49 Psychologic Factors and Diabetes

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Keypoints

- Both type 1 (T1DM) and type 2 diabetes mellitus (T2DM) can affect the psychologic and neuropsychologic status of children and adults. In most instances, these effects are modest in magnitude and are most likely to be associated with certain events that occur during the course of diabetes or its management.
- Children show remarkable psychologic resilience to the diagnosis of diabetes. About one-third report some psychologic distress shortly after diagnosis but this generally subsides within 6 months. This "adjustment disorder" is characterized by increased depressive symptomatology, more anxiety, social withdrawal and sleep disturbances. A similar adjustment reaction is often seen in parents, particularly mothers, of newly diagnosed children. Diagnoses of post-traumatic stress disorder are also more common in parents, occurring at rates comparable with that reported in children diagnosed with cancer. Increased rates of depression are also found in adults newly diagnosed with T1DM, whereas diagnosis of T2DM does not appear to increase the risk of depression unless accompanied by multiple medical co-morbidities.
- During the first 5–10 years of their diabetes, most children and adolescents show adequate psychologic functioning; however, after 10 years of diabetes, their rates of anxiety, depression or eating disorders are markedly increased, with as many as one-third of adolescents with diabetes meeting criteria for one or more psychiatric disorders. Adults with diabetes also show elevated rates of depression which are twice as high as those reported in the general population. At greatest risk are people who have been hospitalized, are older with multiple medical problems, have a history of past psychopathology or are female. Metabolic control is only weakly associated with the occurrence of a mood disorder.
- Macrovascular disease, chronic foot ulceration and proliferative retinopathy increase the risk of psychopathology, an understandable reaction to serious complications; however, lifetime psychiatric disorders such as depression may also increase the risk of later development of complications such as retinopathy. Recurrent diabetic ketoacidosis, particularly in females, is also predicted by poor psychologic functioning, and by high rates of family dysfunction.
- Phobic disorders are more common in adults with diabetes than in the general population. Fear of blood and injury may lead to less blood glucose self-monitoring and poorer control. Fear of hypoglycemia is common and may also lead to premature treatment as blood glucose levels begin to fall, resulting in persisting hyperglycemia.
- Quality of life for those with diabetes does not differ from patients with other chronic conditions, such as arthritis. Poor health-related quality of life is associated with biomedical complications, being female, physical inactivity, low income and recurrently hypoglycemia. Intensive diabetes management is not associated with a deterioration in quality of life.
- Interventions to reduce psychologic distress include individual psychotherapy or counseling, and group therapy; however, the efficacy of either – in terms of affecting mood or metabolic control – has not been studied extensively in clinical trials, but data from smaller studies suggests effects may be weak, at best. A promising technique for depressive symptoms is cognitive–behavior therapy, which teaches patients problem-solving strategies for stressful situations and "thinking away" distorted beliefs. Pharmacotherapy, including selective serotonin reuptake inhibitors and tricyclic antidepressants, has been found to reduce symptom severity but specific drugs may differentially influence glycated hemoglobin values.
- Cognitive dysfunction in diabetes is generally mild, but children diagnosed in the first 5 to 7 years of life have an elevated risk of manifesting clinically significant impairments in all cognitive domains. Those with a later onset of diabetes show modest effects, most evident on measures of intelligence, academic achievement and psychomotor efficiency. Deficits appear early in the course of the disease, and are evident within 2–3 years after diagnosis. Hypoglycemia was long considered to be the cause of this neurocognitive dysfunction but more recent research suggests that adverse effects on cognition may only occur when blood glucose levels are very low for an extended period of time. Although the etiology of neurocognitive changes in children remains poorly understood, a growing body of evidence implicates chronic hyperglycemia and, in particular, the development of microvascular and macrovascular complications.
- In adults with T1DM, neurocognitive deficits are quite modest and are most apparent on measures of intelligence, psychomotor speed and executive function. Older adults with T2DM also manifest marked reductions in memory function and, in both groups, the strongest

Textbook of Diabetes, 4th edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein. © 2010 Blackwell Publishing.

predictor of cognitive dysfunction is chronic hyperglycemia and the presence of biomedical complications, particularly retinopathy and peripheral neuropathy.
- Structural damage to the brain is also common in both children and adults with either T1DM or T2DM. Not only is there a reduction in cortical gray matter density, but white matter structures may be disrupted. Cerebral atrophy is often present, neural slowing is evident on electroencephalography and regional cerebral blood flow is altered.
- Diabetes management and health outcomes are influenced by reciprocal relationships between metabolic control and psychologic variables. The latter include enduring psychologic traits such as locus of control, coping style, temperament and transitory psychologic states (stress, anxiety, depression). Diabetes is also strongly related to family functioning, especially in children and adolescents: low family conflict, good communication, cohesion and marital satisfaction relate to better diabetes control.
- Adherence or self-care behaviors (taking medicine, complying with diet, glucose monitoring, exercise regimens) are only weakly related to diabetic control, but this may reflect the inaccuracy of self-reported behavior. For those who are most seriously non-compliant, psychologic interventions include psychotherapy, family therapy and patient empowerment programs to improve goal-setting, problem-solving, coping, managing stress and self-motivation.
- A psychologist or other mental health care professional should be part of the diabetes care team.

Introduction

Diabetes and psychology have long been linked. More than 50 years ago, the psychosomatic model of medical illness postulated that psychosocial factors could trigger or maintain various disorders, including diabetes. This notion was subsequently abandoned by most scientists, yet the person living with diabetes and managing this behaviorally complex condition may nevertheless identify numerous points where diabetes and psychology interact. This chapter examines three major points of intersection: psychologic reactions to the development of diabetes and the appearance of complications, the neuropsychologic or cognitive consequences of diabetes, and psychologic factors that influence, or are influenced by, the everyday management of diabetes.

Psychologic impact of diabetes

Patients with diabetes ought to manifest significant psychologic distress, or so goes conventional clinical wisdom. After all, they have a disorder that shortens their lifespan, leads to debilitating biomedical complications such as blindness or neuropathy, and requires them to take complete daily responsibility for managing their health with drugs or insulin injections and careful monitoring of diet, exercise and blood glucose levels, for the remainder of their lives. Chronic illnesses like diabetes also mark individuals, particularly children, as different from their healthy peers, and burden families with demanding health care responsibilities that they may be unwilling or unable to meet. Given all of these factors, one should not be surprised to find that many people with diabetes, and their families, have elevated rates of emotional disturbances and behavioral problems.

Psychologic distress shortly after diagnosis

Observations in children and their parents

Children and adults show remarkable psychologic resilience in response to a diagnosis of diabetes. In what may be the most comprehensive prospective psychologic study of children with diabetes and their families, Kovacs *et al.* [1] assessed 95 children, 8–13 years of age, shortly after discharge from their initial hospitalization, and followed them for 6–10 years. Within 3 months of diagnosis, 36% of the children experienced sufficient psychologic distress to meet criteria for a diagnosable psychiatric disorder [2]. Most had "adjustment disorder," defined as a transient reaction that exceeds the normal and expectable response to a stressor, develops within 3 months of onset of the stressor and lasts no more than 6 months. The occurrence of such a disorder signals that the child is beginning to come to terms with the diagnosis of diabetes, and can be considered to be a component of the "mourning process" that often accompanies the development of any chronic illness [3]. As one would expect with an adjustment disorder, recovery was rapid, with 93% showing complete remission of these psychiatric symptoms within 9 months. Other investigators, using different outcome measures, have also demonstrated rapid psychologic adaptation to the diagnosis of diabetes [4–6].

Parents of children newly diagnosed with diabetes also manifest psychologic responses that are analogous to an adjustment disorder. For mothers, the strain associated with caring for a school-aged child with diabetes elicited mild levels of depressive symptomatology, anxiety and generalized distress, but this dissipated within 6 months [7]. Less symptomatology was evident in fathers, both shortly after diagnosis and approximately 1 year later; however, if fathers do report experiencing high rates of emotional dysfunction in the first 2 years following their child's diagnosis, their child is more likely to manifest poorer metabolic control and greater blood glucose variability during the first 5 years of diagnosis [8]. Greatly elevated rates of post-traumatic stress disorder (PTSD) have also been reported in a prospective study of parents evaluated at 6 weeks and 6 and 12 months after their child's diagnosis. Depending on time point, 16–22% of mothers met DSM-IV criteria for a PTSD diagnosis, as did 8–14% of fathers [9]. Theses rates were significantly higher than those reported in the general population but are comparable with those seen in mothers of children diagnosed with cancer. The best predictor of PTSD severity at 12 months was PTSD severity at

6 months. Poorer disease outcomes, particularly episodes of hypoglycemia, were associated with an increased level of PTSD severity.

Elevated rates of worry and concern are also present in parents, but these differ by gender: 46% of mothers reported worry all or almost all of the time, whereas only 13% of the fathers reported similarly high levels of concern [10]. Mourning was the primary coping process engaged in by mothers, whose responses most commonly included feeling sad, worried and/or tired, and who manifested bouts of crying and irritability. As duration of illness increased, levels of psychologic distress, particularly depression, showed slight increments, with the greatest increases occurring in those mothers who were most distressed at the time of their child's diagnosis and in those mothers of higher socioeconomic status. The latter finding may reflect the possibility that these women were more knowledgeable about diabetes, and hence may have been more discouraged about its management and long-term outcomes. Despite the stresses and strains that the diagnosis of diabetes exerts on both the child and the family, there is little evidence of major family disruption in the first 2–3 years following diagnosis. Measures of parental perception of overall quality of family life as well as estimates of the quality of parents' marriage show essentially no change during that period [11].

Diagnosis in adulthood

The onset of diabetes during adulthood ought to produce similar adjustment disorders within several months of diagnosis in both the patient as well as the spouse or other family member. A German sample of newly diagnosed, adult patients (aged 17–40 years of age) with type 1 diabetes mellitus (T1DM) had a rate of major depressive episodes that was twice that of a reference group drawn from a representative national population (5.8% vs 2.7%), although more careful analysis shows that these differences were statistically significant only for women with diabetes (9.3% vs 3.2% in reference group) [12]. There were no differences in rates of major depression between men with diabetes and the reference group (3.6% vs 2.2%), nor for other psychiatric disorders. Because this is a cross-sectional study, it is impossible to determine whether this is truly a "classic" depression or whether it is a transient adjustment disorder, as is typically seen in children and adolescents with diabetes. In contrast, several studies of adults with type 2 diabetes mellitus (T2DM) have found little psychologic morbidity in the first year following diagnosis. One smaller clinical study reported that of the 71 subjects studied, more than 50% expressed no emotional reaction to the diagnosis and felt that they could cope with diabetes [13]. Negative emotional reactions, along with feelings of being incapable of coping with this disorder, were expressed by only 26% of the sample, and this may reflect the fact that these individuals had significantly less social support than the others. A larger, more recent study assessing symptoms of depression, similarly found little evidence of a psychologic reaction in 824 patients newly diagnosed with T2DM [14]. Although there were marked gender differences, with women with diabetes reporting higher rates of significant depressive symptomatology than men with diabetes (16.1% and 8.2%, respectively), those values were comparable to UK normative data for women and men (13% and 8%, respectively). Greater depressive symptomatology was associated with more medical co-morbidities: newly diagnosed patients with diabetes taking both lipid-lowering and antihypertensive medications reported more symptoms of depression than those on only one, or on no concurrent medication.

