

**Fasting plasma C-peptide and micro- and macrovascular complications
in a large clinic-based cohort of type 1 diabetic people**

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Objective: A protective effect of residual β -cell function on microvascular complications of type 1 diabetes has been suggested. Our aim was to retrospectively evaluate the association between fasting plasma C-peptide values and micro- and macrovascular complications.

Research design and methods: We recruited a clinic-based cohort of 471 type 1 diabetic persons, born after 1945 and cared for in period 1994-2004. Centralized measurements and standardized procedures of ascertainment of micro- and macrovascular complications were employed. Individual cumulative average of HbA1c up to 2007 was calculated.

Results: a residual β -cell secretion was detected even many years after diabetes diagnosis. In multivariate linear regression analysis, fasting plasma C-peptide values were positively associated with age at diagnosis ($\beta=0.02$, $p<0.0001$) and triglycerides ($\beta =0.20$, $p=0.05$), and inversely associated with diabetes duration ($\beta=-0.03$, $p<0.0001$), and HDL-cholesterol ($\beta =-0.006$, $p=0.03$). The final model explained 21% of fasting C-peptide variability. With respect to fasting C-peptide values in the lowest tertile (< 0.06 nmol/l), higher values were associated with lower prevalence of microvascular complications (OR=0.59, 95% CI 0.37-0.94), independently of age, sex, diabetes duration, individual cumulative HbA1c average during the study period, hypertension, and cardiovascular diseases. No association was evident with macrovascular complications (OR=0.77, 95% CI 0.38-1.58).

Conclusions: Our study shows an independent protective effect of residual β -cell function on the development of microvascular complications in type 1 diabetes, suggesting the potential beneficial effect of treatment allowing the preservation of even modest β -cell function over time.

Type 1 diabetes is due to a chronic autoimmune destruction of insulin-producing β -cells. Few studies, however, have assessed changes in insulin secretion over time in affected people and its relationship with diabetes complication (1-4). C-peptide has been widely accepted as the most appropriate measure of residual β -cell function, because it is secreted on equimolar basis with insulin and, differently from the latter, is not removed in the first pass through the liver (5). Studies have pointed out the relationship between residual β -cell function and age at diagnosis (6,7), markers of β -cell autoimmunity (8,9) and glycemic control (10). The DCCT Study has pointed out the benefits of higher and sustained levels of C-peptide secretion (4); indeed, in the intensively treated group even modest residual β -cell secretion was associated with decreased incidence of microvascular complications and hypoglycemia (4). The next frontier for treating diabetes is now considered the preservation of β -cell function by reducing the autoimmune stimulus directed at pancreatic islets (11-14). More recently, a potential beneficial effect on micro- and macrovascular complications of administering C-peptide in people with type 1 diabetes has also been suggested, but clinical evidence is still quite limited (15-17). Experimental studies are consistent with a biological effect of C-peptide on Na^+/K^+ -ATPase, eNOS activities and nuclear factor- κB (NF- κB) activation of endothelial cells that, under high glucose conditions, are subject to progressive dysfunction (15, 18-19).

Aims of this study were to describe the residual β -cell secretion and its association with micro- and macrovascular complications of the disease in a large clinic-based cohort of type 1 diabetic people, independently of glycemic control and other risk factors.

