SUPPLEMENTARY DATA

Impact of C-Peptide Preservation on HbA1c, Insulin Dose Requirements and Microvascular Complications in the DCCT

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This Appendix provides the detailed description of: A: the association of the quantitative relationship of the quantitative C-peptide with risk of outcomes, B: the association of *fasting* C-peptide with the risk of outcomes, C: associations within the conventional treatment group, D: associations among those with 5-15 years duration; and E: associations with quantitative or ordinal raw outcome measures.

A: Association of Quantitative C-peptide with Risk of Outcomes

For the primary DCCT outcome, sustained ≥ 3-step progression, a 10% higher C-peptide was associated with a 6.37% lower risk. To facilitate calculations using other differences in C-peptide, **Appendix Table A1** presents the model coefficient and its 95% confidence limits. For example, the change in risk with a 25% higher C-peptide at entry, such as 3.75 versus 3.0 pmol/ml, would be computed as $100*(1.25^{-0.69554} - 1) = -14.4$ or a 14.4% risk reduction. A 50% higher C-peptide would be associated with a change in risk of $100*(1.5^{-0.69088} - 1) = -24.6$ or a 24.6% risk reduction.

Likewise, in order to achieve a given risk reduction, such as a 30% reduction, the required C-peptide increase would be computed as $[1 - 0.3]^{(1/\beta)} = 1.670$ or a 67% difference in C-peptide.

B: Fasting C-peptide

Tables A.2 and A.3 present analyses in the intensive treatment group of the qualitative and quantitative associations of the entry fasting C-peptide with outcomes. The results are described in the text of the main paper.

C: Conventional Treatment Group

Tables A.4 and A.5 present like analyses among those with 1-5 years duration within the conventional treatment group. The results are described in the text of the main paper.

D: 5 – 15 Years Duration

Tables A.6 and A.7 present analyses among those with 5-15 years duration on entry in the intensive treatment group. Those with any detectable levels are compared to those with non-detectable levels. The results are described in the text of the main paper.

E: Quantitative and Ordinal Outcome Measures.

Further analyses examined the association between C-peptide at baseline and the detailed measurements of each outcome: the severity of retinopathy using the ordinal ETDRS scale over 7 years of follow-up, the magnitude of albuminuria using the AER (mg/24 h) and the O'Brien rank score of the severity of neuropathy on a nerve conduction examination at 5 years of follow-up. The methods used for each analysis and the results follow.

Table A.8 describes the average overall characteristics during DCCT follow-up of the 855 subjects with 1-5 years duration. The geometric mean AER mg/24 h over the 7 years of follow-up was somewhat less among responders versus non-responders within the intensive group with little difference in the conventional group. For descriptive purposes the ETDRS scores at year 4 of follow-up are presented (thereafter the N observed declines). In the intensive group the majority of the responders (61%) remain free of retinopathy compared to 42% among non-responders who also had higher fractions at higher levels of retinopathy severity. Within the intensive group the O'Brien composite nerve conduction score was higher (less severe) among responders in the intensive group than non-responders whereas values within the conventional group were worse among both responders and non-responders, with no difference. Additional analyses were conducted within the intensive treatment group alone.

SUPPLEMENTARY DATA

Retinopathy. The severity of retinopathy was assessed using the Early Treatment Diabetes Retinopathy Study (ETDRS) final scale of retinopathy severity (1). Explicit descriptions of the steps along the scale are provided in prior DCCT analyses (2). The Wei-Lachin multivariate rank test (3) with the estimate of the Mann-Whitney difference (4) was used to test the difference between responders and non-responders in the distribution of the EDTRS scores using the scores from the annual follow-up assessments through DCCT year 7. The Mann-Whitney parameter is the probability that a non-responder has a higher (worse) score than a responder minus the probability that a responder has a worse score than a non-responder. The difference in probabilities is used owing to the discrete nature of the scores. The parameter is zero when the distributions are the same in the two groups and is > 0 when the scores among non-responders are higher (worse) than responders.

