

Diabetes Fatigue Syndrome

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ABSTRACT

In this editorial we propose a condition that we refer to as ‘diabetes fatigue syndrome’ (DFS), which is commonly encountered in clinical practice. We define DFS as a multifactorial syndrome of fatigue or easy fatigability that occurs in persons with diabetes. It may be caused by a variety of lifestyle, nutritional, medical, psychological, glycemia/diabetes-related, and endocrine and iatrogenic factors. The authors share clinical pearls which can help the diabetes healthcare provider diagnose DFS, identify its etiologic factors and manage the syndrome. The editorial highlights the need to focus on symptomatic well-being in diabetes, along with efforts to achieve numerical targets.

Keywords: Adrenal; Anemia; Fatigue syndrome; Lifestyle modification; Pituitary; Thyroid; Vascular complications; Vitamin D deficiency

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INTRODUCTION

Fatigue is a condition which interests researchers, clinicians, and public health specialists alike [1]. Most of the published discussion on fatigue has revolved around its description and measurement, its psychological pathogenesis and impact, and its influence on occupational and industrial health [2, 3]. Yet, a consensus on its definition has not yet been reached, and its quantification is still not standardized [1]. Fatigue is a common symptom of diabetes that is not limited to uncontrolled diabetes. Persons may complain of fatigue along with a variety of symptoms, which may together herald comorbid psychological, medical, metabolic or endocrine, and acute or chronic complications. For the diabetes healthcare professional, the debates on fatigue are a distraction from the ultimate clinical challenge, namely, to identify fatigue, diagnose the cause(s) of the fatigue, manage the condition, and prevent worsening of the morbidity.

In this editorial we seek to achieve a working definition of ‘diabetes fatigue syndrome’ (DFS), provide a clinical rubric with which to evaluate this condition, and focus attention on this relatively neglected aspect of diabetes care. Much of the discussion in this article should be relevant to general clinical care as well.

All named authors meet the International Committee of Medical Journal Editors (ICMJE)

criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

THE IMPORTANCE OF SYMPTOMS

Modern diabetes care is characterized by a strong focus on evidence-based, number-driven targets and outcomes. While this approach does have its benefits, it has shortcomings and limitations as well, one of which is that little attention is paid to the symptomatic well-being of the persons with diabetes. At times, in fact, complaints may be neglected, and symptoms sacrificed, to justify the use of particular therapeutic strategies or tools. A casual reading of modern guidelines suggests that the end-target (e.g., a specific glycosylated hemoglobin value, or cardiovascular outcome) is more important than the means (a drug which causes gastrointestinal or genitourinary discomfort). Understandably, such clinical judgment is bound to be met with patient dissatisfaction. One symptom which may be ignored in the quest for optimal numerical end-targets, is fatigue.

FATIGUE

Fatigue is defined as physical and/or mental exhaustion [4] that can be triggered by stress, medication, overwork, or mental and physical illness or disease. Fatigability is a term used to assess how fast someone gets exhausted. Easy fatigability implies the occurrence of physical and/or mental exhaustion at a level of work or stress that should ordinarily not cause such exhaustion. Fatigue impairs physical as well as mental functioning, and it reduces the quality of life. Thus, a person presenting with complaints of fatigue deserves a focused endocrine and medical checkup.

FATIGUE IN DIABETES: A VICIOUS CYCLE

Fatigue is a frequently encountered symptom in the general practice management of diabetes. Fatigue may be the presenting symptom of diabetes, or it may present as one of a constellation of complaints. It may even persist after glycemic control is achieved. All of these clinical situations, irrespective of causality or association, may be grouped together as DFS. Fatigue has been reported to be prevalent in patients with type 1 diabetes or type 2 diabetes [5, 6]. Its association with inflammation, body mass index, insulin treatment, and depression has also been studied [7–9]. The lack of correlation between fatigue on the one hand and hyperglycemia and glycemic variability on the other is also known [10]. The unique features of fatigue in persons with diabetes have also been recognized, prompting the development of disease-specific diagnostic tools [11], as opposed to generic ones [12, 13].

