

## Review

# PSYCHOLOGICAL DISTRESS AND DIABETES: CLINICAL AND METABOLIC CONNECTIONS

Mala Dharmalingam

### ABSTRACT

With less than half of the diabetic population able to maintain a good glycemic control, it is important to look at some of the other factors like psychosocial problems as an important factor in this. Both children and adult face psychological distress on discovering they have diabetes. They require a lot of support from the family as well as health care providers. This article looks into the psychological stress and its relation to metabolic complications

**KEY WORDS:** Psychological; Diabetes; Metabolic complications; Neurocognitive dysfunction

### INTRODUCTION

Diabetes is a major health problem in the world. WHO predicts that the number of people with diabetes will double, from 176 to 370 million people by 2030 (1). Half of the people with this disorder do not achieve satisfactory glycemic control, despite the availability of effective treatments (2). As a consequence, millions of people with diabetes are at elevated risk of suffering needlessly from serious complications of the disease. This importantly also suggests that there are several important areas that have the potential to address these problems (1). The reason for the non achievement of the blood glucose is not only lack of compliance but other important factors like psychological distress.

### DIABETES AND PSYCHOSOCIAL PROBLEMS

Type 1 diabetes imposes considerable demands on patients and their families. Children and adolescents already coping with normal developmental challenges may not be able to deal with the additional burden of diabetes effectively. This is especially true for the demands of intensive management. Families of children with diabetes play a significant role in diabetes management and are instrumental in the implementation of interventions. Diabetes affects both psychosocial and neurocognitive functioning adversely

this thus potentially affects the quality of life of the child and the entire family. Psychosocial factors also influence regimen adherence and glycemic control. Therefore, psychosocial factors are very important to consider in the management of children and adolescents with diabetes.

Many children have adjustment problems soon after the diagnosis of diabetes (3, 4). Although these are resolved within the first year, some of those who do not are at risk for poor adaptation to diabetes, including regimen adherence problems, poor metabolic control, and continued psychosocial difficulties (5-7). In addition, many mothers of newly diagnosed children are at risk for adjustment problems of their own, with significant depressive symptoms observed in approximately one third of mothers; most of these abate within the first year after their child's diagnosis (8).

A study of adolescents with diabetes found that one third had psychiatric disorders, most involving internalizing symptoms (9); other studies have shown that diabetic youth have greater rates of depression (10) and that those with depression have poor glycemic control (11). Depression and low self esteem are the most frequent psychiatric diagnosis, (12). These psychological adjustment problems during adolescent may pass into adulthood (13).

### NEUROCOGNITIVE FUNCTIONING

Studies indicate that children who develop diabetes before 5 years of age and who have frequent episodes of hypoglycemia are at risk for neurocognitive deficits, particularly in visual-spatial functioning (14, 15, 16). In addition, research findings indicate that children with diabetes miss more school and that lower reading achievement was related to more school absences (17). Studies have also shown that diabetic children, especially boys, are more likely to have learning problems (18). Other research has found poorer attention functioning and lower verbal intelligence in children with a history of significant hypoglycemia (19).

---

Associate Professor MSR Medical College, Bangalore, Email [drmala@vsnl.net](mailto:drmala@vsnl.net)

## **QUALITY OF LIFE**

There are very few quality of life studies in children and adolescents with diabetes (20). Quality of life can be reliably measured by self-report (21). Better quality of life in youths is associated with increased self-efficacy and less depression (22), as well as improved metabolic control (23).

## **PSYCHOSOCIAL FACTORS RELATED TO REGIMEN ADHERENCE AND METABOLIC CONTROL.**

Regimen adherence declines over time and is especially poor among some adolescents (24, 25). Metabolic control is worse in single-parent, lower-income youths. (26-28) Low levels of family conflict and stress, high levels of cohesion and organization, good communication skills, and appropriate involvement of both parents and children in diabetes management have been associated with higher levels of regimen adherence (29,30) and better metabolic control (31). High levels of self-efficacy (32) and low levels of learned helplessness (33) are associated with good glycemic control.

## **PSYCHOSOCIAL THERAPIES**

A number of studies have examined the efficacy of psychosocial interventions for diabetic youth. Recent studies indicate that family-based behavioral procedures such as goal-setting, self-monitoring, and appropriately shared responsibility for diabetes management have improved regimen adherence and glycemic control (34). In addition, such interventions can improve the parent-adolescent relationship (35, 36). Psycho-educational interventions with children and their families that promote problem-solving skills and increase parental support early in the disease course have improved long-term glycemic control of children (37).