The analysis was conducted with no adjustment. Then a stratified analysis (5) was conducted that adjusted for membership at baseline in the primary (no retinopathy) versus secondary (mild retinopathy) cohort. Then a further analysis was stratified by cohort and the quartiles of the baseline HbA1c within each cohort to provide a joint adjustment for the baseline retinopathy level and HbA1c. The following are the unadjusted and adjusted results.

The Mann-Whitney Difference in the probability of a worse ETDRS retinopathy score over 7 years of follow-up for non-responders versus responders.

	Mann-Whitney Difference	95% Confidence Limits	p =
Unadjusted	0.131	0.052, 0.211	0.0013
Adjusted for Primary vs Secondary cohort	0.112	0.042, 0.182	0.0018
Adjusted for cohort and baseline HbA1c.	0.114	0.003, 0.226	0.0446

Unadjusted, the probability that a non-responder would have worse retinopathy is 0.131 greater than the probability that a responder would have worse retinopathy, that is highly significant. The result is virtually identical after adjustment for baseline cohort and remains significant after adjusting for baseline cohort and HbA1c.

To examine the association of the quantitative C-peptide value with the ETDRS score, we fit a quantile (median) regression model (6) to the ETDRS scores at year 4 as shown in Table A.8 as a function of the log C-peptide and the results were expressed as the number of steps change in the median on the ETDRS scale per 50% increase in C-peptide. The results are shown in the following table.

Steps change in the median on the ETDRS scale at 4 years of follow-up per 50% increase in C-peptide.

	Steps Lower	95% Confidence Limits	p =
Unadjusted	-0.15	-0.23, -0.07	0.0001
Adjusted for Primary vs Secondary cohort	-0.16	-0.23, -0.08	0.0001
Adjusted for cohort and baseline HbA1c.	-0.029	-0.07, 0.010	0.15

SUPPLEMENTARY DATA

The median number of steps on the ETDRS scale is reduced by about 0.15 steps per 50% higher level of C-peptide that is highly significant both unadjusted and then adjusted for baseline cohort. However, there is no meaningful change in the median number of steps as the C-peptide increases when also adjusting for HbA1c.

Nephropathy. The difference in the log AER between responders and non-responders, and the percentage change per 50% increase in C-peptide were assessed in a longitudinal mixed model adjusted for the follow-up year using values up to 7 years of follow-up. The following table presents the mean percentage change in AER for responders versus non-responders over the 7 years of follow-up

Mean percentage difference in AER over 7 years of follow-up for Responders versus non-responders.

	Percent Difference	95% Confidence Limits	p =
Unadjusted	-22.2%	-11.6, -33.8	0.0001
Adjusted Baseline AER	-16.5%	-7.3, -26.5	0.0003
Adjusted Baseline AER and baseline HbA1c.	-13.8%	-4.5, -23.9	0.0030

Unadjusted, the AER among responders was 22% less than that of non-responders over the 7 years of follow-up. Adjustment for the baseline AER and also for HbA1c diminished this difference somewhat but it remained significantly different.

A like analysis was conducted using the log C-peptide values and the results are presented as the percentage change in AER per 50% increase in C-peptide in the following table

Percentage change in AER over 7 years of follow-up per 50% increase in C-peptide.

	Percent change	95% Confidence Limits	p =
Unadjusted	-2.9%	-4.6, -1.2	0.0011
Adjusted Baseline AER	-1.8%	-3.4, -0.2	0.0260
Adjusted Baseline AER and baseline HbA1c.	-1.4%	-2.95, 0.27	0.1015

Unadjusted, the AER decreased by about 3% per 50% higher C-peptide over the 7 years of follow-up. Adjustment for the baseline AER diminished this effect somewhat but it remained significantly different. Adjustment for HbA1c diminished the effect further that was not significant.

SUPPLEMENTARY DATA

Neuropathy. Nerve conduction assessments were conducted in the complete cohort at 5 years of follow-up and included measurement of 10 components: median motor amplitude, median motor conduction velocity, median motor F-wave latency, median sensory amplitude, median sensory conduction velocity, peroneal amplitude, peroneal conduction velocity, peroneal F-wave latency, sural amplitude, and sural conduction velocity. For each component, the fractional rank was computed for each participant such that higher values represented worse nerve conduction. For the two latencies, the descending fractional ranks were used so that higher values were worse. The mean fractional rank (O'Brien score) was then used in a Mann-Whitney analysis (8). These scores take values between 0 and 1. An adjusted Mann-Whitney analysis was obtained from an analysis of the residuals after fitting a quantile (median) regression model of the 5 year O'Brien scores regressed on either the baseline O'Brien score, or the baseline score and HbA1c. The results are interpreted as above for the analysis of the retinopathy ETDRS scores.