Psychologic reactions emerging in the course of diabetes

Depressive symptomatology in children and adolescents

After resolution of their adjustment disorder, are children able to get on with their lives, or is there an increased likelihood of subsequent psychologic distress in the individual with diabetes? As duration of diabetes continues, it now appears that most children and adolescents with diabetes function well psychologically, although small increases may be evident in depressive symptomatology and internalizing behaviors, such as somatic complaints, social withdrawal, sleep disturbance and symptoms of depression and anxiety). In both school-aged [6,15,16] and pre-school children [17], this was evident after 2–3 years of diabetes, yet the magnitude of these changes was not so large as to be indicative of clinically significant psychopathology. Somewhat higher rates of externalizing, or aggressive, behaviors have also been reported, with this phenomenon especially pronounced in boys with diabetes [15], and strongly associated with consistently elevated blood glucose levels [18]. High levels of family conflict and the occurrence of multiple stressful life events appear to be particularly potent predictors of more aggressive behavior in children and adolescents with diabetes [19].

After 6 years of follow-up, Kovacs *et al.* [16] found trivially small increases in symptoms of depression for all subjects, and increased symptoms of anxiety for girls but not boys. Children who reported more difficulties in managing their diabetes also showed more symptoms of psychologic distress. Level of psychologic distress shortly after diabetes onset was the best predictor of symptomatology 6 years later, whereas the degree of metabolic control, as indexed by glycated hemoglobin (HbA_{1c}) values, was not a viable predictor in this or in most other studies [20,21]. Neither age nor age at onset predicted increased psychologic distress in Kovacs *et al.*'s cohort, although others have found an association between developmental stage and emotional or behavioral problems in so far as adolescents manifested more problems than pre-adolescents [21].

Even after 10 years of diabetes, older adolescents and young adults with childhood onset of diabetes may report little psychologic distress, although they tend to have lower levels of self-esteem and express concerns about their sociability and their physical appearance [22]. What is remarkable, however, is that when patients are formally evaluated with structured psychiatric interviews to assess for clinically significant psychopathology over this extended time period, marked elevations are found in rates of psychiatric disorder. Not only were females more often affected

than males [23,24], but their risk of subsequently experiencing a recurrence of depression was nine times greater than males [25]. Kovacs *et al.* [1] reported that 40% of their sample had experienced at least one episode of a psychiatric disorder during the first 10 years of living with diabetes, and 26% had two different psychiatric disorders. Major depression was the most common diagnosis (26% of sample), followed by some form of anxiety disorder (20%). By comparison, similarly aged, subjects without diabetes drawn from the community had rates of depression that ranged from 9–16%, and rates of anxiety that ranged from 11–25% [26].

Remarkably similar rates of clinically significant DSM-IV disorders have been reported more recently by Northam *et al.* [23], who followed a cohort of newly diagnosed Australian children over a 10-year period. By year 10, 37% of those with diabetes received at least one diagnosis; of those, 60% met criteria for two or more disorders and 55% met criteria for three or more disorders [23]. In that study, mood, anxiety and eating disorders were each present in 17% of the sample; nearly 20% of the sample manifested a behavior disorder. Of note is their observation that those adolescents who met criteria for a DSM-IV psychiatric disorder were also more likely to have manifested significant externalizing problems shortly after diagnosis. Although not evaluated by Northam *et al.*, other investigators have identified maternal psychopathology as a potent predictor of subsequent psychiatric disorder [1] and increased depressive symptomatology in children and adults with diabetes [27].

Significantly elevated rates of suicidal ideation have also been reported for adolescents with diabetes, with lifetime prevalence rates noted to be 26%, compared to rates for adolescents without diabetes ranging from 9–12% [28]. Although the rate of actual suicide attempts is low amongst youth with diabetes (4%), suicidal ideation was associated with greatly increased rates of non-compliance with medical treatment.

Clinically significant mood disorders in adults

The process of psychologic adaptation to the diagnosis of diabetes in adulthood remains incompletely understood, largely because few longitudinal studies have been conducted with adults [29]. In what remains the largest follow-up study of adults with T1DM, the Diabetes Control and Complications Trial (DCCT) Research Group [30] found no change in self-reported psychologic symptomatology over a follow-up period of 6–9 years, and found no relationship between type of treatment (conventional or intensive insulin therapy) and levels of psychologic distress [31]. Rates of clinically significant distress were higher in both treatment groups (25%) compared with rates of depression measured by self-report in the general population (14.4%) [32]. A smaller study that followed adults for 2 years from the diagnosis of T1DM also reported either no changes in psychologic state over time, or a significant improvement in functioning (e.g. reduced depressive symptomatology) [33].

Cross-sectional studies of adults with either T1DM or T2DM have demonstrated repeatedly that rates of psychologic distress, particularly depression and anxiety, tend to be higher than the general population, but are usually comparable to those reported in individuals with other chronic diseases [34–38]. Using self-report measures of psychologic symptoms, Peyrot & Rubin [39] found greatly elevated rates of both depressive (41%) and anxiety symptomatology (49%), with 38% of their entire sample showing elevations in both domains; however, repeated reassessment of these patients over a 6-month period indicated that these effects are quite unstable. Across all three assessments, only 13% of the sample was consistently disturbed. The strongest predictors of persisting distress included being female, having less than a high school education, being middle-aged and having more than two diabetes-associated biomedical complications [40]. Prevalence rates for any depressive disturbance were nearly twice as high in this study [39] than DCCT reports (41% vs 25%, respectively), but this is likely to be because of sampling differences. The DCCT study group was comprised of highly motivated patients with minimal diabetes-associated complications who were vigorously followed by a treatment team that included a psychologist or psychiatrist [41], whereas those patients studied by Peyrot & Rubin included a mix of patients with T1DM and T2DM who were recruited during a 1-week diabetes management outpatient program.

Numerous other studies have also demonstrated high rates of anxiety disorder [42] and depressive symptomatology in adults with either T1DM or T2DM [35,43]. An early analysis of 42 studies indicated that the risk of depression was doubled in people with diabetes, as compared to people without diabetes, and this occurred regardless of type of diabetes (Figure 49.1) [32]. Similar results have been reported in a more recent meta-analysis of 10 studies that included 9028 patients with T2DM and 42 272 adults without diabetes; again, rates of self-reported depression were significantly elevated in patients with diabetes (17.6% vs 9.8%) [44].

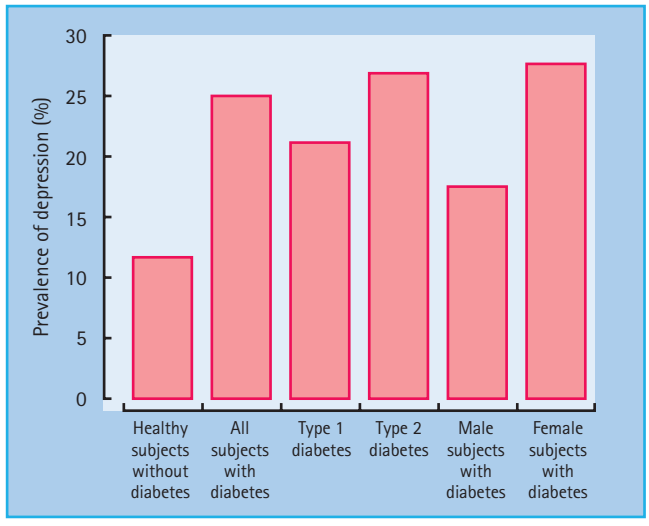

Figure 49.1 The increased prevalence of depression in people with diabetes compared with subjects without diabetes. The data are from a meta-analysis of 42 studies; figures for subjects with diabetes are the aggregate of both controlled and non-controlled studies. Adapted from Anderson *et al.* [32].

Variations in prevalence rates are common across individual studies, and appear to be related to the method used to ascertain depression. Those studies using self-report symptom scales yielded prevalence rates that were nearly three times higher than rates obtained using formal structured interviews with clinically established diagnostic criteria (31% vs 11%) [32]. Discrepancies amongst studies have also been found to be caused by differences in subject characteristics, particularly age and medical history [45,46]. The highest rates of current psychiatric distress tend to be found in hospitalized patients [47] or in older adults with multiple medical co-morbidities [48,49]. Frequently [50,51], but not invariably [45,52], adults with diabetes and more emotional problems also have poorer metabolic control. A review of more than 30 studies indicates that although depression is associated with higher HbA_{1c} values, the magnitude of this effect is extremely small, with the exact value being a function of how depression is ascertained. In studies using symptom self-reports, less than 3% of the variance in HbA_{1c} was explained by depression; when standardized diagnostic interviews are used, approximately 8% of the variance in HbA_{1c} was accounted for by depression [53].

Studies of children with diabetes have indicated that the best predictor of future psychopathology is past psychopathology [16], and the same principle applies to adults. Lustman *et al.* [29] reassessed a group of adults with diabetes 5 years after they had first met criteria for current depression, and found that 67% were depressed at follow-up, whereas only 15% of the initially non-depressed adults met criteria for psychiatric disorder at follow-up. Repeated episodes of depression were common in the initially depressed group, with subjects having an average of 4.2 episodes during the 5-year follow-up period. Recurrence of depression was apparently unrelated to duration of disease, type of diabetes or development of diabetes-associated complications, but it was associated with a family history of psychiatric disorder. A subsequent study found that the severity of recurrent depressive episodes was related to the presence of neuropathy, but no other biomedical complication, at study entry and it has been suggested that the discomfort associated with this complication may serve as a stressor capable of provoking an episode of depression in vulnerable individuals [54]. The generally weak relationship between diabetes-related variables and reoccurrence of a mood disorder suggests that depression is not merely a psychologic reaction to the development of diabetes or its complications, but may be influenced significantly by underlying genetic or constitutional factors [25,55,56].

Depression as a risk factor for subsequent development of type 2 diabetes

Most readers would assume from this literature that the emergence of depression is a direct consequence of coping with its demanding burden of care [48] and/or its associated co-morbid medical conditions [57], but there is growing evidence, at least from studies of older adults with T2DM, that the reverse may be true, and that being depressed greatly increases the risk of subsequently developing diabetes. In a meta-analysis that included 13 comparative prospective studies of depression and T2DM, a robust relationship was noted between depression and the subsequent incidence of T2DM (60% increase in risk), whereas the relationship between having T2DM and subsequently developing depression was modest at best (15% increase in risk) [58]. Although the exact pathologic mechanisms have not yet been established, it is certainly plausible that depression could greatly increase the likelihood of developing diabetes, in so far as depressive symptomatology is associated with a variety of behavioral (e.g. poorer compliance with dietary and weight loss recommendations; less physical activity) [59] and physiologic (e.g. increased activation of the hypothalamic-pituitary-adrenal axis, and increased inflammation) [60] risk factors for T2DM.