RESEARCH DESIGN AND METHODS

Out of a large clinic-based cohort of 1024 persons with type 1 diabetes cared for at the academic diabetes clinic of the “S. Giovanni Battista” Hospital in Turin, we recruited all people born in 1945 or after, who had been examined at least once during period 1994–2004 (n=573). A diagnosis of type 1 diabetes was based on permanent insulin treatment within 6 months of diagnosis. People are generally cared for 3-4 times/year by diabetologists, with centralized measurements, updated clinical information and annual assessment of complications according to standardized procedures. For all patients, the presence of micro- and macrovascular complications at the last clinical assessment was retrieved from clinical chart up to 2007, as well as BMI, blood pressure and plasma values of fasting glucose, lipids and creatinine. Hypertension was defined as either blood pressure 140/90 mmHg and over or current antihypertensive treatment. Cardiovascular disease (CVD) was defined as physician diagnosed myocardial infarction, angina, coronary artery bypass graft, stroke, arterial disease of lower limb or epiaortic arterial trunks. Screening for diabetic nephropathy was performed measuring albumin/creatinine on first morning urine collection and confirming abnormal results with albumin excretion rate on overnight urine collection. Screening for diabetic retinopathy was performed locally by trained diabetologists and ophthalmologists, who also performed laser therapy when indicated. Distal symmetrical polyneuropathy was diagnosed on the basis of presence of one or more neuropathic symptoms, absence of two or more ankle or knee reflexes and abnormal vibration perception threshold, measured by biothesiometers on the right big toe and on the right medial malleolus. Autonomic neuropathy was defined as a loss

of heart rate variability with an R-R ratio <1.04 and/or postural hypotension with a fall in systolic blood pressure ≥ 20 mmHg. Residual β -cell function was assessed at the initial visit at the clinics in prevalent cases or at disease stabilization in incident cases, by measuring fasting plasma C-peptide (DPC, Los Angeles, California, USA; normal values, 0.36–1.17 nmol/l). Out of 573 people of the study base, plasma C-peptide values were available in 471 (82.2%). Median lag-time between C-peptide measurement and last clinical assessment of complications was 4.5 years (interquartile range 2.1–6.8).

Cumulative individual averages of HbA1c over the observational study period (1994–2007) were calculated. Markers of β -cell autoimmunity (GADA, ICA) were assessed at the same time of C-peptide plasma levels. GADA were measured by a radioligand assay using human recombinant GAD 65 as antigen (Medipan Diagnostica-Selchow, Germany); immunocomplexes were precipitated with protein A, according to the method of Schmidli. GADA values > 0.9 U/ml were considered as positive. Anti-islet cell antibodies (ICA) were assayed by indirect immunofluorescence on frozen sections of human blood group 0 pancreas with fluorescein isothio-cyanate-conjugated rabbit antibodies. ICA positivity was expressed in Juvenile Diabetes Foundation units (JDF-u), by a standard curve based on the international JDF-u reference sera sample. An ICA ≥ 5 JDF-u was considered as positive. Both sensitivity and specificity were 100% at the 4th GADA and 13th ICA proficiency programme of the Research Institute for Children, New Orleans, LA, USA (Laboratory ID 13).

Statistical analysis: Data are shown as mean and standard deviation (SD), whereas non-normally distributed variables (triglycerides, C-peptide) were analyzed after a logarithmic transformation and referred in

tables as geometric mean and interquartile range. Pearson correlations were performed. Multiple linear regression analysis was performed to assess variables independently associated with fasting plasma C-peptide. We then performed logistic regression analysis in order to study variables independently associated with microvascular (retinopathy, micro-macroalbuminuria, diabetic neuropathy) and macrovascular complications (myocardial infarction, angina, coronary artery bypass graft, stroke, peripheral arteriopathy). The independent role of C-peptide was examined using tertiles of its distribution (<0.06 nmol/l, 0.06–0.10 nmol/l, 0.11–2.76 nmol/l). ORs in the second and third tertile were similar and were aggregated as reference category in the final analysis and compared with the lowest tertile. Variables assessed in models were age, mean cumulative HbA1c, time gap between measurement of C-peptide and last clinical assessment, positivity of markers of β -cell autoimmunity (ICA, GADA), BMI, micro and macrovascular complications, lipids, blood pressure, smoking, treatment with ACE-inhibitors and sartans. We compared nested models using both the backward and the forward strategy (20). Two models are nested if both contain the same predictors and one has at least one additional predictor. In the final analysis, we included variables which were significantly associated with the independent variable on a LR test basis, or that modified ORs for other variables included (20). All analyses were performed using Stata 10.0.