Diabetes and fatigue seem to have a bidirectional relationship, both feeding and worsening each other, thereby creating a vicious cycle of DFS (Fig. 1). This relationship is strengthened by biochemical, psychological, and lifestyle factors.

THE BIOCHEMISTRY OF DIABETES FATIGUE

The pathophysiology of fatigue centers around biochemical and ionic changes which occur in muscle and subsequently impact the electrical and contractile properties of this organ. Substrate depletion, high levels of hydrogen ions, and the presence of inorganic phosphate and potassium have been implicated in the pathogenesis of fatigue. Evidence suggests, however, that calcium ion availability at the sarcoplasmic reticulum of the mitochondria, which is linked to a decrease in ATP synthesis, may lead to fatigue [14].

In persons with diabetes, lack of insulin (relative to the body's needs) may shift the energy substrate from carbohydrate to fat. When this occurs (once glycogen stores are exhausted), the ADP phosphorylation rate falls and ATP

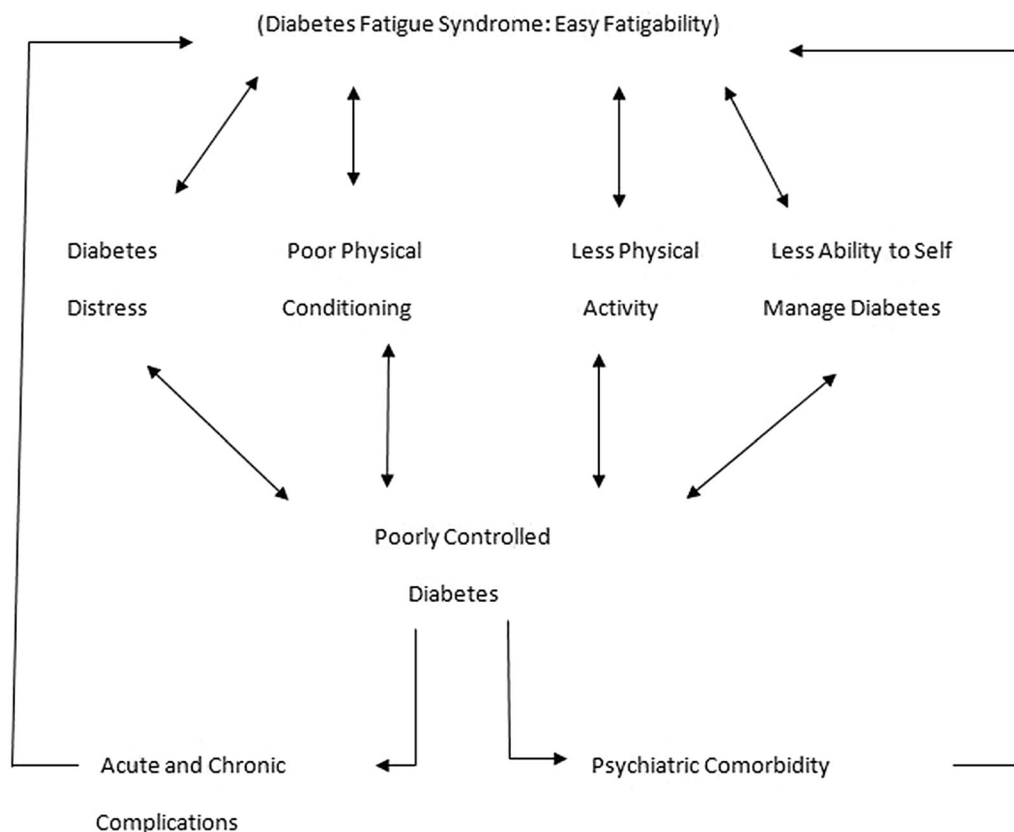


Fig. 1 The vicious cycle of diabetes fatigue syndrome

resynthesis slows down. This process may explain the occurrence of fatigue in diabetes.

