Glycemic Control, Coping, and Internalizing and Externalizing Symptoms in Adolescents With Type 1 Diabetes

A cross-lagged longitudinal approach

Koen Luyckx, PhD1,2
Inge Seiffge-Krenke, PhD3
Sarah E. Hampson, PhD4

OBJECTIVE — This study examines how active coping and withdrawal, psychological (internalizing and externalizing) symptoms, and glycemic control (A1C values) influence each other across time in adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS — One hundred and nine adolescents participated in a four-wave longitudinal study spanning four years (mean age at Time 1 was 13.77). Patients were visited at home and completed questionnaires measuring coping and psychological symptoms. The treating physicians were contacted to obtain A1C values. Cross-lagged path analysis from a structural equation modeling approach was used for data analysis.

RESULTS — Clinically meaningful pathways between coping and glycemic control were found across time. Active coping prospectively predicted lower A1C levels, which, in turn, predicted active coping. Higher A1C levels and higher psychological symptoms consistently predicted avoidance coping across time. Finally, psychological symptomatology constituted an important link in the observed longitudinal chain of effects. More specifically, higher A1C values and symptomatology at Time 1 positively predicted withdrawal at Time 2, which, in turn, positively predicted symptomatology at Time 3. Next, symptomatology at Time 3 positively predicted higher A1C values at Time 4, thus coming full circle.

CONCLUSIONS — Coping with everyday stress, psychological symptoms, and glycemic control were interrelated across time. Evidence was obtained for reciprocal pathways and mutually reinforcing mechanisms, indicating the need to monitor coping strategies and psychological symptoms along with glycemic control in optimizing clinical care in adolescents with type 1 diabetes.

Diabetes Care 33:1424–1429, 2010

Adolescence can be a challenging time when individuals have to deal with several developmental tasks such as growing independent from parents and developing mature peer relationships. Having type 1 diabetes imposes multiple additional demands on the adolescent, invading every aspect of his or her life. Diabetes management requires a great deal of self-discipline and is perceived as being highly stressful (1). Consequently, several studies suggest that adolescents with diabetes are at a greater risk than their healthy peers for developing psychological symptoms (such as internalizing and externalizing symptoms, which are both being assessed in this study) or even psychiatric disorders (e.g., depressive disorder) (2–4). However, other studies did not find increased levels of psychological symptoms in these adolescents (5,6), which could signal their increased competence in managing their illness and coping with age-specific developmental tasks. Psychological symptoms (such as internalizing or, more specifically, depressive symptoms) can negatively influence glycemic control through physiological channels and/or through behavioral pathways thereby reducing treatment adherence (4,7). In turn, such symptoms can also be a consequence of poorly controlled diabetes (e.g., due to repeated stressful episodes of severe diabetic ketoacidosis and diabetic microvascular complications such as retinopathy) (3,8–10). As such, the relationship between psychological symptoms and glycemic control is hypothesized to be a reciprocal one.

Several studies have shown that many adolescents have difficulty coping with various illness-specific and everyday stressors, show low adherence with their prescribed treatment, and/or poor glycemic control (11,12). Seiffge-Krenke et al. (13,14) distinguished between functional and dysfunctional coping. Functional coping refers to efforts to manage a problem by actively seeking support, taking concrete actions, or reflecting on possible solutions. Dysfunctional coping includes efforts to withdraw from or deny the existence of the stressor and to avoid seeking solutions and, as such, risk exacerbating the effects of stress (11). Adolescents using active coping skills were less likely to show a worsening in their glycemic control, implying that their coping competencies had a protective effect (15). The consistent use of withdrawal or avoidance coping has been linked to increases in psychological symptoms in community samples (16). In sum, adolescents with diabetes who use withdrawal coping may be at risk for psychological symptoms and poor glycemic control. Some have suggested that these relationships may be reciprocal (1).

The present study

Despite the burgeoning literature dealing with psychological functioning and dia-

From the 1Catholic University Leuven, Leuven, Belgium; the 2Fund for Scientific Research-Flanders, Flanders, Belgium; the 3University of Mainz, Mainz, Germany; and the 4Oregon Research Institute, Eugene, Oregon.

Corresponding author: Koen Luyckx, koen.luyckx@psy.kuleuven.be.

