Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Online Appendix Supplementary Material

Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes

The DCCT/EDIC Research Group

Writing Group:
Ian H. de Boer, MD, MS, University of Washington, Seattle, WA
Wanjie Sun, MS, The George Washington University, Rockville, MD
Patricia A. Cleary, MS, The George Washington University, Rockville, MD
John M. Lachin, ScD, The George Washington University, Rockville, MD
Mark E. Molitch, MD, Northwestern University, Chicago, IL
Michael W. Steffes, MD PhD, University of Minnesota, Minneapolis, MN
Bernard Zinman, MD, University of Toronto, Toronto, Ontario

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The DCCT/EDIC Study Research Group

The following persons and institutions participated in the DCCT/EDIC Study Research Group:

Study Chairmen - S. Genuth, D.M. Nathan, B. Zinman (vice-chair), O. Crofford (past)

Albert Einstein College of Medicine - J. Crandall, M. Reid, J. Brown-Friday, S. Engel, J. Sheindlin, H. Martinez (past), H. Shamoon (past), H. Engel (past), M. Phillips

Case Western Reserve University - R. Gubitosi-Klug, L. Mayer, S. Pendegast, H. Zegarra, D. Miller, L. Singerman, S. Smith-Brewer, M. Novak, J. Quin (past), W. Dahms (deceased), Saul Genuth (past), M. Palmert (past)

Cornell University Medical Center - D. Brillon, M.E. Lackaye, S. Kiss, R. Chan, V. Reppucci (past), T. Lee (past), M. Heinemann (past)

Henry Ford Health System - F. Whitehouse, D. Kruger, J. K. Jones, M. McLellan (past), J.D. Carey, E. Angus, A. Thomas, A. Galprin (past)

International Diabetes Center - R. Bergenstal, M. Johnson, M. Spencer (past), K. Morgan, D. Etzwiler (deceased), D. Kendall (past)

Joslin Diabetes Center - Lloyd Paul Aiello, E. Golden, A. Jacobson (past), R. Beaser, O. Ganda, O. Hamdy, H. Wolpert, G. Sharuk, P. Arrigg, D. Schlossman, J. Rosenzwieg (past), L. Rand (past)

Massachusetts General Hospital - D.M. Nathan, M. Larkin, M. Ong, J. Godine, E. Cagliero, P. Lou, K. Folino, S. Fritz (past), S. Crowell (past), K. Hansen (past), C. Gauthier-Kelly (past)

Mayo Foundation - J. Service, G. Ziegler

Medical University of South Carolina - L. Luttrell, S. Caulder, M. Lopes-Virella (past), J. Colwell (past), J. Soule (past), J. Fernandes, K. Hermayer, S. Kwon, M. Brabham (past), A. Blevins, J. Parker, D. Lee (past), N. Patel, C. Pittman, P. Lindsey (past), M. Bracey (past), K. Lee, M. Nutaitis, A. Farr (past), S. Elsing (past), T. Thompson (past), J. Selby (past), T. Lyons (past), S. Yacoub-Wasef (past), M. Szpiech (past), D. Wood (past), R. Mayfield (past)

Northwestern University - M. Molitch, B. Schaefer, L. Jampol, A. Lyon, M. Gill, Z. Strugula, L. Kaminski, R. Mirza, E. Simjanoski, D. Ryan

University of California, San Diego - O. Kolterman, G. Lorenzi, M. Goldbaum

University of Iowa - W. Sivitz, M. Bayless

University of Maryland School of Medicine - D. Counts, S. Johnsonbaugh, M. Hebdon (past), P. Salemi, R. Liss, T. Donner (past), J. Gordon (past), R. Hemady (past), A. Kowarski (past), D. Ostrowski (past) S. Steidl (past), B. Jones (past)

University of Michigan - W.H. Herman, C.L. Martin, R. Pop-Busui, A. Sarma, J. Albers, E. Feldman, K. Kim, S. Elner, G. Comer, T. Gardner, R. Hackel, R. Prusak, L. Goings, A. Smith, J. Gothrup, P. Titus, J. Lee, M. Brandle, L. Prosser, D.A. Greene (past), M.J. Stevens (past), A. K. Vine (past)

University of Minnesota - J. Bantle, N. Wimmergren, A. Cochrane, T. Olsen (past), E. Steuer (past), P Rath (past), B. Rogness (past)

University of Missouri - D. Hainsworth, D. Goldstein , S. Hitt, J. Giangiacomo

University of New Mexico - D.S. Schade, J.L. Canady, J.E. Chapin, L.H. Ketai C

University of Pennsylvania – S. Braunstein, P.A. Bourne, S. Schwartz (past), A. Brucker , B.J. Maschak-Carey (past), L. Baker (deceased)

