Effects of comorbid conditions on health-related quality of life in youth with Type 2 diabetes: the TODAY clinical trial

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Abstract

Aim—To explore associations between health-related quality of life (HRQOL) and comorbidities in youth with Type 2 diabetes.

Patients & methods—Of 699 youth in the TODAY study, 685 (98%) had baseline HRQOL data, 649 (93%) at 6 months and 583 (83%) at 24 months. Comorbidities were defined by sustained abnormal values and treatment regimens.

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Results—At baseline, 22.2% of participants demonstrated impaired HRQOL. Only depressive symptoms distinguished those with versus without impaired HRQOL and were significantly related to later impaired HRQOL (p < 0.0001). A significant correspondence between impaired HRQOL and number of comorbidities (p = 0.0003) was noted, but was driven by the presence of depressive symptoms.

Conclusion—Results emphasize the need for evaluation of depressive symptoms. Other comorbidities did not have a significant impact on HRQOL in this cohort.

Type 2 diabetes (T2D) in youth has become a public health concern, and the development of complications appears accelerated when compared with adults with equivalent diabetes duration [1,2]. Initial studies suggest that comorbidities are observed early in the disease course in patients with youth-onset T2D, making prevention or treatment of comorbid conditions of utmost concern in this population [3–5]. Complications such as hypertension, microalbuminuria, dyslipidemia and depression have the potential to add significant health burden and expense, and have been associated with diminished health-related quality of life (HRQOL) in adults [6]. It is important to understand whether the associations between comorbidities and perceived health status observed in the adult population with T2D are present in youth with T2D.

Studies in adults with T2D report that HRQOL worsens as diabetes-related conditions and complications increase in number, severity and duration [6]. The long-term follow-up (>23 years) of individuals with T1D [7] also shows that worsening metabolic control, serious diabetes complications and the emergence of psychiatric conditions are associated with increased HRQOL impairment. However, within an average 2.7 years of diagnosis, T1D youth report very similar HRQOL to their peers without illness [8]. Less is known about how comorbid conditions may influence self-reported health perceptions in adolescents or young adults with T2D. Some studies have found that within the first several years of disease onset, youth with T2D may have poorer HRQOL overall compared with those with T1D [9–11] but more prospective research is needed.

The TODAY randomized clinical trial (Treatment Options for Type 2 Diabetes in Adolescents and Youth) provided an opportunity to explore the effects of select comorbid conditions on HRQOL in a large well-characterized sample. Prior reports from TODAY have found that hypertension, dyslipidemia and microalbuminuria were frequently encountered at baseline and, despite aggressive management and therapies, new cases were diagnosed during follow-up of 2–6.5 years (average 3.9 years) [1,2]. In addition, 15% of TODAY participants had clinically significant depressive symptoms at baseline [12].

The primary objective of this analysis was to report on the association of comorbidities and impaired HRQOL in the TODAY cohort at baseline and during the study. Five comorbidities were examined both singly and in combination: hypertension, microalbuminuria, LDL

dyslipidemia, triglyceride dyslipidemia and clinically elevated depressive symptoms. We hypothesized that the presence and accumulation of comorbid conditions would affect HRQOL in youth with T2D.

Patients & methods

TODAY design & primary results

The collaborative study group included 15 clinical centers, a data coordinating center and central laboratories and reading centers. Study design has been reported [13] and is briefly summarized. Between July 2004 and February 2009, 699 youth were enrolled between the ages of 10 and 17 years, with T2D (pancreatic autoantibody negative) diagnosed by American Diabetes Association criteria of less than 2 years duration, and with a BMI   85th percentile. Medically-related exclusion criteria included: refractory hypertension, hyperlipidemia or anemia (i.e., abnormal values despite appropriate medical therapy); use of steroids or medications known to affect insulin sensitivity or secretion, weight gain or loss, or the metabolism of study drugs; and other significant organ system illness or conditions (including psychiatric or developmental disorders) that would prevent participation in the opinion of the investigator. To be eligible, all TODAY participants had to identify an adult caregiver who agreed to support the youth participant in the study, including accompanying to all visits.

