Myocardial ischemia/reperfusion upregulates the transcription of the Neuregulin1 receptor ErbB3, but only postconditioning preserves protein translation: Role in oxidative stress

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Diabetes-specific variables associated with quality of life changes in young diabetic people: the Turin Registry of Type 1 Diabetes, Italy.

Short running title: Diabetes-specific quality of life in type 1 diabetes

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ABSTRACT

Background and aims: Type 1 diabetes (T1DM) affects young people during the most active years of their life. Our aim was to assess quality of life (QoL) and associated variables in a large cohort of adults with childhood-onset and adult-onset T1DM.

Methods: A cohort of adult patients (18 years and older) from the T1DM Registry of Turin, Italy, was recruited. Clinical characteristics and Diabetes QoL (DQOL) questionnaire were assessed by standardized procedures.

Results: 310 adults completed the questionnaire. Age and diabetes duration at assessment (mean ± SD) were 32.8±7.3 years and 17.3±6.3 years, respectively. DQOL and its subscores were in the lower quartiles of their distributions, indicating a good level of QoL. However, scores were significantly higher in females than in males, particularly for the subscale of diabetes-related worries. In multivariate analysis, lower QoL was independently associated with female sex (β=1.07, 95% CI 1.03-1.11, p=0.003), higher age at onset (β=1.03, 1.00-1.05, p=0.009), lower schooling (β=1.05, 1.00-1.09, p=0.02), higher fasting plasma glucose (β=1.03, 1.01-1.05, p=0.008), daily SMBG >4 (β=1.06, 1.01-1.10, p=0.01), severe hypoglycemia over the last year (β=1.06, 1.01-1.11, p=0.02), lower numbers of diabetologic visits (β=1.07, 1.01-1.13, p=0.02) and hypertension (β=1.06, 1.02-1.10, p=0.005). Autonomic neuropathy was associated with diabetes impact. Female sex (β=4.36, 2.43-7.83) and daily SMBG >4 (β=3.77, 1.72-8.30) were independently associated with worst level and CSII with better level (β=0.22, 0.07-0.68) of diabetes-related worries.

Conclusions: The impact of T1DM on QoL may depend on demographic, metabolic control-related variables, presence of complications and insulin delivery modality.

Type 1 diabetes (T1DM) is a chronic disease affecting young people and influencing the most active years of their life. Current management of T1DM includes self-monitoring of blood glucose (SMBG) and multiple insulin injections under the constant threat of hypoglycemic events and chronic complications (1, 2). The results of the Diabetes Control and Complications Trial (DCCT) focused on the effectiveness of maintaining blood glucose levels as close as possible to the normal range to prevent or delay microvascular complications (3). To do so, patients need appropriate knowledge and skills to make informed choices and behavioural changes (4). Understandably, they feel challenged by diabetes and its day-to-day demands, as they have to make countless decisions for their metabolism to approximate the non-diabetic state. As a result, the psychosocial toll of living with diabetes is a heavy one, possibly reflecting on self-care behavior and quality of life (QoL) (1-2).

Previous reports on QoL in T1DM have either included relatively small numbers of young patients or limited recruitment to childhood-onset T1DM (5-11). The impact of the disease, however, might differ by both age and age at onset of the disease. The Turin Registry has been recruiting incident cases of T1DM in the age group 0-29 years since 1984 (12), and a wide population-based cohort is now available for morbidity (13) and mortality studies (14). Aim of this study was to assess self-reported QoL and its association with demographic and health-related data in a wide cohort of adult people in whom the onset of T1DM had been either in childhood or in adulthood.

Methods

The first Italian population-based registry of T1DM was established in 1984 in Turin, Northern Italy, to monitor the incidence rate of the disease up to age 29 years. As previously described, 1053 incident cases were recruited between 1/1/1984 and 12/31/2000 (14). Since we estimated from

Registry data that the regional pediatric hospital had been the referral center for more than 95% of children of the Province of Turin, we further identified a hospital-based cohort of incident cases of T1DM aged 0-14 years at diagnosis in the period 1974-1983 (n=157), approximating it to a population-based cohort. Therefore, the final incident cohort included 1210 patients with onset of T1DM in period 1974-2000.