The efficacy of group interventions for diabetic youth has also been systematically evaluated. For example, research findings have shown that peer group support and problem-solving have improved short-term glycemic control (38). Group coping skills training has been shown to help optimize glycemic control and quality of life for adolescents involved in intensive insulin regimens (39,40). In addition, stress management and coping skills training has reduced diabetes-related stress (41) and improved social interaction (42) in adolescents.

## **SIGNIFICANCE**

Diabetes is a psychologically and behaviorally

demanding disease; therefore, psychosocial factors are relevant to nearly all aspects of its management. The psychosocial impact of diabetes has been recognized as a stronger predictor of mortality in diabetic patients than many clinical and physiological variables (43). Considering the importance of psychosocial factors in management of diabetes, the rapidly increasing number of adult patients with diabetes (mostly type 2), and the tremendous and growing public health burden of diabetes, the development and clinical implementation of effective psychosocial interventions are critical needs. Such interventions could help patients improve self-care behaviors and glycemic control, thus reducing their risk of health complications and improving their quality of life.

## **PSYCHOSOCIAL FUNCTIONING.**

The prevalence and course of psychiatric disorders, particularly affective and anxiety disorders, in adults with diabetes is well documented.(44). Research findings have demonstrated that depression is more common in patients with diabetes than in the general population; at least 15% of patients have clinical depression (45). Findings indicate that depression is associated with worse glycemic control and health complications (46,47), as well as decreased quality of life (48), and is likely to be persistent (49). A recent meta-analysis confirms the association of depression with hyperglycemia and complications in both adult type 1 and type 2 diabetes (50). Evidence indicates that depression doubles the incidence of type 2 diabetes, independent of other risk factors (51, 52). In patients with preexisting diabetes, depression is an independent risk factor for coronary heart disease and seems to accelerate its presentation (53). Research has also shown that anxiety disorders are common in adults with diabetes and linked with poor glycemic control (54, 55).

There is promising evidence that some of the adverse effects of depression and anxiety on diabetes are reversed by psychiatric treatment. Randomized controlled intervention trials have shown that treatment with either cognitive behavior therapy or antidepressant medication can improve both mood and glycemic control (56, 57). Psychopharmacologic interventions have been shown to reduce anxiety and improve glycemic control (58).

## **QUALITY OF LIFE.**

Diabetes-related quality of life can be reliably measured (59). Quality of life in adults with diabetes

is positively affected by increased physical activity and adequate social support. Improved quality of life has also been demonstrated after intensification of insulin regimens, which can be attributed to patients' greater flexibility in physical activities and diet (60). Quality of life is adversely affected by the presence of comorbid psychiatric disorders and health complications (61), as well as physical complaints and worries about the future (62). In addition, research has shown that quality of life is diminished when diabetes-specific health behaviors are associated with a sense of burden (63).

### **PSYCHOSOCIAL THERAPIES.**

A number of controlled studies have evaluated the effects of psychosocial interventions for adults with diabetes. A recent meta-analytic review of diabetes self-management interventions indicated significant improvements in glycemic control, as well as reductions in diabetes-related hospitalizations and health care costs, particularly when interventions incorporated individually tailored strategies to change behavior (64).

For example, interventions that increase patients' sense of empowerment and self-management skills have resulted in improvements in self-efficacy, self-care behaviors, glycemic control, patient satisfaction, and quality of life (65, 66). These benefits have also been found in studies with older minority patients with type 2 diabetes (67).

Suboptimal diabetes self-management has been identified as one of the possible causes of poor outcomes of diabetes care in general practice.(68). The importance of psychological, social, and behavioral factors for patient self-management has been indicated(69) Access to patient-centered self-management support and education has shown to improve outcomes of diabetes care.(70) Effective communication between patients and providers has been suggested to be important for optimal treatment outcomes. For instance, application of motivational interviewing techniques has been shown to improve the success rate of behavior change consultations. Access to a coordinated interdisciplinary diabetes care team to offer appropriate care, self-management education, medical advice, or psychosocial support, has been identified as an important factor for improving treatment outcomes in diabetes.