Eligible subjects also had to successfully complete a 2–6 month prerandomization runin period that included attaining glycemic control (HbA1c <8% measured monthly for at least 2 months) on 1000–2000 mg of metformin monotherapy, mastering standard diabetes education, demonstrating   80% adherence to study medication (percent of number of pills taken divided by number prescribed by pill count) for at least 8 of 12 consecutive weeks, and attending study visits. Eligible participants were randomized to one of three treatment arms: metformin (M), metformin plus rosiglitazone (M+R) and metformin plus an intensive lifestyle program (M+L). The primary objective was to compare the three arms on time to treatment failure – that is, loss of glycemic control defined as either HbA1c   8% over a 6-month period or inability to wean from temporary insulin therapy within 3 months following acute metabolic decompensation. After an average follow-up of 3.9 years, 319 (45.6%) lost glycemic control; M+R was superior to M (p = 0.006) and M+L was intermediate but not different from M [14].

The protocol was approved by the Institutional Review Boards of the participating institutions; parents signed informed consent for a minor child, and youth signed informed assent according to local practice.

Data collection & measurements

Participants were seen every 2 months in year 1 and quarterly thereafter for purposes of medical monitoring and management and distribution of study drug; physical measurements were made and blood was drawn and sent to a central study laboratory [14]. Outcome data collection visits occurred at baseline, 6 months, 24 months and then annually.

Baseline characteristics—Race-ethnicity was determined by self report on two separate items: participants checked Hispanic/Latino ethnicity either yes or no and checked as many racial categories as needed. Participants were categorized as non-Hispanic black, non-Hispanic white, Hispanic and other (combination of categories too small for separate analysis). Household education was the highest education level attained by parent/guardian or current spouse/partner; 15 categories were collapsed into four for purposes of analysis. Annual household income of all persons living in the household in the past year was collected by self-report of participant and family member(s) present at the baseline visit; nine categories were collapsed into three for purposes of analysis. Participants were also asked whether they lived with their biological mother and/or father and total number living in the household.

Quality of life—The Pediatric Quality of Life Inventory (PedsQL) measured youth perception of HRQOL. The Total Scale Score was computed using all 23 items, the Psychosocial Health Summary Score 15 items and the Physical Health Summary Score 8 items. Each score could range from 0 to 100. Impaired HRQOL was determined by cut-offs (mean – 1 SD) derived from over 5000 healthy youth [15] as follows: 71.19 (= 83.84–12.65) for Total; 67.78 (= 81.87–14.09) for Psychosocial; 74.03 (= 87.53–13.50) for Physical.

Comorbidities—Diagnostic criteria for hypertension, dyslipidemia and microalbuminuria included consistently abnormal values and/or taking appropriate therapy. The cut-offs used have been described in detail elsewhere [4]. Briefly, cut-offs were: blood pressure 30/80 or 95th percentile for age, gender and height; LDL-cholesterol 130 mg/dl; triglycerides 150 mg/dl; and urine albumin:creatinine ratio 30 μg/mg. Once the diagnosis was made, it was treated according to study protocol and considered chronic. Depressive symptoms were assessed using either the Children's Depression Inventory (CDI) for participants <16 years [16] or the Beck Depression Inventory II (BDI-II) for those 16 years [17]. Total scores were calculated for each instrument; a cut-off score 13 on the CDI and 14 on the BDI-II indicated clinically elevated levels of depressive symptoms. Depressive symptoms could be present or absent at each assessment.

Statistical analysis

Hypothesis testing applied χ^2 for categorical data and one-way analysis of variance for continuous data. Significance was defined as $p < 0.05$ with no adjustment for multiple testing; the trial was powered for the primary outcome only.