Received 30 October 2009 and accepted 13 March 2010. Published ahead of print at http://care.diabetesjournals.org on 31 March 2010. DOI: 10.2337/dc09-2017.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
betes, neither adolescents’ coping strategies nor their capacity to achieve adequate glycemic control have been addressed in a single longitudinal design. However, psychological symptoms, coping, and glycemic control are hypothesized to influence each other across time (17). As opposed to cross-sectional relations, which reveal whether two variables are simultaneously related, cross-lagged (longitudinal) relations reveal whether a certain variable is related to changes in another variable. For example, Helgeson et al. (18) found that, although depressive symptoms were not related to glycemic control at a concurrent level in their adolescent sample, depressive symptoms were found to predict decreases in glycemic control across time. Consequently, through the use of cross-lagged path analysis in a longitudinal sample of adolescents with diabetes, the present study examined how coping and psychological symptoms (both internalizing and externalizing) influenced glycemic control across time. We expected that active coping would be related to good glycemic control, whereas withdrawal coping and experiencing psychological symptoms would be related to poor glycemic control across time. Further, we hypothesized that reciprocal mechanisms set in motion a detrimental vicious circle which withdrawal coping and increases in psychological symptoms could not only influence but also could be influenced by poor glycemic control (1).

As noted, the use of active coping was expected to break this chain of mechanisms by improving glycemic control or protecting against psychological symptoms. The present study also took into account possible sex differences as girls generally have higher A1C values due to pubertal acceleration and higher internalizing symptom scores (1,13,18).

**RESEARCH DESIGN AND METHODS**

**Participants and procedure**

Participants were from the German Longitudinal Study on Juvenile Diabetes (1), which received full Institutional Review Board approval from the University of Mainz, Mainz, Germany. All participants provided informed consent. A total of 109 patients with type 1 diabetes (47% girls and 9% of non-German—mainly Turkish, Italian, and Greek—descent) were recruited from 17 pediatric health care services offering outpatient care in two German cities (12% of the patients initially contacted declined to participate mainly due to language problems). The sample was found to be representative of German adolescents of the same age range on different demographic variables (1). The 109 patients participated in a four-wave longitudinal study spanning four years. Participants were visited at home by project team members and were asked to fill out questionnaires. Mean age at Time 1 was 13.77 (SD = 1.41; range 12–16 years with 71% of the sample being 12–14 years). As such, the majority of the participants were in their early adolescent years at Time 1 and in their middle to late adolescent years at Time 4.

Further, with respect to parental educational level, 19% of the patients had fathers who received education to the 10th grade level, 53% to 11th or 12th grade level, and 23% to the college level. Mean duration of diabetes at Time 1 was 4.95 years (SD = 3.48). Illness duration and age were unrelated to all study variables except for a positive association of illness duration with A1C values at Time 1 (r = 0.22; P < 0.05) and of age with psychological symptoms at Time 1 (r = 0.24; P < 0.05).

**Measures**

**Coping with everyday stress.** Active coping and withdrawal were assessed with the German Coping Across Situations Questionnaire (14), consisting of seven potentially stressful domains (parents, peers, leisure time, romantic relationships, self, future, school) and 20 coping strategies. The participants were requested to indicate (either yes or no) which coping strategies they used to deal with a stressor in each of the seven domains. Based on factor analysis (14), each of the 20 coping strategies across all domains could be assigned to one of three coping styles, two of which were used for present purposes. Sample items read “I discuss the problem with my parents” (active coping; 7 items) and “I withdraw because I cannot change anything anyway” (withdrawal; 6 items). Mean scores (ranging between 0 and 7 for active coping and 0 and 6 for withdrawal) indicate the average number of coping strategies used across all domains. Cronbach’s α for these two coping dimensions, summed across all domains, ranged from 0.81 to 0.93 and 0.83 to 0.90, respectively, across waves.

**Internalizing and externalizing symptoms**

The German Youth Self-Report (YSR) (19,20) was used. With a total of 102 items (rated not true, somewhat true, sometimes true, often true, or very often true), the YSR consists of multiple symptoms that can be combined in two broadband scales: internalizing and externalizing symptoms. By collapsing these two scales, a total symptomatology score can be calculated. Norms, reliability, and validity of the YSR are well established (19). Mean sum scores (Table 1) indicate that our participants generally displayed low-to-moderate symptomatology across time outside of the clinical range (1).

