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Associations of dietary protein intake with bone mineral density: An observational study in 70,215 UK Biobank participants

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ABSTRACT

Purpose: Adequate dietary protein intake is important for the maintenance of bone health; however, data in this area is ambiguous with some suggestion that high protein intake can have deleterious effects on bone health. The aim of the current study was to explore the associations of protein intake with bone mineral density (BMD).
Methods: We used baseline data from the UK Biobank (participants aged 40–69 years) to examine the association of protein intake with BMD (measured by ultrasound). These associations were examined, in women (n = 39,066) and men (n = 31,149), after adjustment for socio-demographic and lifestyle confounders and co-morbidities.
Results: Protein intake was positively and linearly associated with BMD in women (β-coefficient 0.010 [95% CI 0.005; 0.015, p < 0.0001]) and men (β-coefficient 0.008 [95% CI 0.000; 0.015, p = 0.044]); per 1.0 g/kg/day increment in protein intake, independently of socio-demographics, dietary factors and physical activity.
Conclusions: The current data have demonstrated that higher protein intakes are positively associated with BMD in both men and women. This indicates that higher protein intakes may be beneficial for both men and women.

1. Introduction

The current dietary recommendation for protein intake is for all adults to consume 0.8 g of protein per kg body mass per day (g/kg/day) [1,2]. There is a wealth of research which has suggested that higher protein intakes may be beneficial for the maintenance of muscle mass [3,4], due to protein's anabolic properties [5]. Furthermore, higher protein intakes have been suggested for weight loss due to proteins ability to reduce hunger and promote fullness [6], mitigate reductions in fat-free mass and resting energy expenditure, and augment reductions in plasma triglycerides and blood pressure [7,8]. There have, however, been some concerns that diets high in protein could result in bone mineral depletion – the acid-ash hypothesis which has contributed to the popularity of the so-called "alkaline diet". According to this hypothesis, diets which result in the metabolic production of acid, such as high protein diets, result in demineralisation of the skeleton and an increase in urinary calcium excretion [9]. The data in support of this hypothesis are limited.

Indeed, systematic review of randomized trials and observational studies found no support for the acid-ash hypothesis [10]. On top of this a meta-analysis of randomized trials and prospective cohort studies did not indicate any differences between high and low protein diets in and their associations with BMD and/or bone mineral content loss over time [11]. It is worth noting that in this meta-analysis the conclusions were limited by the clear heterogeneity in the studies in terms of study design, doses, durations and outcomes, as acknowledged by the authors. A more recent meta-analysis concluded that data tentatively supports the hypothesis that protein intakes above the current recommendations may be beneficial for BMD [12], although again limitations in the data were noted including a high level of heterogeneity. Interestingly some data from a small cohort (n = 2919) has indicated that the relationship between protein and bone may not be the same between sexes, with higher protein intakes being of benefit to women but detrimental to men [13]. Further work, in a larger cohort, is required to determine if

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the associations between protein intake and BMD differ by sex. The UK Biobank data allows us to test the association between protein intake and BMD in the largest cohort studied which also allows us to investigate potential sex differences in associations.

The aim of the current study, therefore, was to explore the associations of reported protein intake with BMD in UK Biobank, a large general population cohort study of participants aged 40–69 years.

2. Methods

2.1. Study design

UK Biobank is a large, population cohort study. Between 2007 and 2010, 502,628 participants, aged 40–69 years, were recruited and participated in baseline assessments at 22 centres across England, Scotland and Wales. Detailed information was obtained via a self-completed, touch-screen questionnaire and face-to-face interview, and trained staff undertook a series of measurements using standard operating procedures. The main outcome measured in this study was BMD. The independent predictor variable of interest was daily protein intake (g/kg/day). We chose to express protein intake in g/kg/day as these are the units in which current recommendations are given. Socio-demographic factors (age, ethnicity and area-based socioeconomic deprivation index), smoking status, body weight, physical activity, grip strength, sedentary behaviour, total energy intake, and dietary intake (total energy, alcohol, fruit and vegetable, calcium and potassium) were treated as potential confounders.

2.2. Study procedures

Dietary information was collected via the Oxford WebQ; a web-based 24 h recall questionnaire which was developed specifically for use in large population studies and has been validated against an interviewer-administered 24 h recall questionnaire [14]. The Oxford WebQ derives energy intake (total and from specific macronutrients) from the information recorded in McCance and Widdowson's, The Composition of Food, 5th edition [15]. For participants who completed more than one online dietary questionnaire, mean values were calculated from all of the information provided. Implausibly low or high energy intakes were defined as < 1.1 times basal metabolic rate (calculated according to Henry equation [16]) ($1.1 * \text{BMR}$), and > 2.5 times basal metabolic rate respectively; the latter being the upper limit of sustained energy expenditure defined by the Scientific Advisory Committee for Nutrition [17]. These participants were excluded from analyses (n = 12,189).