THE PSYCHOLOGY OF FATIGUE

Fatigue also has a strong psychological component [1]. The inability to self-manage diabetes may lead to a sense of fatiguability, which in turn may hamper efforts to manage the condition. Thus, there is a bidirectional relationship between easy fatiguability and diabetes distress, with each feeding on the other, creating a vicious cycle which ultimately leads to DFS.

DIABETES FATIGUE SYNDROME

We define DFS as a multifactorial syndrome of fatigue or easy fatigability that occurs in persons with diabetes. It may be caused by a variety of lifestyle, nutritional, medical, psychological,

glycemic/diabetes-related, endocrine, and iatrogenic factors.

In this section we discuss the common forms of DFS that are encountered in clinical practice and describe the neuropsychiatric, musculoskeletal, and general symptoms and signs that facilitate the diabetes healthcare provider in making the differential diagnosis of DFS (Tables 1, 2). We also list ‘clinical pearls’ which help the healthcare provider to diagnose and manage DFS (Tables 2, 3). Chronic fatigue syndrome is extreme fatigue which persists unabated for at least 6 months and which is not the result of a diagnosed disease or illness. It is just one cause (out of many) of fatigue and does not fall within the range of the subject discussed here.

ETIOLOGY AND PRESENTATION

The possible causes of DFS may be classified as non-endocrine and endocrine factors, respectively.

Table 1 Causes of fatigue in persons with diabetes

Non-endocrine causes	Endocrine causes
Lifestyle related	Glycemic related
Lack of physical conditioning/exercise	High HbA1c in spite of normal glucose levels
Poor sleep hygiene	Postprandial hyperglycemia with normal fasting glucose
Excessive caffeine, alcohol intake	Recurrent hypoglycemia
Substance abuse	High glycemic variability
Drug withdrawal	Complications of diabetes
Diet related	Nephropathy
Excessive caloric intake	Heart failure
Excessive caloric restriction	Myopathy
Protein malnutrition	Neuropathy
Starvation ketosis	Concomitant endocrinopathy
Medical	Hypothyroidism
Anemia	Cushing's syndrome
Dyselectrolytemia	Hypogonadism
Vitamin deficiency	Addison's disease
Diabetes distress	Iatrogenic
	Chronic corticosteroid use
	Statins
	Diuretics
	Beta blockers

HbA1c Glycated hemoglobin

Non-Endocrine DFS

Lifestyle-Related Causes

Non-endocrine factors that may contribute to DFS include an unhealthy lifestyle, inappropriate diet, and suboptimal mental health. Lack of physical conditioning, poor sleep hygiene, substance abuse (including excessive alcohol, caffeine), and drug withdrawal may lead to DFS. These factors are usually identified through history taking. Validated questionnaires may be used to screen for some of these conditions [15, 16]. The treating physician should also be aware of locally prevalent substances of abuse

(such as betel quid, khat, opium) and culture-linked syndromes (e.g., Dhat syndrome) that may contribute to DFS.

Nutritional Causes

Unhealthy diets, which may lead to macronutrient or micronutrient malnutrition or starvation ketosis, can also precipitate DFS. Again, a history taking, with a detailed dietary recall, helps establish the diagnosis.

Medical Causes

Common medical conditions, such as anemia, dyselectrolytemia, and multiple vitamin