The diagnosis and treatment of depression and other psychiatric disorders in patients with diabetes is described in detail in Chapter 55.

Psychologic reactions to biomedical complications

Microvascular and macrovascular complications as triggers for psychologic distress

Diabetic complications may not only disrupt the individual's usual lifestyle and interfere with self-care activities, but may also serve as a reminder that despite their best efforts, patients have failed to manage their disease adequately. In the same way that the child recently diagnosed with diabetes manifests an anxious or depressed mood as part of an adjustment disorder, older patients might be expected to show psychologic distress soon after a complication appears. This conjecture has not been tested empirically: it is not known how adults with diabetes react psychologically shortly after a complication appears, although as a group, adults with complications usually [61], but not invariably [62], have greater levels of psychologic distress.

Three types of diabetic complications are known to increase the risk of psychopathology: macrovascular disorders, chronic foot ulceration and sight-threatening proliferative retinopathy. Adults with diabetes and macrovascular disease often have elevated rates of depression [52] and poorer quality of life [55], although this is not always the case [46,63]. Similarly, patients with chronic unilateral foot ulceration secondary to diabetic neuropathy have higher rates of depression and report greater dissatisfaction with their lives than age-matched adults with diabetes but no history of foot ulceration [64]. Results from a prospective cohort study noted that 24% of adults with diabetes presenting with their first diabetic foot ulcer had clinically significant major depression, and this was associated with a threefold risk of death during an 18-month follow-up period [65]. Other studies have also demonstrated marked increases in depressive symptomatology and peripheral neuropathy, and have attributed this psychologic distress to the physical distress associated with reduced feeling in the feet and unsteadiness, as well as its unpredictability [66,67].

Increased psychiatric symptomatology is also seen in patients with proliferative diabetic retinopathy, compared with those without retinopathy [68]. Both level of visual acuity and duration

of visual problems affect mental health. Wulsin *et al.* [69] followed patients with diabetic retinopathy for 8 months, beginning shortly after a vitreous hemorrhage, and found that greater impairment of visual acuity was associated with increased psychologic distress and poorer coping efforts. Unlike a classic adjustment disorder, these relationships grew stronger, rather than weaker, over time. Fluctuations in visual impairment may also increase psychologic distress [70], although that is not inevitable [71], and it is important to keep in mind that the degree of psychologic distress secondary to visual loss is not unique to patients with diabetes; at least one study of older adults has reported no significant difference in psychologic adjustment between those with and without diabetes, either at the onset of visual loss or when re-evaluated 12 months later [72].

Depression exacerbates the development and course of complications

Distress and depression are usually assumed to be a direct response to the occurrence of a complication, but there is growing evidence for the alternative possibility; that depression, at least under certain circumstances, may increase the likelihood that an individual will subsequently develop complications. The most compelling support for this view remains Kovacs' sophisticated statistical analysis of 10-year follow-up data from their childhood-onset cohort study which demonstrated that severity of retinopathy could be predicted from three antecedent variables [73]. These variables had an additive effect in so far as the likelihood of retinopathy increased with increasing duration of diabetes, with length of time spent in poor control and with overall proportion of time depressed. Depression was not a reaction to retinopathy in this cohort but predated the diagnosis of retinopathy by several years.

An analogous pattern of results has been reported more recently in a study of 483 African-Americans with T2DM who were followed over a 6-year period. Patients with high depression scores at both baseline and 6-year follow-up had significantly higher baseline HbA_{1c} values and were more likely to show progression of diabetic retinopathy (odds ratio 2.44) and progression to proliferative diabetic retinopathy (odds ratio 3.19), compared with patients with low depression scores at both visits [74]. Baseline HbA_{1c} values accounted for 21% of the progression to diabetic retinopathy, while being depressed at both visits accounted for an additional 6% in the regression model.

These intriguing findings suggest that depression may be a risk factor, not only for the development of subsequent psychopathology, but also for the development of subsequent diabetes complications, at least in certain individuals. The physiologic basis for this relationship remains unknown but, as discussed below, depression could interfere with patients' ability to manage their diabetes [75], and so contribute to poor metabolic control. It follows that early treatment of depression may not only improve the individual's mental health, but may improve metabolic control and delay the appearance of diabetic complications [76]. Support for that possibility comes from one small placebo-controlled medication trial clinical study that used a selective serotonin reuptake inhibitor (SSRI) in a group of older adults with T2DM [77], but several other studies, taking a "collaborative care" approach have had no impact on metabolic control or other diabetes-related variables despite marked success in reducing depression in people with diabetes [78,79].

Interactions between acute metabolic complications and psychologic distress

Acute complications of diabetes, particularly recurrent diabetic ketoacidosis (DKA), may also be predicted in children from indicators of poor psychologic functioning in the first year following diagnosis [80]. This is particularly true in girls, for whom more behavior problems and lower levels of social competence were associated with higher rates of DKA. Family dysfunction in the first year following diagnosis was also predictive, with higher levels of family conflict and lower levels of family cohesion associated with more recurrent DKA. Again, this relationship is limited to girls and is independent of variations in HbA_{1c} values. Boys showed relatively low rates of recurrent DKA (6% vs 20%) but very high rates of recurrent hypoglycemia (22.6% vs 3%); the latter were unrelated to psychosocial variables shortly after diagnosis. Even after several years of diabetes, family functioning processes can have a major impact on risk for DKA. Adolescents who reported their parents expressed more negativity to their diabetes regimen had a greater risk of experiencing DKA [81]. It is likely that the link between early behavior problems and DKA in girls is mediated by psychosocial factors, such as poor adherence [82], although definitive evidence for that possibility is currently lacking.

Diabetes treatment-induced fears and phobias

Phobic disorders are twice as common in adults with diabetes than the general population [46]. Earlier work failed to explore the possible reasons for that difference, but an increasing body of research has identified injection or blood and injury phobia, and fear of hypoglycemia, as two sequelae of insulin treatment for diabetes [83]. For example, Berlin *et al.* [84] studied more than 100 adults with T1DM and not only found that 94% of their sample reported at least one phobic symptom, but that patients with poorer glycemic control had more symptoms of fear of blood or injury than did those with better control. Those individuals also measured their blood glucose less frequently and endorsed more symptoms of anxiety and depression. Statistical modeling techniques support the possibility that the association between poorer metabolic control and lower rates of daily blood glucose monitoring is mediated by patients' fear of blood and injury. The prevalence of this phobia remains controversial, with estimates ranging from approximately 1.3% [85] to approximately 25% [86], depending on the questionnaire used to ascertain injection phobia and the criterion used operationally to define the severity of the disorder.

Fear of hypoglycemia is also common in children [87] and adults [88,89] with diabetes, as well as in spouses [90] and parents

[91]. The development of hypoglycemic fear, and the corresponding effort to avoid any situation that may lead to a recurrence of a hypoglycemic event, is not at all surprising. Acute hypoglycemic episodes are uncomfortable and unpredictable. They are accompanied by autonomic arousal characterized by aversive symptoms such as trembling, sweating, light-headedness, pounding heart, nervousness [92], feelings of anger and "tense-tiredness" [93,94] and worries that this episode could lead to a seizure, coma or death if not treated promptly.

Individuals who experienced recurrent hypoglycemia [88], or even a single episode of severe hypoglycemia when accompanied by seizure or coma [95], have higher hypoglycemic fear scores, although this is likely to be a consequence of several factors, including pre-existing personality traits, particularly neuroticism [89] or trait anxiety [96], and current level of psychologic distress [88]. In addition to being associated with higher levels of generalized psychologic distress, fear of hypoglycemia may lead patients with diabetes, and the parents of pediatric patients, to avoid hypoglycemia by treating falling blood glucose levels prematurely and hence maintain ambient blood glucose at higher values than desirable [97]. Programs that teach insulin-treated patients to recognize and anticipate blood glucose fluctuations have also been successful in reducing fear of hypoglycemia [98]. One might expect that fear of microvascular and macrovascular complications would also influence the self-management of the diabetes by the patient, but there has been little formal research on this topic. The recent development of a psychometrically sound "fear of complications" scale is an important first step [99].

Quality of life

Psychologic distress has so far been the primary focus of this discussion, but the extent to which diabetes affects the individual's perceived quality of life is also crucially important. Defining and measuring quality of life remains controversial, although it is generally agreed that this concept should include an understanding of how health-related variables affect physical, social and mental functioning as well as the individual's overall feelings of well-being and satisfaction with life [100].

General health-related quality of life

Large-scale studies of groups of individuals with various chronic illnesses have typically found little evidence that quality of life is differentially disrupted in adults with diabetes. Patients with diabetes do not differ from those with arthritis, renal disease, dermatologic disorders or from the general population on measures of anxiety, depression, positive affect, emotional ties, loss of control or overall mental health [101]. When health-related quality of life was assessed in a large cohort of adults with diabetes with the Medical Outcome Study (MOS-36) questionnaire, patients with diabetes reported more problems in physical and social functioning than patients without chronic conditions, but tended to function better than patients with cardiovascular, pulmonary or gastrointestinal disorders [102].

For individuals with T1DM, poorer health-related quality of life is associated with being older, having biomedical complications, being female, being less physically active and having a lower income [103]. Even the presence of a single biomedical complication can have a measurable impact on quality of life, and as the number of complications increase, there is a corresponding decline in quality of life as assessed by virtually all MOS-36 scales [103,104]. Chronic hyperglycemia, as indexed by higher HbA_{1c} levels, is also associated with poorer general health, even after the presence of complications is taken into account statistically [105]. Recurrent hypoglycemia, defined as one or more episodes a month, also predicts poorer health-related quality of life, particularly on measures of mental health and social function [103] and physical health [105,106]. Many of these same variables are associated with poorer health-related quality of life in older adults with T2DM. Among the best predictors are the presence of diabetes-related complications [107], certain demographic characteristics (female, poorly educated, lower income) and lower levels of physical activity [105,108]. The relationship between metabolic control and health-related quality of life remains controversial, with some [105], but not all [109] studies finding statistically reliable correlations.

Diabetes-specific quality of life

The use of diabetes-specific quality of life measures leads to similar conclusions [104]. The Diabetes Quality of Life (DQOL) measure, first developed to assess changes in quality of life during the course of the DCCT, explicitly examines factors such as satisfaction, impact of diabetes, social/vocational worry and diabetes-related worry [110]. When evaluated with either a generic pediatric quality of life measure [111] or with disease-specific questions, adolescents reported a relatively good quality of life which was only moderately affected by their diabetes, yet there was a great deal of inter-individual variation in response [112]. Differences in metabolic control or other biomedical or psychosocial factors may be responsible for this variability, although there is little consistency across studies. For example, improved metabolic control has sometimes [113], but not invariably [112], been found to be associated with better diabetes quality of life in adolescents.

