Fatigue in Adults with Type 2 Diabetes – An Overview of Current Understanding and Management Approaches

Cynthia Fritschi[1] and Anne M Fink[2]

1. Assistant Professor; 2. Research Associate, Department of Biobehavioral Health Science, University of Illinois at Chicago College of Nursing, Chicago, Illinois, US

Abstract

Patients with type 2 diabetes often experience fatigue, which impacts their self-care and quality of life. There are few data supporting a relationship between fatigue and glucose homeostasis, but fatigue in type 2 diabetes has been associated with higher body mass index (BMI), depression, physical inactivity, sleep disturbances and chronic low-grade inflammation. Although links between fatigue and inflammation are documented in other disease populations, little is known about inflammatory mechanisms specific to type 2 diabetes and associated treatment modalities for type 2 diabetes-related fatigue. Herein we review existing knowledge about fatigue in type 2 diabetes and potential pharmacological and behavioural therapies.

Keywords

Type 2 diabetes, fatigue, inflammation, patient-reported outcomes, symptoms, management

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Correspondence: Cynthia Fritschi, University of Illinois at Chicago College of Nursing (MC 802), 845 South Damen Avenue, Chicago, IL 60612, US. E: Fritschi@uic.edu

Patients with type 2 diabetes commonly experience fatigue, which may be incapacitating and adversely affect self-care regimens.[1–7] Fatigue is a perplexing problem for healthcare providers.[8] Wessely suggests that because fatigue is a non-specific and universal symptom, chronic fatigue is challenging to diagnose and treat.[9] Fatigue researchers do not have a standardised definition, measurement approach, or diagnostic criteria. Diabetes-related fatigue is assumed to correlate with alterations in glucose homeostasis, but few data support this hypothesis.[3,7,10,11] Fatigue in type 2 diabetes may be is associated with higher body mass index (BMI),[1,7,12] the presence of co-morbid conditions,[7,13] depression,[7] physical inactivity,[1,7,14] sleep disturbances[1,15,16] and elevated cytokines.[3,10] Fritschi and Quinn recently provided a detailed review of the correlates of fatigue in diabetes, including conflicting findings regarding the relationship between fatigue and glycaemic control.[8]

Type 2 diabetes is a disorder associated with chronic low-grade inflammation.[17,18] Type 2 diabetes and insulin resistance, especially among obese patients, were linked to an increased production of pro-inflammatory cytokines (e.g., tumour necrosis factor alpha [TNF-α], monocyte chemoattractant protein-1 [MCP-1], interleukin-1β [IL-1β], interleukin-6 [IL-6]) from immune cells as well as increased acute phase reactants (e.g., C-reactive protein [CRP]). Pro-inflammatory cytokines and CRP were associated with high fatigue levels[10,11,19,20] and depression and sleep disturbances in a variety of diseases.[21–24]

There is a considerable gap in the literature, however, about the treatment of fatigue secondary to type 2 diabetes. Anti-inflammatory therapies may ameliorate fatigue with type 2 diabetes. Thus, our discussion of fatigue interventions will focus on the few available pharmacological and behavioural interventions in patients with type 2 diabetes to impact inflammation and fatigue.

Pharmacological Therapy

Pharmacological fatigue therapies are in their infancy. The primary therapeutic target has been reducing symptoms of fatigue, depression, and pain associated with high levels of pro-inflammatory cytokines. Disease-modifying antirheumatic drugs, including etanercept, a TNF-α receptor fusion protein, have been shown to decrease fatigue and improve physical and psychological function in patients with psoriasis, psoriatic arthritis, and rheumatoid arthritis.[25–28]

To date, there are few data regarding pharmacological therapies for inflammation and fatigue in type 2 diabetes. Recent findings from a placebo-controlled, double-blind study of IL-1β antagonism with a monoclonal anti-IL-1β antibody in 30 patients with type 2 diabetes indicated a dose-dependent decrease in fatigue.[3] Anti-inflammatory agents therefore show promise, but further long-term studies are imperative for evaluating the effectiveness and potential for adverse effects. Such agents may place patients with type 2 diabetes at higher risk for infection, and the long-term benefits are unknown. In the place of available pharmacological agents, several behavioural therapies were been associated with reductions in fatigue levels and we discuss these below.

