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Original article

Flavonoid rich dark cocoa may improve fatigue in people with multiple sclerosis, yet has no effect on glycaemic response: An exploratory trial

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SUMMARY

Context: Current research suggests that dark cocoa may reduce fatigue; however, the effect on fatigue in people with MS (pwMS) has never been established. The objective of this feasibility study was to explore the acute effect of high flavonoid cocoa on measures of fatigue and glycaemic response.

Methods: This was a randomised crossover participant blind exploratory study in 12 participants (2 male and 10 female) with MS-related fatigue (>4 on the Fatigue Severity Scale; FSS). After fasting overnight, participants consumed the high flavonoid cocoa drink (350 mg gallic acid equivalents {GAE}/g) or a low flavonoid cocoa control (120 mg GAE/g), consuming the alternative drink on the next visit. Fatigue was self-reported on a 100 mm visual analogue scale at 30-min time intervals for 2 h post cocoa consumption and every 2 h for the rest of the day. Fatigability was monitored using a 6 min walk test (6MWT) at the end of the visit (2 h), and activity monitors worn for 24 h commencing at 12 noon on the day of testing. The feasibility of performing the trial including outcome measures was documented.

Results: A moderate effect was found in self-reported fatigue throughout the day in favour of the high flavonoid group (Cohen's *d* 0.32, 95% non-central t CI −0.57 to 1.20). Fatigability measures did not change. Participants consumed and enjoyed the cocoa, all participants completed the study and outcome measures were accepted.

Conclusion: The results of this study support further trials to investigate the feasibility and efficacy of pure cocoa as a dietary supplement for fatigue in pwMS.

1. Introduction

Fatigue is one of the most debilitating symptoms in people with Multiple Sclerosis (pwMS), greatly affecting quality of life [27]. The exact cause of fatigue in MS is unknown, however various mechanisms may influence fatigue severity.

Foods rich in flavonoids may show potential for reducing fatigue, through several proposed mechanisms. There is currently available evidence that suggests oxidative stress may contribute to the pathology in MS, which in turn may be improved or inhibited by the antioxidant properties in flavonoids [28]. In addition, it has been suggested that the functional properties of flavonoids allow for penetration through the blood–brain barrier, potentially leading to improved neurosignaling, as well as rehabilitation of neuronal function [26]. A pathological inflammatory response may be responsible for the fatigue experienced in MS, for example TNF-alpha levels have been found to be elevated in fatigued pwMS compared to those who were non fatigued [4]. Luteolin, a naturally occurring flavonoid, has been found to benefit the disease course of pwMS, for example by inhibiting activated peripheral blood leukocytes and mast cells and mast cell dependent T cell activation. Katz et al. [15] suggest that cocoa may be beneficial towards MS remission as its flavonoid content may promote blood flow to the brain, and may therefore lead to additional nerve repair, better metabolic clearance from the brain and greater oxygen availability.

Abbreviations: BG, blood glucose; GR, glycaemic response; VAS, visual analogue scale; GAE, gallic acid equivalents; pwMS, people with multiple sclerosis; FFQ, food frequency questionnaire; BI, Barthel Index; FSS, fatigue severity scale.

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Therefore foods containing flavonoids may be used in conjunction with other disease modifying treatments (DMTs) in pwMS to reduce relapses and improve the severity of the symptoms experienced.

Cocoa is rich in flavonoids and is a popular and easily accessible product. A recent systematic review and meta-analysis investigated 42 randomized control trials, and found cocoa to be significantly beneficial for vascular endothelial function and inflammation [14]. Cocoa has been shown to improve fatigue in people with Chronic Fatigue Syndrome (CFS). Sathyapalan et al. [24] conducted a double blinded, randomised, pilot crossover study, daily providing participants with 45 g of high flavonoid chocolate. After eight weeks participants reported significant reductions in fatigue and disability. Poor sleep quality has previously been shown to be significantly correlated with fatigue in MS [2]. Flavonoids have also been shown to improve sleep quality and therefore may reduce daytime fatigue in those with MS [21].

Flavonoid rich foods have also been shown to influence postprandial blood glucose levels [7]. Glucose tolerance may be altered in pwMS [18,29] and an association has been found between the availability of glucose to the brain and perceived fatigue [22]. This has therefore raised the question as to whether improved glucose tolerance may reduce the fatigue experienced in those with the disease. However to date there has been no exploration of the response in this group.

