

SUPPLEMENTARY DATA

Supplementary Table 1. Univariate analysis of risk factors for Sustained Microalbuminuria (AER>30)

Characteristics	Development of sustained microalbuminuria (AER \geq 30mg/24hr) from DCCT closeout through EDIC study year 15-16		
	Event	Nonevent	P value
N	38	160	
Demographic			
Age at EDIC study baseline	32.8 \pm 7.6	34.4 \pm 6.5	0.25
Women (%)	55.3	46.9	0.35
Diabetes duration at EDIC baseline (years)	9.6 \pm 3.9	10.8 \pm 4.8	0.25
DCCT treatment group			
Intensives (%)	47.4	59.4	0.18
Glycemia control			
DCCT mean A1c (%)	8.9 \pm 1.6	7.8 \pm 1.5	<.0001
EDIC mean A1c up to EDIC study year 16 (%)	9.0 \pm 1.3	7.8 \pm 1.0	<.0001
Retinopathy at EDIC baseline (%)			
No retinopathy (10/10)	18.4	33.1	0.11
Microaneurismsonly20/(<)20	44.7	36.9	
Mild NPDR 35/(<)35	21.1	20.6	
Moderate NPDR or worse 43/(<)43 +	15.8	9.4	
Renal at EDIC baseline			
AER (mg/24 hr), median (inter-quartiles)	11.5 (7.2, 20.2)	7.2 (4.3, 10.1)	<.0001

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AER\geq40 (%)	10.5	0	<.0001
Neuropathy at EDIC baseline			
Confirmed clinical neuropathy (%)	10.5	8.8	0.74
Abnormal autonomic function (%)	18.2	5.2	0.012
Skin Collagens at EDIC baseline			
Furosine (pmol/mg)	886 \pm 214	724 \pm 214	<.0001
CML (pmol/mg)	590 \pm 127	515 \pm 128	0.001
Pentosidine (pmol/mg)	29.1 \pm 8.4	24.8 \pm 6.7	0.001
Fluorescence (pmol/mg)	197 \pm 45	182 \pm 50	0.02
Acid-soluble collagen (%)	0.48 \pm 0.2	0.58 \pm 0.3	0.03
Pepsin-soluble collagen (%)	5.7 \pm 2.7	7.1 \pm 3.3	0.003
GSPNE (nmol/mg)	2.8 \pm 0.6	2.4 \pm 0.6	<.0001
CEL (pmol/mg)	158 \pm 98	144 \pm 113	0.22
G-H1 (pmol/mg)	74 \pm 51	64 \pm 29	0.47
MG-H1(nmol/mg)	0.95 \pm 0.6	0.77 \pm 0.4	0.056

~ The nephropathy analyses excluded those who had sustained AER \geq 30mg/24 hr at DCCT closeout (n=18).

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Supplementary Table 2. Summary of multivariable logistic regressions for Sustained Microalbuminuria (AER>30)

Covariate effects from multiple models	Df	X ²	P value	Entropy R ²	OR~ (95% CI)
All AGEs: Furosine,CML,pentosidine, Fluorescence, acid/pepsin soluble,CEL, GH1, MG-H1, GSPNE					
Unadjusted	10	22.6	0.012	0.12	
Adjusted for					
DCCT mean A1c	10	13.4	0.20	0.07	
EDIC mean A1c	10	20.5	0.03	0.11	
Old AGEs published in 2005: Furosine,CML,pentosidine, Fluorescence, acid/pepsin soluble					
Unadjusted	6	20.1	0.003	0.11	
Adjusted for					
DCCT mean A1c	6	10.6	0.10	0.06	
EDIC mean A1c	6	17.4	0.008	0.10	
Backward selected AGEs: Furosine					
Unadjusted	1	14.4	0.0002	0.08	2.0 (1.4, 2.9)
Adjusted for					
DCCT mean A1c	1	2.9	0.09	0.02	1.6 (1.0, 2.5)
EDIC mean A1c	1	7.9	0.005	0.04	2.0 (1.3, 3.2)
CML,pentosidine, Fluorescence, acid/pepsin soluble, CEL, GH1, MG- H1, GSPNE	1	6.7	0.01	0.04	2.0 (1.0, 3.2)
All significant factors: DCCT mean A1c, EDIC mean A1c, Retinopathy, log(AER), and abnormal autonomic function at EDIC baseline	1	5.2	0.02	0.03	2.5 (1.0, 6.3)
DCCT mean A1c effect					
Unadjusted	1	14.0	0.0002	0.07	1.9 (1.4, 2.8)
Adjusted for					
Furosine,CML,pentosidine, Fluorescence, acid/pepsin soluble, CEL, GH-1, MG-H1, GSPNE	1	0.9	0.35	0.01	1.3 (0.7, 2.4)
Backward Selected AGEs: Furosine	1	1.2	0.28	0.01	1.4 (0.8, 2.3)

