Relationships among Stressful Life Events and Physiological Markers, Treatment Adherence, and Psychosocial Functioning among Youth with Type 2 Diabetes

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Objective To examine the relationships between stressful life events and physiological measures, adherence to prescribed oral medication regimens, depressive symptoms, and impaired quality of life (QoL) in adolescents with recent-onset type 2 diabetes (T2D).

Study design Data were collected from 497 ethnically diverse participants (66% female) in the final year of the Treatment Options for Type 2 Diabetes in Adolescents and Youth multicenter clinical trial. Exposure to 32 possible events over the previous year and rating of subsequent distress were collected by self-report and summarized as a major stressors score. This score was analyzed for relationship to glycemic control (hemoglobin A1c and treatment failure), body mass index, diagnosis of hypertension or triglyceride dyslipidemia, adherence to a prescribed oral medication regimen, presence of depressive symptoms, and impaired QoL.

Results The total number of major stressful life events in the adolescents with T2D was calculated, with 33% reporting none, 67% reporting ≥1, 47% reporting ≥2, 33% reporting ≥3, and 20% reporting ≥4. There were no associations between the major stressors score and physiological measures or diagnosis of comorbidities. The odds of medication nonadherence increased significantly from those reporting ≥1 major stressor (OR, 1.58; $P = .0265$) to those reporting ≥4 major stressors (OR, 2.70; $P = .0009$). Significant odds of elevated depressive symptoms and impaired QoL were also found with increased reporting of major stressors.

Conclusion Exposure to major stressful life events is associated with lower adherence to prescribed oral medication regimens and impaired psychosocial functioning in adolescents with T2D. *(J Pediatr 2014;165:504-8)*.

Type 2 diabetes (T2D) in youths was a very uncommon clinical entity before the 1990s, but has emerged as a rising public health concern in conjunction with increases in the rates and associated risks of pediatric obesity.[1] Although the psychosocial impact of obesity,[2] as well as the behavioral sequelae associated with type 1 diabetes (T1D),[3] have been reasonably well established, minimal data are available on the psychosocial course of youths with T2D.

Adolescence presents unique challenges for chronic illness management across diseases and is often characterized by deteriorating adherence to prescribed treatments, lower levels of self-care, and compromised outcomes in patients with chronic illnesses.[4] In adolescents with T1D, both cross-sectional and longitudinal studies have found relationships among exposure to stressful life events, diminished metabolic control, and adherence to treatments[5,6]; thus, it is important to determine the extent and impact of stress exposure in adolescents with T2D. This importance is underscored by emerging research suggesting that youths with T2D face an accelerated trajectory toward metabolic deterioration and secondary comorbidities compared with patients with adult-onset T2D.[7]

The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) clinical trial provides a unique opportunity to assess psychosocial

BMI	Body mass index
HbA1c	Hemoglobin A1c
QoL	Quality of life
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TODAY	Treatment Options for Type 2 Diabetes in Adolescents and Youth

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*A list of members of the TODAY Study Group and funding information are available at www.jpeds.com (**Appendix**).

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factors in youths diagnosed with T2D. The trial was a collaboration of 15 clinical centers designed to evaluate the efficacy of 3 treatment regimens in a large cohort of youths with recent-onset T2D.[8] In the present study, we examined the relationships between exposure to stressful life events and physiological, psychosocial, and treatment adherence factors in youths with T2D. We expected to find correlations between higher levels of stressful life event exposure and poorer physiological markers, specifically diminished metabolic control, increased rates of comorbidities, and more extreme overweight status. Moreover, we anticipated to uncover relationships between exposure to stressful life events and poorer adherence to prescribed oral medication regimens, diminished quality of life (QoL), and increased depressive symptoms. Improved understanding of the impact of stressful life events on illness outcomes and psychosocial correlates will help shape and optimize clinical practice and the development of intervention programs to maximize adherence to treatments and enhance psychological functioning in youths with T2D.