RESULTS

Mean diabetes duration in 471 people recruited for present analyses was 15.8 ± 10.2 years (range 5.2–39 years). As shown in Table 1, characteristics of people by C-peptide tertiles were similar, apart from diabetes duration, plasma triglycerides and HDL-

cholesterol values, which were significantly higher and lower, respectively, in people in the lowest tertile. A residual β -cell secretion was detected even many years after diabetes diagnosis. Indeed, almost 50% of people with C-peptide values in the upper tertile had 10 years and over of diabetes duration. In contrast, no differences among tertiles were found in BMI, blood pressure, glycemic control and LDL-cholesterol. In the whole cohort, frequency of positivity of markers of β -cells autoimmunity (ICA and/or GADA) was high (73.0%); frequency, however, was higher in people with C-peptide values in the upper tertile with respect to those with values in the lower tertile (85.7% vs 65.4%).

In univariate analysis, fasting C-peptide values were positively correlated with age at diagnosis ($r=0.32$, $p<0.0001$), triglycerides ($r=0.14$, $p=0.0002$), BMI ($r=0.11$, $p=0.006$), and negatively with diabetes duration ($r=-0.34$, $p<0.0001$) and HDL-cholesterol ($r=-0.16$, $p<0.0001$), whereas no significant correlations were found with age, HbA1c, blood pressure, total and LDL-cholesterol. In multivariate linear regression analysis, fasting plasma C-peptide values were positively associated with age at diagnosis ($\beta=0.02$, $p<0.0001$) and BMI ($\beta=0.03$, $p=0.02$) and inversely associated with duration of disease ($\beta=-0.03$, $p<0.0001$), independently of positivity for markers of β -cell autoimmunity (ICA and GADA) ($\beta=0.12$, $p=0.27$). After inclusion of HDL-cholesterol ($\beta=-0.006$, $p=0.03$) and triglycerides ($\beta=0.20$, $p=0.05$), however, the association with BMI was no more significant; indeed, BMI was significantly correlated with both HDL ($r=-0.15$, $p<0.0001$) and triglycerides ($r=0.28$, $p<0.0001$). The final model explained 21% of fasting C-peptide variability.

Table 2 shows the characteristics of the cohort by diabetes duration. Age was higher in people with longer diabetes duration, whereas fasting C-peptide levels were

significantly lower. Prevalence of both micro- and macrovascular complications was high, particularly in people with longer diabetes duration: at the final clinical assessment, 90% of the subgroup with duration 30 years and over had at least one microvascular complication and 21.7% had one macrovascular complication.

We then performed logistic regression analyses of variables associated with micro- or macrovascular complications at the last clinical assessment (table 3). As regards microvascular complications, we showed that, with respect to C-peptide values in the lowest tertile (<0.06 nmol/l), higher values conferred a protective effect (OR 0.59, CI 95% 0.37-0.94). This finding was independent of age, sex, diabetes duration, individual cumulative HbA1c average during the study period, hypertension, and cardiovascular diseases; all of these variables conferred significantly increased likelihood of microvascular complications, as shown by point estimates of ORs and lower limits of confidence intervals, both of them exceeding 1. Further adjustment for either lag time between diabetes C-peptide evaluation and final clinical assessment or treatment with ACE-inhibitors/sartans did not modify observed associations.

As regards to macrovascular complications, no independent associations with either fasting plasma C-peptide values (OR 0.77, CI 95% 0.38-1.58) or mean cumulative HbA1c (OR 0.93, CI 95% 0.57-1.50) were found, whereas other well-known risk factors (hypertension, LDL-cholesterol and microvascular complications) provided significant ORs values.

DISCUSSION

Results of our clinic-based study pointed out that 1) people with type 1 diabetes and higher fasting C-peptide values had lower prevalence of microvascular complications, independently of duration of diabetes,

individual cumulative average of HbA1c and other risk factors, whereas no similar association was found with macrovascular complications; 2) a residual β -cell secretion was detected even many years after diabetes diagnosis; 3) 90% of people with diabetes duration 30 years and over had at least one microvascular complication.

