood in individuals with type 1 diabetes (10), adolescents with type 1 diabetes demonstrate reduced peak exercise capacity and decreased cardiac function compared with nondiabetic adolescents (11). Although the mechanisms underlying the reduced peak exercise capacity are poorly understood, we have previously shown that insulin resistance and elevated LDL cholesterol (LDL-C) were associated with low peak volume of oxygen (VO_2 peak) (11).

Elevated albumin-to-creatinine ratio (ACR) and glomerular filtration rate (GFR), which are early manifestations of DN, are also increasingly recognized in children and adolescents with type 1 diabetes (1,12). Increased GFR was shown to be associated with increased cardiovascular mortality in adults (13). Little is known, however, about the possible associations between early renal health and exercise capacity in adolescents with type 1 diabetes, and whether this relationship is independent of insulin sensitivity. Accordingly, we sought to examine the associations between markers of renal health and peak exercise capacity in adolescents with type 1 diabetes. We hypothesized that cardiopulmonary fitness would be directly associated with ACR and inversely related to estimated GFR (eGFR) in adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS

Subjects

Pubertal adolescents between the ages of 12 and 19 years were recruited for a study of diabetes and insulin resistance in youth from type 1 diabetes clinics at the Barbara Davis Center for Diabetes with advertisements. Control subjects were recruited from advertisements on the University of Colorado Anschutz Medical Campus, and in endocrine, adolescent medicine, and pediatric clinics at Children's Hospital Colorado. Sixty-nine adolescents with type 1 diabetes and 13 nondiabetic control subjects had data available for analyses of cardiopulmonary fitness, insulin sensitivity, ACR, and eGFR, as determined by creatinine and cystatin C levels.

Screening included a medical history, physical examination, Tanner staging, and fasting laboratory testing (measurement of glycosylated hemoglobin [HbA_{1c}] and LDL-C levels). Type 1 diabetes was defined by American Diabetes Association criteria plus the presence of glutamic acid decarboxylase and islet cell or insulin autoantibodies, as well as an insulin requirement. The absence of diabetes was confirmed in control subjects by a 2-h, 75-g oral glucose tolerance test. Inclusion criteria included Tanner stage >1 and sedentary status (<3 h regular exercise/week) to minimize pubertal and training effects. Study exclusions included resting blood pressure $>140/90$ mmHg or $>190/100$ mmHg during exercise, hemoglobin level <9 mg/dL, serum creatinine level >1.5 mg/dL, HbA_{1c} level $>11\%$ (97 mmol/mol), smoking, medication-dependent asthma or other conditions precluding exercise testing, use of antihypertensive medications and oral contraceptives, pregnancy, breastfeeding, plans to alter exercise or diet during the study, family history of type 2 diabetes, and use of medications affecting insulin sensitivity (e.g., oral or inhaled steroids, metformin, thiazolidinediones, or atypical antipsychotic agents). Pubertal development was assessed by a single pediatric endocrinologist using the criteria established by Tanner and Marshall for pubic hair and breast development (14). Testicular volume was measured using an orchidometer.

All subsequent tests were performed after a 12-h fast, preceded by 3 days of restricted physical activity and a fixed-macronutrient, weight-maintenance diet (55% carbohydrates, 30% fat, 15% protein). Participants with type 1 diabetes were instructed to monitor blood glucose levels at least four times per day and were excluded if large urine ketones were present on admission to the study. The study was approved by the University of Colorado Denver Institutional Review Board, and appropriate consent and assent were obtained.

Activity Questionnaires and Body Composition

A 3-day pediatric physical activity recall questionnaire was used to estimate habitual physical activity (11,15), reported as a 3-d average of daily metabolic equivalents. Body composition was

assessed by DEXA scan, as previously reported (11,15).

