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Consumption of a whey protein-enriched diet may prevent hepatic steatosis associated with weight gain in elderly women

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Abstract *Background and aims:* Protein consumption has been associated with cardio-metabolic benefits, including weight loss and improved insulin sensitivity, and may have potential benefits for individuals with fatty liver disease (FLD). We investigated the effect of increasing dietary protein intake from whey relative to carbohydrate on hepatic steatosis.
Methods and results: A two-year randomized, double-blind, placebo-controlled trial of 30 g/day whey protein-supplemented beverage (protein) or an energy-matched low-protein high-carbohydrate beverage (control) for cardio-metabolic and bone health in 219 healthy elderly women, recruited from the Western Australian general population. Hepatic steatosis was quantified using computed tomographic liver-to-spleen (L/S) ratio. FLD was defined as liver-to-spleen difference <10 Hounsfield units. At baseline, FLD prevalence was 11.4%. Control and protein groups were similar in body mass index (BMI), insulin resistance, L/S ratio and FLD prevalence at baseline. At two-years, dietary protein increased by 20 g in the protein, but not the control, group. Total energy intake and physical activity remained similar between groups. At two-years, BMI and FLD prevalence increased in both groups, with no between group differences. L/S ratio increased in control, but not protein, group at two-years, with no between group differences. In a within group comparison, change in BMI correlated with changes in L/S ratio in control ($r = 0.37$, $P = 0.0007$), but not with protein group ($r = 0.04$, $P = 0.73$).
Conclusion: Increasing dietary protein intake from whey relative to carbohydrate does not reduce weight, hepatic steatosis or the prevalence of FLD in elderly women. However, it may prevent worsening of hepatic steatosis associated with weight gain.
Clinical trials registration: Australian New Zealand Clinical Trials Registry (Registration no. ACTRN012607000163404).

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Introduction

Fatty liver disease (FLD) encompasses a histological spectrum ranging from simple steatosis to steatohepatitis and is most commonly due to insulin resistance associated with excess adipose tissue accumulation [1–3]. FLD can be found in all age groups; however, the prevalence appears to increase with age, peaking in the sixth and seventh decade [4]. It is, therefore, commonly observed in the elderly and is more likely to be present in females than males after the age of 70 [5]. FLD is associated with an increased risk of cardiovascular disease, diabetes and liver-related complications, the latter predominantly observed in patients with steatohepatitis [5–7]. Consequently, FLD is associated with higher mortality rates than that of the general population [8].

Lifestyle intervention with diet and exercise-induced weight loss improves cardio-metabolic risk profile in FLD, with weight loss $\geq$7% associated with improved liver histology [9]. However, this is achieved in $<$50% of FLD patients, with weight re-gain a common occurrence [10]. Moreover, co-morbidities such as osteoarthritis and ischemic heart disease commonly observed in elderly FLD patients often limit the utility of exercise interventions [8]. Alternative strategies that are safe and effective are, therefore, required.

Beyond traditional macronutrients, dietary supplements may play a role in managing cardio-metabolic risk and liver complications in FLD [11,12]. Emerging evidence from short-term intervention studies in humans suggests that consumption of protein sourced from whey, a milk protein [11,12], may induce weight loss, improve insulin sensitivity and lower plasma lipids [13,14]. In addition, studies in animal models of FLD report that whey protein consumption may improve liver biochemistry and histology [15–17]. Notably, a recent rodent study reported that when all macronutrients except for protein quality (whey *versus* casein) were matched, whey protein consumption reduced liver triglyceride content and inhibited expression of genes that regulate fatty acid metabolism [18]. Of interest, these effects were most pronounced at the highest protein to carbohydrate ratio [18], pointing to a potential role for increasing dietary protein intake from whey relative to carbohydrate in FLD. Whey protein is also relatively inexpensive and well-tolerated with few side-effects [12]. Taken together, whey protein may represent an attractive treatment option for subjects with FLD and merits investigation.

Therefore, the objective of the present study was to investigate the long-term effects of increasing protein intake from whey relative to carbohydrate on hepatic steatosis in elderly women. We also examined the effects increasing protein intake relative to carbohydrate on plasma glucose and insulin concentrations. This study was initially performed as a prospective randomized placebo-controlled trial examining the impact of increasing dietary protein intake from whey relative to carbohydrate on metabolic and bone health in elderly women aged between 70 and 80 years of age [19]. This population was targeted due to the high risk of osteoporosis and metabolic diseases. We hypothesized that increasing protein intake from whey would lead to beneficial changes in hepatic steatosis and body weight, and plasma glucose and insulin concentrations. We also explored associations between hepatic steatosis and body weight.

Methods

Study design

The study was a two-year randomized, double-blind, placebo-controlled trial [19]. Study participants were recruited from the general population between April and September 2007 [19]. A population-based approach was used in which a random selection of women aged 70–80 years on the electoral roll in Western Australia received a letter inviting them to join the study (n = 6055). Over 98% of women of this age are on the Western Australian electoral roll. Of the 829 women who responded to the letter, 256 attended clinic screening and 219 women who met the inclusion criteria joined the study. The present study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Sir Charles Gairdner Hospital Human Research Ethics Committee. Written informed consent was obtained from all subjects. The study was registered with the Australian New Zealand Clinical Trials Registry (Registration no. ACTRN012607000163404). Eligible participants were randomized to one of two treatment groups: protein or control. Group allocation was achieved using a computer-generated randomization sequence with a block size of 10 to assign participants to protein or control in a ratio of 1:1.

Supplements

Participants consumed 250 mL/day of their assigned supplement (beverage) [19]. The 250 mL high-protein (protein) beverage provided 30 g of protein, 2 g of fat, 600 mg of calcium and 3.2 kJ/mL (810 kJ). The 250 mL low-protein (control) beverage provided 2.1 g of protein, 2 g of fat, 600 mg of calcium and 3.3 kJ/mL (820 kJ). The dose of 30 g protein in a single meal was selected to maximize effects on metabolic and bone health, while cognizant of total energy intake. This dose is consistent with current recommendations for optimal dietary protein intake in older individuals [20]. The base product for both beverages was skimmed milk. The high-protein product had whey protein isolate (Alacen 894; Fonterra Brands Limited, Palmerston North, New Zealand) added. Consequently, the exact amount of whey protein intake was 27.1 g per 250 mL high-protein beverage. Carbohydrate (maltodextrin) was used in the low-protein (control) beverage to match for the energy. Alginate natural flavoring and natural emulsifying agents were used to provide a similar texture and flavor to the drinks. The supplements were provided to participants as a powder that was reconstituted to 250 mL with cold water before consumption. Each participant received 36 tins of drinking powder (500 g per tin) each year. To aid compliance, the participants were provided with a diary where they record the consumption of the product. The diary was returned to the