Heel BMD was measured, by trained staff, via ultrasound densitometry (Sahara bone sonometer) using the following formula:

$$\text{BMD} = 0.002592 \times (\text{BUA} + \text{SOS}) - 3.687\ \text{g/cm}^2$$

where BUA is the broadband ultrasound attenuation (dH/MHz) and SOS is the speed of sound (m/s). Single left and right calcaneus measurements were taken and the average used in analysis. The sonometer was turned on for at least 1 h prior to any measurements, with a quality control (QC) phantom inserted and the system QC procedures followed at this point. Further details are available on the UK Biobank Website (http://www.ukbiobank.ac.uk).

Height was measured to the nearest centimetre (cm) using a Seca 202 height measure. The duration of light, moderate and vigorous physical activity undertaken over the previous 7 days was self-reported using the International Physical Activity Questionnaire (IPAQ), as described previously [18]. In addition, participants were asked three questions: 'In a typical day, how many hours do you spend watching TV, using a PC, and driving?', and the combined figure was used as a proxy for overall sedentary behaviour [18]. Grip strength was measured as previously described [19] and the mean of the right and left values was expressed in absolute units (kg) for subsequent analysis. Ethnicity was self-reported and categorized into: white, South Asian, black, Chinese, other and mixed. Smoking status was self-reported and classified as: never, former and current. Area-based socioeconomic status was derived from postcode of residence using the Townsend score [20]. Medical history, including menopause status, was collected from the self-completed baseline questionnaire. Further details of these measurements can be found in the UK Biobank online protocol (http://www.ukbiobank.ac.uk).

2.3. Statistical analyses

Of the 321,778 people with BMD data we excluded from all analyses individuals who reported any of the following conditions (Chronic Obstructive Pulmonary Disease, chronic asthma, chronic liver diseases, cancer, alcohol problems, substance abuse, eating disorders, sleep apnoea, schizophrenia, cognitive impartment, Parkinsons, dementia, chronic pain syndrome, heart diseases, rheumatoid arthritis, other inflammatory polyarthropathies, osteoporosis, and those who indicated they were unable to walk) and restricted analysis to those who also had data on all co-variates (n = 70,215) (Supplementary Fig. S1).

All analyses were performed stratified by sex. Firstly, to explore a possible linear association between protein intake and BMD, protein intake was first modelled as a continuous variable and changes in BMD were estimated per 1 g/kg/day higher protein intake. Secondly, to explore a potential non-linear dose-response relationship between protein intake and BMD, protein was categorized into < 0.8 g/kg/day, 0.8–1.2 g/kg/day, 1.2–1.6 g/kg/day, 1.6–2.0 g/kg/day and > 2.0 g/kg/day. Associations of protein intake (continuous or categorical variable) with BMD were investigated using regression analysis. The following statistical adjustments were made: model 0 = unadjusted; model 1 = adjusted for age, ethnicity and Townsend score; model 2 = model 1 + adjusted for smoking, body weight, physical activity, grip strength, sedentary behaviours and dietary intake (total energy, alcohol, fruit and vegetable, calcium and potassium). As a sensitivity analysis, the associations (models 0–2) were performed again but including participants with the aforementioned conditions and adjusted for these as covariates in model 2.

We investigated whether the associations of protein intake with BMD differed by sex by performing a 2-way interaction analysis and fitting a protein*sex term into our model. We then investigated whether the associations of protein intake with BMD differed by sex and other factors by performing a 3-way interaction analysis and fitting a protein*sex*age or physical activity or smoking term into our model. In women only, we investigated whether the associations of protein intake with BMD differed by menopausal status by performing a 2-way interaction analysis by fitting a protein*menopausal status term into our model. We also investigated whether there were interactions between protein intake and calcium intake by performing a 2-way interaction analysis by fitting a protein*calcium intake term into our models.

3. Results

The baseline characteristics of the participants are presented in Table 1 (by sex in Supplementary Tables 1 and 2) by categories of protein intake and sex. Overall those with higher protein intakes were younger, had lower body weight, were more active and less sedentary, have higher energy, calcium and potassium intake, and more likely to be of non-white ethnicity and never to have smoked.

No interaction ($p = 0.082$) between protein intake*sex on BMD was observed but due to clear sex differences in BMD all analysis was carried out stratified by sex. Within women no interaction ($p = 0.319$) between protein intake*menopausal status on BMD was evident. No interactions were observed between protein intake and calcium (males: $p = 0.939$ and females: $p = 0.440$).

When protein intake was treated as a continuous variable in our model 0 (unadjusted) and model 1 (sociodemographic adjustment)