**Statistical methods**

A total of 83% patients participated at all four time points (91% participated at two and 85% at three time points), and 10.10% of the data at the scale level was missing across time. No significant differences emerged at Time 1 between those who participated at all time points and those who dropped out. To minimize the bias associated with occasional attrition, we used the expectation maximization algorithm to impute missing data. A non-significant (ns) Little’s (21) Missing Completely At Random test [χ²(166) = 16.34, ns] indicated that all missing values could be reliably estimated.

Cross-lagged path analysis was applied from a structural equation modeling approach using Lisrel 8.54. In all models tested, all within-time associations at Times 1–4 and all autoregressive coefficients were included. Consequently, we looked at directional paths across time when controlling for all within-time associations and rank-order stability. We used standard model fit indexes. The Satorra-Bentler scaled (SBS) χ² index should be as small as possible; the root mean square error of approximation (RMSEA) should be less than 0.08; and the comparative fit index (CFI) should exceed 0.90 and preferably 0.95.
Glycemic control, coping, and psychological symptoms

Table 1—Mean-level changes (SD) across time in the study variables

| Variable                      | Time 1       | Time 2       | Time 3       | Time 4       | F (3,105) | \( \eta^2 \) |
|-------------------------------|--------------|--------------|--------------|--------------|-----------|-------------|
| Active coping                 |              |              |              |              |           |             |
| Total sample (N = 109)        | 2.17 (1.33)  | 3.36 (1.22)  | 3.30 (1.31)  | 3.37 (1.33)  | 27.03***  | 0.44        |
| Boys (n = 58)                 | 1.91 (1.21)  | 3.26 (1.28)  | 3.13 (1.33)  | 3.20 (1.31)  | 0.53†     | 0.01        |
| Girls (n = 51)                | 2.46 (1.33)  | 3.46 (1.16)  | 3.48 (1.28)  | 3.56 (1.29)  |           |             |
| Withdrawal                    |              |              |              |              |           |             |
| Total sample                  | 1.00 (0.91)  | 1.27 (1.02)  | 1.18 (1.01)  | 1.17 (0.96)  | 2.36      | 0.07        |
| Boys                          | 0.85 (0.78)  | 1.42 (1.01)  | 1.27 (0.94)  | 1.14 (0.85)  | 4.01***   | 0.10        |
| Girls                         | 1.17 (1.02)  | 1.11 (1.01)  | 1.08 (1.09)  | 1.20 (1.07)  |           |             |
| A1C (%)                       |              |              |              |              |           |             |
| Total sample                  | 7.85 (2.41)  | 7.73 (1.92)  | 8.30 (1.55)  | 8.26 (1.66)  | 3.66*     | 0.10        |
| Boys                          | 7.76 (1.91)  | 7.79 (1.68)  | 8.20 (1.29)  | 8.18 (1.37)  | 0.41†     | 0.01        |
| Girls                         | 7.96 (3.09)  | 7.65 (2.17)  | 8.41 (1.80)  | 8.36 (1.94)  |           |             |
| Total symptomatology (raw score) |            |              |              |              |           |             |
| Total sample                  | 35.23 (16.82)| 33.86 (17.95)| 33.32 (18.57)| 30.79 (16.73)| 3.65*     | 0.09        |
| Boys                          | 33.95 (14.95)| 34.23 (16.01)| 33.09 (18.12)| 29.20 (19.84)| 1.36†     | 0.04        |
| Girls                         | 36.68 (18.77)| 33.45 (20.09)| 33.57 (19.25)| 32.60 (18.27)|           |             |
| Internalizing symptoms        |              |              |              |              |           |             |
| Total sample                  | 11.93 (7.09) | 10.75 (7.39) | 10.76 (7.54) | 10.25 (6.59) | 2.77*     | 0.07        |
| Boys                          | 11.07 (6.21) | 10.17 (6.87) | 10.17 (7.77) | 9.13 (5.91)  | 0.60†     | 0.02        |
| Girls                         | 12.92 (7.92) | 11.51 (7.99) | 11.53 (7.51) | 11.68 (7.13) |           |             |
| Externalizing symptoms        |              |              |              |              |           |             |
| Total sample                  | 11.00 (5.15) | 11.25 (5.55) | 10.94 (5.80) | 9.77 (5.35)  | 5.21**    | 0.13        |
| Boys                          | 11.16 (5.07) | 11.73 (5.90) | 11.63 (5.91) | 9.99 (4.99)  | 0.62†     | 0.02        |
| Girls                         | 10.82 (5.28) | 10.67 (5.11) | 10.12 (5.60) | 9.43 (5.73)  |           |             |

