

# STRESS IN THE CAUSE AND COURSE OF DIABETES

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## ABSTRACT

Stress may be defined as a state of threatened homeostasis. Stress has been shown to have a role in the cause of diabetes and certainly in the management of the disease. There may be cortisol mediated intra abdominal fat deposition, modulated by chronic stress, leading to metabolic syndrome or Syndrome X. Hypothalamic-pituitary-axis (HPA) activity has also been postulated to have a significant role in intrauterine programming. The Hoorn study has shown that stressful life events may be associated with visceral adiposity and type 2 diabetes mellitus. In the management of type 2 diabetes mellitus, compliance depends on personality traits and healthcultural beliefs. In childhood diabetes, emotional pain of coping may be taken as a paradigm in planning management for the child as well as the family. Diabetes specific psychological instruments for quality of life, well being and treatment satisfaction, could prove useful in clinical practice and in clinical audit.

**KEY WORDS:** Glucocorticoids; Allostatic load; HPA activity; Bjorntop's hypothesis; Intrauterine programming; Quality of life; Well being; Childhood diabetes.

## INTRODUCTION

In a broad sense, stress may be defined as a 'state of disharmony or threatened homeostasis' (1). Stress by itself is not bad and to an extent is necessary for maintaining life (2). Selye called 'good stress' as 'eustress', in contrast to 'distress' which is a noxious homeostatic mechanism (1).

## PHYSIOLOGY OF THE STRESS RESPONSE

Stress inducing agents set into motion both central and peripheral responses. Centrally, neural pathways are activated to induce arousal, alertness, vigilance and focussed attention. There is simultaneous inhibition of feeding and reproduction. Peripherally, oxygen and nutrients are directed to central nervous system (CNS) and the site that is stressed. These changes are useful when stress-inducing events occur in bursts, with long periods of stress-free intervals. However, if the stress occurs at a low

constant level as in modern life, the stress response leads to 'distress'. It then loses its adaptive quality.

The difference between 'eustress' and 'distress' could in part depend on hereditary traits such as metabolic response, expression of genes for hormone, receptor or an enzyme. Glucocorticoids mediate the stress response. Difference between eustress and distress was ascribed to salutary response to noxious stimuli and prevention of natural recovery phase on chronic exposure to stress (3).

## STRESS, ADAPTATION AND DISEASE

'Allostasis' is the name given to 'stability through change' or adaptation in the face of potentially stressful challenges. Our current concepts of stress are subjective and generally do not account for differences in coping among individuals. Secondly, many aspects of daily living may be stressful, although they are not generally regarded as stressful (4).

Adaptation or allostatic load comes at a price when allostatic systems are either overworked or fail to shut off after the stressful event. Allostatic load or 'distress' can result from different types of stress: frequent stress, the frequency and intensity of stressor determining the allostatic load. In failed shut-down, there is chronic stress response which is not shut off, and finally in inadequate response, there is failure to respond to challenge. The failed shutdown is generally responsible for obesity and type 2 diabetes.

## STRESS AND DIABETES

Management of diabetes mellitus has been described as being the most complex of all common metabolic disorders (5). Type 2 diabetes, which is a disease of lifestyle, has an impact on all aspects of living: having to follow a schedule of diet, doing exercise regularly, taking medicines and getting tested periodically.

Stress can result in causing diabetes mellitus and might also contribute to difficulties in management. There is also evidence that chronic persistent stress may cause type 2 diabetes mellitus. We examine both these issues, viz. stress in the etiology and course of diabetes mellitus.

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## **METABOLIC SYNDROME, OBESITY AND HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS**

Type 2 diabetes mellitus is now well recognized to be a syndrome encompassing hyperglycemia, insulin resistance, truncal obesity, dyslipidemia and hypertension. Hyperglycemia should therefore not be considered in isolation, either in the management or in the prognosis of type 2 diabetes.