Our study extends previous knowledge (1-3), being based on a large series of patients cared for in a single health care structure, with centralized measurements of all examined variables and standardized procedures of complications assessment. A study conducted on 97 type 1 diabetic people showed that measurable C-peptide levels in urine were significantly associated with lower HbA1c and lower prevalence of retinopathy and microalbuminuria (1). In another study recruiting 160 diabetic people, higher levels of urinary C-peptide excretion were associated with lower prevalence of diabetic retinopathy (2), whereas negative findings were reported in a study including 62 subjects only (3). Our results, although based on an observational study design, are consistent with results obtained from the DCCT study, showing that preservation of even small residual pancreatic secretion confers a lower risk for microvascular complications, independently of glycemic control (4). Indeed, among intensively treated patients, the risk of developing diabetic retinopathy was 3.2 times higher in people with unmeasurable fasting plasma C-peptide than in those with higher residual pancreatic secretion, whereas data from conventionally treated patients did not reach statistical significance (4).

Studies conducted over the last 15-20 years have shown that a strict glycemic control since diabetes diagnosis allows to prevent both micro and macrovascular complications and the concept of "metabolic memory" has been emphasized. In our study,

the protective effect of fasting C-peptide values was independent of cumulative individual average of HbA1c during the study period, suggesting that the effect could be directly due to the biological properties of C-peptide. Indeed, recent trials have suggested that plasma C-peptide levels might have a beneficial effect on both diabetic nephropathy and neuropathy, but evidence is still quite limited (16-17). On a molecular level, C-peptide would interact with its own membrane receptor and activate two enzymes scarcely represented in type 1 diabetic people: the Na-K ATPase and the endothelial NO synthase (15).

Limitations of our study should be taken into account. At first, our results are based on a prevalence cohort, so that results might have been affected by survival bias. However, mortality rate in this relatively young cohort is quite low, thus allowing to rule out a major effect of survival bias on our results. Second, the retrospective study design does not allow to examine the role of both C-peptide and glycemic control since diabetes onset; the centralized assessment of laboratory data, however, allowed to include in the analyses both retrospective and prospective data over a long period of time. Third, C-peptide levels were obtained at variable times both from diagnosis and from the clinical outcome. Diabetes duration is associated with both increased prevalence of complications and lower fasting C-peptide levels. Our results were virtually unmodified in multivariate analyses after further adjustment for diabetes duration; however, residual confounding effect on our data cannot be ruled out.

Strengths of the study are the large number of examined people, the centralized measurements and standardized procedures employed over time, the high level of C-peptide measurements available in the cohort.

In conclusion, our study, based on a large cohort of type 1 diabetic people,

underlines a protective effect (-41%) of plasma C-peptide levels >0.06 nmol/l on microvascular complications, independently of diabetes duration, glycemic control and other confounders. Prospective studies are needed to confirm the hypothesis that early therapeutic interventions aimed to preserve even small residual β -cell secretion may

modify the natural history of diabetes.

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Table 1: Characteristics of the clinic-based cohort of 471 people with type 1 diabetes, by C-peptide tertile.