SD is within parentheses. Total, externalizing, and internalizing symptoms are reported as raw scores. †Represents the F-value for the interaction-term with gender. *P < 0.05, **P < 0.01, ***P < 0.001.

RESULTS

Preliminary mean-level analyses

Table 1 presents all mean values at Times 1–4. A series of ANOVAs revealed limited sex differences with girls scoring higher than boys on active coping at Time 1 (F [1,108] = 4.90, P < 0.05, \( \eta^2 = 0.04 \)) and on internalizing symptoms at Time 4 (F [1,108] = 4.15, P < 0.05, \( \eta^2 = 0.04 \)). Repeated-measures ANOVAs with sex as a between-subjects variable indicated that, for the total sample, active coping and A1C levels increased across time whereas symptomatology decreased across time. Mean-level changes were moderated by sex (but not by age, illness duration, and level of paternal education). Whereas girls showed virtually no change across time in withdrawal, boys showed a quadratic trend with initial increases followed by later decreases.

Cross-lagged path analyses

The baseline model included all within-time associations and stability coefficients \([\text{SBS}x^2 (84) = 150.26 (P < 0.001); \text{RMSEA} = 0.09; \text{CFI} = 0.91]\). Next, we included cross-lagged paths from coping to symptoms and A1C, from symptoms to coping and A1C, and from A1C to coping and symptoms, resulting in a model with an acceptable fit \([\text{SBS}x^2 (54) = 101.35 (P < 0.001); \text{RMSEA} = 0.09; \text{CFI} = 0.94]\) and a significantly better fit than the baseline model \([\text{SBS}x^2 (36) = 49.87, P < 0.05]\). A total of eight cross-lagged paths were significant at \(P < 0.10\). All the remaining cross-lagged paths were trimmed and resulted in the final model \([\text{SBS}x^2 (76) = 110.81 (P < 0.01); \text{RMSEA} = 0.07; \text{CFI} = 0.94]\), which had a comparable fit to the previous, less parsimonious model \([\text{SBS}x^2 (22) = 13.85, P = 0.91]\).

Figure 1 presents all standardized stability and cross-lagged coefficients from this final model (see Table 2 for within-time associations). Total symptomatology at Times 1 and 2 and positively predicted withdrawal at Times 2 and 3, respectively. Active coping at Time 1 negatively predicted A1C levels at Time 2, which, in turn, negatively predicted active coping at Time 3. A1C levels at Times 1 and 3 positively predicted withdrawal at Times 2 and 4, respectively. Further, withdrawal at Time 2, in turn, positively predicted total symptomatology at Time 3, which again positively predicted A1C levels at Time 4. The total effects from A1C levels and psychological symptoms at Time 1 to A1C levels at Time 4 reached significance \((z = 1.87, P < 0.10)\) and \((z = 2.39, P < 0.05)\), respectively.

Next, a multigroup analysis was performed in which we compared a constrained model (with all eight significant cross-lagged paths set as equal across sex) against an unconstrained model (with these cross-lagged paths allowed to vary across sex). No significant difference emerged between both models \((\Delta \text{SBS}x^2 [8] = 8.07, P = 0.43)\) and, hence, the more parsimonious constrained model was favored, indicating that the final model fitted equally well for boys and girls.