University of Pittsburgh - T. Orchard, N. Silvers, C. Ryan, T. Songer, B. Doft, S. Olson, R.L. Bergren, L. Lobes, P. Paczan Rath, D. Becker, D. Rubinstein, P.W. Conrad, S. Yalamanchi, A. Drash (past)

University of South Florida - A. Morrison, M.L. Bernal, J. Vaccaro-Kish (past), J. Malone, P.R. Pavan, N. Grove, M.N. Iyer, A.F. Burrows, E.A. Tanaka (past), R. Gstalder (past)

University of Tennessee - S. Dagogo-Jack, C. Wigley, H. Ricks, A. Kitabchi, M. B. Murphy (past), S. Moser (past), D. Meyer (past), A. Iannacone (past), E. Chaum, S. Yoser (past), M. Bryer-Ash (past), S. Schussler (past), H. Lambeth (past)

The University of Texas Southwestern Medical Center at Dallas - P. Raskin, S. Strowig

University of Toronto - B. Zinman, A. Barnie, R. Devenyi, M. Mandelcorn, M. Brent, S. Rogers, A. Gordon

University of Washington - J. Palmer, S. Catton, J. Brunzell, H. Wessells, I. H. de Boer, J. Hokanson, J. Purnell, J. Ginsberg, J. Kinyoun, S. Deeb, M. Weiss, G. Meekins, J. Distad, L. Van Ottingham (past)

University of Western Ontario - J. Dupre, J. Harth, D. Nicolle, M. Driscoll, J. Mahon, C. Canny *Vanderbilt University* - M. May, J. Lipps, A. Agarwal, T. Adkins, L. Survant, R. L. Pate, G. E. Munn, R. Lorenz (past), S. Feman (past)

Washington University, St. Louis - N. White, L. Levandoski, I. Boniuk, G. Grand, M. Thomas, D. D. Joseph, K. Blinder, G. Shah, Boniuk (past), Burgess (past), J. Santiago (deceased)

Yale University School of Medicine - W. Tamborlane, P. Gatcomb, K. Stoessel, K. Taylor (past)J. Goldstein (past), S. Novella (past), H. Mojibian (past), D. Cornfeld (past)

Clinical Coordinating Center (Case Western Reserve University) - R. Gubitosi-Klug, J. Quin, P. Gaston, M. Palmert (past), R. Trail (past), W. Dahms (deceased)

Data Coordinating Center (The George Washington University, The Biostatistics Center) - J. Lachin, P. Cleary, J. Backlund, W. Sun, B. Braffett, K. Klumpp, K. Chan (past), L. Diminick, D. Rosenberg (past), B. Petty (past), A. Determan (past), D. Kenny (past), B. Rutledge (past), Naji Younes (past), Williams (past), L. Dews, M. Hawkins

National Institute of Diabetes and Digestive and Kidney Disease Program Office - C. Cowie, J. Fradkin, C. Siebert (past), R. Eastman (past)

Central Fundus Photograph Reading Center (University of Wisconsin) - R. Danis, S. Gangaputra, S. Neill, M. Davis (past), L. Hubbard (past), H. Wabers, M. Burger, J. Dingledine, V. Gama, R. Sussman

Central Biochemistry Laboratory (University of Minnesota) - M. Steffes, J. Bucksa, M. Nowicki, B. Chavers

Central Carotid Ultrasound Unit (New England Medical Center) - D. O'Leary, J. Polak, A. Harrington, L. Funk (past)

Central ECG Reading Unit (University of Minnesota) – R. Crow (past), B. Gloeb (past), S. Thomas (past), C. O'Donnell (past)

Central ECG Reading Unit (Wake Forest University) – E. Soliman, Z.M. Zhang, R. Prineas (past), C. Campbell

Central Neuropsychological Coding Unit – C. Ryan, D. Sandstrom, T. Williams, M. Geckle, E. Cupelli, F. Thoma, B. Burzuk, T. Woodfill

Central ANS Reading Unit (Mayo Clinic) – P. Low, C. Sommer, K. Nickander

Computed Tomography Reading Center (Harbor UCLA Research and Education Institute) – M. Budoff, R. Detrano (past), N. Wong, M. Fox, L. Kim (past), R. Oudiz

Johns Hopkins Medical Institutions – J. Lima, D. Bluemke, E. Turkbey, R. J. van der Geest, C. Liu, A. Malayeri, A. Jain, C. Miao (past), H. Chahal (past), R. Jarboe (past)