Results

Participant characteristics

Of the TODAY cohort of 699, 685 (98%) had HRQOL data at baseline, 649 (93%) at 6 months, and 583 (83%) at 24 months. At baseline, average PedsQL Total Scale Score was 88.4 (SD 12.5, range 37–100) and 22.2% had impaired HRQOL. Table 1 gives baseline characteristics overall and by HRQOL status (impaired/not impaired). Age, sex and race-ethnicity were representative of youth-onset T2D. Although the total sample was

predominantly obese, participants with impaired HRQOL at baseline were significantly heavier than those not impaired (BMI z-score 2.33 vs 2.19, p = 0.0008; BMI 95th percentile 95.4 vs 86.3%, p = 0.0068). Several indicators of socioeconomic status (household highest level of education, total annual household income, total number in household) were not different between the two subgroups, but percent living with both biological parents was significantly different (30.2% impaired vs 41.4% not impaired; p = 0.0036).

Distribution of impaired HRQOL for each comorbidity

Figure 1 shows the relationship of baseline impaired HRQOL with baseline status of each of the five comorbidities. Only the presence or absence of depressive symptoms distinguished those with impaired HRQOL from those without. The analysis was repeated at 6 and 24 months and for the two HRQOL subscales with identical results (data not shown).

There was a significant negative correlation (r = −0.483, p < 0.0001) between total scores on the BDI and PedsQL at baseline in the TODAY cohort. Comparison of the PedsQL and the BDI shows some overlap between the PedsQL Psychosocial Health Summary Score (15 items addressing problems with feelings, getting along with others and school) and the BDI. The analysis was rerun testing for association between presence/absence of depressive symptoms and HRQOL separated into the Physical and Psychosocial Health Summary Scores. Figure 2 shows that, although much less pronounced in the subscale combining items addressing health and activities, there remains a significant association for both Physical and Psychosocial constructs.

Effect of early comorbidity on later HRQOL

We examined whether the presence of a comorbidity had a 'predictive' effect on future HRQOL by testing the relationship between baseline comorbid condition versus impaired HRQOL at 6 months and at 24 months, and between comorbid condition early (at baseline or 6 months) versus impaired HRQOL at 24 months. In all cases, only depressive symptoms were significantly related to subsequent impaired HRQOL (all p < 0.0001).

Cumulative effect of comorbidities on HRQOL

Participants were categorized as having 0, 1, or 2 or more comorbidities at each of the three time points. Figure 3 shows results at baseline. When all five comorbidities were included there was a significant correspondence between higher percent with impaired HRQOL and number of comorbidities (p = 0.0003). However, when the analysis was repeated with only four comorbidities not including depressive symptoms, there was no relationship between number of comorbidities and percent with impaired HRQOL. Results were the same at 6 and 24 months.

Trend in HRQOL over time

Participants were categorized as either having declined in HRQOL (defined as changing from not impaired to impaired categories between visits) or improved (defined as changing from impaired to not impaired). Participants who were impaired at all visits (n = 28) or not impaired at all visits (n = 376) were excluded from this analysis. The groups were compared

by whether the participant ever had the comorbidity over the 24 months of study. There was no relationship between decline or improvement in HRQOL and presence of any comorbidity.

Discussion

This study examined the impact of comorbid medical conditions including hypertension, microalbuminuria, dyslipidemia and depressive symptoms on HRQOL over time in a large sample of youth with T2D. At baseline, less than a quarter of the TODAY cohort reported poor perceived HRQOL. Of the comorbid conditions examined, only the presence of clinically elevated depressive symptoms significantly predicted HRQOL impairment at any time point. Roberto *et al.* [18] reported similar results, with a significant negative correlation (r = −0.548, p < 0.01) between total scores on the BDI and PedsQL in a sample of adolescents (ages 14–18 years) enrolled in a bariatric surgery program at a large, urban medical center. The relationship between elevated depressive symptoms and impaired HRQOL was consistent across TODAY study visits (baseline, 6 and 24 months). There was no cumulative effect of other medical comorbidities on perceived health, nor any relationship between perceived health declines or improvements and the presence of any other comorbidity.