Finally, we investigated whether the final cross-lagged model could be replicated for internalizing and externalizing symptoms. In the case of internalizing symptoms \([\text{SBS}x^2 (77) = 105.39 (P < 0.05); \text{RMSEA} = 0.06; \text{CFI} = 0.95]\), similar results were obtained as can be seen in Figure 1, except that the path from internalizing symptoms at Time 1 to withdrawal at Time 2 failed to reach significance. In the case of externalizing symptoms \([\text{SBS}x^2 (77) = 118.96 (P < \)
Indeed, the longitudinal findings pointed to a detrimental vicious circle operating across time. A worsening of glycemic control and psychological symptoms at Time 1 were associated with increases in withdrawal at Time 2, which, in turn, was associated with an increase of symptomatology at Time 3. Symptomatology at Time 3 again was associated with a worsening of glycemic control at Time 4. Apparently, suboptimal levels of glycemic control and the presence of psychological symptoms early in adolescence could set in motion a chain of events or mechanisms leading to poor glycemic control several years later. Improving active coping strategies through intervention efforts could help to interrupt this chain of events (22). Active coping at Time 1 was associated with better glycemic control at Time 2, which, in turn, was associated with increases in active coping at Time 3, pointing to an important reciprocal mechanism. Good glycemic control, in turn, was associated with decreases in withdrawal coping across time (i.e., from Time 1 to Time 2 and from Time 3 to Time 4). Apparently, active coping could have protective functions by lowering A1C values 1 year later, whereas obtaining adequate levels of glycemic control seemed to protect against the use of withdrawal coping.

In sum, whereas several longitudinal findings tended to be replicated across time (such as poor glycemic control and psychological symptoms influencing withdrawal), other longitudinal mechanisms were found to operate at specific periods in time. A first explanation could be our relatively small sample size, which decreased the power of the statistical tests. A second explanation might be that these mechanisms become somewhat apparent depending on the adolescent’s developmental stage. Active coping was a stronger predictor of glycemic control when the participants were younger, whereas psychological symptoms were a stronger predictor of glycemic control at the end of the study. With respect to the latter, as adolescents become older, they are increasingly responsible for their illness management. During this process, internalizing and externalizing symptoms may adversely affect glycemic control partially due to their negative impact on self-management and self-care behaviors. They point to important mechanisms that could be addressed in clinical settings provided that the obtained findings are scrutinized and replicated in future studies. A regular screening of maladaptive coping strategies and for providing education or training in optimizing the use of active, problem-focused coping to maintain adequate levels of glycemic control might be warranted in adolescents with diabetes.

The findings for the overall symptomatology score were quite similar to those...
found in separate analyses for internalizing or externalizing symptoms. Although “externalizing” and “internalizing” describe a basic distinction in symptomatology that is extensively validated (23), these two types of symptoms often co-occur in adolescence. Our separate analyses on internalizing and externalizing symptoms indeed demonstrated that comparable time-dependent mechanisms occurred. It should be noted that, for most participants, the magnitude of psychological symptoms did not meet the threshold for being labeled as psychopathology. However, the fact that these symptom scores represented rather normal variants does not downgrade the importance of our findings. Apparently, intraindividual changes in psychological symptoms outside the clinical range also have the potential to influence variables such as glycemic control. In addition, subclinical levels of psychological symptoms could hinder adolescents from mastering normative developmental tasks and render them more vulnerable for developing psychopathology later in life (24).

To conclude, partially due to our small sample size, we found limited sex differences. Future studies involving larger samples should incorporate gender as a variable. Despite these limitations, the present study demonstrates that adolescents with diabetes should be routinely screened for psychological symptoms and for the extent to which they make use of adaptive or maladaptive coping strategies not only in dealing with diabetes but also in dealing with everyday stressors. In addition, the present study demonstrates that the impact of these factors on glycemic control could be moderated by individual differences in psychological symptomatology (22). To conclude, partially due to our small sample size, we found limited sex differences. Future studies involving larger samples should incorporate gender as a variable. Despite these limitations, the present study demonstrates that adolescents with diabetes should be routinely screened for psychological symptoms and for the extent to which they make use of adaptive or maladaptive coping strategies not only in dealing with diabetes but also in dealing with everyday stressors. In addition, the present study demonstrates that the impact of these factors on glycemic control could be moderated by individual differences in psychological symptomatology (22).
3. Kovacs M, Goldston D, Obrosky DS, Bohnar LK. Psychiatric disorders in youths with IDDM: rates and risk factors. Diabetes Care 1997;20:36–44.

4. Gendelman N, Snell-Bergeon JK, McFann K, Kinney G, Paul Wadwa R, Bishop F, Rewers M, Maahs DM. Prevalence and correlates of depression in individuals with and without type 1 diabetes. Diabetes Care 2009;32:575–579.