The following are the unadjusted and adjusted results.

The Mann-Whitney Difference in the probability of a worse O'Brien nerve conduction score at 5 years of follow-up for non-responders versus responders.

	Mann-Whitney Difference	95% Confidence Limits	p =
Unadjusted	0.158	0.027, 0.288	0.018
Adjusted for baseline O'Brien score	0.080	0.054, 0.213	0.25
Adjusted for baseline O'Brien score and baseline HbA1c.	0.066	0.068, 0.200	0.34

Unadjusted, the probability that a non-responder would have worse neuropathy is 0.158 greater than the probability that a responder would have worse neuropathy. After adjusting for the baseline neuropathy score alone, or the baseline score and HbA1c, the difference between responders versus non-responders is diminished.

Quantile (median) regression models were then used to assess the change in the median O'Brien score at 5 years as a function of the log C-peptide unadjusted and then adjusted. The change in the median rank per 50% increase in C-peptide is presented in the following table

Change in the median O'Brien score at 5 years of follow-up per 50% increase in C-peptide

	Change	95% Confidence Limits	p =
Unadjusted	0.003	-0.007, 0.012	0.58
Adjusted Baseline O'Brien score	0.002	-0.003, 0.007	0.38
Adjusted Baseline O'Brien score and baseline HbA1c.	0.001	-0.003, 0.006	0.55

There is no association between the quantitative C-peptide value and the O'Brien score.

SUPPLEMENTARY DATA

Supplementary Table 1. Coefficient (β) for the effect of the log of the C-peptide level (pmol/ml) on risk of progression of microvascular complications in the DCCT intensive treatment in a Proportional Hazards model with no adjustments, adjustment for the entry complication status, and with adjustment for the entry HbA1c.

	Unadjusted	Adjusted for Entry Status * and HbA1c
	β (95% CI)	β (95% CI)
Retinopathy ≥ 3 Step Progression	-0.30456 (-0.50728, -0.10185)	-0.28257 (-0.49621, -0.06893)
Sustained ≥ 3 Step Progression	-0.69544 (-1.11057, -0.28031)	-0.66947 (-1.11153, -0.22741)
Nephropathy		
AER > 40 mg/24 h	-0.24201 (-0.51351, 0.029491)	-0.13921 (-0.42205, 0.14363)

* Entry status is presence or absence of retinopathy on entry for analysis of retinopathy, and the log (AER) on entry for nephropathy.

SUPPLEMENTARY DATA

Supplementary Table 2. Adjusted mean difference over 7 years of DCCT follow-up between intensively treated fasting C-peptide responders (≥ 0.075pmol/mL) versus non-responders with up to 5 years duration (< 60 months), and the change per 50% increase in C-peptide obtained using log(C-peptide) in a linear model*. A. HbA1c %; B. Total insulin dose U/kg/day.

A. HbA1c %.

	Fasting Non-Responders	Fasting Responders		Fasting C-peptide quantitatively	
	LS Mean (95% CI)	LS mean (95% CI)	p <	Change in HbA1c insulin per 50% increase in C-peptide (95% CI)	p <
Unadjusted*	7.3 (7.21, 7.46)	7.2 (7.0, 7.31)	0.0576	-0.0299 (-0.0419, -0.0178)	0.0001
(adj for cohort + duration only)	7.4 (7.23, 7.53)	7.2 (7.02, 7.34)	0.0707	-0.0648 (-0.1157, -0.0139)	0.0130
Adjusted†	7.3 (7.14, 7.40)	7.3 (7.12, 7.43)	0.9602	0.0032 (-0.0179, 0.0136)	0.5513

