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Title: Effect of calcium intake on fat oxidation in adults: a meta-analysis of randomized, controlled trials

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Conflicts of interest: None

Summary

Calcium intake is likely to increase body fat loss during energy restriction. Part of this effect may be explained by increased fat oxidation in the presence of a similar energy balance, yet studies have not provided a conclusive answer. Therefore a meta-analysis was performed to determine whether chronic or acute high-calcium intake increases fat oxidation. Randomized, controlled trials of high-calcium intake in human adults where measures of fat oxidation were taken were included. A random-effects meta-analysis was performed on outcomes expressed as standardized mean differences.

Chronic high-calcium intake increased fat oxidation by a standardized mean difference of 0.42 (95% confidence intervals: 0.14, 0.69; $P = 0.003$; estimated to correspond to an 11% increase), displaying low heterogeneity ($I^2 = 18\%$) which was more prominent when habitual calcium intake was low ($< 700 \text{ mg d}^{-1}$). Acute high-calcium intake increased fat oxidation by a standardized mean difference of 0.41 (0.04, 0.77; $P = 0.03$), with low heterogeneity ($I^2 = 19\%$), yet sensitivity analysis revealed that this effect was relatively weak. In conclusion, chronic high-calcium intake is likely to increase rates of fat oxidation. The effects of acute high-calcium intake appear to point in the same direction but further work is needed to permit a greater degree of certainty.

Introduction

Calcium intake has been inversely associated with BMI and body fat content (1-15), although not all studies have demonstrated a significant relationship (16-19).

Intervention trials have provided variable results, and a meta-analysis concluded that when adjusted for baseline body mass, calcium supplementation does not appear to influence body mass (20). Yet, a benefit of calcium supplementation may have been

hidden by biases introduced by weak allocation methods, as suggested by the authors (20). The only study identified, which was explicitly designed and powered to determine the impact of calcium supplementation on body mass was Zemel *et al.* (21). This study demonstrated that a high-dairy calcium, energy-restricted (~500 kcal) diet for 24 weeks augmented fat loss by ~2.4 kg and body mass loss by ~4.5 kg compared to a low-calcium control group.

Three major mechanisms have been proposed to play a role in the relationship between calcium and fat/body mass, for a recent review see Soares *et al.* (22). It is likely that dietary fat absorption is impaired when consumed in conjunction with calcium, as insoluble calcium soaps are formed with free fatty acids and/or bile which reduces the efficiency of fat absorption (23-29). A meta-analysis has confirmed this hypothesis (30), and suggested that increasing the calcium content of the diet by 800-6000 mg d⁻¹ would result in additional fat excretion of ~2g d⁻¹, equating to 0.7 kg y⁻¹. Calcium intake may also exert some control on appetite. Suggestions have been made based on animal models that calcium deficiency results in “calcium seeking” behavior which may result in increased energy intake. Whereas, if calcium sufficiency is maintained under energy restriction, then individuals are less likely to seek out additional energy (31). This is an area with great scope for future work, and recent human studies support a modest effect (32-34).

Calcium intake suppresses parathyroid hormone (35) and 1,25-dihydroxyvitamin D (36) concentrations. It is thought that lower concentrations of these hormones can increase lipolysis and attenuate lipogenesis in adipocytes thereby increasing fatty acid availability for oxidation (37, 38). It is also well known that calcium signaling is involved in mitochondrial biogenesis (39) and 1,25-dihydroxyvitamin D₃ has been shown to reduce mitochondrial mass and palmitate oxidation in myocytes (40, 41),

providing a pathway through which calcium intake may influence fat oxidation in muscle.

Increasing fat utilisation may confer some protection against obesity/adiposity, since lower rates of fat oxidation (independent of energy expenditure) are associated with weight gain (42), and higher rates of fat oxidation with weight loss following exercise training (43).

There has been some research interest in the effects of calcium intake on fat oxidation in humans (9, 24, 25, 34, 44-48), yet results have been equivocal possibly due to the variety of doses and types (supplemental vs. dairy products) of calcium intake and/or the participant characteristics (habitual calcium intake, age, sex and BMI). The time-course of the putative effects of calcium are also unclear. Changes in parathyroid hormone concentrations occur within 60 min of calcium ingestion (49), yet partly as there is no concrete evidence of the mechanisms involved, the delay between intake and changes in metabolism is not known. As such, it is pertinent to investigate whether a single bolus of calcium can affect fat oxidation, or whether supplemental loading over a period of days/weeks is necessary to alter substrate oxidation. Accordingly, the aim of this study was to perform a meta-analysis of randomized, controlled trials to investigate the effectiveness of both chronic (more than 24 h) and acute (single-meal) calcium supplementation on fat oxidation in adult humans.

Methods

Identification of relevant studies

Medline and the Cochrane Central Register of Controlled Trials were searched for English-language studies reporting the effects of both chronic and acute calcium intake on fat oxidation. Databases were searched up to February 2012 with the

following keywords: calcium, dairy, fat oxidation, lipid utilization, macronutrient oxidation. References from retrieved articles were used to identify further potentially suitable articles.