Exercise Testing

Measurements were made during bicycle ergometer testing using a metabolic cart. For all bicycle tests, VO_2 , volume of carbon dioxide, and minute ventilation were measured, breath-by-breath, at rest and during exercise. Arm blood pressures (by auscultation) and heart rates (measured by 12-lead electrocardiogram) were obtained every minute during exercise. Cardiac status was continuously monitored throughout each test by 12-lead electrocardiogram. The respiratory exchange ratio was calculated as the volume of carbon dioxide-to- VO_2 ratio. Subjects were excluded if the peak respiratory exchange ratio was ≤ 1.1 .

To determine VO_2 peak in all participants, a graded bicycle riding protocol was performed until subject exhaustion, and was carried out, as previously reported (11), on a cycle ergometer (Medgraphics; Medical Graphics Corp., St. Paul, MN) while breathing into the mouthpiece of the metabolic cart (Medgraphics CPX/D; Medical Graphics Corp.). VO_2 peak was reported in milliliters per kilogram per minute and milliliters per lean kilogram determined from DEXA scan per minute, as previously reported (11,15). Blood sugar levels were closely monitored in participants with type 1 diabetes, and short-acting insulin or carbohydrates were administered to achieve a goal pre-exercise range of 100–150 mg/dL.

Insulin Sensitivity

Insulin sensitivity (glucose infusion rate [GIR] in milligrams per kilogram per minute) was calculated from a hyperinsulinemic-euglycemic clamp ($80 \text{ mU} \cdot \text{m}^{-2} \cdot \text{min}^{-1}$ insulin) after an overnight intravenous insulin infusion to normalize glycemia, as previously described (11,15).

Renal Measurements

Samples for serum creatinine and cystatin C measurements were collected after 3–4 h of euglycemia (100 mg/dL) and 16 h of bed rest, eliminating the effects of acute glycemia and exercise on eGFR (16–18). The cystatin C and creatinine samples were analyzed in batches, reducing the effects of temporal systemic shifts on the assays. Serum cystatin C levels were measured by immunoturbidimetric methodology

(Kamiya Biomedical), and serum creatinine levels were measured by enzymatic methodology (Beckman Coulter). Because of the absence of chronic kidney disease and expected normal to elevated GFRs for age, we used the Bouvet equation to estimate GFR: $eGFR = 63.2 \cdot (\text{serum creatinine}/96)^{-0.35} \cdot (\text{serum cystatin C}/1.2)^{-0.56} \cdot (\text{weight}/45)^{0.30} \cdot (\text{age}/14)^{0.40}$ (19). This equation has shown to have the best performance in estimating GFR in adolescents without chronic kidney disease (19). Spot urine samples were also collected upon study admission for measurement of urinary albumin and creatinine levels, and ACR was calculated. Albuminuria was defined as microalbuminuria or greater with $ACR \geq 30$ mg/g.

Statistical Analysis

Analyses were performed in SAS (version 9.3 for Windows; SAS Institute, Cary, NC). Variables were checked for the distributional assumption of normality using normal plots. Differences between continuous parametric variables were examined with the *t* test, continuous nonparametric variables were examined with the Wilcoxon signed rank test, and dichotomous variables were examined with the χ^2 test. eGFRs determined by the Bouvet equation (low <94, middle range 94–106, and high >106 mL/min/1.73 m²) and ACR (low <5.50, middle range 5.50–9.13, and high >9.13 mg/g) were stratified into tertiles. ANOVA with a Tukey-Kramer *P* value adjustment was used for the comparison of continuous variables across the three groups (low, middle, and high tertiles), and least squares means (LSMs) were calculated for the tertile groups.

Pearson correlation, and univariate and multivariable linear regression models were used to examine the associations between eGFR determined by Bouvet equation and the natural log of ACR (log transformed for these analyses because of skewed distribution) and VO₂peak, unadjusted and adjusted for Tanner stage, sex, insulin sensitivity, HbA_{1c} level, systolic blood pressure (SBP), and LDL-C level. Significance was based on an α -level of ≤ 0.05 .

RESULTS

Table 1 shows participant characteristics stratified by diabetes status.