B. Total insulin dose U/kg/day.

	Fasting Non-Responders	Fasting Responders		Fasting C-peptide quantitatively	
	LS Mean (95% CI)	LS mean (95% CI)	p <	Change in insulin per 50% increase in C-peptide (95% CI)	p <
Unadjusted*	0.7655 (0.7370, 0.7940)	0.6626 (0.6244, 0.7008)	0.0001	-0.0299 (-0.0419 - 0.0178)	0.0001
Adjusted‡	0.7224 (0.6942, 0.7506)	0.7476 (0.7131, 0.7820)	0.2180	0.00317 (-.00725 0.013586)	0.5513

*Model including responder versus non-responders and year alone, all year 1-7 values as repeated measures.
†Model including primary versus secondary cohort and duration of diabetes, and HbA1c on entry.
‡ Model including primary versus secondary cohort and duration of diabetes, insulin dose and HbA1c on entry.

SUPPLEMENTARY DATA

Supplementary Table 3. Risk Reduction (RRd %) of progression of microvascular complications in the DCCT intensive treatment group per 50% higher fasting C-peptide value, and also comparing fasting C-peptide responders (≥ 0.075 pmol/L) on entry versus non-responders (< 0.075 pmol/L), with no adjustments, and also with adjustment for the entry complication status and HbA1c.

	Unadjusted	Adjusted for Entry Status* and HbA1c
	RRd % (95% CI)	RRd % (95% CI)
Retinopathy Progression		
≥ 3 Step		
Responders vs non-resp p =	58% (-3, 59) 0.0685	43% (-13, 135) 0.1596
Per 50% higher C-peptide p =	8.8% (-1.9, 18.5) 0.1045	8.7% (-2.2, 18.5) 0.1141
Sustained ≥ 3 Step		
Responders vs non-resp p =	247% (2, 1081) 0.0464	190% (-15, 892) 0.0905
Per 50% higher C-peptide p =	28.6% (9.5, 43.6) 0.0052	27.0% (7.6, 42.3) 0.0090
Nephropathy Progression		
Responders vs non-resp p =	146% (19, 411) 0.0156	217% (-1, 333) 0.0538
Per 50% higher C-peptide p =	12% (-2, 24) 0.0958	8.6% (-6.3, 21.5) 0.2419
Neuropathy† at 5 years		
Responders vs non-resp p =	60% (-24, 87) 0.1135	59% (-29, 87) 0.1267
Per 50% higher C-peptide p =	16% (-7.5, 35) 0.1644	16% (-8.5, 35) 0.1839
Severe Hypoglycemia		
Responders vs non-resp p =	45% (38, 52) <0.0001	47% (40, 53) <0.0001
Per 50% higher C-peptide p =	9.8% (7.5, 12.1) <0.0001	10.8% (8.5, 13.0) <0.0001

* Entry status is presence or absence of retinopathy on entry for analysis of retinopathy, and the log (AER) on entry for nephropathy.

SUPPLEMENTARY DATA

Supplementary Table 4. Adjusted mean difference over 7 years of DCCT follow-up between conventionally treated stimulated C-peptide responders (≥ 0.2pmol/mL) versus non-responders with up to 5 years duration (< 60 months), and the change per 50% increase in C-peptide obtained using log(C-peptide) in a linear model*. A. HbA1c %; B. Total insulin dose U/kg/day.

A. HbA1c %.

	Stimulated Non-Responders	Stimulated Responders		Stimulated C-peptide quantitatively	
	LS Mean (95% CI)	LS mean (95% CI)	p <	Change in HbA1c insulin per 50% increase in C-peptide (95% CI)	p <
Unadjusted*	9.3 (9.15, 9.47)	9.2 (9.03, 9.45)	0.5683	-0.0046 (-0.05578, 0.04657)	0.8600
(adj for cohort + duration only)	9.3 (9.14, 9.54)	9.3 (9.01, 9.49)	0.5247	-0.0069 (-0.0608, 0.0470)	0.8022
Adjusted†	9.2 (9.08, 9.41)	9.4 (9.23, 9.63)	0.0901	0.0645 (0.0209, 0.10806)	0.0039