	C-Peptide tertile (nmol/l)			p
	< 0.06	0.06 – 0.10	0.11 – 2.76	
Number of cases	201	148	122	-
Males (%)	111 (55.2)	79 (53.4)	75 (61.5)	0.38
Age (years)	38.2 ± 10.5	38.6 ± 9.4	39.1 ± 9.7	0.79
Diabetes duration (years)	13.9 (7.5 – 19.8)	11.1 (4.9 – 19.2)	4.0 (0.8 – 8.5)	0.001
< 10	38 (23.0%)	43 (26.1%)	84 (50.9%)	<0.0001
10-19	79 (48.8%)	58 (35.8%)	25 (15.4%)	
20-29	56 (55.4%)	34 (33.7%)	11 (10.9%)	
≥30	28 (65.1%)	13 (30.2%)	2 (4.7%)	
BMI (Kg/m²)	24.1 ± 3.4	24.5 ± 3.6	24.5 ± 4.1	0.50
Systolic blood pressure (mmHg)	123.1 ± 15.8	121.9 ± 15.2	120.3 ± 14.9	0.29
Diastolic blood pressure (mmHg)	74.4 ± 9.9	74.4 ± 9.1	75.1 ± 8.9	0.74
Glucose (mmol/l)	12.4 ± 5.8	12.9 ± 5.2	12.1 ± 5.3	0.51
HbA1c (%)	8.2 ± 1.3	8.2 ± 1.3	8.0 ± 1.4	0.44
Positivity for autoimmunity (%)	119 (65.4)	98 (72.1)	102 (85.7)	0.001
Total cholesterol (mmol/l)	5.20 ± 1.00	5.28 ± 1.05	5.00 ± 1.18	0.10
HDL-cholesterol (mmol/l)	1.56 ± 0.47	1.57 ± 0.47	1.41 ± 0.45	0.005
LDL-cholesterol (mmol/l)	3.14 ± 0.83	3.18 ± 0.85	2.96 ± 0.96	0.12
Triglycerides (mmol/l)*	0.96	1.01	1.11	0.05

Data are expressed as mean ± SD, or percentage (%) or geometric mean (25th-75th percentile).

Table 2: Characteristics of the clinic-based cohort of 471 people with type 1 diabetes, by diabetes duration.

	Duration of diabetes (years)				p
	<10	10-19	20-29	≥30	
Number of cases	165	162	101	43	-
Males (%)	116 (63.4%)	99 (53.5%)	73 (50.3%)	29 (48.3%)	0.05
Age (years)	34.2 ± 9.7	37.3 ± 9.0	41.6 ± 8.4	47.5 ± 6.1	<0.001
C-peptide (nmol/l)	0.12 (0.08-0.27)	0.05 (0.02-0.10)	0.04 (0.02-0.10)	0.03 (0.01-0.10)	<0.0001
Retinopathy					
Background	18 (9.8%)	54 (29.2%)	60 (41.4%)	29 (40.3%)	<0.0001
Preproliferating	0	5 (2.7%)	9 (6.2%)	0	
Proliferating	0	15 (8.1%)	23 (15.9%)	13 (21.7%)	
Diabetic nephropathy	2 (1.1%)	17 (9.2%)	24 (16.6%)	12 (20.0%)	<0.0001
Autonomic or periferal neuropathy	26 (14.2%)	62 (33.5%)	73 (50.3%)	43 (71.7%)	<0.0001
All microvascular complications	39 (21.3%)	103 (55.7%)	110 (75.9%)	54 (90.0%)	<0.0001
CVD	2 (1.1%)	5 (2.7%)	27 (18.6%)	13 (21.7%)	<0.0001

Data are expressed as mean ± SD or percentage (%)

Table 3: Logistic regression of variables associated with either microvascular or macrovascular complications in a cohort of 471 people with type 1 diabetes.

Microvascular complications	Odds Ratio*(95% CI)
Duration of diabetes (per year)	1.12 (1.08-1.15)
Cumulative average of HbA1 (per 1%)	1.20 (1.01-1.41)
CVD	
no	1.00
yes	4.69 (1.01-21.84)
Hypertension (mmHg)	
no	1.00
yes	1.51 (0.95-2.40)
Fasting C-peptide (nmol/l)	
<0.06	1.00
≥ 0.06	0.59 (0.37-0.94)
Macrovascular complications	
Duration of diabetes (per year)	1.05 (0.99-1.11)
Hypertension (mmHg)	
no	1.00
yes	3.90 (1.40-10.89)
Microvascular complications	
no	1.00
yes	9.66 (1.18-78.86)
LDL-cholesterol (per 1 mmol/l)	1.90 (1.12-3.22)
Mean HbA1c (per 1 %)	0.93 (0.57-1.50)
C-peptide (nmol/l)	
<0.06	1.00
≥ 0.06	0.77 (0.38-1.58)

*ORs were adjusted for age, sex, and all other variables in the model