External Evaluation Committee– G. Weir (Chairman), M. Espeland, B. Klein, T Manolio, L. Rand, D. Singer, M. Stern, A.E. Boulton, C. Clark (past), R. D'Agostino (past)

Molecular Risk Factors Program Project (Medical University of South Carolina) - M. Lopes-Virella, W.T. Garvey (past), T.J. Lyons, A. Jenkins, R. Klein, G. Virella, A. Jaffa, Rickey Carter, D. Lackland (past), M. Brabham (past), D. McGee (past), D. Zheng (past), R. K. Mayfield (past)

Genetic Studies Group (Hospital for Sick Children) - A. Paterson, A. Boright, S. Bull, L. Sun, S. Scherer (past), B. Zinman (past)

SCOUT (Veralight) – J. Maynard

Epigenetics (Beckman Research Institute of City of Hope Medical Center) – R. Natarajan, F. Miao, L. Zhang, Z. Chen

Editor, EDIC Publications - D.M. Nathan

Suplementary Methods

Calibration to achieve consistent serum creatinine concentrations across time in the DCCT/EDIC Study

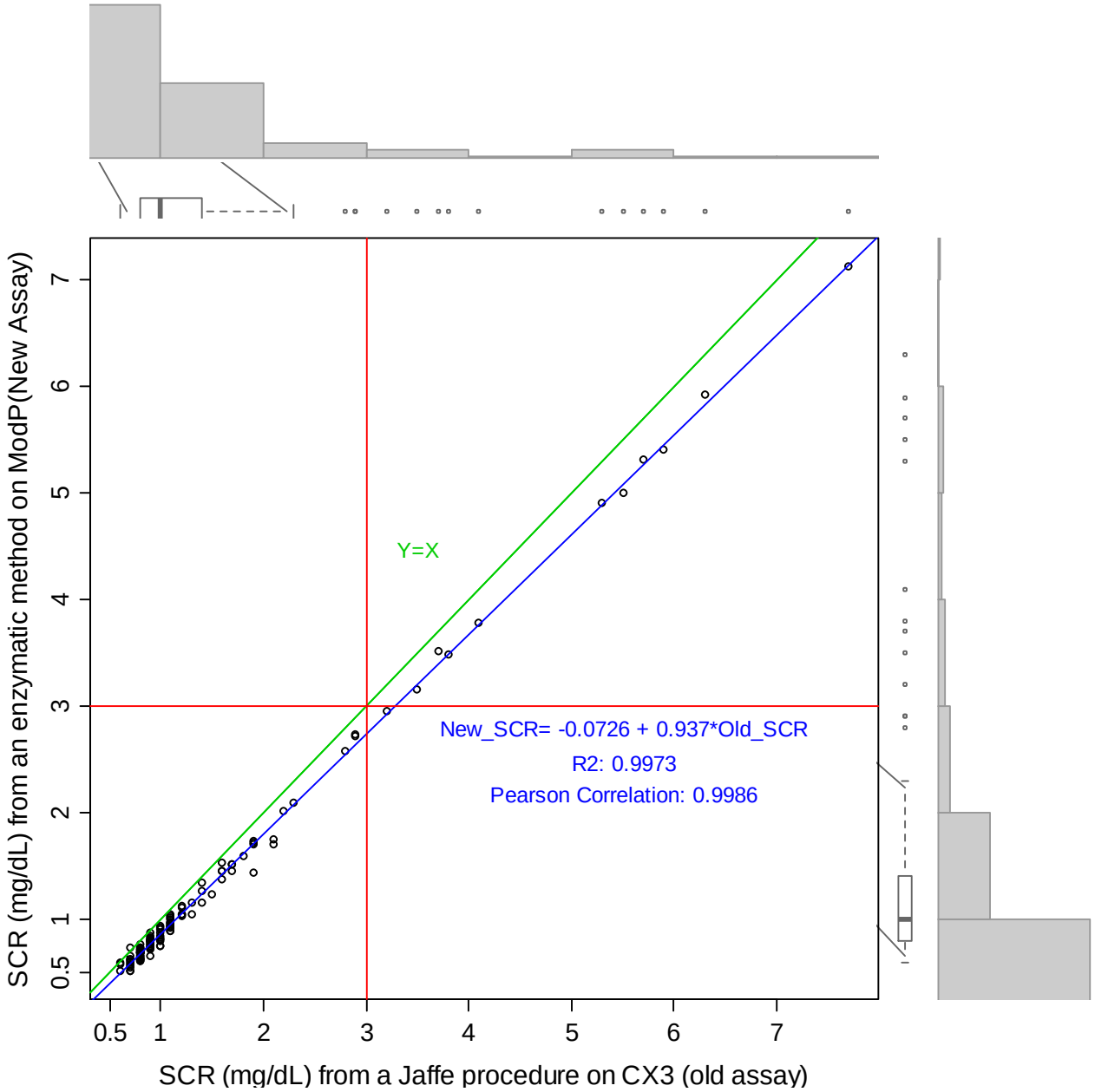
From 1983 through mid-2007, DCCT/EDIC creatinine concentrations were measured on the Beckman Astra and Synchron CX3 Chemistry Analyzers (CX3), using a modified rate Jaffé procedure. Beginning in mid-2007, measurements were transferred to an enzymatic method on the Roche/Hitachi Modular P Chemistry Analyzer (ModP). In addition, creatinine concentrations were then traceable to materials with values assigned by National Institute of Standards and Technology (NIST) Isotope Dilution Mass Spectrometry (IDMS).