Healthy adults with T1DM also report being satisfied overall with life, and indicate that diabetes has had little impact on their lives [114]. These relationships occur regardless of type of treatment (conventional or intensive insulin therapy) [31], or type of diabetes-associated quality of life measures employed [115]. Despite the demands made on individuals treated with intensive therapy, there is no evidence that treatment over a long period of time (6–9 years) adversely affects quality of life [31]; in fact, over a short-term (4 month) period, it is associated with improvements in diabetes quality of life [116]. The relatively benign experience of intensively treated patients participating in the DCCT may be a consequence of the greater level of psychologic and medical support that is provided to the participants in such clinical trials [41] or, alternately, may reflect the relative insensitivity

of a measure like the DQOL to small changes in quality of life over time [100]. More recent studies evaluating changes in quality of life associated with the use of continuous subcutaneous insulin infusion have been mixed, with some indicating no benefit, while others suggesting modest benefit [117], particularly amongst children and their parents [118].

Age at onset of diabetes may also affect certain aspects of life quality. One survey of marital satisfaction found that adults diagnosed with T1DM before 9 years of age were more satisfied with their marriage, and were more likely to have children than those diagnosed later [119]. Those authors suggest that individuals diagnosed earlier in development may be more adept at integrating the disease as part of their lifestyle and thus find less disruption from diabetes later in life. More recent work also suggests that the linkages between marital satisfaction, higher levels of diabetes-related satisfaction and better metabolic control may reflect better psychosocial adaptation to a variety of illness-related and marital role stresses and strains [120].

Diabetes-specific quality of life measures have been used less frequently with older adults with T2DM, but those studies have typically obtained results that do not vary appreciably from those noted in patients with T1DM [104]. When quality of life is operationally defined by measures of mood, cognitive mistakes or work symptoms, most adults with T2DM report little disruption in most areas of life, although an appreciable minority (27%) report loss of enjoyment from previously valued activities, particularly social eating and drinking [121]. Worse quality of life seems to be especially evident in patients with T2DM treated with insulin [122], although several studies, including the UK Prospective Diabetes Study, have found no effect of intensive therapy regimens on quality of life [123].

Interventions to reduce psychologic distress

Traditional psychotherapy

Individual or group psychotherapy or supportive counseling should be as effective in children or adults with diabetes as in individuals without diabetes but with similarly high levels of psychologic distress [124]. Many recommendations have been made for such interventions [16,125], and while there are now a large number of studies that have made use of these, data from several recent meta-analyses have generally found them to have, at best, modest effects in reducing psychologic distress and in improving metabolic control [126–128].

Traditional individualized and group therapy has been used to provide emotional support for both children and adults with diabetes, and may be particularly beneficial for patients who are confronting the development of complications such as blindness [129,130]. Studies of individual psychotherapeutic interventions are rare, but data from a single, very small randomized trial are quite promising. When a time-limited problem-oriented individualized treatment was compared with standard insulin treatment counseling in adults with T1DM, patients receiving the psychotherapeutic treatment showed greater reductions in both problem severity and in HbA_{1c} values than those receiving conventional diabetes care [131].

Group therapy programs, which are far more common, have similarly shown either very small positive effects or no reduction in distress. Such groups are typically led by mental health professionals, have 4–12 participants, meet weekly or fortnightly for 90 minutes; they may run for as long as a year [132], although interventions as brief as 7 weeks have been conducted [129]. A major focus for such groups, at least early on, is to provide participants with more medical information about diabetes [130,132]. Over time, participants become more comfortable in discussing personal concerns, diabetes-related and otherwise. The broad range of topics discussed may include coming to terms with unfinished grieving over diabetes-associated problems, dealing with guilt that they may have caused their own complications and coping with fears about loss of independence [133]. As with individual psychotherapy, the efficacy of formal group therapy, in terms of improved mood or metabolic control, has not been studied extensively in large, carefully designed studies [134] and the quality of the current research is considered "weak" from a methodologic perspective [128]. Anecdotal reports suggest that many participants leave the group happier, or better adjusted, and various "curative factors" have been identified by patients as being a major benefit of group therapy, including interpersonal learning, the experience of catharsis, development of insight into problems and an understanding that the individual is not alone in experiencing disease-related psychologic distress [135,136], but analyses of outcomes from formal clinical trials with children and adults with diabetes have been less sanguine [126,128,137].

Cognitive–behavioral therapy

Of the different psychotherapeutic modalities available, cognitive–behavioral therapy (CBT) appears to be particularly promising in reducing the severity of depressive symptomatology. CBT teaches patients to use problem-solving strategies to reduce stressful situations and trains them to use cognitive techniques to "think away" their distorted beliefs, and replace them with more accurate and adaptive thoughts. Comparing 10 weeks of individualized CBT with non-therapeutic diabetes education (control condition), Lustman *et al.* [138] found that 85% of patients with T2DM receiving CBT achieved remission of depressive symptoms, in contrast to 27% in the control condition; at 6-month follow-up, similar rates of remission were seen (70% vs 33%). Individuals who are most likely to benefit from CBT are those with fewer complications and/or better compliance with blood glucose monitoring [139]. Variations of this approach have been used in studies of adults with T1DM, and while there were marked reductions in diabetes-related distress and in symptoms of depression, they were no differences between those subjects treated with group CBT and those in an active comparator condition who were treated with blood glucose awareness training. In neither group were there meaningful changes in glycemic control at 6 or 12 months after therapy initiation, but both were equally effective in lowering depressive symptoms to a modest degree

[140]. The fact that blood glucose awareness training, which has a minimal psychologic component, is effective in reducing psychologic distress is quite surprising, and emphasizes the potential effects that simple training in diabetes management may have on an individual's level of psychologic distress.

Pharmacotherapy

Diabetes-related depression and anxiety disorders have also been treated successfully with pharmacotherapy [141,142]. Placebo-controlled studies have demonstrated that SSRIs such as fluoxetine [143] and sertraline [77], and tricyclic antidepressants such as nortriptyline [144] effectively reduce severity of depression and its subsequent recurrence in patients with diabetes, whereas the benzodiazepine alprazolam [145] effectively reduces anxiety. These different psychoactive drug classes differentially affect metabolic control. Nortriptyline produces a sustained increase in HbA_{1c} values; in contrast, both fluoxetine and alprazolam reduce HbA_{1c} values significantly. The physiologic basis for these differential effects remains unknown, but most experts believe that pharmcotherapy-induced hyperglycemia can be handled readily with appropriate adjustments to the diabetes management regimen [146].

Pharmacotherapy alone, or paired with a form of psychotherapy such as CBT, may not only improve mental health, but it may also reduce the risk of death, as recently demonstrated in the PROSPECT trial [147]. In that medical practice-based study, older depressed adults with and without diabetes were randomized to usual care or to an intervention in which trained depression-care managers monitored psychopathology, adherence to treatment regimens, patients' responses and side effects, and provided subjects either with a first-line antidepressant medication (an SSRI) or interpersonal psychotherapy. All subjects were followed for a median of 52 months, and only mortality outcomes were reported. There was a significant reduction in all cause mortality, but only for those depressed patients with diabetes who received this simple depression management strategy, demonstrating that even minimal management of depression can have salutary effects in the health of older adults with diabetes. Given the nature of that study's design, however, it is impossible to identify the processes underlying these effects.

Neuropsychologic impact of diabetes

Diabetes has long been thought to affect cognition, as well as emotion, but it was not until the development of clinical neuropsychology (the study of brain–behavior relationships) that researchers were able to demonstrate unequivocally that mental efficiency can be disrupted by diabetes, its complications and its management, and that this neuropsychologic dysfunction reflects changes occurring in the CNS. The magnitude of these effects is relatively modest in most individuals, and few patients with diabetes manifest cognitive changes that would be characterized as being "clinically significant" – unless they developed diabetes early in life. Until very recently, when cognitive dysfunction was found in patients with diabetes it was invariably attributed to the adverse effects of severe and/or recurrent hypoglycemia on the CNS. New research suggests that chronic hyperglycemia, and the metabolic and vascular complications that are associated with it, underlie the development of most structural and functional changes to the CNS, particularly in adults. Although hypoglycemia can never be considered to be entirely benign, it may have a relatively small role in the etiology of neurocognitive changes in patients with diabetes [148,149].

CNS sequelae of diabetes in children and adolescents

Cognitive manifestations

The nature and extent of cognitive dysfunction in children and adolescents differs depending on age of diagnosis. Those diagnosed in the first 5–7 years of life appear to have an elevated risk of manifesting a moderately severe cognitive impairment which is evident across a broad range of cognitive domains, including measures of attention, mental flexibility, psychomotor efficiency, learning, memory, problem-solving and overall intelligence [150–156]. In contrast, those diagnosed after that early "critical period" show very mild cognitive dysfunction which is limited primarily to measures of overall intelligence and to performance on speeded tasks, particularly those having a visuoperceptual component [156]. Learning, memory and problem-solving skills are largely intact in this "later onset" patient population, or are only very minimally [157] and inconsistently affected [158,159]. Regardless of age at diagnosis, children with diabetes also tend to achieve lower scores than their peers without diabetes on measures of academic achievement [157,160], and have somewhat poorer grades in school [161], with these latter effects especially pronounced in children with a very early onset of diabetes [162].

The magnitude of the cognitive dysfunction seen in children with diabetes tends to be quite modest, as demonstrated by a formal meta-analysis of 19 pediatric studies encompassing 1393 children with diabetes and 731 healthy comparison subjects. When effect sizes were calculated (between-group difference divided by pooled standard deviation: "Cohen's **d**" [163]) for studies comparing later-onset children with control subjects, **d** values were approximately 0.20 or less – indicative of "small" to negligible effects. In contrast, effect sizes were more than twice as large when comparing early-onset subjects with diabetes with their peers without diabetes [156]. Using clinical rather than statistical criteria, one similarly finds marked differences between children with an early, as compared with a later, onset of diabetes. One large study found that 24% of children with an early onset of diabetes meet criteria for clinically significant impairment, as compared with only 6% of children with a later onset of diabetes, and 6% of a comparison group without diabetes [153].

This age at onset phenomenon has also been reported in adults diagnosed with diabetes early in life. Young adults who developed diabetes before 7 years of age performed more poorly on measures of information processing speed, and earned lower performance IQ scores than their peers with diabetes diagnosed at or after

age 7 [164]. Abnormalities in brain structure are also evident. Magnetic resonance imaging (MRI) scans showed higher rates of mild to moderate ventricular atrophy (61% vs 20%), as well as somewhat higher rates of small punctate white matter lesions within the hippocampus (14% vs 2%). Smaller brain volumes were also correlated with poorer cognitive test performance, supporting the view that cognition dysfunction is necessarily linked to changes in CNS morphology.

Neurocognitive abnormalities appear relatively early in the course of diabetes, having been reported within 2–3 years of diagnosis. In the largest longest prospective pediatric study to date, a representative sample of 90 newly diagnosed youngsters with diabetes and 84 healthy children drawn from the community have been followed over a 12-year period. No between-group differences were evident at study entry [165] but, 2 years later, those children diagnosed before age 4 manifested developmental delays in so far as their scores on both the Wechsler Vocabulary and Block Design subtests improved less over time, relative to either children with a later diabetes onset or to community control subjects [166]. After 6 years of follow-up, children with diabetes – regardless of age at diagnosis – performed worse than their peers without diabetes on measures of intelligence, attention, processing speed, long-term memory and executive skills. Children with an early age at onset were particularly affected, and performed significantly worse on measures of attention and executive function than those with a somewhat later onset of diabetes [151]. After 12 years of follow-up, these children with diabetes – now young adults – continued to earn lower verbal and full-scale IQ scores, demonstrating that these effects are not a "developmental delay," but reflect a true, albeit modest, loss in cognitive efficiency, relative to those without diabetes [167]. Several other reports have also noted gradual decline in IQ scores as diabetes duration increases [161,167,168].