### **Central Obesity, HPA and Stress**

Cortisol and obesity are closely associated. Earlier studies suggested that in obesity, both secretion and clearance of cortisol are increased, resulting in normal or low circulating levels. Environmental stress and the pattern of cortisol secretion may both contribute to the pathogenesis of obesity. Other contributing factors are, conversion of cortisol to its metabolites, perinatal factors and the programming of the HPA axis (6).

Central obesity has been called the 'Cushings disease of the omentum': viz., constant exposure of glucocorticoids specifically to the adipose tissue in the omentum may be responsible for central obesity (7).

### **Bjorntop's Hypothesis**

Bjorntop postulated that stress could be responsible for sympathetic nervous system activation, hormone abnormalities and obesity (8,9). Arousal along both axes occurs at the hypothalamus, corresponding to the 'defense' and 'defeat' reactions. There is evidence for this in animal models. In humans, unambiguous demonstration is not possible due to complex responses and counter responses. Bjorntop's hypothesis postulates that psychosocial stress triggers the onset of visceral obesity and the other components of Syndrome-X. Different persons may show 'eustress' and 'distress' responses to the same stimulus (10).

### **HPA activation and Obesity**

HPA axis is more active in centrally obese men and in centrally obese women but not post-menopausally (11). Central obesity in women was associated with differential cortisol secretory response to a meal and with enhanced clearance capability of cortisol (12,13). There could also be a spontaneous, subtle, differential regulation of HPA axis in android versus gynecoid obesity (14). Similarly, it could be more specifically targeted to key tissues such as liver and visceral fat, leading to adverse metabolic consequences (15).

Fat was preferentially deposited in the abdomen due to activity of enzymes that metabolize

glucocorticoids. The activity of 11 beta HSD activity was highly related to body fat distribution and with central obesity (16). The 11 beta HSD oxo-reductase activity in subcutaneous abdominal fat tissue was increased in obesity (17). This increase may activate local glucocorticoid receptors and promote obesity (18).

### **HPA Activation and Intrauterine Programming**

There is some evidence that exposure to stress may activate HPA axis even in utero. Adult metabolic Syndrome-X and low birth weight may be linked to cortisol activation, at least in populations undergoing health transition (19). Prenatal glucocorticoid exposure may also participate in fetal programming, along with maternal malnutrition.

In experimental animals, prenatal exposure to dexamethasone resulted in lower birth weight, permanent elevation of blood pressure and hyperinsulinism. These responses may be due to a resetting of neuroendocrine pathways.

Low birth weight in humans was associated with elevated glucocorticoid concentrations in later life. What is unclear is whether this is a cause or a consequence. In a study of young, non-obese subjects from South Africa, low birth weight and glucose intolerance, blood pressure and dyslipidemia were compared with HPA responsiveness and cortisol metabolism (19). Both systolic and diastolic blood pressures significantly correlated with current adult weight, waist circumference, height, basal plasma cortisol and post-ACTH cortisol. HPA axis could thus be a primary target for early life programming.

## **GENE-ENVIRONMENT INTERACTION**

It is evident that not that all stressors result in an identical response. Genetic and other environmental factors such as the use of tobacco and alcohol, dietary and sedentary habits may all contribute. Interventions to correct stress are possible at many levels to lower the allostatic load (20,21). In animal studies altered circadian rhythm in serum cortisol was affected by aging (22).

### **Testing Bjorntop's Hypothesis-The Hoorn Study**

A recent clinical study tested whether chronic psychological stress was associated with prevalence of type 2 diabetes and with visceral adiposity (23). In 2,262 Caucasian adults aged 50-74 years without a history of diabetes mellitus, the number of major stressful life events experienced during the preceding five years were assessed by a questionnaire. This

was followed by an oral glucose tolerance test. The number of stressful events was positively associated with the prevalence of hitherto undiagnosed diabetes. These findings were partially consistent with Bjorntop's hypothesis that stressful life events were associated with undetected type 2 diabetes and with visceral adiposity.