B. Total insulin dose U/kg/day.

	Stimulated Non-Responders	Stimulated Responders		Stimulated C-peptide quantitatively	
	LS Mean (95% CI)	LS mean (95% CI)	p <	Change in insulin per 50% increase in C-peptide (95% CI)	p <
Unadjusted*	0.6871 (0.6634, 0.7108)	0.6161 (0.5854, 0.6468)	0.0003	-0.044199 (-0.017921, 0.00535)	0.2905
Adjusted‡	0.6548 (0.6347, 0.6749)	0.6856 (0.6611, 0.7101)	0.0243	0.03068 (0.001307, 0.012441)	0.0159

*Model including responder versus not and year alone, all year 1-7 values as repeated measures.
†Model including primary versus secondary cohort and duration of diabetes, and HbA1c on entry.
‡ Model including primary versus secondary cohort and duration of diabetes, insulin dose and HbA1c on entry.

SUPPLEMENTARY DATA

Supplementary Table 5. Risk Reduction (RRd %) of progression of microvascular complications in the DCCT conventional treatment group with duration < 5 years per 50% higher stimulated C-peptide value on entry, and also comparing stimulated C-peptide responders (≥ 0.2 pmol/L) versus non-responders (< 0.2 pmol/L), with no adjustments, and also with adjustment for the entry complication status and HbA1c.

	Unadjusted	Adjusted for Entry Status* and HbA1c
	RRd % (95% CI)	RRd % (95% CI)
Retinopathy Progression		
≥ 3 Step		
Responders vs non-resp p =	13% (-27, 37) 0.4110	-13% (-58, 20) 0.4919
Per 50% higher C-peptide p =	2.9% (-3.1, 8.6) 0.3359	-1.6% (-8.5, 4.8) 0.6314
Sustained ≥ 3 Step		
Responders vs non-resp p =	6% (-46, 39) 0.7946	-25% (-96, 20) 0.3218
Per 50% higher C-peptide p =	3.3% (-4.9, 10.7) 0.4215	-2.5% (-12.0, 6.2) 0.5812
Nephropathy Progression		
Responders vs non-resp p =	9% (-48, 44) 0.7143	-2% (-68, 37) 0.9262
Per 50% higher C-peptide p =	7.8% (-1.1, 15.8) 0.0840	4.8% (-4.6, 13.4) 0.3079
Neuropathy† at 5 years		
Responders vs non-resp p =	23% (-43, 59) 0.4093	13% (-65, 54) 0.6746
Per 50% higher C-peptide p =	1.4% (-10.9, 12.4) 0.8094	1.4% (-14.8, 10.4) 0.8250
Severe Hypoglycemia		
Responders vs non-resp p =	38% (22, 50) <0.0001	44% (30, 56) <0.0001
Per 50% higher C-peptide p =	5.5% (2.1, 8.9) 0.0017	7.8% (4.4, 11.1) <0.0001

* Entry status is presence or absence of retinopathy on entry for analysis of retinopathy, and the log (AER) on entry for nephropathy.

SUPPLEMENTARY DATA

Supplementary Table 6. Adjusted mean difference over 7 years of DCCT follow-up between intensively treated patients with a detectable stimulated C-peptide (> 0.03pmol/mL) versus those undetectable with 5-15 years duration (≥ 60 months). A. HbA1c %; B. Total insulin dose U/kg/day.

A. HbA1c %.

	Stimulated undetectable	Stimulated Detectable	
	LS Mean (95% CI)	LS mean (95% CI)	p <
Unadjusted*	7.3 (7.15, 7.39)	7.2 (6.96, 7.39)	0.4414
(adj for cohort + duration only)	7.5 (7.12, 7.81)	7.2 (6.84, 7.64)	0.0675
Adjusted†	7.4 (7.04, 7.68)	7.2 (6.87, 7.60)	0.2618

B. Total insulin dose U/kg/day.

	Stimulated undetectable	Stimulated Detectable	
	LS Mean (95% CI)	LS mean (95% CI)	p <
Unadjusted*	0.7187 (0.6909, 0.7465)	0.7363 (0.6842, 0.7883)	0.5573
Adjusted‡	0.7631 (0.6797, 0.8233)	0.8021 (0.7272, 8771)	0.0923

*Model including responder versus not and year alone, all year 1-7 values as repeated measures.
†Model including primary versus secondary cohort and duration of diabetes, and HbA1c on entry.
‡ Model including primary versus secondary cohort and duration of diabetes, insulin dose and HbA1c on entry.