Weight Reduction and Dietary Changes

Fatigue was strongly associated with increased BMI and obesity in both the general population[29–31] and patients with type 2 diabetes.[7,32,33]

Obesity was also correlated with inflammation; however, the data were conflicting about:

- the temporal relationship between obesity, inflammation and fatigue;
- the type of fat (visceral versus subcutaneous) with the most influence on inflammation and fatigue; and
- whether pro-inflammatory cytokines mediate the effects of obesity on fatigue levels or if obesity is the causal factor in fatigue.[34–36]

Whether through reduction in inflammation or simply reduction in fat mass, evidence supports the fatigue-reducing effects of weight loss. Longitudinal data from the Bypass Angioplasty Revascularization Investigation 2 Diabetes Trial (BARI 2D) of 2,163 patients with diabetes and stable ischaemic heart disease who were obese at baseline revealed significant improvements in functional capacity and feelings of energy through weight reduction.[33] High dietary fat-induced obesity has been associated with greater levels of low-grade inflammation, especially increased IL-6 and TNF-α.[37]

Dietary interventions successfully reduced obesity and inflammation, but few investigators measured the concurrent influences on fatigue. A recent study compared the effects on measures of inflammation, BMI and glycaemia of a low glycaemic index (LGI) diet to a high glycaemic index (HGI) diet plus aerobic exercise in obese, insulin-resistant adults.[38] Both interventions resulted in decreased BMI and fasting plasma glucose and insulin levels. Only the LGI diet group had decreased plasma TNF-α, MCP-1, and IL-6 compared to baseline. These data suggest that an LGI diet may have the benefits of both improved glycaemic control and a reduction in systemic inflammation in patients with type 2 diabetes.[38] In a secondary analysis of data from the NHANES cohort, King reported that adults who were obese, had hypertension or diabetes, and consumed high dietary fibre (> 20 g/day) had significantly lower levels of CRP than did those adults who consumed lower fibre.[39] Similarly, Esposito conducted a study of 120 obese, healthy, pre-menopausal women. Half the group was assigned to a reduced-calorie Mediterranean-style diet and exercise and a control group received healthy lifestyle information only. Women in the intervention group consumed fewer calories, less saturated fat and cholesterol and more high-complex carbohydrates, fibre and mono-unsaturated fats compared to the control group. After two years, women in the intervention group demonstrated a significantly greater weight loss and lower insulin resistance compared to those in the control group. In addition, serum pro-inflammatory cytokine levels IL-6 and IL-18 decreased significantly in the intervention group compared to controls.[40] Decreased serum CRP was also measured in adults over age 60 who ate a diet high in omega 3 fatty acids for eight weeks[41] and in adults with type 2 diabetes and nephropathy who replaced 50 % of their meat protein intake with soy protein.[42] The same authors reported a linear relationship between consumption of red meat and increased risks for metabolic syndrome and inflammation.[43]

Modest caloric restriction was also shown to reduce systemic inflammation over time.[44,45] For example, Khoo et al. randomised men with type 2 diabetes to an eight-week very low calorie diet (approximately 1,000 kcal/day) or to a low-fat, low-carbohydrate, high-protein diet (prescribed to reduce intake by approximately 600 kcal/day compared to their usual diet); after eight-weeks all subjects followed the latter diet for another 44 weeks. Interestingly, upon conclusion of the study, only subjects originally assigned to the high-protein, low-fat, low-carbohydrate diet had decreased CRP and IL-6 compared to baseline levels, and significant reductions in these inflammatory molecules were still evident one year later.[44] Both groups, however, experienced significant reductions in weight and blood glucose. In another study, Snel et al. measured the long-term effects of a four-month very low calorie diet with exercise in obese men and women with type 2 diabetes. Although subjects experienced weight loss, there were no significant changes in pro-inflammatory cytokines upon the conclusion of the intervention. At six-month follow-up (after weight loss when subjects resumed a eucaloric diet), however, plasma levels of CRP, interferon-γ (INF-γ), IL-1, IL-2, IL-6, IL-8 and TNF-α were all significantly decreased compared to baseline.[45]

Collectively, the above findings indicate that weight loss, increased consumption of fibre, omega 3 fatty acids and vegetable-based proteins, with reductions in saturated fats and calories may help to reduce low-grade inflammation and some of its associated sickness behaviours, including fatigue. More extreme caloric restriction, however, does not appear to have a beneficial effect on cytokine profiles despite weight loss.