Inclusion and exclusion criteria

Studies were included in the review if : (i) they were of crossover design or included a control group; (ii) calcium intakes differed by more than 200 mg between intervention and control using either supplements or dairy products; (iii) participants were randomly assigned to the order of intervention or group; (iv) the study had been peer-reviewed, (v) fat oxidation was measured at rest for at least 30 min. Studies were excluded if: (i) meals/diets were not isoenergetic or macronutrient-matched; (ii) studies did not use adult humans. Acute studies were defined as ingestion of a single high-calcium meal, whereas chronic studies were defined as an increase in calcium intake for longer than 24 h.

Data abstraction

A standardized data extraction form (Microsoft Excel® spreadsheet) was used to accumulate data and included: (i) Characteristics of articles valid for review, (ii) The Cochrane Collaboration's tool for assessing risk of bias and (iii) outcome data suitable for successive analyses which included the rate of fat oxidation, standard deviation or standard error of the mean and the sample size for intervention and control groups. Also collected were data in trial design (crossover/parallel), participant characteristics (age, sex, BMI, habitual calcium intake), the type of intervention (dosage and duration of calcium supplementation, supplement/dairy), the

period of fat oxidation measurement and the principal conclusions of the authors regarding fat oxidation.

The Cochrane Collaboration's tool for assessing risk of bias was applied by assessing the following for each intervention: randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, attrition bias, reporting bias and other bias (including funding and conflicts of interest). Each component was provided with a high, unclear or low risk of bias and ascribed A, B and C, respectively (<http://www.cochrane-handbook.org/>). This was performed independently and in duplicate by J.T.G. and P.L.S.R.

Statistical analysis

Missing standard deviations were calculated from standard errors (50). Absolute outcome measures were converted into the standardized mean difference (SMD; μ experimental – μ control/ σ) with 95% confidence intervals (CI) and were used as the summary statistic. The SMD expresses the size of the treatment effect relative to the variability observed in that trial. A random-effects meta-analysis (51) was employed to estimate between-study variance (τ^2) using Review Manager (RevMan) 5.1.4 (The Cochrane Collaboration). Heterogeneity between trials was assessed using the χ^2 statistic with the significance level set at $P < 0.10$ and the I^2 value where 0-40% suggests heterogeneity might not be important, 30-60% may represent moderate heterogeneity, 50-90% may represent substantial heterogeneity and 75-100% represents substantial heterogeneity (52, 53). Publication bias was examined by funnel plots. Subgroup analyses were also performed for supplementation only, and dairy only. To examine whether conclusions concerning calcium intake and fat

oxidation depend on a single study, sensitivity analyses were employed by repeating the analyses with each study omitted, in turn.

Results

Results of the search

Twenty-nine potentially relevant papers were initially located (Figure 1). Of these, six were review papers and therefore did not provide novel data, three were not performed in adult humans (cellular/animal models; adolescents), two were published as conference proceedings only, a further two used multivitamin and mineral supplements rather than increasing calcium intake alone, whilst one was a cross-sectional study. Therefore the remaining fifteen studies were examined in detail. Of these, four did not meet the criteria set for fat oxidation measurement whilst two did not meet dietary criteria. The eight studies outstanding were included in the review (24, 34, 44-48, 54). These included studies based on chronic (Table 1) and acute (Table 2) calcium intake, providing a total of 12 and 8 comparable conditions, respectively. Where studies used more than one experimental condition (eg. high vs. low calcium in energy balance or energy deficit, differing dosages/sources of calcium), separate effect size estimates were generated.

The meta-analysis of chronic studies included a total of 94 participants (30 males and 64 females). Calcium intakes ranged from 350 to 673 mg d⁻¹ on control/placebo trials compared to a range of 986 to 2500 mg d⁻¹ on experimental trials and the range of duration of the interventions were from 7 d to 1 y.

The meta-analysis of acute studies included a total of 38 participants (10 males and 28 females). Calcium intakes ranged from <100 mg to 248 mg on control trials,

compared to a range of 531 to 543 mg on experimental trials. The range of the duration of the measurement period in acute studies was 4 to 6 h.

Chronic intake

Chronic high-calcium intake resulted in an increase in rates of fat oxidation compared to control/placebo (Figure 2) with a SMD of 0.42 (95% CI: 0.14, 0.69; $Z = 3.00$; $P = 0.003$). The degree of heterogeneity was relatively low ($I^2 = 18\%$) and removal of any individual study did not impact on the significance of the results with effect sizes ranging from 0.33-0.50 (All $P < 0.02$). The weighted mean increase in calcium intake was 958 mg and resulted in an 11% (95% CI: 4-18%) increase in fat oxidation vs. placebo/control. When separate analyses were performed, it became apparent that the supplemental sources were more effective than dairy with SMDs of 0.58 (95% CI: 0.12, 1.04; $Z = 2.47$; $P = 0.01$) and 0.35 (95% CI: 0.00, 0.71; $Z = 1.95$ $P = 0.05$), respectively. Habitual calcium intake also influenced the efficacy of the interventions with low ($< 700 \text{ mg d}^{-1}$) habitual calcium intake demonstrating an effect size of 0.78 (95% CI: 0.22, 1.33; $Z = 2.47$; $P = 0.006$) whereas those with higher ($> 700 \text{ mg d}^{-1}$) habitual intakes showed an effect size of 0.25 (95% CI: -0.05, 0.54; $Z = 1.66$; $P = 0.1$). Three outcomes were studied under energy deficit and/or weight loss and displayed a non-significant effect size of 0.54 (95% CI: -0.06, 1.13; $Z = 1.77$; $P = 0.08$) compared to 0.38 (95% CI: 0.06, 0.70; $Z = 2.32$; $P = 0.02$) for the remaining studies which were performed in energy balance or no weight loss occurred. Neither BMI (> 25 vs. $< 25 \text{ kg m}^2$), duration ($> 1 \text{ wk}$ vs. $< 1 \text{ wk}$) nor dose ($> 500 \text{ mg d}^{-1}$ vs. $< 500 \text{ mg d}^{-1}$) of supplementation impacted upon effect size estimates.

