

# **Diabetes, Type 1**

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## **Abstract**

This chapter provides an overview of the role of psychological stress in Type 1 diabetes. Studies relating to stress and Type 1 diabetes onset and control, as well as the evidence relating to stress management training in people with Type 1 diabetes are discussed.

*Published in:*

G. Fink (Ed) *Encyclopedia of Stress, Second Edition*. Oxford: Academic Press, 792-796.

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**B or beta cells** the cells in the islets of Langerhans in the pancreas that produce insulin.

**diabetes mellitus** a heterogeneous group of disorders, characterised by hyperglycaemia, and disturbances of carbohydrate, fat and protein metabolism which are associated with absolute or relative deficiencies of insulin secretion and/or insulin action.

**glycosuria** sugar in the urine.

**hyperglycaemia** excessive levels of glucose in the blood. This is a feature of untreated or undertreated diabetes mellitus.

**hypoglycaemia** abnormally low levels of glucose in the blood. Symptoms are idiosyncratic but may include trembling, faintness, sweating, palpitations, mental confusion, slurred speech, headache, loss of memory and double vision. Severe, untreated hypoglycaemia may lead to fits or coma and on rare occasions, death. It can be caused by an overdose of insulin.

**islet cell antibodies (ICAs)** antibodies which are present in the blood when the body develops an autoimmune reaction to the pancreatic islet cells. The presence of ICAs indicates that the process of destruction has started which will eventually lead to Type 1 diabetes. This process appears to take several years

before diabetes is clinically manifested.

**insulin** a peptide hormone produced in the beta cells of the Islets of Langerhans in the pancreas. Insulin facilitates and accelerates the movement of glucose and amino acids across cell membranes. It also controls the activity of certain enzymes within the cells concerned with carbohydrate, fat and protein metabolism.

TYPE 1 DIABETES MELLITUS, previously known as insulin-dependent diabetes mellitus (IDDM), juvenile-onset diabetes, or ketosis-prone diabetes, is the commonest form of diabetes to occur in children and young adults of European origin. Age at clinical onset of the condition is usually under the age of 40 years and often under 30 years. People who have Type 1 diabetes lose the ability to produce insulin. Exogenous insulin, usually delivered by injection, will be needed continuously throughout the lifetime of a person with Type 1 diabetes with the possible exception of a brief honeymoon period which may occur within a year of clinical onset when endogenous insulin production is temporarily restarted. The onset of Type 1 diabetes is abrupt with severe thirst, excessive urination and dramatic weight loss. Individuals usually present to the doctor with one or more of these symptoms and an elevated blood glucose level.

Once developed, Type 1 diabetes can be managed by balancing a combination of insulin injections, intake of carbohydrates in the diet, and energy expenditure. The goal of treatment is to maintain blood glucose levels as close to the normal

range as possible in order to reduce the risk of chronic complications while also avoiding the dangers of blood glucose falling to hypoglycaemic levels.

### **I. Stress and Type 1 Diabetes Onset**

Although it has not been possible to determine the exact pathogenesis involved in the expression of Type 1 diabetes, it is clear that genetics play an important role. The genetic component of the condition is indicated by the increased prevalence of Type 1 diabetes in first degree relatives of 5% compared with less than 1% in the general population. However, genetic susceptibility is not sufficient to cause diabetes since the majority of people with disease-associated alleles do not develop Type 1 diabetes. Environmental factors play an important role in the overt expression of Type 1 diabetes, although the mechanisms are still unclear. Psychological stress may have a role in increasing vulnerability to viral infection or impairing defence mechanisms against infection, thereby facilitating the progression of the hidden pathological process. For example, stress-related changes in immune function may increase the likelihood of viral or bacterial disease, which may provide the initial insult to the B (or beta) cells. A second mechanism whereby stress may be implicated in diabetes onset may occur around the time when diabetes becomes symptomatic. Stress-related counter-regulatory hormone activity may aggravate the metabolic disturbance that has already developed. In fact, if the already elevated blood glucose level increases to beyond the renal threshold, glycosuria will cause dehydration which may then produce the first symptoms of overt diabetes. Many anecdotal accounts and

descriptive reports of life stresses occurring synonymously with symptomatic Type 1 diabetes onset may reflect this second mechanism where stress triggers overt manifestation of symptoms.