Adolescents with type 1 diabetes had reduced peak exercise capacity compared with nondiabetic control subjects (VO₂peak 31.5 ± 6.3 vs. 36.2 ± 7.9 mL/kg · min, *P* = 0.046; VO₂peak/lean kg 43.7 ± 7.0 vs. 51.0 ± 8.6 mL/lean kg · min, *P* = 0.007), despite similar age, Tanner stage, BMI, and habitual level of physical activity. When adjusting for eGFR, the differences in Tanner stage and sex-adjusted means for VO₂peak/kg (LSMs ± SE 32.3 ± 1.0 vs. 34.2 ± 1.5, *P* = 0.30) and VO₂peak/lean kg (LSMs ± SE 49.0 ± 2.1 vs. 45.0 ± 1.4, *P* = 0.09) between adolescents with and without type 1 diabetes lost significance.

In adolescents with type 1 diabetes, eGFR correlated strongly with VO₂peak (*r* = −0.55, *R*² = 30.22%, *P* = 0.002) and VO₂peak/lean kg (*r* = −0.44, *R*² = 19.58%, *P* = 0.02), and remained significantly associated with VO₂peak and VO₂peak/lean kg after adjusting for sex and Tanner stage (Tables 2 and 3). Additional adjustments for insulin sensitivity, HbA_{1c} level, SBP, or LDL-C level did not attenuate the significance of the associations among eGFR, VO₂peak, and VO₂peak/lean kg; however, the association between eGFR and VO₂peak/lean kg became less significant (*P* = 0.048; Table 3). In contrast, the associations between eGFR and VO₂peak/kg and VO₂peak/lean kg in adolescent control subjects were not significant in fully adjusted models (data not shown). In contrast to eGFR, LnACR did not correlate with VO₂peak ($\beta \pm SE$ −1.42 ± 1.49, *P* = 0.35) and VO₂peak/lean kg ($\beta \pm SE$ −2.24 ± 1.71, *P* = 0.20) when adjusted for sex and Tanner stage.

When stratifying eGFRs into tertiles, subjects in the highest eGFR tertile had significantly lower VO₂peak (LSM ± SE 26.91 ± 1.52 vs. 35.53 ± 1.88, *P* = 0.002) and VO₂peak/lean kg (LSM ± SE 39.65 ± 2.07 vs. 46.18 ± 2.55, *P* = 0.048) adjusted for sex and Tanner stage, compared with those in the lowest eGFR tertile (Fig. 1). Stratifying ACR into tertiles demonstrated no differences in VO₂peak or VO₂peak/lean kg among the three groups (data not shown).

CONCLUSIONS

Our major observation in this study was that in adolescents with type 1 diabetes, a disease characterized by

reduced exercise capacity, eGFR was independently and negatively associated with cardiopulmonary fitness, independent of insulin sensitivity and other important risk factors.

We previously demonstrated reduced peak exercise capacity, and cardiac and vascular function in otherwise healthy, nonobese adolescents with type 1 diabetes, compared with well-matched nondiabetic control subjects of similar BMI, pubertal stage, and habitual level of physical activity (11). Furthermore, we found that insulin sensitivity correlated strongly with VO₂peak in youths with type 1 diabetes, as did LDL-C level to a lesser degree (11). In this report, we present for the first time an independent relationship between renal health and cardiopulmonary fitness that is independent of insulin sensitivity, LDL-C level, and other important covariates. This association may represent a novel pathway of a cardiorenal connection in type 1 diabetes separate from atherosclerosis. Type 1 diabetes is associated with shortened life span, and cardiac and vascular dysfunction, independent of coronary artery disease (20). In fact, low fitness levels in adults with and without diabetes are associated with CVD mortality and decreased longevity (21,22). Control of conventional risk factors such as glucose level, cholesterol level, and blood pressure is important, but does not abolish the cardiovascular risk in subjects with type 1 diabetes (2,23). Although not without controversy, the Finnish Diabetic Nephropathy Study (24) and the Pittsburgh Epidemiology of Diabetes Complications Study (3) demonstrated no increase in mortality in adults with type 1 diabetes compared with nondiabetic control subjects in the absence of DN. In contrast, The Coronary Artery Calcification in Type 1 Diabetes study (9) demonstrated strong associations among eGFR, ACR, and progression of coronary artery calcification in adults with type 1 diabetes in the absence of established DN, suggesting that renal health may be associated with early cardiovascular pathophysiology that may take years to manifest clinically. The specific mechanisms underlying the association between renal and cardiovascular health, however, remain unclear, but increasing evidence supports the importance of shared risk factors and pathogenic pathways, including