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EDIC mean A1c effect					
Unadjusted	1	32.0	<.0001	0.17	2.9 (1.9, 4.3)
Adjusted for					
Furosine,CML,pentosidine, Fluorescence, acid/pepsin soluble, CEL, GH-1, MG-H1, GSPNE	1	23.1	<.0001	0.13	2.7 (1.7, 4.2)
Backward Selected AGEs: Furosine	1	21.4	<.0001	0.12	2.5 (1.6, 3.8)

~ Odds ratio is based on 1 standard deviation increase in the continuous variables (DCCT mean A1c: 1.6%; EDIC mean A1c: 1.1%; furosine: 231 pmol/mg)).

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Supplementary Table 3. Spearman correlation among skin collagen modifications and with HbA1c

	Furosine	Fructose-lysine	CML	Pentosidine	Fluorescence	Acid Soluble	Pepsin Soluble	GSPNE	CEL	G-H1	MG-H1	DCCT mean HbA1c
Fructose-lysine	0.70 (<.001)											
CML	0.40 (<.001)	0.36 (<.001)										
Pentosidine	0.42 (<.001)	0.37 (<.001)	0.62 (<.001)									
Fluorescence	0.38 (<.001)	0.29 (<.001)	0.44 (<.001)	0.48 (<.001)								
Acid Soluble	-0.26 (<.001)	-0.22 (0.001)	-0.34 (<.001)	-0.34 (<.001)	-0.21 (0.002)							
Pepsin Soluble	-0.51 (<.001)	-0.45 (<.001)	-0.56 (<.001)	-0.62 (<.001)	-0.37 (<.001)	0.69 (<.001)						
GSPNE	0.52 (<.001)	0.56 (<.001)	0.50 (<.001)	0.57 (<.001)	0.43 (<.001)	-0.38 (<.001)	-0.53 (<.001)					
CEL	-0.06 (NS)	0.12 (NS)	0.02 (NS)	-0.04 (NS)	-0.07 (NS)	-0.02 (NS)	0.03 (NS)	0.11 (NS)				
G-H1	0.07 (NS)	-0.01 (NS)	0.10 (NS)	0.19 (0.005)	0.24 (<.001)	0.04 (NS)	-0.05 (NS)	0.08 (NS)	-0.57 (<.001)			

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MG-H1	0.13 (NS)	0.26 (<.001)	0.34 (<.001)	0.42 (<.001)	0.17 (0.01)	-0.17 (0.01)	-0.30 (<.001)	0.41 (<.001)	0.40 (<.001)	0.29 (<.001)		
DCCT mean HbA1c	0.72 (<.001)	0.63 (<.001)	0.38 (<.001)	0.37 (<.001)	0.37 (<.001)	-0.26 (<.001)	-0.47 (<.001)	0.48 (<.001)	-0.03 (NS)	0.09 (NS)	0.11 (NS)	
EDIC mean HbA1c	0.29 (<.001)	0.27 (<.001)	0.07 (NS)	0.02 (NS)	0.07 (NS)	-0.09 (NS)	-0.15 (0.02)	0.21 (0.002)	-0.02 (NS)	0.05 (NS)	0.04 (NS)	0.40 (<.001)