Effects of hypoglycemic episodes on brain function

Hypoglycemia has long been considered to be the cause of these neuropsychologic deficits, particularly in children with an early onset of diabetes [153,155]. Not only are rates of severe hypoglycemia significantly higher in children younger than 5 years of age, compared with children older than 5 (48% vs 13%), but hypoglycemia is also more likely to reccur in this younger group [169]. Behavioral factors could also contribute to the high rates of hypoglycemia early in life. Falling blood glucose levels may go unrecognized and untreated because very young children cannot adequately communicate that they are developing hypoglycemic symptoms. Although that view seems quite plausible, recent large well-designed cross-sectional [164,170] and longitudinal [171,172] studies completely failed to find any relationship between recurrent episodes of hypoglycemia and cognitive impairment, whereas others have reported only very weak and inconsistent findings [159] or have data sets in which severe hypoglycemia and age at onset tend to be confounded [173]. Similarly, both animal neuropathology [174] and human neuroimaging studies [167,175,176] are consistent with that view. For example, no changes in neuronal morphology were found in very young (1 month old) rats despite recurrent bouts of experimentally induced severe hypoglycemia, whereas 2 months of insulin-controlled diabetes caused a reduction in dendritic branching and fewer dendritic spines on neurons, and this was associated with poorer performance on measures of spatial memory [174]. These findings suggest that hypoglycemia is unlikely to be sufficient to induce significant brain dysfunction in most children, at least in those diagnosed with diabetes after the age of 7 years; however, for children with an early onset of diabetes, hypoglycemia may have a contributory role in the development of brain dysfunction [154,159].

Other CNS changes associated with diabetes in childhood

In addition to cognitive dysfunction, children with diabetes manifest multiple other changes in the CNS. Slowed neural activity is a very robust phenomenon. Compared with their peers without diabetes, adolescents with diabetes in good metabolic control showed significant increases in delta and theta (slow wave) activity, significant declines in alpha peak frequency in frontal brain regions, and declines in alpha, beta and gamma fast wave activity in posterior temporal regions [177]. When electroencephalogram (EEG) recordings were evaluated clinically, one large study noted that 26% of their subjects with diabetes had abnormal EEG records, compared to only 7% of healthy controls [178]. Both earlier age of diabetes onset and episodes of severe hypoglycemia were strong predictors of abnormality in that study, as well as in several earlier studies [179]. When auditory or visual evoked potentials were recorded, children and adolescents with a 2 years or more history of diabetes showed significant neural slowing, as evidenced by increased latencies, whereas those with less than 2 years of diabetes had normal latencies [180].

Cerebral blood flow has been measured only infrequently in children with diabetes, but the one study that used single photon emission computed tomography (SPECT) found lower levels of cerebral blood flow in children with diabetes than in healthy comparison subjects [181]. The greatest reductions in brain perfusion were found in the basal ganglia and frontal regions, followed by parietal and temporal areas. This pattern is similar to that reported in adults with T1DM [182], and provides limited support for the view that changes in brain perfusion may occur relatively early in the course of diabetes. The extent to which these cerebrovascular changes contribute to cognitive dysfunction remains to be determined.

Brain structure anomalies, documented with MRI, have only recently been reported in children with diabetes. The one study that focused exclusively on children with an early onset of diabetes noted greatly elevated rates of a very unusual brain anomaly – mesial temporal sclerosis. Within this cohort, 16% manifested this anomaly compared to less than 1% of the general pediatric population [175]. These anomalies apparently developed within a relatively brief period of time (mean duration of diabetes in this sample was approximately 7 years), and were unrelated to a past history of hypoglycemia. By contrast, children who experienced

one or more episodes of severe hypoglycemia (seizure or coma) had smaller gray matter volumes than those with no such history (724 vs 764 cm^3), regardless of whether the hypoglycemic event occurred early in life or at a somewhat later age.

A second neuroimaging study used a semi-quantitative voxel-based morphometry technique to ascertain gray and white matter volumes in 108 children with diabetes and 51 age-matched children without diabetes who were 7–17 years of age [176]. Total brain volume was comparable in the two groups, but those children with diabetes who experienced one or more episodes of severe hypoglycemia had a slight reduction in gray matter in the left (but not right) temporal occipital region. This pattern of highly circumscribed effects, localized primarily to the left hemisphere, is consistent with what has been reported in adults with a long history of childhood-onset diabetes [183], as well as in several case reports [184]. Lifetime HbA_{1c} values, used to estimate of chronic hyperglycemia, were associated with less cortical volume in the right posterior brain regions (particularly the right cuneus and precuneus), also replicating findings in adults with diabetes [183]. Chronic hyperglycemia was also associated with less white matter, and these effects were most pronounced in parietal brain regions.

At this point, the underlying pathophysiologic basis for the development of CNS dysfunction in children remains unresolved, because at least some studies have found relationships between neurocognitive outcomes and both hypoglycemia and chronic hyperglycemia; however, there is increasing interest in studying the many metabolic – and potentially neurotoxic – events that occur around the time of diabetes diagnosis such as changes in brain glucose during the peri-onset period, dramatic metabolic perturbations, including the occurrence of DKA, that now seem to have the potential to alter the structure of the developing brain in the child with diabetes [154,185].

Brain structure and function in adults with type 1 diabetes

Neurocognitive manifestations

A highly circumscribed pattern of mild cognitive dysfunction characteristic of adults with T1DM has been identified from a systematic meta-analysis of data from 31 studies published in English between 1980 and 2004 that compared the performance of subjects with and without diabetes on multiple cognitive domains [186]. As illustrated in Table 49.1, subjects with diabetes, who were 18–50 years of age and in relatively good health, performed significantly more poorly on measures of intelligence, attention, psychomotor speed, cognitive flexibility and visual perception, whereas no between-group differences were found on measures of language, learning and memory. Even when differences were detected, they were modest at best, with effect sizes (**d**) ranging from 0.3 to 0.8 standard deviation units. It is important to note that not all cognitive domains were affected. Learning and memory skills, which are generally considered to be sensitive to early brain damage [187], were well preserved in this diverse patient population, despite an average of 20 or more years of T1DM. Moreover, with only one exception ("crystallized intelligence"), virtually all of the cognitive tasks on which patients with diabetes perform more poorly were those that also required rapid responding. That is, mental slowing appears to be the fundamental deficit associated with T1DM in adulthood [188]. A similar pattern of results has been found in adults with T1DM who are over the age of 60 [189]. Remarkably, the magnitude of the cognitive differences found in these older adults was similar (**d** = 0.3–0.5) to that reported in their younger counterparts, despite their longer duration of diabetes.

Table 49.1 Cognitive characteristics of adults with T1DM, based on a meta-analysis of published papers. Standardized effect sizes (Cohen's **d**) for each cognitive domain reflect differences between subjects with and without diabetes. Adapted from Brands *et al.* [186].

Domain	Effect size	Significance	Total number	Studies
Overall cognition	0.40	$P < 0.001$	660	16
Intelligence				
Crystalized	0.80	$P < 0.01$	276	5
Fluid	0.50	$P < 0.01$	168	4
Language	0.05	NS	144	4
Attention				
Visual	0.40	$P < 0.001$	195	5
Sustained	0.30	$P < 0.01$	217	3
Learning and memory				
Working memory	0.10	NS	244	8
Verbal learning	0.20	NS	204	5
Verbal delayed memory	0.30	NS	157	3
Visual learning	0.10	NS	187	5
Visual delayed memory	0.10	NS	157	4
Psychomotor speed	0.60	$P < 0.05$	368	8
Cognitive flexibility	0.50	$P < 0.001$	364	9
Visual perception	0.40	$P < 0.001$	202	5

NS, non-significant.

As noted in studies of children with diabetes, adults with diabetes also manifest slowed neural processing on measures of brainstem auditory evoked potentials [190,191], visual evoked potentials [192] and EEG recordings [193]. The magnitude of these effects is greatest in those individuals who have clinically significant microvascular complications [194–196]. Multiple studies have also demonstrated that cerebral blood flow patterns are abnormal in adults with diabetes, with these effects greatest in frontal and frontotemporal brain regions [197]. Changes in cerebral perfusion, measured by SPECT, are common. In one large study, 85% of middle-aged adults with diabetes showed hypoperfusion in one or more region of interest compared to 10% of controls; similarly, 58% of subjects with diabetes showed hyperperfusion, compared to 20% of controls [182]. Again, these effects were greatest in subjects with microvascular complications.

Changes in gray and white matter

Marked reductions in brain matter density, as demonstrated by voxel-based morphometry, are also associated with T1DM. Compared with a group of healthy individuals without diabetes, young adults with a childhood onset of diabetes manifested significantly less gray matter (approximately 5%) in the right superior temporal gyrus, and in several left hemisphere regions, including the temporal gyrus, angular gyrus, medial frontal gyrus, inferior parietal lobule and thalamus [183]. These structures are especially important for attention, memory and language processing. The strongest predictor of gray matter density reduction was degree of chronic hyperglycemia in so far as higher lifetime HbA_{1c} values were consistently correlated with lower gray matter density.

Similar findings have been reported in a case–control study demonstrating that individuals with diabetic proliferative retinopathy manifest small but statistically reliable reductions in gray matter density in the left middle frontal gyrus, the right inferior frontal gyrus, the right occipital lobe and the left cerebellum, whereas the gray matter values of patients with diabetes without retinopathy were comparable to adults without diabetes [198]. Reductions in white matter volume have also been noted, with effects being greatest amongst adults with a longer history of chronic hyperglycemia and microvascular complications [199].

Retinopathy as a risk factor for CNS abnormalities

In reviewing these structural and functional findings it appears that a long history of chronic hyperglycemia, as indexed by the occurrence of microvascular complications, is a robust risk factor for neurocognitive abnormalities. The most direct support for this possibility comes from a longitudinal study that followed a group of young and middle-aged adults with a childhood onset of T1DM over a 7-year period [200]. Subjects who had clinically significant proliferative diabetic retinopathy at study entry, or who developed retinopathy during the course of the follow-up period, showed a significant decline in psychomotor efficiency, compared to demographically similar subjects without diabetes. In contrast, those without retinopathy at either time showed no evidence of psychomotor slowing. The risk of cognitive change was predicted by four variables: the presence or development of proliferative retinopathy, the presence of autonomic neuropathy, elevated systolic blood pressure and longer duration of diabetes. The resulting statistical model identified, with 83% accuracy, subjects who showed significant cognitive decline and explained 53% of the variance.