Improved Sleep

Sleep disturbances, including obstructive sleep apnoea (OSA) and disrupted sleep due to restless leg syndrome, nocturia and pain are common in type 2 diabetes and have been associated with a variety of sickness behaviours, including depressed mood, reduced physical activity, excessive daytime sleepiness and fatigue.[46–49] Disturbed sleep has been associated with both poor glucose control[50–52] and obesity. Again, the temporal nature of these relationships has yet to be elucidated; however, there is strong evidence that these phenomena explain only part of sleep issues and are all intertwined with low-grade, systemic inflammation.[21,22,34,53,54] Sleep disturbances, while common in type 2 diabetes, often go undetected. Prevention of nocturia-induced awakenings through improved glycaemic control is the starting point for improving sleep and thus fatigue in type 2 diabetes. In patients with OSA and type 2 diabetes, use of continuous positive airway pressure (CPAP) treatment has been associated with improved sleep parameters, as well as improved glycaemic control,[55,56] which may affect subjective fatigue levels. Bardwell reported that, in patients with OSA, higher levels of depressive symptoms predicted higher fatigue, even after controlling for the OSA,[57] while Hong reported that low physical activity predicted fatigue better than OSA after controlling for BMI in obese individuals.[58] In summary, disturbed sleep is common among patients with type 2 diabetes and may affect fatigue levels either directly or indirectly through higher levels of inflammation alone, or in congruence with obesity, depression, poor glucose control, or physical inactivity.

Exercise

Much evidence supports the positive effects of regular exercise on fatigue and energy.[59] Data from observational studies suggest that low levels of physical activity are associated with higher levels of fatigue in adults with type 2 diabetes.[1,7,14] While there have been no clinical trials of the effects of an exercise intervention on fatigue symptoms in type 2 diabetes, results from exercise trials in both healthy and diverse disease populations have shown that regular exercise may be an effective strategy for decreasing fatigue. Among healthy, sedentary adults with persistent fatigue of unknown origin, six weeks of low-intensity exercise training resulted in decreased fatigue, despite no changes in aerobic fitness level.[60] The largest body of evidence in support of exercise therapy in reducing fatigue comes from the cancer literature. A recent meta-analysis of exercise interventions aimed at decreasing fatigue among cancer patients and survivors showed that regular exercise, especially aerobic exercise, resulted in significantly decreased levels of fatigue.[61] The physiological mechanisms underlying these effects were not elucidated; however, both cancer and type 2 diabetes are associated with higher levels of inflammatory cytokines and exercise may have anti-inflammatory properties.[62,63] In overweight patients with type 2 diabetes, participation in aerobic training interventions lasting six months and 12 weeks, respectively, resulted in reduction in cytokines (e.g., IL-6 and IL-18) despite participants' having no significant weight loss exercise.[64,65] The effects of physical activity on the cytokine profile may be related to the particular exercise modality. In a four-group, randomised, controlled trial, Balducci and colleagues compared biomarkers among patients with type 2 diabetes randomised to a sedentary group, a lifestyle counselling group, an aerobic training group and an aerobic training plus strength training group.[66] The most noteworthy differences were found in the latter mixed-training group who had significantly decreased serum levels of CRP, IL-1β, TNF-α, and INF-γ compared to baseline. In addition, cytokines with anti-inflammatory properties – IL-4 and IL-10 – were also increased compared to baseline in the mixed-training group. These alterations in the cytokine profile support the American Diabetes Association and American College of Sports Medicine recommendation for patients with type 2 diabetes to incorporate both aerobic and conditioning exercises into their exercise programmes.[67]

Summary

Fatigue associated with type 2 diabetes has multiple causal factors and the pathophysiological mechanisms are poorly understood. Low-grade inflammation, however, may be a key mechanisms that can be ameliorated by dietary and exercise interventions. Pharmacotherapeutics may reduce inflammation, and therefore fatigue and this area requires further research. Lifestyle interventions resulting in weight loss, improved detection and treatment of sleep disorders and depression, and inclusion of regular physical activity, including both aerobic and strength-training components, may reduce fatigue in patients with type 2 diabetes. ■

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