Table 2 Fatigue and depression: differential diagnosis

Parameter	Fatigue	Depressive disorder
Definition	Used to refer to loss of energy with complaints of increased fatigue after mental effort, often associated with some decrease in occupational performance or coping efficiency in daily tasks. Mental fatigability is typically described as an unpleasant intrusion of distracting associations or recollections, difficulty in concentrating, and generally inefficient thinking	A mood disorder characterized by depressed mood, loss of interest and enjoyment, and reduced energy leading to increased fatigability and diminished activity
Symptoms	Physical symptoms: reduced activity, low energy, tiredness, decreased physical endurance, increased effort to do physical tasks, general weakness, heaviness, slowness or sluggishness, nonrestorative sleep, and sleepiness. Cognitive symptoms: decreased concentration, decreased attention, decreased mental endurance, and slowed thinking. Emotional symptoms: decreased motivation or initiative (apathy), decreased interest, feeling overwhelmed, feeling bored, aversion to effort, and feeling low	Depressed mood, loss of interest and enjoyment, and reduced energy leading to increased fatigability and diminished activity
Definite diagnosis	Definite diagnosis requires the following: (1) Either persistent and distressing complaints of increased fatigue after mental effort, or persistent and distressing complaints of bodily weakness and exhaustion after minimal effort; (2) At least two of the following: - Feelings of muscular aches and pains - Dizziness - Tension headaches - Sleep disturbance - Inability to relax - Irritability - Dyspepsia (3) Any autonomic or depressive symptoms present that are not sufficiently persistent and severe to fulfil the criteria for any other disorders, including depressive disorders	Definitive diagnosis requires that the individual usually suffers from (1) depressed mood, (2) loss of interest and enjoyment, and (3) reduced energy leading to increased fatigability and diminished activity. Marked tiredness after only slight effort is common. Other common symptoms are: - Reduced concentration and attention - Reduced self-esteem and self-confidence - Ideas of guilt and unworthiness (even in a mild type of episode) - Bleak and pessimistic views of the future - Ideas or acts of self-harm or suicide - Disturbed sleep - Diminished appetite <u>Mild</u> : at least two of three main symptoms and at least two of the other common symptoms <u>Moderate</u> : at least two of the three main symptoms and at least three of the other common symptoms <u>Severe</u> : all of the three main symptoms and at least four of the other common symptoms
Associated morbidity	Associated with decrease in occupational performance or coping efficiency in daily tasks	Associated with significant distress and/or dysfunction
Instruments for severity rating	Fatigue Questionnaire and the Fatigue Associated with Depression scales (FasD)	Beck's Depression inventory, Hamilton Depression Rating Scale

deficiencies, are also characterized by fatigue. Such morbidities are as plausible in persons with diabetes as in those without. Specific symptoms and signs may point towards these comorbid causative factors of DFS. Many of these conditions coexist with dietary inadequacy. A history of breathlessness on exertion, excessive blood loss, worm infestation, and pallor on examination suggest anemia. Dyselectrolytemia usually leads to neurological

symptoms and signs. Proximal muscle weakness, together with musculoskeletal aches, pains, and easy fatigability, implies vitamin D deficiency.

Psychological Causes

At times, DFS may be worsened by psychological impairment. Diabetes distress is defined as an emotional response, characterized by extreme apprehension, discomfort, or dejection

Table 3 Pragmatic suggestions**Pragmatic suggestions**

Every person with diabetes must be asked about fatigue at each clinical encounter

Every person with DFS should be screened clinically for lifestyle, drug intake, and medical and endocrine factors, and by history taking and physical examination

Every person with a suggestive history or physical examination findings should be assessed for specific medical conditions and endocrinopathies

Relevant investigations for DFS must be prescribed based upon index of clinical suspicion and economic considerations

A therapeutic trial of vitamin D and calcium may be considered in South Asian persons with fatigue, taking the ubiquitous occurrence of vitamin D deficiency into consideration

Hormone replacement or supplementation should be not initiated as a treatment for DFS without documentation of endocrine deficiency or insufficiency

DFS Diabetes fatigue syndrome

due to a prescribed inability to cope with the challenges and demands of living with diabetes. This adjustment disorder is characterized by a discomfort disorder that in turn is characterized by discomfort, and it may be reported as fatigue, possibly contributing to, overlapping with, or mimicking DFS. Yet another differential diagnosis of fatigue may be major depressive disorder. The differences between fatigue and depression are highlighted in Table 2 [17, 18].

Endocrine DFS

If lifestyle, nutritional, and medical causes are ruled out, a targeted gluco-endocrine evaluation must be done to pinpoint the cause of DFS.

Diabetes-Related Causes

Diabetes-related causes include poor glycemic control, diabetic complications, and concomitant endocrinopathies. A suboptimal gluco-phenotype, involving any or all of the glycemic hexad (hyperglycemia, hypoglycemia, excessive glycemic variability), can lead to DFS. Similarly, fatigue may be the presenting symptom, or it may herald an insidious onset of vascular complications, such as heart failure and nephropathy. Lesser known comorbidities of diabetes, including chronic venous disease and

Alzheimer's disease, may also present with fatigue.