Delayed initiation of medication therapies to prevent long-term complications is commonly observed in general practice settings. Both patient

and provider beliefs appear to contribute to the delayed use of effective therapy (e.g., misconceptions of the consequences of initiating medication, that medication is not efficacious or may have serious side effects (71). These factors lead to a reluctance to intensify treatment regimens, which may be overcome through improved communication.

### **RELATIONSHIP WITH HEALTH CARE PROVIDERS**

The quality of patient-provider relationships was rated high by patients; 88.8% reported that they have a good relationship with the people who care for their diabetes. However, most providers reported that they need to better understand the psychological consequences of diabetes (69.8%) and the various ethnic cultures that they deal with (78.8%).

The paradigm for treating diabetes care is changing on a global scale. Governments, health insurers, health care professionals, and nongovernmental organizations are increasingly recognizing the importance of new partnerships and new ways of adopting more effective approaches to helping people with diabetes better self-manage the medical and psychosocial challenges associated with the disease. Continuous and increasing collaborative efforts are needed to transform care for diabetes and other chronic diseases from the acute to the chronic care model. Future focus needs to be placed on implementation and translational research, with international sharing of effective tools for furthering a person-centered approach to chronic disease management and prevention.

### **CONCLUSIONS**

It has been well demonstrated that psychosocial factors play an integral role in the management of diabetes in both children and adults. Research has demonstrated the efficacy of a number of psychosocial therapies that can improve regimen adherence, glycemic control, psychosocial functioning, and quality of life. There is an increasing need to develop psychosocial intervention programs for specific patient populations and to demonstrate the cost-effectiveness of these approaches. Any chronic disorder like diabetes requires an approach which is slightly different from the conventional approach of patient management. This requires a change in relationship with the patient as well empowering the patient with better management skills. There is an increasing need for studies which look at these factors scientifically and in clinical setting.