Recruitment of the cohort

In January 2004, a follow-up investigation was set up in order to ascertain life status of all members of the overall cohort (14). Out of 1210 incident cases, 1113 were still living in the Province of Turin and formed the study base for the morbidity study (13). In this paper, data referring to 1039 patients aged 18 years and over at the clinical examination (2006-2007) were analysed. In the first phase of recruitment, the registry contacted the diabetologists who had performed the initial diagnosis in order to obtain active consent to recruit their patients (acceptance rate=98%). In the second phase, a letter indicating the aims of the study, their diabetologist's consent and an invitation to contact our diabetes clinic was sent to all patients. Those who did not answer the letter within two weeks were then called by phone either by their diabetologists or by ourselves every fortnight for up to three times to plan an appointment. To further increase adherence to the study, the list of non-recruited patients was re-examined by all diabetologists in search for any who had been seen over the previous months. The response rate of adult patients with T1DM was 33% (343/1039).

Examination of the cohort

The study was approved by the local ethics committee and carried out in accordance with the principles of the Helsinki Declaration. All adult patients who provided written consent (343/1039) were examined in 2006-2007 by trained investigators who performed fundus examination, a 12-lead resting ECG and tests for autonomic and peripheral neuropathy. For each patient we collected, by

standardized procedures, demographic data, schooling level, smoking habits, daily alcohol intake (grams per day), current insulin therapy, number and units of daily insulin administrations, frequency of SMBG, any previous hospitalization due to diabetes, any hypoglycemic event serious enough to require the help of another person and the number of diabetologic visits over the previous 12 months.

All blood specimens were centrally analyzed, including measurements of HbA1c and plasma lipids. Blood pressure was measured twice while recumbent (after 10-min rest and 2-min apart), and 1 min and 2 min after standing up. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. BMI was calculated as kg/m^2 and overweight and obesity defined by values between 26 and 29 kg/m^2 and 30 kg/m^2 and over, respectively. Microvascular complications were defined by standardized procedures, according to the EURODIAB protocol (15). Retinopathy was assessed by retinal photographs taken according to the EURODIAB protocol and graded by one diabetologist expert in diabetic retinopathy (MP) and classified as absent (level 0), non-proliferative (levels 1-3 for mild, moderate or severe), proliferative (level 4) and maculopathy. Nephropathy was defined as either overnight albumin excretion rate (AER) ≥20µg/min or albumin/creatinine ratio (A/C) ≥30 µg/mg on a spot urine sample. No patient had end-stage renal disease. Cardiovascular disease (CVD) was considered as the composite of any documented episode of myocardial infarction, stable or unstable angina, lower limb peripheral arteriopaty, and hemodinamically significant stenosis of epiaortic vessels.

Quality of life ascertainment

Perception of QoL was assessed by the self-administered Diabetes QoL (DQOL) questionnaire translated and validated into Italian (16, 17). The DQOL questionnaire was designed by the DCCT Research Group and contains 46 items which the patient rank on 5-point Likert scales ranging from 1 to 5 (1=never, 5=all the time). Four subscales measure diabetes impact on daily life (20 items,

range 20-200), diabetes-related worries (4 items, range 4-20), satisfaction (15 items, range 15-75), and social worries (7 items, range 7-35). The DQOL score is the algebraic sum of the four scores and ranges between the minimum value of 46, corresponding to the highest level of quality of life, and a maximum of 230, corresponding to the lowest level of quality of life. This instrument has good evidence of reliability and internal and external validity, both for the original version (16) and the Italian translation (17).

Statistical analysis

Normally distributed variables are presented as mean ± standard deviation (SD), whereas variables with skewed distribution (DQOL and its subscales) were analyzed after logarithmic transformation and the results presented as geometric means and interquartile range. Differences in clinical characteristics of patients were assessed by t test for continuous variables and χ^2 *test* for categorical ones. P-values refer to differences for either log-transformed DQOL score or its subscores among different groups of comparison. Pearson's correlation coefficients between continuous variables and log-transformed DQOL and subscales scores were performed.