### **COPING WITH DIABETES, CORRELATION WITH STRESSORS**

Considering that diabetes mellitus is an insidious, omnipresent, lifestyle condition, studies looked at conditions that might facilitate or impede diabetes care. Differences in personality traits were correlated with variations in glycemic control in diabetes (24). In a longitudinal cohort study on 105 type 2 diabetes patients, lower average blood glucose values were associated with higher scores for personality domain of neuroticism. The relative tendency to experience fewer negative emotions and to focus on the needs of others instead of oneself could prove to be a risk factor for poor glycemic control.

Health beliefs also affect management of diabetes. Differences in cultural and health beliefs must be considered when attempting to improve diabetic control (25). Besides, diabetes self-care behavior is also dependent on the family and community support. Interventions must be directed at the family, which is the unit providing support for the individual, and could consider appropriate involvement of religious institutions (26). Characteristics of the family setting are linked to self-care behavior, which again depend on ethnicity (27). Multiple targets for intervention are thereby available, which must however be compatible with the setting of disease management.

Besides the patient, one must consider the stress in family members. Family support for carers improve quality of life in families with patients of cerebrovascular accidents (28).

### **PSYCHOLOGICAL FACTORS IN CHILDHOOD DIABETES**

Childhood diabetes forms a small percentage of the diabetic population reported from our country (29). However, to those affected, it entails considerable stress in management — the child, the family and the health-care team. Medical skills and psychosocial support are nowhere more crucial than in the management of the very young child with diabetes (30). Where trained manpower in supportive fields such as social work, psychology and nutrition is not available, the treating physician must often take

on the additional role of providing psychosocial support for the child and the family. The extended family structure, which is still common in our country, offers additional family members in sharing the burden. However, managing the young child with diabetes requires empathy, tact, understanding and ingenuity.

### **Access To Diabetes Care And Compliance**

Among type 1 diabetic persons at Diabetes Research Centre, Chennai, the proportion of females was higher in the high income group (>Rs 2000/- per month; 115/119; 0.967) compared to that in the low income group (<Rs 2000/- per month; 178/202; 0.88) (31). It is possible that the difference could at least be in part due to difference in access in medical care between boys and girls (29,32). Childhood and adolescence being a period of intense change, compliance is likely to be poor during this time. At All India Institute of Medical Sciences, more girls were likely to be regular than boys, in their contact and follow-up with diabetes education programme (33).

### **Parenting**

In the management of a child with diabetes, the mother tends to carry a disproportionate share of the burden of diabetes care (34). When fathers do not participate in the initial period of diabetes management, they feel out of touch with the complexities of its management. Therefore care should be taken to distribute the responsibility between the two parents (29).

### **Pain as a Paradigm in Dealing with Childhood Diabetes**

The painful processes of managing diabetes in childhood can be considered as two components. (a) Physical pain of enduring hyperglycemic symptoms, and the pain of pricks from blood glucose testing procedures and insulin injections (b) emotional pain in the child, family and others, of having to bear the entire management process.

### **Child's Conceptualization of Coping with Pain**

The way a child views the value, function and consequences of pain may impact the coping process. A child who focusses on potential secondary gain, may view pain as an opportunity to gain sympathy or a reward, which may undermine attempts to cope effectively and ultimately lead to a maladaptive outcome. On the other hand a child who views a medical procedure as unnecessary discomfort or punishment, it may be catastrophic, whereas a child who understands the rationale or

necessity of a procedure may try to feel better by focussing on its benefits (35).

### **Parenteral Influence**

The way parents react to a situation influence the reaction in the child. Children with anxious mothers tend to exhibit greater anxiety in their presence, whereas children with low-fear mothers show more distress in their absence. It is essential to understand the parental reactions to stressors, their attempts to promote coping and children's coping responses.

### **Cognitive Appraisal of Coping**

Appraisals are beliefs that presumably influence adjustment to a stressor, the selection of coping strategies and the nature of the outcome (35).