## REFERENCES

1. World Health Organization: Diabetes: total number of people with diabetes [article online]. Available online at [www.who.int/ncd/dia/databases4.htm](http://www.who.int/ncd/dia/databases4.htm)
2. Kristensen JK, Bro F, Sandbaek A, Dahler-Eriksen K, Lassen JF, Lauritzen T: HbA<sub>1c</sub> in an unselected population of 4438 people with type 2 diabetes in a Danish county. *Scand J Prim Health Care* 2001; 19: 241–6.
3. Jacobson AM, Hauser ST, Wertlieb D, Woldsdorf J, Orleans J, Viegra M: Psychological adjustment of children with recently diagnosed diabetes mellitus. *Diabetes Care* 1986; 9: 323–9
4. Kovacs M, Feinberg TL, Paulauskas S, Finkelstein R, Pollock M, Crouse-Novak M: Initial coping responses and psychosocial characteristics of children with insulin-dependent diabetes mellitus. *J Pediatr* 1985; 106: 827–34,
5. Grey M, Cameron M, Lipman T, Thurber F: Psychosocial status of children with diabetes in the first 2 years after diagnosis. *Diabetes Care* 1995; 18: 1330–6.
6. Jacobson AM, Hauser ST, Lavori P, Willett JB, Cole CF, Wolfsdorf JI, Dumont RH, Wertlieb D: Family environment and glycemic control: a four-year prospective study of children and adolescents with insulin-dependent diabetes mellitus. *Psychosom Med* 1994; 56: 401–9.
7. Kovacs M, Ho V, Pollock MH: Criterion and predictive validity of the diagnosis of adjustment disorder: a prospective study of youths with new-onset insulin-dependent diabetes mellitus. *Am J Psychiatry* 1995; 152: 523–8
8. Kovacs M, Finkelstein R, Feinberg TL, Crouse-Novak M, Paulauskas S, Pollock M: Initial psychologic responses of parents to the diagnosis of insulin dependent diabetes mellitus in their children. *Diabetes Care* 1985; 8: 568–75.
9. Blanz B, Rensch-Riemann B, Fritz-Sigmund D, Schmidt M: IDDM is a risk factor for adolescent psychiatric disorders. *Diabetes Care* 1993; 16:1579–87
10. Mayou R, Peveler R, Davies B, Mann J, Fairburn C: Psychiatric morbidity in young adults with insulin-dependent diabetes mellitus. *Psychol Med* 1991; 21: 639–45
11. Kovacs M, Goldston D, Obrosky D, Bonar L: Psychiatric disorders in youths with IDDM: rates and risk factors. *Diabetes Care* 1997; 20: 36–44
12. Jacobson AM, Hauser ST, Willett J, Wolfsdorf JI, Herman L, de Groot M: Psychological adjustment to IDDM: 10-year follow-up of an onset cohort of child and adolescent patients. *Diabetes Care* 1997; 20: 811–8
13. Rydall AC, Rodin GM, Olmsted MP, Devenyi RG, Daneman D: Disordered eating behavior and microvascular complications in young women with insulin-dependent diabetes mellitus. *N Engl J Med* 1997; 336: 1849–54
14. Holmes C, Richman L: Cognitive profiles of children with insulin-dependent diabetes. *J Dev Behav Pediatr* 1985; 6: 323–6
15. Rovet J, Ehrlich R, Hoppe M: Specific intellectual deficits associated with the early onset of insulin-dependent diabetes mellitus in children. *Child Dev* 1988; 59: 226–34.
16. Ryan C, Vega A, Drash A: Cognitive deficits in adolescents who developed diabetes early in life. *Pediatrics* 1985; 75: 921–7
17. Ryan C, Longstreet C, Morrow L: The effects of diabetes mellitus on the school attendance and school achievement of adolescents. *Child Care Health Dev* 1985; 11: 229–40
18. Holmes C, Dunlap W, Chen R, Cornwell J: Gender differences in the learning status of diabetic children. *J Consult Clin Psychol* 1992; 60: 698–704
19. Grey M, Boland EA, Yu C, Sullivan-Bolyai S, Tamborlane WV: Personal and family factors associated with quality of life in adolescents with diabetes. *Diabetes Care* 1998; 21: 909–14
20. Guttman-Bauman I, Flaherty BP, Strugger M, McEvoy RC: Metabolic control and quality-of-life self-assessment in adolescents with IDDM. *Diabetes Care* 1998; 21: 915–8 [Abstract]
21. Jacobson AM, Hauser ST, Lavori P, Wolfsdorf J, Herskowitz R, Milley J, Bliss R, Gelfand E, Wertlieb D, Stein J: Adherence among children and adolescents with insulin-dependent diabetes mellitus over a four-year longitudinal follow-up: I. The influence of patient coping and adjustment. *J Pediatr Psychol* 1990; 15: 511–26
22. Johnson SB, Kelly M, Henretta JC, Cunningham WR, Tomer A, Silverstein JH: A longitudinal analysis of adherence and health status in childhood diabetes. *J Pediatr Psychol* 1992; 17: 537–53 [Abstract]
23. Auslander WF, Thompson S, Dreitzer D, White NH, Santiago JV: Disparity in glycemic control and adherence between African-American and Caucasian youths with diabetes: family and community contexts. *Diabetes Care* 1997; 20: 1569–75.
24. Delamater AM, Albrecht DR, Postellon DC, Gutai JP: Racial differences in metabolic control of children and adolescents with type I diabetes mellitus. *Diabetes Care* 1991; 14: 20–5
25. Delamater AM, Shaw K, Applegate B, Pratt I, Eidson M, Lancelotta G, Gonzalez-Mendoza L, Richton S: Risk for metabolic control problems in minority youth with diabetes. *Diabetes Care* 1999; 22: 700–5.
26. Miller-Johnson S, Emery R, Marvin R, Clarke W, Lovinger R, Martin M: Parent-child relationships and the management of insulin-dependent diabetes mellitus. *J Consult Clin Psychol* 1994; 62: 603–10
27. Schafer LC, Glasgow RE, McCaul KD, Dreher M: Adherence to IDDM regimens: relationship to psychosocial variables and metabolic control. *Diabetes Care* 1983; 6: 493–8. Anderson BJ, Miller JP, Auslander WF, Santiago JV: Family characteristics of diabetic adolescents: relationship to metabolic control. *Diabetes Care* 1981; 4: 586–94.
28. Anderson BJ, Ho J, Brackett J, Finkelstein D, Laffel L:

- Parental involvement in diabetes management tasks: relationships to blood glucose monitoring adherence and metabolic control in young adolescents with insulin-dependent diabetes mellitus. *J Pediatr* 1997; 130 :257–65.
29. Wysocki T: Associations among teen-parent relationships, metabolic control, and adjustment to diabetes in adolescents. *J Pediatr Psychol* 1993; 18: 441–52.
  30. Charron-Parochownik D, Becker M, Brown M, Liang W, Bennett S: Understanding young children's health benefits and diabetes regimen adherence. *Diabetes Educator* 1983; 19: 409–18.
  31. Wysocki T, Harris M, Greco P, Bubb J, Danda C, Harvey L, McDonell K, Taylor A, White N: Randomized, controlled trial of behavior therapy for families of adolescents with insulin-dependent diabetes mellitus. *J Pediatr Psychol* 2000; 25: 23–34.
  32. Anderson BJ, Wolf F, Burkhart M, Cornell R, Bacon G: Effects of peer-group intervention on metabolic control of adolescents with IDDM: randomized outpatient study. *Diabetes Care* 1989; 12: 179–83.
  33. Kaplan R, Chadwick M, Schimmel L: Social learning intervention to promote metabolic control in type I diabetes mellitus: pilot experimental results. *Diabetes Care* 1985; 8: 152–5.
  34. Boland EA, Grey M, Oesterle A, Fredrickson L, Tamborlane WV: Continuous subcutaneous insulin infusion: a new way to lower risk of severe hypoglycemia, improve metabolic control, and enhance coping in adolescents with type 1 diabetes. *Diabetes Care* 1999; 22: 1779–84.
  35. Grey M, Boland EA, Davidson M, Yu C, Sullivan-Bolyai S, Tamborlane WV: Short-term effects of coping skills training as adjunct to intensive therapy in adolescents. *Diabetes Care* 1998; 21: 902–8.
  36. Mendez F, Belendez M: Effects of a behavioral intervention on treatment adherence and stress management in adolescents with IDDM. *Diabetes Care* 1997; 20: 1370–5.
  37. Davis WK, Hess GE, Hiss RG: Psychosocial correlates of survival in diabetes. *Diabetes Care* 1988; 11: 538–45.
  38. Gavard JA, Lustman PJ, Clouse RE: Prevalence of depression in adults with diabetes: an epidemiological evaluation. *Diabetes Care* 16:1167–1178, 1993; Peyrot M, Rubin RR: Levels and risks of depression and anxiety symptomatology among diabetic adults. *Diabetes Care* 1997; 20: 585–90.
  39. Jacobson AM, de Groot M, Samson JA: The effects of psychiatric disorders and symptoms on quality of life in patients with type I and type II diabetes mellitus. *Qual Life Res* 1997; 6: 11–20.
  40. Peyrot M, Rubin RR: Persistence of depressive symptoms in diabetic adults. *Diabetes Care* 1999; 22: 448–52.
  41. Lustman PJ, Anderson R, Freedland K, De Groot M, Carney R, Clouse R: Depression and poor glycemic control: a meta-analytic review of the literature. *Diabetes Care* 2000; 23: 934–42.
  42. Eaton W, Armenian H, Gallo J, Pratt L, Ford D: Depression and risk for onset of type II diabetes: a prospective, population-based study. *Diabetes Care* 19: 1097–1102,
  43. Kawakami N, Takatsuka N, Shimizu H, Ishibashi H: Depressive symptoms and occurrence of type 2 diabetes among Japanese men. *Diabetes Care* 1996; 22: 1071–6.
  44. Forrest K, Becker D, Kuller L, Wolfson S, Orchard T: Are predictors of coronary heart disease and lower-extremity arterial disease in type 1 diabetes the same? A prospective study. *Atherosclerosis* 2000; 148: 159–69.
  45. Lustman PJ, Griffith L, Freedland K, Kissel S, Clouse R: Cognitive behavior therapy for depression in type 2 diabetes: a randomized controlled trial. *Ann Intern Med* 1998; 129: 613–21.
  46. Lustman PJ, Freedland K, Griffith L, Clouse R: Effects of fluoxetine on depression and glycemic control in diabetes: a double-blind, placebo-controlled trial (Abstract). *Ann Behav Med* 1999; 21: S158.
  47. Lustman PJ, Griffith LS, Clouse RE, Freedland KE, Eisen SA, Rubin EH, Carney RM, McGill JB: Effects of alprazolam on glucose regulation in diabetes: results of a double-blind, placebo-controlled trial. *Diabetes Care* 1995; 18: 1133–9
  48. Affentio SG, Backstrand JR, Welch GW, Lammi-Keefe CF, Rodriguez NR, Adams CH: Subclinical and clinical eating disorders in IDDM negatively affect metabolic control. *Diabetes Care* 1997; 20: 182–4.
  49. Glasgow RE, Toobert DJ: Social environment and regimen adherence among type II diabetic patients. *Diabetes Care* 1988; 11: 377–86
  50. Peyrot M, McMurry JF, Kruger DF: A biopsychosocial model of glycemic control in diabetes: stress, coping, and regimen adherence. *J Health Soc Behav* 1999; 40: 141–58
  51. Gonder-Frederick L, Carter W, Cox DJ, Clarke W: Environmental stress and blood glucose change in insulin-dependent diabetes mellitus. *Health Psychol* 1990; 9: 503–15.
  52. Halford WK, Cuddihy S, Mortimer RH: Psychological stress and blood glucose regulation in type I diabetic patients. *Health Psychol* 1990; 9: 516–28
  53. Bott U, Muhlhauser I, Overmann H, Berger M: Validation of a diabetes-specific quality-of-life scale for patients with type 1 diabetes. *Diabetes Care* 1998; 21: 757–69.
  54. Polonsky W: Understanding and assessing diabetes-specific quality of life. *Diabetes Spectrum* 2000; 13: 36–4.
  55. Rubin RR, Peyrot M: Quality of life and diabetes. *Diabetes Metab Res Rev* 1999; 15: 205–18.
  56. Glasgow RE, Ruggiero L, Eakin EG, Dryfoos J, Chobanian L: Quality of life and associated characteristics in a