We then performed multivariate linear regression analysis to assess variables independently associated with DQOL (total and subscales). On the basis of a *a priori* hypothesis, we assessed nested models examining the associations of DQOL with metabolic control-related variables and complications, taking into account the role of demographic variables as potential confounders. Both backward and forward strategies of model selection were employed and variables retained if they added significantly to the model or to the estimated coefficients of predictors. Examined variables were age, age at onset, duration of diabetes, fasting plasma glucose, HbA1c, lipids, BMI (continuous variable), sex, schooling (primary school vs secondary school or higher), microvascular complications, numbers of daily insulin injections (<4 and ≥4), daily SMBG (0-4 and >4), previous hospitalizations (yes vs no), use of continuous subcutaneous insulin infusion (CSII), number of

diabetologic visits over the previous 12 months (≤2, >2), severe hypoglycemic episodes over the previous 12 months (yes vs no). For continuous variables (fasting plasma glucose, age and age at onset of T1DM) β values for each increment of 1 SD are shown in Table 3. Analyses were performed with STATA software, version 10.0.

Results

Out of the incident cohort, 343 adults were recruited, 310 of whom correctly completed the DQOL questionnaire and were included in the analysis. Among 696 non-recruited adults, 410 (58.9%) could not be traced, 214 (30.8%) were not interested in the study and 72 (10.3%) had difficulties in obtaining leave of absence from work. Compared to recruited people, they were similar with respect to sex, age, age at diagnosis and diabetes duration (data not shown).

Patients included in the analyses (n=310, 53.5% males) had mean age at follow-up of 32.8 ± 7.3 years (range 19.5-48.6 years) and mean duration of diabetes of 17.3 ± 6.3 years (range 5.9-32.0 years), 144 (46.5%) of them were aged 0-14 years and 166 (53.5%) 15-29 years at diabetes onset. Fasting plasma glucose and HbA1c were 184.5± 85.8 mg/dl and 8.4±1.3%, respectively, with 36 subjects (11.6%) having HbA1c values <7.0%. Multiple daily insulin injections (≥4) were used by 95.2% of the cohort, and out of them 32 (10.3% of the cohort) used CSII. Mean values of systolic and diastolic blood pressure were 114 ± 12.2 and 79.0 ± 8.6 mmHg, respectively, and 29.7% of the patients were hypertensive. Most of the patients had normal weight, whereas 25.5% were overweight and 5.5% were obese. Ten patients (3.2%) had CVD, 137 (44.2%) any grade diabetic retinopathy, 56 (18.1%) micro-macroalbuminuria, 34 (11.0%) peripheral neuropathy and 52 (16.8%) autonomic neuropathy. With regard to schooling, 83 (26.8%) patients had attended primary school and 227 (73.2%) secondary school or higher.

As shown in Table 1, scores of DQOL and its subscales were in the lower quartiles of their distributions, indicating a fairly good level of perceived QoL. Values, however, were significantly

higher in females than in males for both DQOL and subscales referring to diabetes impact, diabetes-related worries and social worries.

DQOL correlated positively with age at onset (r=0.15, p=0.009), daily frequency of SMBG (r=0.25, p<0.0001), fasting blood glucose (r=0.18, p=0.001) and HbA1c (r=0.13, p=0.02). In addition, the number of severe hypoglycemic episodes over the previous year correlated positively with the subscale of diabetes impact (r=0.12, p=0.02).

Scores referring to diabetes-related worries were positively associated with daily SMBG (r=0.29, p<0.0001) and negatively associated with the number of daily insulin injections (r= -0.14, p=0.02). The scores of satisfaction were positively associated with age (r=0.14, p=0.02), HbA1c (r=0.22, p<0.0001), fasting glucose (r=0.16, p=0.005), daily SMBG (r=0.12, p=0.05) and diastolic blood pressure (r=0.11, p=0.06). The scores referring to social worries were associated negatively with age (-0.13, p=0.02) and positively with daily SMBG (r=0.13, p=0.03).

As shown in Table 2, other variables associated with higher DQOL in univariate analyses were both peripheral (p=0.02) and autonomic neuropathy (p=0.01), ≤2 diabetologic visits vs >2 over the previous year and low educational level (p<0.001). Neither retinopathy nor hospitalizations due to diabetes were associated with DQOL (data not shown). Similar results were found for other subscales, apart from satisfaction, which was also associated with hypertension (p=0.009) (online Table 1).