Table 1—Characteristics for adolescents with type 1 diabetes

	Lean control subjects (n = 13)	Adolescents with type 1 diabetes (n = 69)	P value
Age (years)	15.1 ± 2.2	15.5 ± 2.2	0.55
Type 1 diabetes duration (months)		75 ± 46	
Ethnicity (%)			0.38 ^a
Non-Hispanic white	83	86	
Hispanic	0	7	
Black	17	3	
Other	0	4	
Tanner stage (%)			0.74 ^a
Tanner 2	8	4	
Tanner 3	8	13	
Tanner 4	38	26	
Tanner 5	46	57	
BMI (kg/m ²)	20.6 ± 2.4	22.9 ± 4.7	0.09
GIR	20.3 ± 4.1	11.7 ± 4.3	<0.0001
HbA _{1c} (%)	5.0 ± 0.3	8.5 ± 1.4	<0.0001
HbA _{1c} (mmol/mol)	31.0 ± 3.3	69.0 ± 15.3	<0.0001
SBP (mmHg)	109 ± 6	116 ± 12	0.06
DBP (mmHg)	62 ± 6	69 ± 8	0.003
LDL-C (mg/dL)	81 ± 25	82 ± 24	0.84
Serum creatinine (mg/dL)	0.75 ± 0.15	0.68 ± 0.15	0.14
Serum cystatin C (mg/dL)	1.00 ± 0.17	0.94 ± 0.16	0.18
eGFR by Bouvet equation (mL/min/1.73 m ²)	89 ± 14	101 ± 19	0.03
ACR ^b (mg/g)	7.3 (5.1–9.2)	6.7 (4.4–12.9)	0.48
Mean habitual exercise (METs)	58 ± 10	64 ± 13	0.15
VO ₂ peak/kg (mL/kg · min)	36.2 ± 7.9	31.5 ± 6.3	0.046
VO ₂ peak/lean kg (mL/lean kg · min)	51.0 ± 8.6	43.7 ± 7.0	0.007

Data are reported as LSMs ± SE, unless otherwise indicated. METs, metabolic equivalents. ^aχ² test. ^bData are reported as the median (Q25–Q75).

atherosclerosis (6,7,11,25–28). Reduced exercise capacity and its association with renal health highlighted in this article, taken together with the established relationship between fitness and premature CVD mortality, may provide an alternative and novel pathway explaining the premature mortality of subjects with type 1 diabetes (21,22).

There is currently no generally accepted definition for renal hyperfiltration (29), but it is increasingly recognized that elevated GFR is an early hemodynamic abnormality seen in diabetes that is linked with an increased risk of DN (1). The meta-analysis from the Chronic Kidney Disease Prognosis Consortium (30,31) demonstrated significantly greater all-cause mortality and cardiovascular