Our main finding that depressive symptoms are a dominant predictor of HRQOL impairment over 2 years is consistent with the finding in previous studies of adults with diabetes that depression or a history of psychiatric events relates to HRQOL [19] even over long periods of time [7]. A study of the relationship of HRQOL to depressive symptoms in children and adolescents with T1D also found significant associations [9]. Our study extends these findings to youth with recent-onset T2D. The negative toll depression may have on a youth's quality of life should be discussed with youth and with their families; this is particularly important given the challenges faced by families in following through with referrals for diagnosis and treatment of mood disorders [20]. Youth with either T2D or T1D are at elevated risk for mood disorders [21,22] and their healthcare providers should be equipped with resources to screen and/or make appropriate referrals. Interdisciplinary teams, including psychologists within the clinic or hospital, could assist in addressing this vital need [23], particularly since depression has been shown to be successfully treated in youth in this age group [24].

Analysis of TODAY data also revealed that, unlike findings in adults with T2D [6], the presence of hypertension, dyslipidemia and micro-albuminuria (alone or in combination) does not appear to significantly affect the HRQOL of youth with T2D at this early stage in their illness. In our sample, these seemingly 'silent' comorbidities did not have any measurable impact on the day-to-day functioning of youth based upon their reported HRQOL. As with T1D, the psychological and social needs and demands of adolescence may simply supersede the needs and demands of this chronic medical condition. Very similar findings have been reported in obese adolescents without diabetes [25]. Therefore, one challenge presented by this finding is how to implement strategies to promote positive self-management behaviors for youth with T2D who are not affected by chronic health concerns, given an apparently accelerated development of diabetic complications.

The robust relationship between HRQOL and elevated depressive symptoms and the lack of a relationship between HRQOL and the other comorbidities may suggest that those patients with indicators of depression may develop barriers to diabetes self-care management. Thus it may be appropriate to address psychosocial needs of youth with T2D as a first step to a more broad-based discussion of chronic illness self-management and other self-care behaviors (including weight management). We also found that at baseline, family composition was related to HRQOL – that is, youth who were living with both biological parents were less often in the impaired HRQOL group. While inclusion of this information as part of a clinical assessment would require an individualized approach appreciating the diversity of family circumstance, the association warrants further investigation.

This study has several strengths including the large sample size, the repeated measurements over time and the determination of comorbid conditions applying standardized criteria and measurements made by certified staff and/or laboratories. Limitations include the fact that the TODAY sample may not be representative of youth with T2D at large due to the stringent eligibility criteria. In addition, the BDI/CDI and PedsQOL rely entirely on self-report and the former indicate presence of depressive symptoms but not a diagnosis of depression.

Conclusion

In summary, impaired HRQOL in the TODAY cohort of youth with T2D was related only to clinically elevated depressive symptoms assessed by self report survey. This relationship was consistently identified over a 2-year period, and contrary to expectation, the presence of the other comorbidities or of multiple comorbidities did not significantly impact HRQOL at any time point. Additional correlates, though not the primary focus of this study, were identified at baseline including degree of obesity and absence of one or both biological parents from the home. These findings, taken together, may assist in identifying youth who may be vulnerable to challenges in self-management and need additional screening and support to cope with their chronic condition. They also point to the importance of implementing interventions to target weight control that take into account the psychological and overall health perspectives of youth in the early stages of their T2D diagnosis.

In conclusion, these results support the importance of early screening for depressive symptoms in youth with T2D. Whether treatment for depression will improve HRQOL is a subject for future research.

Future perspective

Youth with T2D may present with varying degrees of psychological vulnerability that may be compounded by challenging socio-economic environments and comorbidities. The TODAY clinical trial addressed the need to document the extent of this phenomenon. Our findings suggest that screening for depression is an integral part of any comprehensive approach to the clinical management of T2D in this population. In addition, we recommend that future research continue to evaluate and document the impact psychological health plays in the clinical management of T2D with this ever increasing group. An examination of the

association between time since diagnosis and measures of psychological health may provide insights; because eligible participants in TODAY had to have been diagnosed <2 years, the range was too narrow in the TODAY cohort to perform a meaningful analysis.