In multivariate analysis (Table 3), higher DQOL scores were positively and independently associated with demographic variables (sex, age at onset, low educational level), diabetes control-related factors (fasting plasma glucose, severe hypoglycemia over the previous year, 2 and less diabetologic visits over the previous year, daily SMBG >4), and complications (hypertension). Other microvascular and cardiovascular complications did not add significantly to the model, either separately or as a composite variable. This model explained 17% of the entire variability. We then

performed separate models for each DQOL subscale (online Table 2). Results were similar using diabetes impact as dependent variable, apart from the number of diabetologic visits, which was no longer significant, and autonomic neuropathy, which was significantly associated. In contrast, diabetes-related worries showed a strong positive association with female sex (β=4.36, 2.43-7.83) and daily SMBG >4 (β=3.77, 1.72-8.30), whereas CSII was negatively associated (β=0.22, 0.07-0.68). With regard to satisfaction, associated variables were female sex, fasting plasma glucose, 2 or less diabetologic visits over the last year, hypertension and low schooling. Social worries were associated negatively with age and positively with daily SMBG >4 and autonomic neuropathy.

Discussion

Integrating diabetes into one's life and self-identity is a complex and challenging process, which poses considerable demands on people's coping, self-esteem and mood (18, 19). This paper suggests that, in spite of all the above demands, T1DM may not play a markedly detrimental role in the life of adult patients, at least in the case of males, whereas females appear to be marginally more vulnerable to the pressures of the disease on their QoL, with specific reference to diabetes impact, diabetes-related worries and social worries. In any event, the average scores and interquartile ranges for all subareas of the DQOL, a tool that was specifically designed for patients with T1DM enrolled in the DCCT (16), are within the first quartile of the available ranges, connected with acceptably good QoL. Being a disease-specific questionnaire, the DQOL does not allow direct comparisons between diabetic and non diabetic persons. Similarly, there are no normal ranges for DQOL reported in the literature, whether in overall diabetic population samples or in specific age groups of patients. Our study was performed in adult patients, whereas previous studies using the DQOL questionnaire to analyze QoL in diabetic patients had limited recruitment to children and adolescents. Nonetheless, associations among QoL and the variables examined in our study were similar to those observed in

studies of younger patients. In particular, they showed lower QoL in girls than boys and in older adolescents, and higher QoL in patients using insulin pumps (20-24). A recent study compared QoL through the KINDL-R questionnaire in diabetic people aged 11-17 with onset of disease at age 4 and lower and in a large control group of non diabetic people, providing evidence of similar scores of QoL in both groups (7). In our study, variables associated with worse quality of life were: having developed diabetes later in life, lower schooling, higher fasting blood glucose, more frequent SMBG, and having had severe hypoglycemic attacks and less diabetes consultations over the previous year. Interestingly, HbA1c levels were not associated with QoL, and only a small percentage of the patients had values <7%, which is far from recommendations of scientific societies guidelines (25). The literature is not consistent on the association of QoL with metabolic control, with some studies showing no correlation and others showing lower QoL in those with worse glycemic control (20-24).

The influence of chronic complications was negligible, with the exception of autonomic neuropathy. The size of the effects of the above associations on overall QoL, however, was fairly small, and diabetes-related worries was the only subarea that showed large fourfold effects of being female and doing more frequent SMBG whereas, interestingly, being on CSII was associated with a similarly sized improvement of the score. It remains to be established whether better QoL was a result of these technical opportunities or rather it was patients with different psychological characteristics who availed themselves of these practices.

The results of this survey do suggest that patients in our area receive satisfactory support from the local network of diabetes clinics. There is however scope for further improvement, by implementing new approaches to care which involve a major redefinition of the roles and relationships between health care professionals and patients (2). In a previous study, we measured similar DQOL scores in adult patients with T1DM followed by usual care and an improvement after

3 years of an approach which substituted traditional top-down one-to-one visits with interactive group education sessions (26). Further addition of a structured carbohydrate counting programme improved not only QoL but also HbA1c and coping skills (27).