mortality in individuals with the highest GFR values (>105 mL/min/1.73 m²). Similarly, the Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6) recently reported (13) significantly greater odds of both carotid atherosclerosis and left ventricular hypertrophy in participants in the highest GFR quartile (>101.2 mL/min/1.73 m²). It is, however, also plausible that the mechanisms underlying the association between renal health and exercise capacity in adolescents with type 1 diabetes differ from the link seen with atherosclerosis. The mechanisms responsible for the relationship between renal health and exercise capacity are not yet clear. Adults with type 1 diabetes and elevated GFR demonstrate cardiovascular dysfunction, including increases in arterial stiffness and altered flow-mediated dilatation (32,33). We previously demonstrated reduced forearm blood flow in youths with type 1 diabetes (11) as evidence of vascular dysfunction, which correlated with reduced VO₂peak. Moreover, alterations in arterial stiffness have also been reported to be present in youths with type 1 diabetes (34). Elevated GFR is associated with endothelial dysfunction via cyclooxygenase-2 activity and nitric oxide synthase inhibition, and relatively higher blood pressures (35–37), both of which could directly impact exercise capacity. Elevated GFR is also associated with increased carotid intimal medial thickness and left ventricular hypertrophy in nondiabetic individuals, further suggesting that increased GFR potentially reflects a generalized change in vascular function rather than simply reflecting intrarenal abnormalities (13). Endothelial dysfunction could also contribute to elevated GFR, thus the relationships could be bidirectional. We did not observe a significant association between ACR and peak exercise capacity, potentially because increasing evidence supports the distinction of albuminuria as a risk factor for DN and not an early phenotype of DN (38). Furthermore, the prevalence of microalbuminuria (n = 9) was low due to the young age of our population.

Our study does have important limitations. First, our sample size was relatively small. However, to minimize the effect of sample size, we used careful and detailed physiological measurements,

Table 2—Associations between eGFR and VO₂peak/kg

	VO ₂ peak/kg*	VO ₂ peak/kg†	VO ₂ peak/kg‡
eGFR by Bouvet equation	−0.18 ± 0.05; 0.002	−0.18 ± 0.05; 0.002	−0.19 ± 0.07; 0.02
Tanner stage	1.09 ± 1.45; 0.46	0.94 ± 1.53; 0.54	0.62 ± 1.62; 0.71
Female sex	−4.92 ± 2.43; 0.06	−4.78 ± 2.51; 0.07	−4.88 ± 2.70; 0.09
GIR		0.10 ± 0.24; 0.70	0.22 ± 0.27; 0.42
HbA _{1c}			0.66 ± 0.95; 0.49
SBP			−0.01 ± 0.10; 0.94
LDL-C			−0.08 ± 0.06; 0.21

Data are reported as β ± SE; P value. Age was not adjusted for because it is part of the Bouvet eGFR equation. *Adjusted for Tanner stage and sex. †Adjusted for Tanner stage, sex, and GIR. ‡Adjusted for Tanner stage, sex, GIR, HbA_{1c} level, SBP, and LDL-C level.

Table 3—Associations between eGFR and VO₂peak/lean kg

	VO ₂ peak/lean kg*	VO ₂ peak/lean kg†	VO ₂ peak/lean kg‡
eGFR by Bouvet equation	−0.16 ± 0.07; 0.03	−0.16 ± 0.07; 0.03	−0.19 ± 0.09; 0.048
Tanner stage	0.73 ± 1.92; 0.71	0.70 ± 2.03; 0.73	0.12 ± 2.05; 0.96
Female sex	−1.46 ± 3.22; 0.65	−1.46 ± 3.33; 0.67	−1.21 ± 3.43; 0.73
GIR		0.02 ± 0.32; 0.95	0.27 ± 0.34; 0.45
HbA _{1c}			1.31 ± 1.20; 0.29
SBP			0.04 ± 0.13; 0.78
LDL-C			−0.14 ± 0.08; 0.09

Data are reported as β ± SE; P value. Age not adjusted for because it is part of the Bouvet eGFR equation. *Adjusted for Tanner stage and sex. †Adjusted for Tanner stage, sex, and GIR. ‡Adjusted for Tanner stage, sex, GIR, HbA_{1c} level, SBP, and LDL-C level.