### **A Animal Studies**

It has been shown that stress may be associated with the onset of Type 1 diabetes in the genetic model for this type of diabetes. In the diabetes-prone BB Wistar rat, thirty to seventy percent of these animals have impaired glucose tolerance with hypo-insulinemia and hyperglycaemia by 150 days of age. It has been shown that these rats developed diabetes earlier, when exposed to restraint and crowding. It has also been found in the BB rat, that chronic stress significantly increases the incidence of phenotypic expression of the gene for Type 1 diabetes. Eighty percent of the stressed males and 70% of the stressed female animals developed diabetes, compared with 50% in both control groups (Lehman et al., 1991). However, because of the range of additional immune and endocrinological abnormalities evident in the BB rats, generalisability of these findings to humans is limited.

### **B. Human Studies**

Research has shown that people who go on to develop Type 1 diabetes are more likely to suffer a major family loss or an increase in other stressful life events before diagnosis. Some of these studies have been poorly controlled and were also prone to recall bias, where the pattern of life events reported may

reflect an attempt to find an explanation for diabetes onset rather than a difference in the events actually encountered. However, a more carefully controlled study of life events which avoided problems of recall bias has also shown that people with diabetes had significantly more severe life events within the 3 years before diagnosis than either non-diabetic siblings or matched controls (Robinson and Fuller, 1985). It is possible that life events experienced over longer time periods may play a role in the aetiology of Type 1 diabetes. It is clear from prospective studies of ICAs that many years may elapse between the actions of the possible stress-related causal agents to initiate cell damage and the appearance of symptomatic diabetes.

Clear evidence of the effect of stress on diabetes onset is difficult to establish. Some difficulties include methodological problems and interpretation of the findings which would involve expensive large prospective studies or reliance on retrospective methods to identify the relationship between stressful experiences and the onset of the disease. However even in a seemingly large trial, it can be difficult to delineate the effects of stress, if a broad age range of people are recruited into the trial. It is often the case that differences in the type and intensity of life changes are associated with different ages (Llyod et al., 2005). The relationship between stress and diabetes control is more amenable to study.

## **II. Stress and Type 1 Diabetes Control**

It is widely recognised among people with diabetes and their clinicians that psychological stress can impair glycaemic control. Theoretically, stress-related

hyperglycaemia should be greater in Type 1 patients (compared to Type 2 patients) because Type 1 patients have little or no endogenous insulin to offset increased blood glucose levels. Stress may affect diabetes control in at least two ways:

- i a direct psychophysiological effect via sympathetic and pituitary activity resulting in the elevation of catabolic hormone levels and the suppression of anabolic hormones. In people with diabetes, this may result in increased blood glucose levels, although, for a small minority, less readily understood decreases in blood glucose levels result.
- ii a behavioural mechanism whereby stress leads to behavioural changes capable of disrupting self-care behaviour. For example, the occurrence of unexpected, frustrating events may disrupt the diabetes self-care routines.

### **A Acute Stress and Blood Glucose Control**

Pioneering work examining the relationship between stress and diabetes was most often conducted in the laboratory, and the stresses induced were normally acute. Early research by Hinkle and others in the early 1950s, induced stress in some of their patients by a psychiatric interview and found changes in their blood ketone levels that remitted when the stress was removed. These researchers carried out a series of studies which showed that individuals without diabetes and individuals with diabetes (both Type 1 and Type 2 patients were studied) have a metabolic response to psychological stress which included changes in urine glucose, blood glucose and blood ketones, but the response of those with

diabetes was greater. Research in the 1960s included investigations of stress under hypnosis and examination stress, which resulted in a decrease in blood glucose levels. However, early studies have been criticised on methodological and conceptual grounds. There was concern that the stressors used were not sufficiently potent or reproducible. Furthermore, the grouping together of heterogeneous patients with Type 1 and 2 diabetes and those with different degrees of blood glucose control in studies of very small groups were also a focus of criticism.