Limitations of this study include its cross-sectional design, which does not allow to draw causal relationships between perceived QoL and associated factors. Secondly, selection bias cannot be ruled out, as people who were not recruited in spite of proactive strategies to increase the response rate may include a higher proportion of either highly active individuals, possibly with a better QoL, or people with negative perceptions of their disease and/or invalidating complications and worse QoL. Although previous cross-sectional studies on young T1DM reported higher overall response rates, they were performed either in clinic-based cohorts (23) or through administrative data (28). When active participation to a protocol was requested with a population-based approach, response rates were similar to ours (29-30). Conversely, strengths of our survey include being based upon a population incidence registry, which allowed to check for differences between recruited and non recruited individuals. In addition, to our knowledge, this is one of the largest studies of QoL perception among young adult people with T1DM. The DCCT had reportedly measured QoL by the DQOL tool (3), but detailed results were not published. Other studies that addressed the issue were either based on smaller samples or cohorts of childhood-onset T1DM aged <18 years at recruitment (5-11).

In conclusion, this study suggests that QoL may be acceptably good in patients with T1DM, although females and patients with specific problems may fare worse. If confirmed in other cohorts, this suggests that strategies should be put in place to address the residual problems of a disadvantaged population by training providers to treat not only the pathophysiology of diabetes but also the psychosocial aspects of daily life with the disease. Our experience (21, 22) and that of others support the notion that, by empowering patients in their efforts to self-manage their diabetes

and address psychological barriers, education and psychological care are instrumental in achieving

more satisfactory medical and emotional outcomes.

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References

1. Rubin RR, Peyrot M (1999) Quality of life and diabetes. Diabetes Metab Res Rev 15: 205-218
2. Rose M, Fliege H, Hildebrandt M et al (2002) The network of psychological variables in patients with diabetes and their importance for quality of life and metabolic control. Diabetes Care 25: 25-42
3. The DCCT Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 329:977-986
4. Peyrot M, Skovlund SE, Landgraf R (2002) Epidemiology and correlates of weight worry in the multinational Diabetes Attitudes, Wishes and Needs study. Curr Med Res Opin 2009; 25:1985-93
5. Skinner TC, Hampson SE, Five-Schaw C (2002) Personality, personal model beliefs, and self-care in adolescents and young adults with type 1. Health Psychol 21: 61-70
6. Beaufort C, Swit PGF, Skinner TC et al. (2007) Continuing stability of center differences in peadiatric diabetes care: do advances in diabetes treatment improve outcome? Diabetes Care 30:2245-2250
7. Stahl A, Straßburger K, Lange K et al (2012) Health-related quality of life among German youths with early-onset and long-duration type 1 diabetes. Diabetes Care 35:1736-42

8. Wagner VM, Müller-Godeffroy E, von Sengbusch S, Häger S, Thyen U (2005) Age, metabolic control and type of insulin regime influences health-related quality of life in children and adolescents with type 1 diabetes mellitus. Eur J Pediatr 164:491-6
9. Bryden KS, Peveler RC, Stein A, Neil A, Mayou RA, Dunge DB (2001) Clinical and psychological course of diabetes from adolescence to young adulthood: a longitudinal cohort study. Diabetes Care 24:1536-40

10. Hislop AL, Fegan PG, Schlaeppi MJ, Duck M, Yeap BB (2008) Prevalence and associations of psychological distress in young adults with Type 1 diabetes. Diabet Med 25:91-6

11. Luyckx K, Vanhalst J, Seiffge-Krenke I, Weets I (2010) A typology of coping with Type 1 diabetes in emerging adulthood: associations with demographic, psychological, and clinical parameters. J Behav Med 33:228-38.

12. Bruno G, Novelli G, Panero F et al (2009) The incidence of type 1 diabetes is increasing in both children and young adults in Northern Italy: 1984-2004 temporal trends. Diabetologia 52:2531-5
13. Yau JW, Rogers SL, Kawasaki R et al; Meta-Analysis for Eye Disease (META-EYE) Study Group (2009) Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care 35:556-64
14. Bruno G, Cerutti F, Merletti F et al (2009) Piedmont Study Group for Diabetes Epidemiology. Short-term mortality risk in children and young adults with type 1 diabetes: the population-based Registry of the Province of Turin, Italy. Nutr Metab Cardiovasc Dis 19:340-4
15. Tesfaye S, Stevens LK, Stephenson JM et al (1996) Prevalence of diabetic peripheral neuropathy and its relation to glycaemic control and potential risk factors: the EURODIAB IDDM Complications Study. Diabetologia 39:1377-1384