Endocrine Causes

Persons with diabetes, especially type 1 diabetes, are more prone to endocrinopathy. Diseases such as hypothyroidism, Addison's disease, Cushing's syndrome, and hypothyroidism, if left unrecognized and/or untreated, may worsen DFS. The symptoms, sign, and laboratory anomalies specific to these diseases, coupled with a high index of clinical suspicion, help in their identification.

Iatrogenic Causes

At times, DFS may be iatrogenic. Drugs such as corticosteroids, beta blockers, diuretics, and statins are known to cause fatigue. Their use must be looked into during the evaluation of DFS.

CLINICAL APPROACH

Diabetes fatigue syndrome is a multifactorial multifaceted condition which should not be evaluated from a purely gluco-centered or endocrine-oriented prism. The appropriate strategy to addressing DFS should follow a simple hierarchy (Table 2; Fig. 2) which

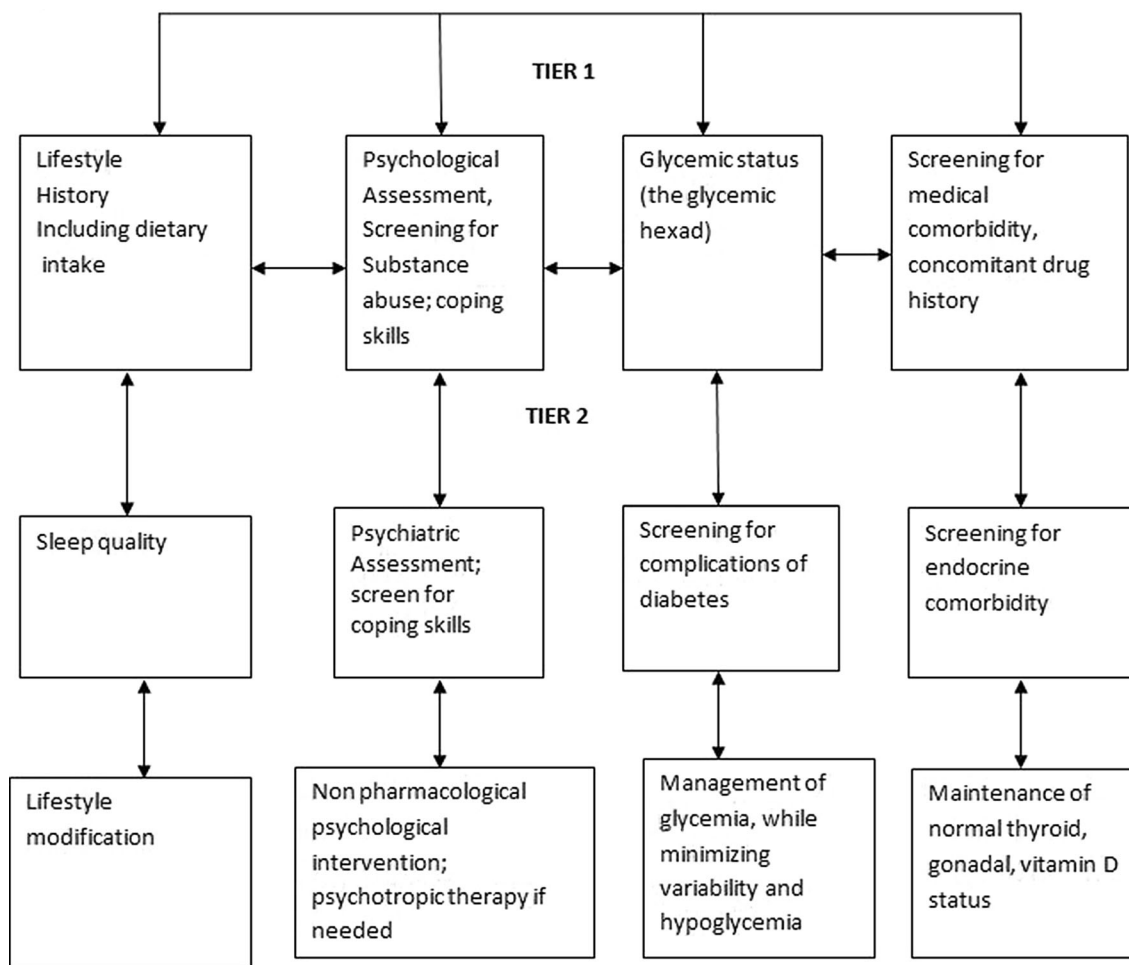


Fig. 2 Approach to diagnosing diabetes fatigue syndrome

evaluates the biomedical and psychosocial causative factors in parallel. Lifestyle- and diet-related factors are evaluated prior to factors related to medical and endocrine dysfunction. Deficiencies of macronutrients, micronutrients, electrolytes, sleep, and exercise, solely or in combination, must be ruled out before further evaluation. While glycemic control is assessed along with screening for diabetic complications, a detailed drug history must be taken to rule out iatrogenic causes of fatigue, such as statins, beta blockers, centrally acting antihypertensives, and diuretics. Fatigue corrected by eating food indicates hypoglycemia, and early morning headache or fatigue may indicate nocturnal hypoglycemia.

A careful history and physical examination may reveal clues which can help in choosing focused investigations to confirm common medical and endocrine diagnoses. Sudden onset fatigue in persons with well-controlled diabetes, accompanied by pallor, and reduction in anti-diabetic drug requirements should prompt investigation for nephropathy and hypothyroidism. Fatigue with breathlessness and inability to exercise in diabetes should prompt investigation for heart failure. Proximal muscular symptoms should prompt assessment for vitamin D deficiency, osteomalacia and Cushing’s syndrome, while predominant neuropathic symptoms suggest a diagnosis of diabetic neuropathy, hypothyroidism or hypoparathyroidism. Fatigue with predominant skeletal