Several seemingly well-controlled acute stress studies conducted in the 1980s reported no significant changes in blood glucose control in response to potential stressors such as mental arithmetic and public speaking. However, in an attempt to meet the criticisms levelled at the earlier studies, these later studies have overlooked the possibility that individual differences in response to stress might be real and interesting and not a reflection of methodological inadequacies. More recent studies of experimental stress have examined physiological mechanisms hypothesised to mediate the relationship between stress and blood glucose control. There is evidence that reduced blood flow to the insulin injection site and insulin resistance over several hours may cause increased blood glucose levels in individuals with Type 1 diabetes in response to acute laboratory stressors. There is also evidence that the level of blood glucose rises in some patients, and falls in others in response to a laboratory stressor (Stroop test), and that these changes can be largely explicable in terms of changes in injection-site blood flow. Vasodilation at the subcutaneous insulin injection site may in some cases lead to

a paradoxical hypoglycaemic effect during acute stress via an increased rate of absorption of insulin, an effect which will be counterbalanced to a greater or lesser degree by increases in counter-regulatory hormones. More commonly, absorption of insulin may fall during stress as a result of vasoconstriction and reduced skin blood flow and contribute to hyperglycaemia.

Idiosyncratic blood glucose responses which were reliable across a 12-week time period within individuals with Type 1 diabetes have been reported in response to caffeine and to the competitive playing of a video game. Researchers have therefore begun to consider individual differences in response to stress to be real and interesting and not a reflection of methodological inadequacies. The inconsistent findings of previous research may have arisen at least in part because of differences in the stress-responsiveness of the individual patients recruited.

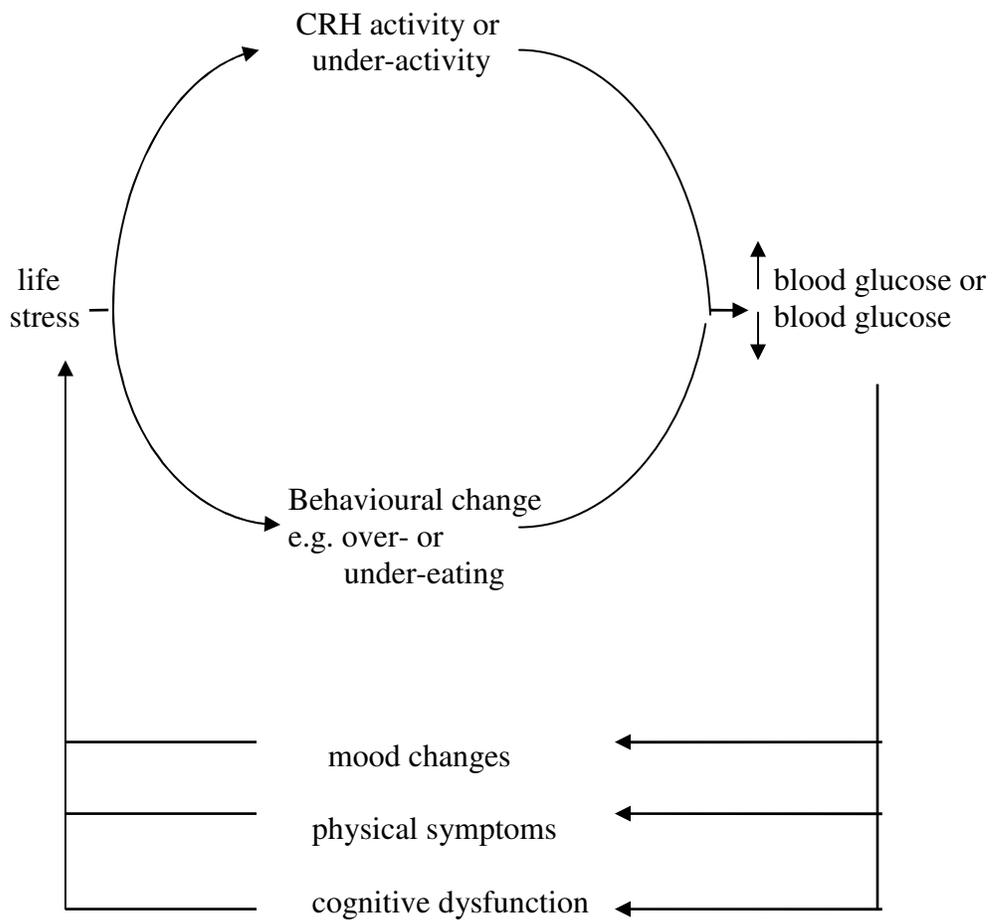
## **B. Life Stress and Diabetes Control**