#### *Primary Appraisal*

A child may view management restrictions in daily living with diabetes as a punishment. Threat appraisals may be reflected as potentially interfering with opportunities to participate in activities or sports with peers. Primary appraisals may influence children's approach to coping: a child who perceives an injection as threatening, may be more likely to adopt an antagonistic coping response, whereas a child who appraises it in terms of its curative value, may engage in adaptive coping. This also depends on the age of the children. Adolescents were more likely to focus on the implications of the disease, whereas children were more likely to focus on the symptoms.

#### *Parent Child Alienation*

One of the major fall-outs is diabetes-related conflict between parents and children. It could start out as erosion of self-esteem in response to frustration over the child's inability to adhere to the diabetes treatment and / or to consistently achieve euglycemia. Repeated family conflicts over non-adherence to treatment or severe parental or child distress or depression over blood sugar readings, should be indications for professional psychological and family counselling.

### **COGNITIVE FUNCTION IN CHILDHOOD DIABETES**

Diabetes mellitus is known to be associated with neurobehavioral and neuropsychological changes involving learning, memory, mental speed and eye-hand coordination (36).

### **Frequency of Cognitive Dysfunction**

Children with diabetes were shown to have greater psychological disability compared to children with

other chronic disorders (37). Cognitive dysfunction identified by electrophysiological tests may antedate abnormal psychometric tests (38). Lower performances on IQ scores were demonstrated one year after onset of childhood diabetes, when associated with ketonuria and hospitalizations (39), along with other mild neuropsychological dysfunction, such as information processing speed, acquisition of new knowledge and conceptual reasoning (40). Similarly, there was an inability to express emotions verbally — alexithymia, as a form of emotional suppression (41).

### **Studies in India**

There are few published Indian studies, except for the report by Seshiah et al (42). Children with diabetes scored less compared to controls on all scores: Wechsler's coding, digit span test and Raven's colored progressive matrices. However, there was no correlation with duration of diabetes or early onset of diabetes. It was concluded that the lower scores were due to psychosocial factors in addition to metabolic control. In a recent study at our centre, it was shown that cognitive function was poorer compared to control children on reaction time and memory. Sixteen children with diabetes (8 boys, 8 girls) aged 8-16 were compared to 32, age and sex matched controls. Diabetic children had longer reaction times than controls. Similarly, they scored poorly on memory scales including memory span, logical memory and associated learning. However, there was no statistically significant difference in intelligence quotient between children with diabetes and controls (43).

### **Significance of Cognitive Impairment**

Children with diabetes missed school more often, performed more slowly and obtained lower scores than controls (44). Cognitive impairment is associated with increased risk of learning problems (45). This underscores the necessity for ascertaining educational skills in diabetic children when planning diabetic treatment regimens, especially with early onset long duration diabetes, who may be especially vulnerable (46).

### **Adult Psychosocial Stress**

Sexual dysfunction is an important expression of stress. Besides vascular and neural dysfunction leading to sexual dysfunction in men, stress can also result in reversible sexual dysfunction (47). Shift work and adverse work conditions also contribute to sleep disorders and sexual dysfunction.

Sleep disturbances are four times common in diabetes mellitus compared to controls (48). The stress of having the disease, along with physical symptoms, psychosocial factors including shift work may all contribute to sleep disturbances. Women were shown to have more sleep disturbances than men (49).

### **Apprehension of Complications and Likely Disability**

Onset of complications brings on extra psychosocial problems. The single deciding factor is the degree of handicap resulting from complications and how well the individual can cope with the resulting limitation. The health care team along with the individual's family form the major source of support in coping.

### **MEASURES OF TREATMENT SATISFACTION**

The outcome of treatment in acute conditions such as infectious diseases is measured by duration of illness and recovery. Diabetes mellitus cannot be evaluated similarly. The traditional measure of signs, symptoms and biochemical investigations form the doctors' 'preoccupation with the disease process' (50).