Cross-sectional studies of young adults have similarly demonstrated that background retinopathy is associated with white matter abnormalities on MRI and poorer performance on measures of attention, fluid intelligence and information processing speed [201]. Abnormal brain activation patterns during the performance of a working memory task have also been identified in patients with clinically significant retinopathy who were evaluated with functional MRI [202]. Other microvascular complications, particularly peripheral neuropathy, are also associated with changes in brain function and structure [177,193,196,203,204].

Because middle-aged adults without diabetes who have retinal microaneurysms also show a pattern of cognitive decline that is characterized by psychomotor slowing [205], it has been suggested that retinopathy may serve as a general marker of cerebral microangiopathy [148,206]. This is quite plausible, given the well-known homology between the retinal and cerebral microvascular systems [207]. In patients with clinically significant diabetic retinopathy, the resulting microangiopathy could lead to cerebral hypoperfusion and thereby contribute to the development of abnormalities in brain structure and function by interfering with the efficient delivery of glucose and other key substances to neural tissue [148,198]. The relationship often reported between peripheral neuropathy and brain dysfunction in patients with diabetes may simply reflect the fact that microvascular complications tend to appear contemporaneously and have a common origin [208,209]. That is, microvascular disease may be the primary mechanism underlying the development of neurocognitive dysfunction in young and middle-aged adults [150].

Repeated episodes of severe hypoglycemia and cognitive dysfunction

The widespread belief that moderately severe hypoglycemia will induce cognitive impairment in adults with diabetes appears to have little support from a growing body of research on this topic. The most compelling negative data come from the DCCT and its follow-up natural history study, the Epidemiology of Diabetes Interventions and Complications (EDIC). Cognitive functioning was assessed over an 18-year period in 1144 patients with T1DM who were between 29 and 62 years of age (mean 46 years) at the time of their final cognitive evaluation. Lifetime rates of severe hypoglycemia, defined as including a seizure or coma, were high, with a total of 1355 episodes reported in 453 subjects over the course of the study. Despite that, no relationship whatsoever was found between the cumulative number of severe hypoglycemic episodes and performance on a comprehensive battery of cognitive tests [210].

Cross-sectional studies have also failed to find robust relationships between cognition and episodes of severe hypoglycemia [186,201]. Several earlier studies did note a link between hypoglycemia and brain damage [211], but all relied on small samples of highly selected subjects who were assessed with a limited number of cognitive tests which yielded a pattern of results that was not entirely consistent with brain damage. For example, subjects with repeated hypoglycemia performed slower, but no less accurately, on a number of tests, and earned somewhat lower scores on the Performance subtests of the Wechsler Adult Intelligence Scale, yet learning and memory skills were intact. This latter finding is unexpected because of the well-known associations between memory and the hippocampus, a major focus of structural damage following profound hypoglycemia in rodents [212], nonhuman primates [213] and humans [184,214]. Whether moderately severe bouts of hypoglycemia adversely affect brain structure

remains controversial, with some [215] but not all [174] studies finding evidence of neuronal necrosis in rodent models. In human studies it can be quite difficult to make attributions specifically to hypoglycemia, rather than to chronic hyperglycemia, because patients who experience hypoglycemia also have a history of poor metabolic control [177].

As described in Chapter 33, severe and profound hypoglycemia can induce significant structural and function brain damage, but the prevalence of this phenomenon in adults with diabetes seems extremely low.

Hyperglycemia and neurocognitive dysfunction associated with T2DM

Older adults with T2DM also show evidence of psychomotor slowing [216–218] and, in that way, are somewhat similar to young and middle-aged adults with poorly controlled T1DM. In addition, elderly adults with T2DM consistently learn new verbal and non-verbal information more slowly, and remember less of it over a brief delay, compared with subjects without diabetes [219–221]. Interestingly, this phenomenon appears to be limited to individuals over 60 years of age; younger adults with T2DM rarely show memory impairments [222]. Other cognitive skills, particularly problem-solving ability, may also be affected in older adults with T2DM [221], but those skills have been assessed less frequently (for reviews, see [219,223,224]).

The cognitive effects associated with T2DM are similar in magnitude to those reported in younger adults with T1DM. One recent study comparing 119 patients with T2DM (mean age 66 years; mean HbA_{1c} 6.9% [52 mmol/mol]) with 55 age-matched healthy subjects without diabetes found the subjects with diabetes to perform worse only on measures of information processing speed (**d** = 0.50), memory (**d** = 0.43) and attention and executive function (**d** = 0.43) [225]. The strongest predictor of poorer cognitive function was poorer metabolic control; neither duration of diabetes nor severity of peripheral neuropathy were related to any cognitive outcome variable [226]. Other studies have also noted strong negative relationships between HbA_{1c} values and cognition. For example, one very large epidemiologic study has demonstrated that each 1.0% (11 mmol/mol) increase in HbA_{1c} was associated with significantly poorer performance on tests of psychomotor speed, memory and executive function [227].

Despite their often brief duration of diabetes, patients with T2DM also manifest evidence of neural slowing [190,196], overall reductions in cerebral blood flow [228,229] and significant changes in brain structure, including smaller gray matter volumes (appriximately 22 mL reduction), greater subcortical atrophy (approximately 7 mL increase in lateral ventricle volume) and larger white matter lesion volume (approximately 57% increase) [230]. Structural changes appeared to be more prominent in women and were associated with higher HbA_{1c} values and older age, but were unrelated to diabetes duration, hypertension or hyperlipidemia. Compared with patients with T1DM, those with T2DM showed significantly greater cortical atrophy and deep white matter lesions, with effect sizes ranging between 0.50 and 0.66 [231], even though the patients with T2DM had diabetes for a shorter period of time (7 vs 34 years) and had lower rates of clinically significant microvascular complications (laser-treated retinopathy: 8% vs 38%). The higher rates of macrovascular disease and atherosclerotic risk factors may underlie the development of the CNS changes seen in the T2DM cohort, although there is evidence to suggest that impairments in glucose and/or insulin regulation may be contributory [232,233]. The hippocampus, which has only infrequently been evaluated in most modern neuroimaging studies, was also found to be reduced in a group of relatively healthy adults with T2DM compared to healthy controls (5.4 vs 6.2 cm^3; **d** = 1.4) [234]. This could explain, at least in part, the poor memory function seen in many older adults with T2DM. The best predictor of hippocampal atrophy was HbA_{1c} values.

Much attention has recently been focused on rates of dementia in older patients with T2DM and it has been argued that diabetes is a significant risk factor for the subsequent development of Alzheimer disease or vascular dementia. Several recent studies and review articles have noted an increased risk of dementia that ranges 1.2–2.3 for Alzheimer disease and 2.2–3.4 for vascular dementia [235–237]. T2DM also has a significant negative impact on activities of daily living, with rates of functional disability doubled (e.g. ability to do housework efficiently and without assistance; walk 2–3 blocks) [238].

The degree of chronic hyperglycemia, as indexed by HbA_{1c} levels, is the best (albeit imperfect) predictor of impairment in the older patient with diabetes, although a growing body of research has identified other diabetes-related conditions, including hyperinsulinemia [239,240], hypertension [220] and hypercholesterolemia [241]. Many patients with T2DM are beset with multiple medical problems or diabetic complications, some of which, such as cerebral atherosclerosis, could contribute to cognitive decline [219,224]. Nevertheless, it is clear that factors other than vascular disease must play a part in the etiology of these cognitive impairments because they can be identified in otherwise healthy adults with T2DM who have no clinically apparent vascular complications [217].

Diabetes management and psychologic processes

The management of diabetes is an extraordinarily complex endeavor. The person with T1DM must take responsibility for injecting insulin two or more times each day, carefully monitor food intake at each meal, periodically measure glucose in blood, and readjust insulin, food and/or exercise during acute illnesses or in response to excessively high or low blood glucose values. Similar demands are placed on those with T2DM. The medication regimen may be less onerous, but dietary and lifestyle changes are often harder to tolerate. In either instance, patients and their families assume primary responsibility for these self-

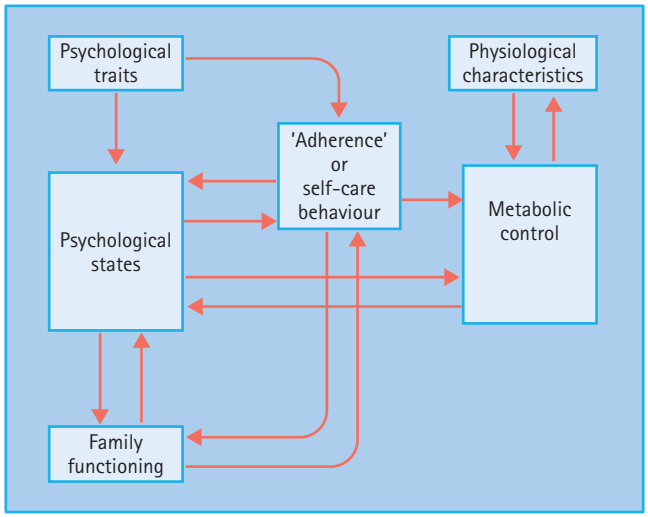

Figure 49.2 A systems model of the relationships between psychological and metabolic variables.

care behaviors, all of which are directed at maintaining optimal metabolic control. Good control signals that the patient's management efforts have been successful, while poor control may be interpreted as evidence that the patient has failed. This latter outcome may adversely affect mood and general psychologic well-being. Conversely, certain personality traits or coping styles that are intrinsic to an individual's psychologic make-up may modulate the patient's ability to manage diabetes self-care activities, as may environmental and psychosocial factors such as peer pressure to engage in certain "forbidden" activities, disruptive interpersonal conflicts and the normal stresses and strains of everyday life. Overall, an individual's "psychology" may influence, and be influenced by, the process of diabetes management.

According to a systems model of health, there is no simple direct relationship between any single psychologic variable and metabolic control [242]. Rather, health outcomes are determined by a system of reciprocal relationships amongst multiple psychologic, behavioral and physiologic variables. Figure 49.2 shows one such model of this process. Psychologic traits are relatively enduring characteristics that include personality, temperament and coping style. These may have a direct impact on self-care behaviors (adherence), and may also have a direct impact on emotional state. Psychologic states are more transitory and reflect emotions or feelings at a given point in time. Both family interactions and self-care behaviors may affect, and be affected by, the individual's mood or level of stress. Theoretically, at least, certain emotional states, especially stress, may also influence metabolic control directly via the autonomic nervous system or, indirectly, by interfering with the patient's ability to manage his/her diabetes. Family functioning, including conflicts and degree of family cohesiveness, can affect psychologic state (and vice versa), but can also influence self-care behaviors. Self-care or adherence behaviors include medication use, diet, exercise and monitoring, and these behaviors serve as the primary final common pathway to metabolic control. The frequently reported absence of a strong relationship between adherence and glycemic levels may reflect the effects of physiologic characteristics, such as intercurrent illness or hormonal fluctuations secondary to puberty.