### **1. Major life events**

Studies of major life events and diabetes control have produced fairly consistent results which have suggested that increased life events (over past several months to a year) are associated with raised blood glucose levels, usually measured by glycosylated haemoglobin (GHb) or the related measures of haemoglobin A1 (HbA1) and haemoglobin A1c (HbA1c). These measures reflect average blood glucose levels over the previous six to eight weeks. In some studies, more life events were reported by groups showing a stronger association

between life events and HbA1c levels. This could be due to a perceptual bias which may have lead people who experienced greater disturbance in association with life events to be more likely to recall the occurrence of life events. It could be that the subgroups did not actually differ in the number of life events reported, but only in their recollection of the events. However, a two-way causal link in which life events cause disruptions in diabetes control, which in turn cause increased life events has been suggested (Bradley, 1988; see figure 1). There is evidence that glycaemic fluctuations themselves can contribute to behavioural changes. It is now well-established that both hypo- and hyperglycaemia can impair cognitive functioning. Cognitive impairment may in turn cause inadvertent behavioural changes (e.g. in poor self-care responses to feedback from blood glucose monitoring) which can affect blood glucose control. Poorly controlled diabetes may also result in mood changes causing interpersonal conflict and thereby increasing stress levels and associated physiological reactivity. Physical symptoms are also caused by extreme blood glucose levels, e.g. fatigue is often associated with high blood glucose levels. Hypoglycaemic comas may have many consequences including accidents, job loss, and relationship problems. Such associations are described in the stress-blood glucose model shown in Figure 1.

**Figure 1. An elaborated two-way causal model of relationships between life stress and diabetes control. CRH = counter-regulatory hormone**



from Bradley (1988)

The practice of aggregating life stresses and blood glucose levels across time, incorporated by the majority of the life event studies, assumes minimal within-individual variation in stress and in blood glucose response. Such assumptions are not supported by common experience or by the literature which suggests that stress experienced varies within individuals from day to day. Information about the variability of blood glucose levels is lost when measures of GHb are used which give only an average of blood glucose control. Hypoglycaemia is not reflected in GHb measures because of its transient nature. Multiple observations of stress are required together with serial blood glucose measurement. Recent research has focused on the relationship between minor daily events and diabetes control (using serial blood glucose measurements) in order to overcome these methodological limitations.

## **2. Minor daily events**

Investigations of minor events have provided more interpretable results with studies reflecting individual differences in response to stress that were also seen in some of the laboratory-based acute stress studies. Although the overall picture suggests that increased daily stress correlates with increased blood glucose levels in people with Type 1 diabetes, examination of individuals' blood glucose responses to stress indicates that some people display blood glucose reactivity to stress and some people do not. Approximately half of 15 participants with Type 1 diabetes had significant associations between stress and blood glucose levels independent of the effects of diet and exercise self-management (Halford

et al., 1990). In a small study by Kramer et al (2000), 2 of 9 participants had significant correlations between stress and HbA1c, whereas 6 participants exhibited significant associations between stress and daily level or variability of glucose readings. In a larger study by Riazi et al (2004) with 54 participants, for approximately one-third of the sample, stress was significantly associated with either same- or next-day blood glucose levels. Within those people who display stress-reactivity, most show an increase in blood glucose but there is also evidence to suggest that a smaller proportion of people show a decrease in blood glucose. Therefore, in order for people with Type 1 diabetes to take appropriate action to prevent or correct stress-related disruptions in diabetes control, they need to discover empirically how their own blood glucose levels respond to different kinds of stress.