- large national sample of adults with diabetes. *Diabetes Care* 1997; 20: 562–7.
57. Chantelau E, Schiffers T, Schutze J, Hansen B: Effect of patient-selected intensive insulin therapy on quality of life. *Patient Educ Counseling* 1997; 30: 167–73
  58. Aalto AM, Uutela A, Aro AR: Health related quality of life among insulin-dependent diabetics: disease-related and psychosocial correlates. *Patient Educ Counseling* 1997; 30: 215–25.
  59. Watkins KW, Connell CM, Fitzgerald JT, Klem L, Hickey T, Ingersoll-Dayton B: Effect of adults' self-regulation of diabetes on quality-of-life outcomes. *Diabetes Care* 2000; 23: 1511–5.
  60. Anderson RM, Fitzgerald JT, Wisom K, Davis W, Hiss R: A comparison of global versus disease-specific quality-of-life measures in patients with NIDDM. *Diabetes Care* 1997; 20: 299–305.
  61. Jacobson AM, de Groot M, Samson JA: The evaluation of two measures of quality of life in patients with type I and type II diabetes. *Diabetes Care* 1994; 17: 267–74.
  62. Clement S: Diabetes self-management education. *Diabetes Care* 1995; 18: 1204–14.
  63. Anderson RM, Funnell M, Butler P, Arnold M, Fitzgerald J, Feste C: Patient empowerment: results of a randomized controlled trial. *Diabetes Care* 1995; 18: 943–9.
  64. Pieber TR, Brunner GA, Schnedl WJ, Schattenberg S, Kaufmann P, Krejs GJ: Evaluation of a structured outpatient group education program for intensive insulin therapy. *Diabetes Care* 1995; 18: 625–30.
  65. Rubin RR, Peyrot M, Saudek C: Effect of diabetes education on self-care, metabolic control, and emotional well-being. *Diabetes Care* 1989; 12: 673–9.
  66. Rubin RR, Peyrot M, Saudek C: The effect of a diabetes education program incorporating coping skills training on emotional well-being and diabetes self-efficacy. *Diabetes Educator* 1993; 19: 210–4.
  67. Glasgow RE, Toobert DJ, Hampson S, Brown J, Lewinson P, Donnelly J: Improving self-care among older patients with type II diabetes: the "Sixty Something... " study. *Patient Educ Counsel* 1992; 19: 61–74.
  68. Cox DJ, Gonder-Frederick L, Polonsky W, Schlundt D, Julian D, Clarke W: A multicenter evaluation of blood glucose awareness training-II. *Diabetes Care* 1995; 18: 523–8.
  69. Cramer JA: A systematic review of adherence with medications for diabetes. *Diabetes Care* 2004; 27: 1218–24.
  70. World Health Organization: Adherence to long-term therapies . Geneva, World Health Org., 2003.