Methods

The rationale for, design of, and methodology of the TODAY study have been reported previously.[8] Between July 2004 and February 2009, the study enrolled 699 multiethnic youths who were aged 10-17 years inclusive, had been diagnosed with T2D within the previous 2 years, were in the ≥85th percentile for body mass index (BMI), were negative for diabetes autoantibodies, and had a fasting C-reactive peptide level >0.6 ng/mL. Exclusion criteria included the presence of another significant condition, such as a major psychiatric or developmental disorder, that investigators believed would prevent full participation in the study protocol. The protocol was approved by an external evaluation committee convened by the National Institute of Diabetes and Digestive and Kidney Diseases and by the Institutional Review Board of each participating institution. All participants provided both informed parental consent and minor child assent. Materials developed and used for the TODAY standard diabetes education program and the intensive lifestyle intervention program are available to the public at https://today.bsc.gwu.edu/.

Participants were randomly assigned to 1 of 3 treatment arms: metformin monotherapy, metformin plus rosiglitazone, or metformin plus an intensive lifestyle intervention program. The primary objective of the present study was to compare the 3 treatment arms in terms of time to treatment failure (ie, loss of glycemic control), defined as either hemoglobin A1c (HbA1c) ≥8% over a 6-month period or inability to wean from temporary insulin therapy within 3 months after acute metabolic decompensation. Almost one-half of the cohort (45.6%; n = 319) achieved the primary outcome after an average follow-up of 3.9 years (range, 2-6.5 years). The metformin plus rosiglitazone combination was found to be superior to metformin monotherapy ($P = .006$); metformin plus lifestyle intervention was not statistically significantly different from metformin alone.[9]

In the final year of the trial, participants completed a self-report questionnaire capturing life event exposure. The survey was based on the Yeaworth Adolescent Life Change Event Scale.[10,11] The instrument provided the ability to assess both the frequency and the self-rated level of distress associated with the occurrence of life events having to do with family, friends, relationships, job, school, and other factors in the previous year. The survey was modified to include several supplemental items from the Holmes and Rahe Social Readjustment Rating Scale.[12] Participants responding to the questionnaire first indicated whether the event had occurred (yes/no), and for "yes" responses then rated how upsetting the event was (0, not at all upset; 1, a little upset; 2, somewhat upset; 3, very upset; or 4, extremely upset). The questionnaire contained 33 items, but 1 item for girls related only to menstrual cycles was excluded from the present analysis. Three composite scores were derived: (1) occurrence of discrete events, or tally score, the number of "yes" responses; (2) a severity score, derived from summing upset ratings; and (3) a major stressors score, computed as the number of events classified as somewhat, very, or extremely upsetting.[11] The tally score provides a cumulative measure of events experienced by the participant, the severity score reflects the level of distress caused by the events experienced, and the major stressors score reflects both the frequency and the degree of severity of events reported.

Data on physiological measures, oral medication adherence, QoL, and depressive symptoms were also collected during the final year of the study. Height and weight were measured by trained staff with standard methods and equipment[8] and used to compute BMI. A central study laboratory provided HbA1c measurements. Adherence to the prescribed oral medication treatment was estimated based on pill counts; nonadherent was defined as a rate of pill use <80% of the prescribed dose. Depressive symptoms were assessed using the Children's Depression Inventory for participants aged <16 years or the Beck Depression Inventory II for those aged ≥16 years. Total scores were calculated for each instrument; a cutoff score ≥13 on the Children's Depression Inventory and ≥14 on the Beck Depression Inventory II indicated clinically significant levels of depressive symptoms.[13-15] The Pediatric Quality of Life Inventory measured youths' perception of QoL, with impaired QoL defined as 1 SD below the mean for the entire sample (74.6).[16] Data on BMI, HbA1c, and adherence from quarterly study visits in the final year of the study were averaged. Once treatment failure (ie, loss of glycemic control) occurred, participants were treated with insulin and metformin; during the last year, 40% of the sample had HbA1c values on this regimen. The depression inventory and Pediatric Quality of Life Inventory were administered at the final study visit.

The other 3 outcome status measures represented evaluations performed once, as occurred during the TODAY study. Treatment failure was as defined above. A diagnosis of hypertension was defined as blood pressure ≥130/80 mm Hg or ≥95th percentile for age, sex, and height (based on Centers for Disease Control and Prevention normative data)