5. Kovacs M, Iyengar S, Goldston D, Stewart J, Obrosky DS, Marsh J. Psychological functioning of children with insulin-dependent diabetes mellitus: a longitudinal study. J Pediatr Psychol 1990;15:619–632.

6. Wilkinson G, Borsey DQ, Leslie P, Newton RW, Lind C, Ballinger CB. Psychiatric morbidity and social problems in patients with insulin-dependent diabetes mellitus. Br J Psychiatry 1988;153:38–43.

7. Delamater AM, Bubb J, Kurtz SM, Kuntze J, Smith JA, White NH, Santiago JV. Physiologic responses to acute psychological stress in adolescents with type 1 diabetes mellitus. J Pediatr Psychol 1988;13:69–86.

8. Aikens JE, Perkins DW, Lipton B, Piette JD. Longitudinal analysis of depressive symptoms and glycemic control in type 2 diabetes. Diabetes Care 2009;32:1177–1181.

9. Lustman PJ, Skor DA, Carney RM, Santiago JV, Cryer PE. Stress and metabolic control. Lancet 1983;1:588.

10. Cohen ST, Welch G, Jacobson AM, De Groot M, Samson J. The association of lifetime psychiatric illness and increased retinopathy in patients with type I diabetes mellitus. Psychosomatics 1997;38:98–108.

11. Hanson CL, Cigrang JA, Harris MA, Carle DL, Relyea G, Burgan GA. Coping styles in youths with insulin-dependent diabetes mellitus. J Consult Clin Psychol 1989;57:644–651.

12. Wysocki T. Associations among teen-parent relationships, metabolic control, and adjustment to diabetes in adolescents. J Pediatr Psychol 1993;18:441–452.

13. Seiffge-Krenke I, Aumola K, Nummi JE. Changes in stress perception and coping during adolescence: the role of situational and personal factors. Child Dev 2009;80:259–279.

14. Seiffge-Krenke I. Stress, coping, and relationships in adolescence. Hillsdale, NJ, Lawrence Erlbaum Associates, 1995.

15. Graue M, Wentzel-Larsen T, Bru E, Hanestad BR, Søvik O. The coping styles of adolescents with type 1 diabetes are associated with degree of metabolic control. Diabetes Care 2004;27:1313–1317.

16. Seiffge-Krenke I, Klessinger N. Long-term effects of avoidant coping on adolescents’ depressive symptoms. J Youth Adolesc 2000;29:617–630.

17. Malik JA, Koot HM. Explaining the adjustment of adolescents with type 1 diabetes: role of diabetes-specific and psychosocial factors. Diabetes Care 2009;32:774–779.

18. Helgeson VS, Simmermto L, Escobar O, Becker D. Predictors of metabolic control among adolescents with diabetes: a 4-year longitudinal study. J Pediatr Psychol 2009;34:254–270.

19. Achenbach TM, Edelbrock CS. Manual for the Youth Self-Report and Profile. Burlington, VT, University of Vermont, Department of Psychiatry, 1987.

20. Løsel F, Blesener T, Köferl P. Erlebens- und verhaltensprobleme bei jugendlichen: Deutsche adaptation und kulturvergleichende überprüfung der Youth Self-Report form der child behaviour checklist. Z Klin Psychiatr Psychother 1991;20:22–51 [in German].

21. Little RJA. A test of missing completely at random for multivariate data with missing values. J Am Stat Assoc 1988;83:1198–1202.

22. de Ridder D, Schreurs K. Developing interventions for chronically ill patients: is coping a helpful concept? Clin Psychol Rev 2001;21:205–240.

23. Achenbach TM, McConaughy SH, Howell CT. Child/adolescent behavioral and emotional problems: implications of cross-informant correlations for situational specificity. Psychol Bull 1987;101:213–232.

24. Petersen AC, Compas BE, Brooks-Gunn J, Stemmler M, Ey S, Grant KE. Depression in adolescence. Am Psychiatr 1993;48:155–168.

25. Silverstein J, Klingensmith G, Copeland K, Plotnick L, Kaufman F, Laffel L, Deeb L, Gray M, Anderson B, Holzmeister LA, Clark N, American Diabetes Association. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. Diabetes Care 2005;28:186–212.