symptoms suggests a diagnosis of hyperparathyroidism, osteomalacia or osteoporosis.

Fatigue with periodicity suggests a diagnosis of dyselectrolytemia or premenstrual syndrome. Fatigue with loss of libido or other sexual dysfunction may suggest a diagnosis of hypogonadism, including menopause or andropause. Psychological morbidity, such as diabetes distress, should be ruled out prior to diagnosing psychiatric conditions.

The astute physician should be able to correlate the patient's symptoms and sign and apply 'good clinical sense' to order relevant investigations. At the same time, DFS is multi-etiological, and the treating physician must take the opportunity to optimize lifestyle, nutritional intake psychological status, and medication usage in persons with fatigue. Table 3 lists some pragmatic suggestions which reinforce this clinical approach.

MANAGEMENT OF DFS

The psychological aspect of DFS can be minimized by effective management of diabetes distress. Diabetes distress occurs due to the person's inability to cope with the demands of life with diabetes. Therefore, its management is best done by following a four pronged strategy: enhancing self-perception, enhancing coping skills, minimizing the discomfort of change, and utilizing external support. An effective coping adjustment with diabetes may help mitigate not only psychological distress, but also psychosomatic symptoms such as fatigue as well.

Lifestyle optimization, including a healthy diet, physical activity regimen, stress control, and a good sleep pattern, will help mitigate fatigue precipitated by unhealthy living habits.

Effective and safe glycemic control, along with maintenance of optimal endocrine, medical, and metabolic function, is necessary to tackle the physical component of DFS. A focus on euglycemia, with minimal hypoglycemia and glycemic variability, is required to ensure efficient mitochondrial function and achieve maximal musculoskeletal efficiency.

SUMMARY

Diabetes fatigue syndrome is defined as a multifactorial syndrome of fatigue or easy fatigability, occurring in persons with diabetes, which may be caused by a variety of lifestyle, nutritional, medical, psychological, glycemia/diabetes-related, endocrine, and iatrogenic factors. Though this communication, we share a pragmatic approach to the identification and management of DFS. We highlight clinically relevant issues which will help improve the quality of care provided to persons with diabetes.

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