16. The DCCT Research Group (1988) reliability and validity of a diabetes quality-of-life measure for the Diabetes control and Complications Trial (DCCT). Diabetes Care 11:725-732

17. Mannucci E, Mezzani B, Conti A, Rotella CM (1994) Valutazione della qualità della vita nei pazienti adulti diabetici tipo 1. Il Diabete 6:223-228

18. Whittemore R. Dixon J (2008) Chronic illness: the process of integration. J Clin Nurs17: 177-187

19. Kakleas K, Kandiyla B, Karayianni C, Karavanaki K (2009) Psychological problems in adolescents with type 1 diabetes mellitus. Diabetes Metab 35: 339-350

20. Graue M, Wentzel-Larsen T, Hanestad BR, Båtsvik B, Søvik O (2003)Measuring self-reported, health-related, quality of life in adolescents with type 1 diabetes using both generic and disease-specific instruments. Acta Paediatr 92:1190-6

21. Guttmann-Bauman I, Flaherty BP, Strugger M, McEvoy RC (1998) Metabolic control and quality-of-life self-assessment in adolescents with IDDM. Diabetes Care 21:915-8

22. Grey M, Boland EA, Yu C, Sullivan-Bolyai S, Tamborlane WV (1998) Personal and family factors associated with quality of life in adolescents with diabetes. Diabetes Care 21:909-14

23. O'Neil KJ, Jonnalagadda SS, Hopkins BL, Kicklighter JR (2005) Quality of life and diabetes knowledge of young persons with type 1 diabetes: Influence of treatment modalities and demographics. J Am Diet Assoc 105:85-91

24. Lawrence JM, Yi-Frazier JP, Black MH, Anderson A, Hood K, Imperatore G, Klingensmith GJ, Naughton M, Mayer-Davis EJ, Seid M; SEARCH for Diabetes in Youth Study Group (2012) Demographic and clinical correlates of diabetes-related quality of life among youth with type 1 diabetes. J Pediatr 161:201-7

25. Bruno G, De Micheli A, Frontoni S, Monge L (2010) Working Group on the Standards of care for Diabetes: Highilights from Italian Standards of Care for diabetes mellitus 2009-2010. Nutr Metab Cardiovasc Dis 21:302-314

26. Trento M, Passera P, Borgo E et al (2005) A 3-year prospective randomized controlled clinical trial of group care in type 1 diabetes. Nutr Metab Cardiovasc Dis 15: 293-301

27. Trento M, Trinetta A, Kucich C, Grassi G, Passera P, Gennari S, Paganin V, Tedesco S, Charrier L, Cavallo F, Porta M (2011) Carbohydrate counting improves coping ability and metabolic control in patients with type 1 diabetes managed by Group Care. J Endocrinol Invest 34:101-5

28. Lepore G, Bruttomesso D, Nosari I et al (2002) Glycaemic control and microvascular complications in a large cohort of Italian Type 1 diabetic out-patients. Diabetes Nutr Metab 15:232-9

29. Eeg-Olofsson K, Cederholm J, Nilsson PM et al (2010) Glycemic control and cardiovascular disease in 7,454 patients with type 1 diabetes: an observational study from the Swedish National Diabetes Register (NDR). Diabetes Care 33:1640-6

30. Margeirsdottir HD, Larsen JR, Brunborg C et al (2008) High prevalence of cardiovascular risk factors in children and adolescents with type 1 diabetes: a population-based study. Diabetologia 51:554-61

Table 1: DQOL and subscales scores among 310 adults recruited by the T1DM Registry of Turin. Values are geometric mean and interquartile range. Higher scores indicate worse quality of life. P-values refer to differences for either log-transformed DQOL score or its subscores between sexes.