Trial Registration: ClinicalTrials.gov NCT00081328

Acknowledgements

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Practice points

- Impaired HRQOL in the TODAY cohort of youth with Type 2 diabetes (T2D) was related only to clinically elevated depressive symptoms assessed by self report survey.

- The presence of the other comorbidities or of multiple comorbidities did not significantly impact HRQOL at any time point.

- The main finding that depressive symptoms are a dominant predictor of HRQOL impairment over 2 years is consistent with findings in previous studies of adults with diabetes.

- Additional correlates were identified including degree of obesity and absence of one or both biological parents from the home.

- The findings, taken together, may assist in identifying youth who need additional screening and support to cope with their chronic condition.

- The findings point to the importance of implementing interventions to target weight control that take into account the psychological and overall health perspectives of youth in the early stages of their T2D diagnosis.

- The results support the importance of early screening for depressive symptoms in youth with T2D.
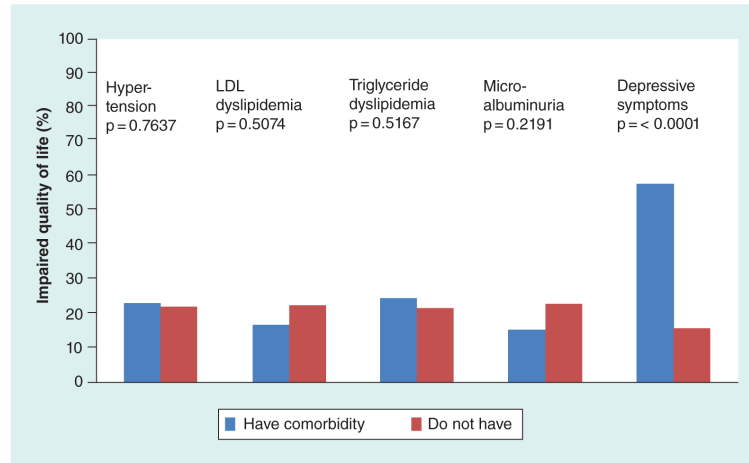
Figure 1. Distribution of impaired HRQOL by each comorbidity at baseline

Only the presence of clinically significant depressive symptoms (by self-report) was associated with impaired HRQOL.
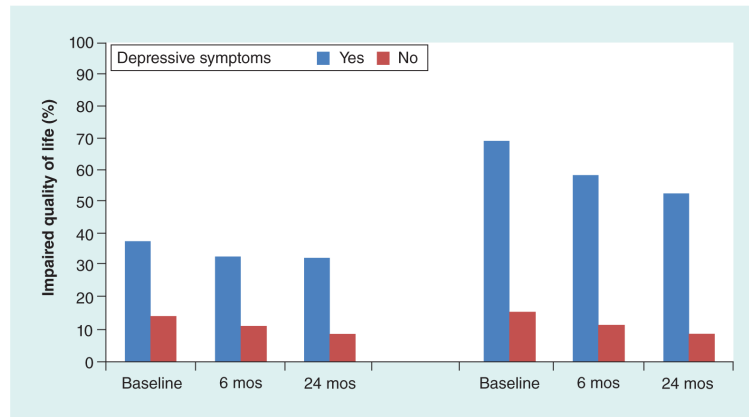
Figure 2. Percent impaired HRQOL by presence of clinically depressive symptom summary subscales across visit month