The current randomised crossover exposure response participant blind exploratory study will assess the effect of high flavonoid cocoa versus low flavonoid cocoa on fatigue and fatigability as measured by mobility in pwMS. Glycaemic response (GR) after the consumption of the drink, was also measured.

2. Method

This was a randomised crossover participant blind exploratory study in 12 participants (aged 54 ± 10.56 years, 2 male and 10 female) with MS-related fatigue. Participants were expected to attend two test visits at Oxford Brookes University and in a randomised order (determined electronically by a random number table) consumed either the low flavonoid control or the high flavonoid cocoa on different days, with at least three days between test visits (Fig. 1). The present study was approved by the Oxford Brookes University Research Ethics Committee: UREC Registration No: 150938. All procedures were carried out accordingly to Declaration of Helsinki guidelines and policies, and retained data was managed accordingly to the Oxford Brookes University's policy on Academic Integrity.

2.1. Procedure

PwMS were recruited from local support groups throughout the Thames Valley and via advertisements posted at Oxford Brookes University. After expressing interest in the study, participants were provided with the study information sheet and were given a minimum of 24 h to review the information and ask the researchers any questions regarding the trial. Once potential participants agreed to take part in the trial and after initial eligibility was checked over the phone, a combined screening and first test visit was arranged where signed consent was taken.

Participants were asked to keep a 24 h food diary the day before each visit, and to repeat this diet before the next test day. In addition to reduce variability in testing, participants were also asked to avoid vigorous exercise, and to limit their alcohol and caffeine intake on the day prior to testing (≤2 units and ≤3 cups respectively). Additionally, participants were asked to fast overnight for 10–12 h prior to visits, which began between 7 and 10 am, and on the first assessment visit a health questionnaire was administered (asking about smoking habits, current or previous diseases, current medication or supplement intake, dietary habits).

2.2. Screening and descriptive data

At the screening/first test visit demographics were recorded including MS subtype, compliance with the fasting protocol, blood pressure (mmHg) was recorded and mean fasting blood glucose (BG) was measured. Participant independence in daily living was assessed using the Barthel Index (BI; [20]). Each test occasion lasted no longer than 3 h, and participants were required to leave a minimum of 24 h between test days.

2.3. Participants

Participants were excluded if they reported any sudden changes in MS symptoms within the last three months, had a change in their DMTs and/or medications that could influence fatigue in the past three weeks, had a metabolic disease or were presently on medication interfering with insulin or glucose metabolism, had been diagnosed with a condition other than MS affecting the CNS, had an allergy or intolerance to ingredients used during testing, experienced fatigue from any condition other than MS, were pregnant or lactating, were clinically depressed, had a BMI outside 18.5–30 kg/m^2 (body composition was confirmed using Tanita BC-418MA), had impaired glucose tolerance (7.8–11.1 mmol/l), or had a fatigue severity score less than 4 on the Fatigue Severity Scale (FSS; [17]). This scale asks nine questions about various aspects of perceived fatigue, 1 = not fatigued at all and 7 = very fatigued with a global fatigue score ranging from 1 to 10 (1 = not fatigued at all and 10 = very fatigued).

2.4. Acute response to flavonoid drink/intervention

Participants were randomly administrated a high polyphenol test or low polyphenol control cocoa drink (Table 1), to consume within a maximum time of 15 min. Drinks were matched as closely as possible for available carbohydrate (avCHO) and energy content. Due to the idea that pwMS are following the Overcoming Multiple Sclerosis (OMS) diet, which excludes diary from the diet, the drink was made with Alpro rice milk (Tesco, UK). The total polyphenol content of the drinks had previously been established [23], with the high flavonoid cocoa powder containing 350 mg gallic acid equivalents (GAE)/g, whilst the low flavonoid control powder had instead been established to contain 120 mg GAE/g.

2.5. Fatigue VAS

Fatigue was recorded on a horizontal 100 mm VAS every 30 min following drink consumption and throughout testing, categorizing 0 mm as ‘not at all fatigued’ and 100 mm as ‘extremely fatigued’ [16]. Participants continued to record fatigue every 2 h after testing was completed, until 6 h after leaving the lab.

2.6. Fatigability

Fatigability was monitored using a 6 min walk test (6MWT) performed at the end of the visit (2 h), and through activity monitoring.

2.7. Activity monitoring

A GENEActiv (Geneactive, UK) was used to record physical activity for a 24 h period. Data was sampled at 100 Hz at a ±8 g range at 3.9 mg resolution and recorded from the non-dominant wrist. Post measurement, data was epoched to 1 s samples and analysed