	Total (n=310)	Males (n=166)	Females (n=144)	P value
DQOL (46 items, score 46-230)	78.2 (69-87)	75.5 (68-84)	81.5 (71-89)	<0.001
Diabetes impact (20 items, score 20-100)	31.5 (27-36)	30.2 (27-33)	33.0 (28-37)	<0.001
Diabetes-related worries (4 items, score 4-20)	7.1 (5-9)	6.5 (5-8)	7.9 (6-9)	<0.001
Satisfaction (15 items, score 15-75)	30.2 (26-36)	29.7 (25-35)	30.7 (26-37)	0.23
Social worries (7 items, score 7-35)	8.6 (8-9)	8.4 (8-8)	8.9 (8-9)	0.041

Table 2: Univariate analyses of characteristics of the adult population recruited by the T1DM Registry of Turin, by DQOL. Higher scores imply worse QoL. P-values refer to differences for either log-transformed DQOL score among different groups of comparison.

		N (%)	DQOL	p
Hypertension	**no**	218 (70.3)	77.3 (68-86)	0.08
	yes	92 (29.7)	80.4 (70-91)	
Normoalbuminuria		254 (81.9)	77.6 (69-86)	0.08
Micro-macroalbuminuria		56 (18.1)	81.2 (70-92)	
Peripheral neuropathy	**no**	276 (89.0)	77.6 (69-86)	**0.02**
	yes	34 (11.0)	83.8 (70-96)	
Autonomic neuropathy	**no**	258 (83.2)	77.3 (69-86)	**0.01**
	yes	52 (16.8)	82.9 (72-92)	
Daily SMBG (n)	**0-4**	82 (27.9%)	82.1 (71-92)	**0.002**
	>4	212 (72.10	76.4 (68-86)	
Diabetologic visits over the previous year (n)	**0-2**	46 (14.9)	83.0 (72-86)	**0.016**
	3 +	223 (71.9)	77.5 (68-88)	
Severe hypoglycemia	**no**	240 (77.4)	77.1 (69-86)	**0.007**
	yes	70 (22.6)	82.3 (71-93)	
Schooling	**primary school**	83 (26.8)	82.6 (71-92)	**0.001**
	middle school and higher	227 (73.2)	76.7 (69-86)	

Table 3: Multivariate analysis of variables independently associated with DQOL among adults recruited by the T1DM Registry of Turin. Exponentiated β coefficients (95% confidence interval) from multivariate models. P values from Likelihood Ratio (LR) test for nested models. Higher scores imply worse QoL

DQOL	β (95% CI)	P value
Sex (females vs males)	1.07 (1.03-1.11)	0.003
Age at onset (per 8 years)	1.03 (1.00-1.05)	0.009
Schooling (primary school vs middle school and higher)	1.05 (1.00-1.09)	0.02
Fasting plasma glucose (per 86 mg/dl)	1.03 (1.01-1.05)	0.008
Daily SMBG (>4 vs ≤4)	1.06 (1.01-1.10)	0.01
Severe hypoglycemic attack over previous year (yes vs no)	1.06 (1.01-1.11)	0.02
Diabetologic visits over previous year (0-2 vs >2)	1.07 (1.01-1.13)	0.02
Hypertension (yes vs no)	1.06 (1.02-1.10)	0.005

Online Table 1: Univariate analyses of characteristics of the adult population recruited by the T1DM Registry of Turin, by DQOL subscales. Higher scores imply worse QoL. P-values refer to differences for either log-transformed DQOL subscores among different groups of comparison