The significant association between presence of clinically depressive symptoms (total score) and impaired HRQOL was repeated for each subscale: **(A)** Physical Health Summary Score and **(B)** Psychosocial Health Summary Score: all $p < 0.0001$. The difference was less pronounced for the Physical Score than the Psychosocial Score **(B)**, likely due in part to some overlap between the PedsQL Psychosocial Score (15 items addressing problems with feelings, getting along with others and school) and the BDI.
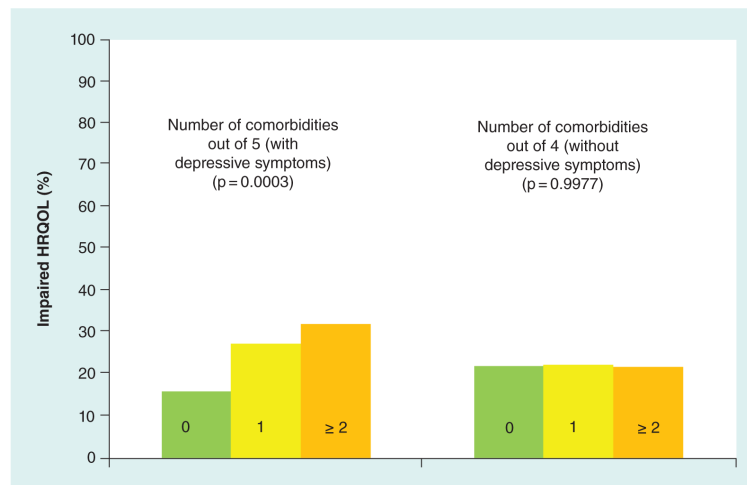
Figure 3. Percentage impaired HRQOL by presence of multiple comorbidities at baseline
Participants were categorized as having 0 (56%), one (32%) or two or more (12%)
comorbidities. When all five comorbidities were included there was a significant
correspondence between impaired HRQOL and number of comorbidities (p = 0.0003).
However, when the analysis was repeated with only four comorbidities not including
depressive symptoms, there was no relationship between number of comorbidities and
impaired HRQOL. Results were the same at 6 and 24 months.

Table 1

Descriptive statistics (mean [standard deviation] or percentage) for demographics and characteristics at baseline overall and by impaired health-related quality of life at baseline.

Characteristics determined at baseline	Overall (n = 685)	HRQOL		
		Impaired (n = 152; 22.2%)	Not impaired (n = 533; 77.8%)	p-value
Age (years); mean (SD)	14.0 (2.0)	13.9 (2.0)	14.0 (2.0)	0.5442
Female	65.0%	69.1%	63.8%	0.2279
BMI z-score; mean (SD)	2.22 (0.47)	2.33 (0.41)	2.19 (0.48)	0.0008
BMI percentile:				0.0068
– Overweight (85% to <95%)	10.2%	4.6%	11.8%	
– Obese (95%)	88.3%	95.4%	86.3%	
Race:				0.2189
– Non-Hispanic black	32.5%	36.2%	31.5%	
– Hispanic	39.6%	32.2%	41.6%	
– Non-Hispanic white	20.6%	23.0%	20.0%	
– Other	7.3%	8.6%	6.9%	
Household highest level education:				0.3023
– Less than high school	26.5%	21.6%	27.9%	
– High school or equivalent	25.0%	29.1%	23.9%	
– Some college or associates degree	31.8%	30.4%	32.2%	
– Graduate degree	16.7%	18.9%	16.0%	
Total annual household income:				0.2622
– <US$25,000	41.5%	42.1%	41.3%	
– US$25,000–49,999	33.7%	37.9%	32.4%	
– US$50,000	24.8%	20.0%	26.3%	
Lives with biological parents:				0.0036
– Both biological parents	39.0%	30.2%	41.4%	
– Biological mother only	46.7%	52.3%	45.1%	
– Biological father only	5.1%	2.7%	5.8%	
– Neither biological parent	9.2%	14.8%	7.7%	
Total number in household:				0.3810
– 2	9.5%	13.4%	8.4%	
– 3	18.7%	16.8%	19.2%	
– 4	30.9%	30.9%	30.9%	
– 5	21.5%	18.8%	22.3%	
– >5	19.4%	20.1%	19.2%	
Treatment group assignment:				0.7869
– Metformin alone	32.9%	33.5%	32.7%	

Characteristics determined at baseline	Overall (n = 685)	HRQOL		
		Impaired (n = 152; 22.2%)	Not impaired (n = 533; 77.8%)	p-value
– Metformin + rosiglitazone	33.9%	31.6%	34.5%	
– Metformin + lifestyle program	33.2%	34.9%	32.8%	