**Quality of Life Questionnaire:** Diabetes quality of life questionnaire (DQOL), was originally developed for use in Diabetes Control and complications trial (DCCT) to evaluate the discomfort of intensive insulin therapy compared with conventional therapy. The questionnaire evaluates the satisfaction, impact and worries, associated with diabetes treatment. It can be used in both type 1 and type 2 diabetic patients using insulin, or diet and oral hypoglycemic agents (51). It is acceptable, easy-to-use and is not difficult to understand.

**Well Being Questionnaire:** The well being questionnaire was specifically designed (52) and scored so that diabetes related symptoms are not mistakenly attributed to depressed mood.

**Diabetes Treatment Satisfaction Questionnaire (DTSQ):** Was designed to measure satisfaction with diabetes treatment regimens in people with diabetes (53). It is intended to measure satisfaction with treatment and is not designed to measure satisfaction with other aspects of the diabetes care service. It is a measure of psychological outcome, to measure benefits of new treatments that can improve patients' quality of life rather than just the blood glucose control. However, DTSQ scores should not be interpreted in isolation, but should be corroborated with other measures of

metabolic control. Or else patients are likely to desire a treatment regimen that is 'easy' to follow, but which does not achieve metabolic control.

### **Application of these Instruments**

The use of QOL instruments has shown that management of diabetes correlates with positive well being and improved QOL. A study done in a bi-ethnic population in San Luis Valley showed that the individuals with type 2 diabetes rated their perceived quality of life lower than controls. Rather, control and treatment strategies should reflect an understanding of the impact that diabetes has on social functioning, leisure activities and physical and mental health (54). Similarly, higher levels of blood glucose were related to a decreasing quality of life, caused in part by the presence of diabetic complications (55).

In a series of more than 200 persons with diabetes, quality of life was a function of the gender and age. Women reported poorer quality of life compared to men (56). They reported lesser satisfaction with the time available to manage the disease and its influence on their daily work. Men on the other hand stated the disease had no substantial impact on their work life. Diabetic persons aged less than 40 years reported better satisfaction with the treatment and management of the disease and a better quality of life. Duration of diabetes had no significant influence on quality of life.

Similarly, gender and age of diabetes had a significant influence on reported well-being. Women and those aged above 58 years had poorer well being and experienced more depression. Men and those aged between 41 and 48 years reported better positive well-being. Duration of diabetes had no significant influence on well-being (57).

In general, adjustment to diabetes was significantly influenced by the gender, men reporting better adjustment, especially with coping and integration of the illness. Diabetic persons with normal blood glucose levels accepted the regimen of diabetes management and a medically dependent attitude towards its management. There was a tendency for this difference to occur in a subgroup of lean type 2 diabetics (58).

In longitudinal studies over one year, psychological well-being improved as a result of personalized care, attention and possibly the supply of medicines (59,60). Given the potential availability of personnel in India, improvement in psychological well-being can be ensured even before attempts at

achieving euglycemia are possible.

Similarly, we examined the psychological correlates of work life among persons with diabetes compared to those without diabetes. Men perceived a poorer quality of work life, poorer well-being and greater fatigue compared to controls. (61).

We evaluated the social support received by patients with type 2 diabetes mellitus based on the first quartile (good well-being) or last quartile (poor well-being) on Bradley WHO well-being scale. A self-reliant approach to the management of diabetes was shown to enhance the well being (62).

In a related evaluation on effective living with diabetes, we constructed the living with diabetes (LVD) score from scores on quality of life, well-being and psychological adjustment to diabetes. Subjects were categorized into those living effectively (those in the first quartile on LVD score) and those not living effectively (those in the last quartile). In the sample studied, men lived more effectively than women. Women must be encouraged to develop a more positive attitude towards the disease and its management (63).

In conclusion, stress may be expressed in myriad ways: emotionally, physically and biochemically. The different facets may cause diabetes, and certainly operate in the course of diabetes. The future holds promise to translate 'distress' to 'eustress'.

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