	Impact of diabetes	p	Diabetes-related worries	p	Satisfaction	p*	Social worries*	p*
Hypertension **no**	31.2 (27-35)	0.23	7.1 (5-9)	0.93	29.5 (25-35)	**0.009**	8.7 (8-9)	0.34
yes	32.1 (28-36)		7.1 (6-8)		31.9 (27-38)		8.3 (8-8)	
Normoalbuminuria	31.2 (27-35)	0.07	7.1 (7-9)	0.81	29.9 (25-35)	0.11	8.6 (8-9)	0.80
Micro-macroalbuminuria	32.9 (28-38)		7.2 (6-8)		31.6 (26-38)		8.6 (8-9)	
Retinopathy **no**	31.1 (27-35)	0.25	7.0 (5-9)	0.29	29.6 (25-35)	0.10	8.6 (8-8)	0.77
yes	31.9 (27-36)		7.3 (6-9)		30.9 (27-36)		8.6 (8-9)	
Peripheral neuropathy **no**	31.2 (27-35)	0.06	7.0 (5-9)	0.16	29.9 (25-35)	**0.03**	8.6 (8-9)	0.36
yes	33.4 (28-37)		7.7 (6-10)		32.8 (26-42)		8.9 (8-9)	
Autonomic neuropathy **no**	31.0 (27-35)	**0.005**	7.1 (6-9)	0.53	29.9 (25-36)	0.12	8.5 (8-9)	0.06
yes	33.8 (28-39)		7.3 (5-10)		31.6 (27-37)		9.1 (8-9)	
Daily SMBG **(n)** **0-4**	30.6 (28-37)	**<0.001**	7.6 (6-11)	**0.008**	30.9 (26-38)	0.19	9.0 (8-9)	**0.04**
>4	33.5 (27-34)		6.9 (5-9)		29.6 (25-35)		8.5 (8-9)	
Diabetologic visits over the previous year (n) 0-2	32.5 (28-36)	**0.24**	7.1 (6-9)	0.87	34.1 (30-38	**<0.001**	8.6 (8-9)	0.85
3 +	31.3 (27-35)		7.1 (5-9)		29.5 (25-35)		8.6 (8-8)	
Hospitalizations **no**	31.0 (27-36)	0.25	7.1 (5-9)	0.79	30.3 (26-36)	0.83	8.7 (8-8)	
yes	31.8 (28-36)		7.1 (6-9)		30.1 (25-36)		8.7 (8-9)	0.59
Severe hypoglycemia **no**	30.7 (27-34)	**<0.001**	6.9 (5-8)	**0.03**	30.0 (25-36)	0.33	8.6 (8-8)	
yes	34.1 (28-39)		7.7 (6-10)		30.9 (27-36)		8.7 (8-9)	0.53
Schooling **primary school**	33.4 (28-39)	**0.001**	7.5 (6-10)	0.06	32.1 (27-38)	**0.007**	8.5 (8-8)	0.71
middle school and higher	30.8 (27-34)		6.9 (5-9)		30.2 (25-35)		8.7 (8-9)	

Online Table 2: Multivariate analysis of variables independently associated with DQOL subscales among adults recruited by the T1DM Registry of Turin. Exponentiated β coefficients (95% confidence interval) from multivariate models. P values from Likelihood Ratio (LR) test for nested models. Higher scores imply worse QoL

Diabetes impact		
Sex (females vs males)	1.07 (1.03-1.12)	<0.001
Age at onset (per 8 years)	1.03 (1.01-1.05)	0.003
Schooling (primary school vs middle school and higher)	1.05 (1.00-1.10)	0.05
Fasting plasma glucose (per 86 mg/dl)	1.02 (1.00-1.05)	0.02
Daily SMBG (>4 vs ≤4)	1.07 (1.02-1.13)	0.003
Severe hypoglycemic attack over previous year (yes vs no)	1.09 (1.04-1.15)	0.005
Hypertension (yes vs no)	1.05 (1.01-1.10)	0.03
Autonomic neuropathy (yes vs no)	1.07 (1.00-1.13)	0.03
Diabetes-related worries		
Sex (females vs males)	4.36 (2.43-7.83)	<0.001
Daily SMBG (>4 vs ≤4)	3.77 (1.72-8.30)	<0.001
CSII (yes vs no)	0.22 (0.07-0.68)	0.008
Satisfaction		
Age at onset (per 8 years)	1.03 (1.00-1.06)	0.02
Schooling (primary school vs middle school and higher)	1.08 (1.02-1.15)	0.005
Fasting plasma glucose (per 86 mg/dl)	1.04 (1.01-1.06)	0.006
Diabetologic visits over previous previous year (≤ 2 vs >2)	1.15 (1.07-1.23)	<0.001
Hypertension (yes vs no)	1.09 (1.03-1.15)	0.005
Social worries		
Age (per 7 years)	0.97 (0.95-0.99)	0.02
Daily SMBG (>4 vs ≤4)	1.06 (1.00-1.12)	0.04
Autonomic neuropathy (yes vs no)	1.09 (1.01-1.17)	0.02