In order to accommodate changes in methods and have all DCCT/EDIC creatinine results traceable to IDMS, 127 serum specimens with a broad range of creatinine concentrations (0.6-7.7 mg/dL) were measured simultaneously on both chemistry platforms. These data were used to indirectly calibrate all results generated by the Jaffé procedure on the CX3 to IDMS-traceable values obtained with the enzymatic method on the ModP. While correlation of the two assay methods was excellent (Pearson correlation coefficient 0.9986), median serum creatinine concentration from the CX3 was 0.18 mg/dL higher than that of the ModP: CX3 1.0 mg/dL (interquartile range 0.8, 1.4 mg/dL); ModP 0.82 mg/dL (0.69, 1.26 mg/dL), **Supplementary Figure 1**. The mean and standard deviation revealed a similar trend (1.44±1.25 mg/dL CX3 vs. 1.27±1.17 mg/dL ModP). A Bland Altman plot demonstrated consistent difference, with all points above the reference line of 0 mg/dL, meaning that measurements from the CX3 were consistently higher than those from the ModP. Pearson correlation showed that the difference between tCX3 and ModP was positively associated with the mean of the two methods (0.77), meaning that the difference between the two assays was larger for higher serum creatinine concentrations.

Linear regression was used to develop an equation to calibrate CX3 serum creatinine concentration to IDMS traceable concentrations: $SCr_{calibrated} = -0.0726 + 0.937 \times SCr_{CX3}$. The distribution of the calibrated CX3 serum creatinine concentration was almost identical to that of ModP serum creatinine: mean ± standard deviation 1.27±1.17 mg/dL; median (interquartile range): 0.86 mg/dL (0.68, 1.24 mg/dL). A repeat Bland Altman plot including calibrated CX3 creatinine and original ModP creatinine demonstrated a balanced distribution of data points above and below the reference line of 0 mg/dL, with the majority within +/- 0.1 mg/dL, suggesting no obvious overestimation or underestimation between the two measures; Pearson correlation showed that the difference and mean of the two measures were not correlated (-0.03, P=0.72). The test of homoscedasticity revealed a constant variance of the error term (P=0.23). Log-transformation of CX3 and ModP serum creatinine concentrations prior to linear regression did not improve results. Analysis of mean serum creatinine concentrations in DCCT/EDIC before 2007 (calibrated CX3 creatinine) and after 2007 (ModP creatinine) demonstrated no break in temporal trend during 2007.

Supplementary Figure

Supplementary Figure S1. Calibration of serum creatinine



Suplementary Figure S1. Calibration to achieve consistent serum creatinine concentrations across time in the DCCT/EDIC Study: comparison of creatinine concentrations measured by a Jaffé procedure (CX3, old assay) to those measured simultaneously by an IDMS-traceable enzymatic method (ModP, new assay). Regression line (blue) is superimposed on a scatter plot and line of identity (orange). Histograms and box plots reflecting distributions of serum creatinine concentrations are shown outside the X and Y axes.

Supplementary Tables

Supplementary Table S1. Effects of intensive diabetes therapy on mean estimated glomerular filtration rate and change in estimated glomerular filtration rate over time (slope) by period of assessment (DCCT vs. EDIC).