SUPPLEMENTARY DATA

Supplementary Table 7. Risk Reduction (RRd %) of progression of microvascular complications in the DCCT intensive treatment group comparing those with a detectable stimulated C-peptide (> 0.03pmol/mL) on entry versus those undetectable with 5-15 years duration (≥ 60 months), with no adjustments, and with adjustment for the entry complication status and HbA1c.

	Unadjusted	Adjusted for Entry Status* and HbA1c
	RRd (95% CI)	RRd (95% CI)
Retinopathy Progression		
≥ 3 Step		
Detectable vs undetectable p =	1.79 (1.01, 3.17) 0.0474	1.61 (0.90, 2.86) 0.1071
Sustained ≥ 3 Step		
Detectable vs undetectable p =	1.17 (0.56, 2.43) 0.6794	0.978 (0.47, 2.056) 0.9539
Nephropathy Progression		
Detectable vs undetectable p =	0.96 (0.53, 1.75) 0.9036	0.78 (0.42, 1.43) 0.4178
Neuropathy† at 5 years		
Detectable vs undetectable p =	0.91 (0.35, 2.39) 0.8529	0.92 (0.35, 2.42) 0.8638
Severe Hypoglycemia		
Detectable vs undetectable p =	22 (12, 32) 0.002	23 (12 33) <0.0001

* Entry status is presence or absence of retinopathy on entry for analysis of retinopathy, and the log (AER) on entry for nephropathy.

SUPPLEMENTARY DATA

Supplementary Table 8. Outcome characteristics among those with < 60 months duration of diabetes (N=855) classified as C-peptide responders with Stimulated C-peptide ≥ 0.2 pmol/mL on study entry versus non-responders (Stimulated C-peptide < 0.2 pmol/mL).

	INTENSIVE		CONVENTIONAL	
	Responders N=138	Non-Responders N=274	Responders N=165	Non-Responders N=278
Ordinal or quantiative outcome characteristics§				
AER (geometric mean x/÷ GSD)*	8.13 x/÷ 2.20	9.94 x/÷ 1.78	11.1 x/÷ 2.84	11.5 x/÷2.30
Year 4 Retinopathy levels				
1 = 10, no retinopathy	73 (61%)	107 (42%)	58 (40%)	91 (35%)
2 = 20/10, very mild NPDR	27 (23%)	79 (31%)	35 (24%)	64 (25%)
3 = 20/20	18 (15%)	52 (20%)	28 (19%)	62 (24%)
4 = 35/<35, mild NPDR	1 (0.8%)	12 (5%)	16 (11%)	28 (11%)
5 = 35/35	0	3 (1%)	2 (1%)	9 (3%)
6 = 43/<43, Moderate NPDR(1)	0	2 (0.8%)	4 (3%)	3 (1%)
7 = 43/43, Moderate NPDR(1)	0	0	0	3 (1%)
8 = 47/<47, Moderate NPDR(2)	0	1 (0.4%)	0	0
9 = 47/47, Moderate NPDR(2)	1 (0.8%)	0	1 (0.7%)	0
Neuropathy O'Brien score at year 5 median (25,75 percentiles)	0.62 (0.50, 0.71)	0.56 (0.47, 0.66)	0.45 (0.35, 0.59)	0.47 (0.36, 0.58)

* From a longitudinal regression model of the natural log(AER) with a class effect for the 7 years of follow-up comparing responders versus non-responders, with separate models within each treatment group. Results presented as a geometric mean (exp(mean log(x)) and geometric standard deviation (exp(stddev(log(x)))

† Steps on the final ETDRS scale of retinopathy severity where X/<X designates that the worse eye is at level X and the other eye at a lesser level, X/X designates that both eyes are at level X. NPDR equals non-proliferative diabetic retinopathy. Values were missing for 36 intensive and 39 conventional patients that are excluded from denominator

§ The O'Brien mean fraction rank among the 10 nerve conduction components, a value 0.5 refers to the median O'Brien score in the cohort. Lower O'Brien scores reflect increasing severity of nerve conduction defects..

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