Psychologic traits and their impact on metabolic control

These encompass a series of overlapping psychologic concepts that include "personality," "temperament" and "coping style." Individuals with personality characteristics indicative of a strong need for achievement and a high level of responsivity to social demands enjoy better metabolic control [243]. By contrast, HbA_{1c} values tend to be higher in adults who are opportunistic and alienated [244] or who have poor impulse control, a propensity for self-destructive behaviors and difficulty maintaining interpersonal relationships [245]. Being a worrier or highly emotional, as reflected by elevated neuroticism scores or higher levels of trait negative affect, may also be associated with poorer metabolic control [246,247], although there is not complete agreement [248,249]. Indeed, in adults with T2DM, higher neuroticism levels were associated with better metabolic control, and it has been suggested that moderate levels of worry may be needed to motivate these older adults to manage their diabetes [250].

Locus of control is another psychologic trait that may affect glycemic state. Individuals who have an "internal" locus of control believe that they are responsible for their health, whereas those who have an "external" locus believe that they are at the mercy of chance, or some other outside force. In general, individuals with an internal locus seem more likely to have better metabolic control [251–253], although that is not invariably the case [33,254,255]. One would expect that individuals with an internal locus of control would do a better job of managing their diabetes, and that this would lead to better metabolic control, yet most studies have failed to demonstrate a strong link between locus of control and adherence [252,256]. Reconciliation of these discrepancies may require a reconceptualization of the locus of control construct. For example, internal locus of control may have multiple dimensions such as autonomy and self-blame that are not typically measured in a systematic fashion yet may lead to somewhat different health outcomes [257]. Multidimensional measures that examine different aspects of sense of control as well as different modes of control and motivation for control may ultimately provide investigators with more accurate insights into the complex inter-relationships between perception of control and optimal diabetes management but, to date, they have been used only infrequently [258].

The complexity of these interactions has recently been underscored in a study that measured locus of control, self-efficacy and outcome expectancy, and used this information to predict patients' HbA_{1c} values. Within a sample of patients with T2DM from a predominantly disadvantaged background, those with an internal locus of control who reported low self-efficacy and low outcome expectancy tended to be in better metabolic control, whereas those with an internal locus of control but also expressed

low self-efficacy and high outcome expectancy tended to be in poorer metabolic control [259]. Having an internal locus of control may be particularly beneficial to those patients with little confidence in their ability to follow their physicians' recommendations (i.e. low self-efficacy), as well as little confidence that following those recommendations will actually improve their health (low outcome expectancies).

Coping styles, broadly categorized as emotion-focused and problem-focused [260], serve to modulate the individual's response to stressful situations. Emotion-focused or cognitive coping attempts to reduce threats from the environment by reinterpreting or reappraising the situation ("Stay calm, it really can't hurt you"). Problem-focused coping, in contrast, seeks to change the environment and thereby eliminate the threat (e.g. reduce excessive carbohydrate consumption by removing all high fat snacks). Within each of these categories, specific behavioral strategies may be differentially effective. Some may actually exacerbate stress (e.g. emotion-arousing strategies that include anger, impatience or anxiety), while others (e.g. stoicism) may reduce or "buffer" the effects of stress [261]. In adults with T1DM, higher levels of stress were associated with poorer metabolic control, but only in people who use ineffective coping styles that tend to increase emotional arousal [262]. In adolescents, emotion-focused coping styles (e.g. behavioral and mental disengagement; aggressive coping) was also associated with poorer metabolic control and reduced diabetes-related quality of life, whereas the use of active coping strategies directed at approaching and making a direct effort to change the situation causing psychologic distress was linked to better metabolic control [263]. Data from a meta-analysis of 21 studies have shown that the use of approach coping was associated with both better overall psychologic adjustment and with somewhat better metabolic control [264].

If traits truly reflect enduring behavioral characteristics, they ought to predict long-term adherence. Support for that possibility has been provided by Jacobson *et al.* [256] in their longitudinal study of children and adolescents with diabetes. Coping style assessed soon after diabetes onset predicted adherence behaviors 4 years later. Those children who used more mature defense mechanisms and showed greater adaptive capacity such as higher stress tolerance or greater persistence shortly after diagnosis were most likely to manage their diabetes satisfactorily in the long term.

Psychologic states: stress, depression and anxiety

Many adults with diabetes consider stress to be a powerful determinant of their ability to maintain good metabolic control [265]. Higher levels of stress are associated with poorer glycemic control in adolescents [266,267] and adults [262,268], although there are very high levels of inter-individual variability. Like depression and other negative mood states [269], stress may affect metabolic control indirectly by disrupting the individual's ability to manage diabetes effectively [242,267]. Furthermore, elevated stress levels may affect metabolic control more directly by stimulating the autonomic nervous system to initiate a series of neuroendocrine responses that raise circulating blood glucose and catecholamine levels [270] and alter the activity of the hypothalamic-pituitary-axis, which may, in turn, further disrupt metabolic regulation and brain function [271]. Although this mechanism is theoretically attractive, several physiologic studies using carefully controlled acute stressors failed to find evidence of acute metabolic derangements in children and adults with T1DM [272–274]. No experimental studies have systematically examined the relationship between chronic stress and long-term metabolic changes, and it remains possible that both indirect (behavioral) and direct (neuroendocrine) pathways are involved in mediating the relationship between heightened stress and poor metabolic control [242].

Investigators have also considered the possibility that high levels of stress may trigger the appearance of diabetes in genetically susceptible individuals [275]. Although there is evidence that children with diabetes experienced greater stress (particularly actual or threatened losses within the family) prior to diagnosis than healthy control subjects assessed in the same fashion [276–278], no evidence of a similar relationship has been found in young adults newly diagnosed with T1DM [279]. Nevertheless, the occurrence of major stressful life events [280], or pre-existing depression [281], increases the risk of T2DM by as much as 37% [282]. Although the physiologic basis for this effect remains incompletely understood, it is generally assumed that stress induces a dysregulation of glucose metabolism [283] and/or disrupts insulin signaling processes within the CNS [271] in individuals genetically and constitutionally predisposed to develop diabetes.

Depression and anxiety has been found by some [284–286] but not all studies [45,73,256] to be associated with poorer metabolic control. Some of the strongest evidence for a link between affect and glycemic state comes from an early study in which adults with diabetes were followed during 36 weeks of treatment [287]. As glycemic control improved, symptoms of depression and anxiety declined; as control worsened, depression and anxiety increased, giving the appearance that success (or lack thereof) in managing diabetes led to corresponding changes in mood state. Taking a different approach, more recently researchers focused their attention on the extent to which changes in depressive symptomatology over a 12-month follow-up period influenced HbA_{1c} values [288]. Although there was a marked reduction in depressive symptoms regardless of type of diabetes, there was no corresponding improvement in metabolic control over time, leading to the conclusion that mood state has no meaningful impact on metabolic control.

The absence of an obvious relationship between depression and metabolic control [288] is not only counterintuitive, but it is inconsistent with the growing body of literature that suggests that the presence of depression adversely affects the medication adherence and self-care behaviors of people with diabetes. Particularly in older adults with T2DM, major depression is associated with less physical activity, a more unhealthy diet and poorer adherence to complicated medication regimens that

includes taking multiple oral hypoglycemic, antihypertensive and lipid-lowering drugs at various times during the day [75,289–291]. Given those relationships, one would expect that reducing the level of depression would lead to corresponding improvements in their metabolic control as the person with diabetes begins to take better care of themselves but, to the best of our knowledge, no data support that possibility. The only prospective data available demonstrate that the presence of depressive symptoms at baseline predicts poorer adherence 9 months later [292]. Whether adherence would improve as depressive symptoms reduce in severity remains unexamined.

Family characteristics

Diabetes can dramatically disrupt the entire family, particularly when the patient is a child or adolescent [293]. Children, especially younger ones, enjoy better metabolic control when their parents take an active role in managing their diabetes, whereas adolescents are in better control when parents share management responsibilities with them [294–297]. Within the family, low levels of conflict [298], including sibling conflict [299], high levels of cohesion [8,300] and better communication skills [301] are associated with better control, as is a higher level of social support from family and friends [302]. Parental marital satisfaction also predicts control [300], perhaps because it serves as a surrogate for family cohesion and lack of conflict. Maternal trait anxiety [303] and parental intelligence also predict the child's metabolic control [304]; whether this association is mediated by better diabetes management or by less family conflict remains to be determined. Family factors such as lower adherence levels associated and greater levels of family stress, more family conflict and less family cohesion and sociodemographic variables (e.g. single-parent households) are also thought to explain the clinically significant disparity in metabolic control between African-American and Caucasian adolescents in the USA (mean HbA_{1c} 10.1 ± 2.1% [87 ± 2.3 mmol/mol] vs 8.6 ± 1.3% [70 ± 14 mmol/mol], respectively) [305,306]. Consistent with those data is the observation that children raised by single mothers have poorer metabolic control than those from two-parent families [307]. In adults with diabetes, better marital satisfaction is associated with better diabetes-related quality of life and marginally better glycemic control [308] but, not surprisingly, more global variables such as family [309] and work environment [310] do not predict glycemic control, although they do predict degree of psychologic adjustment.

The relationship between family characteristics and glycemic control in children is most likely mediated via a purely behavioral pathway whereby family conflicts disrupt performance of self-care behaviors. Support for this interpretation comes from Jacobson *et al.*'s [311] and Hauser *et al.*'s [312] seminal 4-year follow-up study of recently diagnosed youngsters with diabetes. Degree of family conflict and extent of family organization at diagnosis were the best predictors of both short and long-term adherence to diet, exercise, insulin administration and self-monitoring. Children whose families had less conflict as well as a family structure for planning activities and responses to problems were more likely to manage their diabetes satisfactorily [312] and to have better metabolic control [311]. This pattern of results has subsequently been supported by other large prospective [305] and cross-sectional analyses [313].

Self-care or "adherence" behaviors

The terms "adherence" and "compliance" have been used interchangeably, and refer to the extent to which an individual follows a medical management regimen. Adherence to a diabetes regimen cannot easily be determined, however, because there is no standard against which the person's actual behavior can be compared [314]; for example, few physicians provide a written management plan that specifies all aspects of diabetes care. Because it is the patient, and not the health care professional, who is responsible for nearly all diabetes care [315], an increasing number of writers have suggested that diabetes management efficacy be assessed by determining the extent to which a patient engages in "self-care" behaviors [316,317]. The shift in terminology from "adherence" to "self-care behaviors" acknowledges the behavioral complexity of diabetes management, and takes into account recent data demonstrating that specific self-care behaviors (e.g. taking medication, diet, monitoring and exercise) are not strongly related to one another in either adults [318] or children [319].

Certain self-care behaviors are far more likely to be followed than others. For example, data from a large survey of more than 2000 adults with diabetes indicated that 97% of insulin requiring patients and 93% of oral medication requiring patients always or usually took their medications as recommended, but only 77% reported that they always or usually followed blood glucose self-monitoring recommendations, and even fewer followed diet (63%) and exercise (40%) recommendations [320]. These findings are consistent with earlier studies demonstrating that more behaviorally complex activities such as diet and exercise are performed less consistently than medication-taking and blood glucose monitoring [321]. Not all self-care activities are equally predictive of glycemic control for children or adults [314,322] but, overall, the more self-care behaviors that are performed well, the greater should be the improvement in blood glucose control [257].