	DCCT (1983/1989-1993)		EDIC (1994-2009)	
	Mean (95% CI)	**P value**	**Mean (95%)**	**P value**
Mean at baseline (mL/min/1.73m^2)				
Intensive therapy	126.0 (112.2, 139.9)		116.0 (103.0, 129.0)	
Conventional therapy	126.2 (111.7, 140.8)		117.8 (104.1, 131.5)	
Difference*	-0.2 (-1.7, 1.3)	0.8	-1.8 (-3.2, -0.4)	**0.002**
Model 1†				
Mean at year 1 (mL/min/1.73m^2)				
Intensive therapy	121.8 (121.3, 122.2)		114.6 (114.2, 115.0)	
Conventional therapy	123.2 (122.8, 123.7)		113.0 (112.6, 113.3)	
Difference*	-1.4 (-2.2, -0.6)	**0.0003**	1.6 (1.1, 2.2)	**<.0001**
Rate of change (slope, mL/min/1.73m^2/yr)				
Intensive therapy	-1.26 (-1.42, -1.10)	**<.0001**	-1.32 (-1.45, -1.19)	**<.0001**
Conventional therapy	-1.19 (-1.36,-1.03)	**<.0001**	-1.55 (-1.68, -1.43)	**<.0001**
Difference*	-0.06 (-0.29, -0.16)	0.6	0.23 (0.05, 0.41)	**0.01**
Model 2‡				
Overall Mean (mL/min/1.73m^2)				
Intensive therapy	118.4 (117.9, 118.9)		104.7 (104.0, 105.5)	
Conventional therapy	120.1(119.6, 120.5)		102.2 (101.5, 103.0)	
Difference*	-1.7 (-2.3, -1.0)	**<.0001**	2.5 (1.4, 3.6)	**<.0001**

* Difference comparing intensive to conventional diabetes therapy, with positive numbers indicating higher values for intensive therapy (higher mean estimated glomerular filtration rate or less rapid loss of estimated glomerular filtration rate over time) and negative numbers indicating lower values for intensive therapy (lower mean estimated glomerular filtration rate or more rapid loss of estimated glomerular filtration rate over time).

†Model 1 assessed mean eGFR and its change over time ("slope") by allowing random intercepts and random slopes. For DCCT results, independent variables included DCCT treatment assignment, interaction term of DCCT treatment assignment and time, and DCCT baseline eGFR. For EDIC results, independent variables included DCCT treatment assignment, interaction term of DCCT treatment assignment and time, age, gender, diabetes duration, DCCT cohort (primary vs. secondary), and EDIC baseline eGFR. Estimated GFR was imputed as 10 mL/min/1.73m^2 for study visits occurring after the development of ESRD.

‡Model 2 assessed only mean eGFR by incorporating the same covariates as Model 1 except the interaction term of DCCT treatment assignment and time. No random intercepts or random slopes were specified.

Supplementary Table S2. Iothalamate glomerular filtration rate (GFR) and its change over time among subsets of DCCT/EDIC participants with available measurements.

Time interval	Intensive Diabetes Therapy	Conventional Diabetes Therapy	Difference (Intensive - Conventional Diabetes Therapy)	P-value for difference
DCCT baseline to DCCT closeout				
N	177	189		
Time between measurements (years)	4.8 (0.6)	4.9 (0.6)		
DCCT baseline GFR (mL/min/1.73m^2)	126.5 (18.4)	127.7 (18.7)	-1.2 (-2.6, 5.0)	0.53
DCCT close-out GFR (mL/min/1.73m^2)	117.3 (16.5)	124.8 (22.2)	-7.4 (-11.5, -3.4)	**0.0003**
Difference in GFR (mL/min/1.73m^2, DCCT closeout - baseline)	-9.2 (-45.4, 27.0)	-3.0 (-42.9, 36.9)	-6.2 (-10.2, -2.2)	**0.0025**
EDIC Baseline to EDIC Year 1 or 2				
N	499	471		
Time between measurements (years)	2.1 (0.5)	2.1 (0.5)		
EDIC Baseline GFR (mL/min/1.73m^2)	118.0 (17.8)	122.7 (19.7)	-4.6 (-7.0, -2.3)	**0.0001**
EDIC year 1 or 2 GFR (mL/min/1.73m^2)	116.4 (20.5)	115.7 (24.5)	0.8 (-2.1, 3.6)	0.59
Difference in GFR (mL/min/1.73m^2, EDIC Year 1 or 2 - EDIC Baseline)	-1.6 (-35.9, 32.7)	-7.0 (-50.9, 36.9)	5.4 (2.9, 7.9)	**<.0001**

Cell contents are mean (SD) for time between measurements and absolute values of iothalamate GFR or difference (95% confidence interval) for differences in iothalamate GFR within and between groups. Differences with confidence intervals and P values are generated from the General Linear Model.

GFR was measured by iothalamate clearance periodically during the DCCT and at years 1 or 2 of EDIC (half of the cohort per year) using standardized methods (Kidney Int 1995;47:1703-20). EDIC baseline is equivalent to DCCT closeout.