including gold standard fitness testing and hyperinsulinemic-euglycemic clamp studies. We also chose groups similar in habitual physical activity, pubertal stage, sex, and BMI, and controlled for pre-study diet and physical activity. Another limitation to the current study included the cross-sectional design, which prevents the determination of causality, and whether the association holds true longitudinally; for that reason, the data should be viewed as hypothesis generating. The direction of the association between renal health and exercise capacity (i.e., whether renal health leads to reduced exercise capacity or vice versa) is also difficult to determine with the available data. Results from this study may also not be generalizable to older people with type 1 diabetes or to cohorts with a different ethnic distribution. Finally, we used an estimate of GFR to assess renal function; however, to estimate the GFR we used the Bouvet equation, which was shown to have the best performance in estimating GFR in children

and adolescents with normal to elevated GFRs (18). The mean eGFR in our lean nondiabetic control subjects is slightly lower than GFRs measured by insulin level in adolescents in some studies (39), but is consistent with GFRs estimated by creatinine and cystatin C levels in adolescents in large-scale studies (40).

In conclusion, in adolescents with type 1 diabetes, a disease characterized by reduced peak exercise capacity compared with nondiabetic adolescents, there was a strong relationship between eGFR and cardiopulmonary fitness, independent of directly measured insulin sensitivity and other important risk factors. This observation provides further evidence for the broad interactions observed between renal and cardiovascular function in type 1 diabetes. Further research is needed to investigate the longitudinal relationships between renal and cardiopulmonary health in adolescents with type 1 diabetes, and to elucidate the specific mechanisms

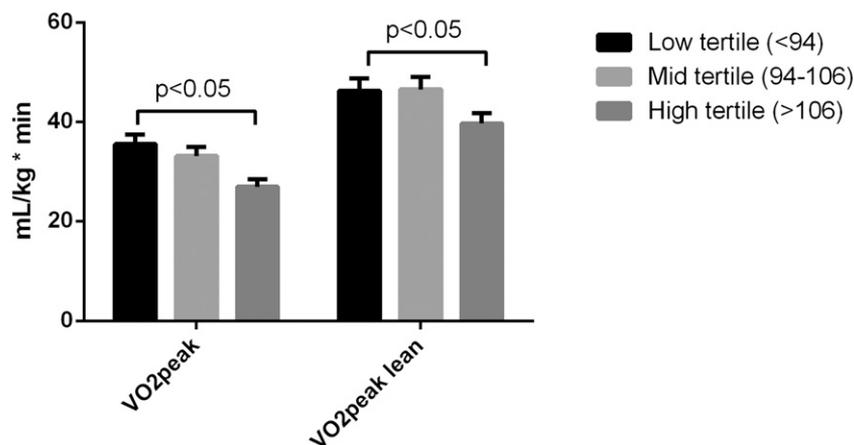


Figure 1—Tanner stage- and sex-adjusted means for VO₂peak/kg and VO₂peak/lean kg stratified by tertiles of eGFR. Data are presented as LSMs ± SE.

underlying this relationship as potential therapeutic targets.

Funding. Support for this study was provided by National Center for Research Resources grant K23-RR-020038-01, National Institutes of Health (NIH)-Building Interdisciplinary Research Careers in Women's Health grant K12-5K12-HD-057022-04, American Diabetes Association grants 7-11-CD-08 and 1-11-JF-23, JDRF Award 11-2010-343, NIH-Department of Health and Human Services grant R56-DK-088971, NIH-National Center for Advancing Translational Sciences-Colorado Clinical and Translational Sciences Institute grant UL1-TR-000154, the Center for Women's Health Research, and a U.S. Department of Veterans Affairs Merit Review Award.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. P.B. researched, wrote, and formulated the analytic plan; contributed to the discussion and analytic plan; and reviewed and edited the manuscript. M.C.-G. and A.B. contributed to the research, and reviewed and edited the manuscript. D.M.M. and D.Z.C. contributed to the discussion and analytic plan and reviewed and edited the manuscript. L.P. reviewed and edited the analytic plan and the manuscript. J.G.R. and J.E.R. contributed to the discussion and reviewed and edited the manuscript. K.J.N. contributed to the research and the discussion and helped to write, review, and edit the manuscript. P.B. and K.J.N. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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