Blood glucose self-monitoring frequency ought to be a particularly salient self-care activity. A large medical registry study found that adults with T1DM who self-monitored blood glucose three or more times daily subsequently had HbA_{1c} values that were 1% (11 mmol/mol) lower than those who monitored less frequently; for T2DM adults, the difference was somewhat smaller (0.6%, 7 mmol/mol), albeit statistically significant [323]. Other studies have provided less positive results. For example, studies of patients with T2DM have either failed to find any evidence whatsoever that traditional fingerstick self-monitoring of blood glucose (SMBG) had any impact in reducing HbA_{1c} values over a 1-year period [324] or have noted only weak and inconsistent effects [325]. Similarly pessimistic conclusions have been drawn from several studies of children and adults with T1DM. Data

from a recent clinical trial comparing continuous subcutaneous glucose monitoring HbA_{1c} with SMBG technique found the degree of change in HbA_{1c} values to be quite small, ranging from a 0.5% (6 mmol/mol) improvement to essentially no change over a 26-week time period. Moreover, somewhat surprising, the superiority of the CGM technique was limited to those subjects who were 25 years of age or older [326]. These data suggest that simply monitoring blood glucose values, and not using that information to adjust insulin or oral medications frequently and systematically, may have little meaningful impact on patients' long-term metabolic control.

Treatment adherence varies at different ages and changes with time. Younger children with diabetes tend to show better adherence (perhaps because of greater parental involvement) than adolescents [256,322]. Even after controlling for age, however, a longer duration of diabetes tends to be associated with declines in adherence [16,256], at least during adolescence. Other factors associated with better adherence are good family support [296], more shared responsibility between the child with diabetes and parent for self-care behaviors [327], greater cognitive maturity [328], more knowledge of diabetes and its management and better memory skills [319]. The nature of the physician–patient relationship can also influence adherence behaviors [329]. Doctor-centered discussions discourage patients from asking questions and increase their level of uncertainty and discomfort [330], whereas patient-centered communications are predictive of better self-reported adherence [331].

The generally weak relationship between self-care behaviors and metabolic control remains problematic for any model purporting to predict successful diabetes management. To some extent, this could reflect the possibility that the HbA_{1c} concentration is not the most appropriate measure of metabolic control [314], but it is more likely that the unexplained variance in glycemic control reflects unspecified physiologic or situational characteristics, as well as difficulties inherent in measuring self-care behaviors [317]. Because adherence is typically assessed by asking subjects to describe their behavior, rather than by direct observation, it is possible that self-reports may exaggerate or otherwise misrepresent the extent to which patients performed a particular self-care behavior [317].

Psychologic interventions to improve adherence

More traditional psychotherapeutic approaches

Several psychologic interventions have been developed to improve adherence in patients with diabetes. For adults who are most seriously non-compliant and whose consistent refusal to follow medical advice has led to "brittle diabetes," Boehnert & Popkin [332] have recommended a therapeutic approach that begins with crisis management, followed by psychotherapy of the sort typically used with patients diagnosed with "borderline personality." Intensive inpatient psychoanalytic psychotherapy, with 3–5 weekly sessions over a 5–28 week period, has also been found to improve metabolic control over a 1-year period [333], but this may be the least practicable way of treating brittle diabetes, because relatively few hospital settings offer this type of psychotherapy to children.

For less severe adherence problems, a variety of behavioral and psychosocial interventions have been used to improve diabetes management [334,335]. These differ from more traditional group therapy programs in so far as they use several sessions to target one or more self-care behaviors and/or the psychologic factors that may interfere with good adherence. A typical self-management program may meet once or twice monthly for seven or more sessions, discuss specific self-care strategies (e.g. blood glucose monitoring; exercise), role play appropriate behaviors, use homework assignments to practice what has been learned and resolve problems or barriers encountered during diabetes management [336].

Variations on this basic theme include the use of "booster" sessions, scheduled 6 or 12 months following the end of the program and designed to review and reinforce previously learned material. Interventions may include spouses or family members at some or all of the sessions, or incorporate separate but concurrent sessions for parents and adolescents with diabetes [337,338]. The program content also varies. Some focus on basic diabetes management and the acquisition of effective problem-solving skills [336,338] while others emphasize handling stress [339,340] or other psychologic issues that are especially problematic for participants, including fears about hypoglycemia or the development of hyperglycemic complications [130]. Most include homework assignments and extensive self-monitoring [336,340]. Interventions developed initially for patients without diabetes with high levels of psychologic distress are increasingly being applied to patients with diabetes, and both CBT [140] and "motivational interviewing" [341,342] or "motivational enhancement therapy" [127] programs have led to modest improvements in HbA_{1c} levels and in self-reported quality of life.

Family-focused behavioral interventions have been found to be particularly successful in improving diabetes management in children. In one of the largest studies of its kind, Wysocki *et al.* [343] randomized 119 families of adolescents to either 10 sessions of behavioral family systems group therapy, 10 sessions of an education and support group or standard diabetes therapy (with minimal psychologic support). Behavioral family systems therapy included four modules: problem-solving training which focused on conflict resolution; communication skills training; cognitive restructuring to identify and change those attitudes and beliefs that impede effective communication; and specialized family therapy interventions. In the 12 months following treatment, adolescents who participated in behavioral family systems therapy showed long-term improvement in relationships with their parents compared with adolescents in the other two treatment groups, and also manifested improved adherence to their diabetes management regimen, although these behavioral and psychologic changes were not associated with improvements in metabolic control [344]. Similar interventional approaches have also been applied to older adults with T2DM and, as is the case with children and adults with T1DM, there are reductions in psychologic

distress and occasionally, but not invariably, small improvements in long-term glycemic control [345].

Cognitive–behavioral approaches

Coping skills training programs have also been found to be effective in improving the diabetes management skills of adolescents treated with intensive insulin therapy [346]. Based on a cognitive–behavioral skills-building model, coping skills training presents participants with a series of social situations that are particularly problematic for adolescents, and asks them to demonstrate how they would resolve that situation (e.g. manage food choices with friends). As implemented by Grey *et al.* [346], groups of 2–3 adolescents role play each scenario with a highly trained group leader who provides correction and models appropriate coping behavior. Sessions last 60–90 minutes and, in the typical training program, subjects participate in six weekly sessions followed by monthly visits. Over a 12-month follow-up period, adolescents randomized to coping skills training plus intensive diabetes management had significantly lower HbA_{1c} values (7.5% vs 8.5%; 58 vs 69 mmol/mol) and reported higher levels of self-efficacy as well as less difficulty in coping with diabetes and less depression when compared with adolescents who received intensive diabetes management alone [297].

Another successful approach is to "empower" patients, and encourage them to take personal responsibility in managing their diabetes [347]. Empowerment programs aim to improve patients' ability to identify and set realistic goals, apply problem-solving strategies to overcome barriers to those goals, develop more effective coping strategies in general, manage stress more effectively, increase levels of social support and improve self-motivation [348,349]. Results from a randomized controlled trial demonstrated that following a 6-week patient empowerment program, adults with diabetes showed a significant decline in HbA_{1c} level as well as increases in ability to set goals, manage stress, obtain external support and make decisions about diabetes management [348].

Individually tailored programs have also been used to help patients manage stress. If elevated levels of stress are a barrier to optimal metabolic control, then the stress-reduction effects of biofeedback-assisted relaxation training ought to reduce blood glucose levels appreciably. Results from various studies are mixed, with some [350], but not all [351,352] reporting significant improvements in glucose control following relaxation training. Results from a recent study suggest that the effectiveness of stress management programs may be determined, at least in part, by the patient's underlying personality. Patients with T2DM who were anxious, angry or hostile showed improved metabolic control following a stress management program that included progressive muscle relaxation training [352].

In their very thoughtful and thorough review of behavioral and psychosocial interventions in diabetes, Peyrot & Rubin [334] discuss the utility of including both problem-focused and emotion-focused interventions as part of an integrated behavior change support program. According to their model, interventions must occur in a particular sequence of five steps:

Table 49.2 Behavioral and/or psychosocial interventions: a step-by-step approach. From Peyrot & Rubin [334].

Intervention	Sample question
Problem-focused interventions	
1 Start with the patient's problem	"What's the hardest thing about managing your diabetes?"
2 Specify the problem	"Can you give me an example?"
3 Negotiate an appropriate goal	"What is your goal for changing your self-care behavior?" "Is that realistic?"
4 Identify barriers to goal attainment	"What could keep you from reaching your goal?" "Why would that keep you from reaching your goal?"
5 Formulate strategies to achieve the goal	"How can you overcome that barrier to reaching your goal?" "How have you successfully dealt with that before; would that work now?"
6 Contract for change	"What are your criteria for defining success?" "How will you reward yourself for success?"
7 Track outcomes	"How will you keep track of your efforts?"
8 Provide on-going support	"What will you do if you slip in your efforts to reach your goal; what can I do to help?"
Emotion-focused interventions	
9 Identify diabetes distress	"Do you feel overwhelmed by diabetes?"
10 Alleviate diabetes distress	"What are you saying to yourself when you deal successfully/unsuccessfully with a diabetes-related challenge?"
11 Identify depression	"In the past 2 weeks have you felt depressed or lost interest or pleasure in things?"
12 Treat disorder or refer for treatment	"Would you like to talk to someone who can help you resolve these problems?"

1 Specify the patient's problem;
2 Translate the patient's intentions to change into concrete, attainable goals;
3 Collaborate with the patient to identify barriers to reach those goals and formulate effective strategies;
4 Establish a "contract" with the patient to meet, or approach, those goals; and
5 Provide continuing support.

The framework provided by these commentators makes much sense from a clinical perspective, and their step-by-step approach is summarized in Table 49.2. The extent to which such an approach will be successful in initiating lasting clinically significant changes in mood, behavior and metabolic control remains unknown at the present time, but it is certainly an approach worth evaluating in formal clinical trials.

Conclusions

This chapter closes with a discussion of psychologic intervention programs because it is here where psychologists and diabetolo-

gists can work together effectively to improve their patients' mental as well as their physical health. One of the greatest problems facing mental health professionals is the failure, or inability, of many physicians to identify patients with psychologic distress quickly and provide appropriate treatment. A plethora of complex psychologic tests and questionnaires have been developed for research studies with patients with diabetes [353], yet the easiest way to determine whether a patient is having psychologic problems is to ask them explicitly. When psychologic problems are uncovered, immediate referral should be made to a mental health professional who is familiar with diabetes-related psychologic issues. It has been argued that it is the physicians who should diagnose and treat emotional disorders in their patients with diabetes, but that view is unrealistic. Few physicians have the expertise or the time to provide appropriate psychotherapeutic interventions. A far better solution is to add a psychologist, psychiatrist or social worker to the diabetes treatment team [41]. This approach was taken in the DCCT, and it may be one of the reasons why overall levels of psychopathology were so low, and perceived quality of life was so high, despite the arduous demands made on patients.

From this chapter it is clear that patients with diabetes have a remarkable level of psychologic resilience but, like anyone else, they are likely to experience psychologic distress at some time. Psychologists and diabetologists must continue to develop better ways of delivering psychologic support in order to alleviate their distress.

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