### **C Investigation of correlates of stress-reactivity**

There is some evidence to suggest that people with poor control of their diabetes may be more stress-reactive (stress being either laboratory-based or in the form of life events). This supports the model in Figure 1. There is also evidence that children with Type 1 diabetes who are classified as having Type A personality characteristics show elevated blood glucose levels after playing a stressful video game, whereas Type B children with Type 1 diabetes showed a decrease in blood glucose levels (Stabler, 1986). However, there is also evidence that internality and self-esteem did not relate to stress-reactivity in the group of women with Type 1 diabetes studied by Aikens and colleagues (1994). It is likely

that individual differences in stress response are mediated by both physiological and psychological processes. For example, stress-reactive individuals in comparison to non-stress-reactive individuals, had both high HbA1c values and significant relationships between emotion-focused coping and blood glucose levels (Riazi et al., 2004). However further research is necessary to clarify the associations between these variables and stress-reactivity.

### **III Stress Management Training and Type 1 Diabetes Control**

The overly simple model of life stress causing raised blood glucose levels has inspired the use of stress management training, as an aid to diabetes control. There is now self-help guidance (Surwit and Bauman, 2004) for people with diabetes who are interested in achieving better diabetes control through stress management training, in particular, relaxation training. Relaxation is thought to decrease the levels of both cortisol and catecholamines, and hence is expected to prevent stress-induced increases in blood glucose levels.

The research to date supports the view that stress management techniques may be valuable to aid diabetes management for some people but not for others. It has been suggested that relaxation techniques are unlikely to do harm except when blood glucose is already tightly controlled and the insulin dosage is not appropriately reduced to balance the effects of relaxation on insulin requirements (which may well be reduced) and/or when used at a time when blood glucose is already low (<4 mmol/l) and there is a risk of hypoglycaemia. It is important to take the precaution of measuring blood glucose immediately before all relaxation

training or practice sessions. Twenty minutes of relaxation can lead to a drop in blood glucose by as much as 3 mmol/l. Such a substantial fall is only likely if blood glucose is well above the normal range of 4-6 mmol/l to start with and probably results from a suppression of catecholamine secretion. It is recommended that relaxation training should not be conducted at blood glucose levels below 4 mmol/l because of the risk of hypoglycaemia. Relaxation training might be continued if the anticipated reduction in blood glucose were counteracted with pre-training intake of slow release carbohydrate (e.g. an apple). A further precaution of measuring the blood glucose after a relaxation session, before leaving the therapist's office, is also recommended to avoid the risk of hypoglycaemia while travelling home.

Several studies have reported some success with improvements in diabetes control following relaxation training (sometimes involving EMG biofeedback) in people with Type 1 diabetes. There is evidence to suggest that relaxation training is least useful for those people whose glycaemic control is good to start with and most useful when used by people who not only have poor control of their diabetes but who feel that stress disrupts their diabetes control and who are currently experiencing stressful events. Although some studies have found no significant differences between relaxation and control groups in HbA1c levels or insulin requirements after relaxation training, information about the variability of the individual patients was rarely reported. In addition, lack of selection of patients likely to benefit from relaxation training may be responsible for the nonsignificant findings of some studies.

What is emerging from the studies of relaxation training in people with Type 1 diabetes, is that it is most demonstrably useful for those who are showing stress-related disturbance of blood glucose control at the time. Assessment of patients' stress-reactivity before embarking on relaxation training in future studies will help in the identification of patients most likely to show benefit from relaxation training. To date, most studies have incorporated biofeedback into the relaxation training. Relaxation instructions alone would be more practical and less costly. Evaluation of low-technology forms of relaxation training with patients shown to be stress reactive would be a useful contribution to the state of present research. Such evaluation needs to take account of the fact that the benefits of relaxation training for blood glucose control will only be apparent during periods of stress when stress-reactive relaxation-trained individuals would be expected to have more stable blood glucose control than stress-reactive individuals who have not been trained. Improvements in blood glucose control will be more apparent if recruitment to such a study is restricted to individuals who show increased blood glucose under stress.

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