Acute intake

Acute high-calcium intake increased fat oxidation vs. control (Figure 3) to a similar extent as chronic intake with a pooled SMD of 0.41 (95% CI: 0.04, 0.77; $Z = 2.18$; $P = 0.03$). Again, the degree of heterogeneity was low ($I^2 = 19\%$). However, when individual studies were removed, the effect became non-significant ($P > 0.05$) with each comparison removed, apart from two [Gunther *et al.* (48) 2005 DA1 and DA3 in Figure 3].

Risk of bias

Out of all the studies in the review, only one outcome was from a double-blind study (45), reflected in the high degree of uncertainty/high risk evident in assessment blinding (Figures 4A and 4B). There was a similar number of studies with impartial funding compared to funding by a dairy council or dairy-related company. No obvious asymmetry was observed by inspection of funnel plots (Figures 5A and 5B), however the small number of studies included, particularly with acute studies would make detection difficult.

Discussion

The results of this meta-analysis demonstrate that chronic high-calcium intake significantly increases fat oxidation by ~11%. The efficacy is dependent upon the habitual calcium intake of the participants, whereby those who have low calcium intakes gain the greatest increases in fat oxidation on a high-calcium diet. The findings also show that acute calcium supplementation significantly increases fat oxidation, possibly to a similar extent as chronic supplementation.

If it is considered that daily fat oxidation is in the region of 100 g [based on the control conditions of 24-h measures in Boon *et al.* and Melanson *et al.* (44, 46)], and

the assumption is made that no compensation occurs, then the 11% increase would result in a loss of ~3.7 kg body fat over 1 y (equating to ~1.7 kg over 24 wk).

Including the ~0.7 kg (0.3 kg over 24 wk) proposed to result from fat excretion (30) this entirely explains the 2.4 kg reduction in body fat seen in the 24-wk intervention by Zemel *et al.* (21) and indicates that, when energy intake is matched (negating any putative appetite effects) calcium intake can enhance body fat loss by a combination of reduced fat absorption and enhanced fat oxidation. To place the degree of fat oxidation effects in context, this increase is of comparable magnitude to that seen with caffeine supplementation (55).

It was apparent that those with low calcium intakes at baseline gained the most benefit from calcium supplementation. Calcium absorption efficiency is dependent on numerous factors (56). Two of which, are the calcium and vitamin D status of the individual. When calcium deficiency exists, the efficiency of calcium absorption is improved (57) which would explain why the present findings suggest that those with low habitual calcium intakes received the most benefit from the supplementation. Vitamin D deficiency on the other hand, decreases calcium absorption (58). Vitamin D status was not determined in all the studies in this review and therefore including this in the analysis was not possible. It would therefore be interesting to investigate the impact vitamin D status plays in the efficacy of calcium supplementation regarding fat oxidation, particularly as vitamin D status *per se* has been linked with obesity (59).

Calcium supplements appeared to be more effective than dairy calcium at augmenting fat oxidation. This is an interesting finding, particularly as dairy calcium has been shown to be more effective during fat loss trials (21) and regarding fat excretion (30). However, dairy contains a variety of additional compounds which have powerful

effects on appetite and body composition such as whey protein (60, 61) for example, and is fortified with vitamin D in certain countries which could directly and/or indirectly influence the response as previously discussed. The greater effectiveness of supplemental calcium that has been observed in the present analyses may be down to supplemental groups being placebo-controlled. Dairy groups, by nature of the design, were not blinded or placebo-controlled as the diet was modified. Thus, bias may be introduced by the participants in the dairy, and dairy control groups due to the knowledge of group assignment.

The SMD was larger when calcium supplementation was provided under energy deficit compared to the remaining studies under energy balance, yet the SMD did not reach statistical significance under energy deficit. This is likely due to the low number of outcomes assessed under energy balance and therefore more data is needed to establish whether energy status/availability can influence the effectiveness of calcium intake on fat oxidation. Some have shown that calcium/dairy is more potent at eliciting fat loss, under energy-restricted diets (62). Although speculative, it may be that the lipolysis during weight loss releases stored lipid-soluble vitamin D from adipocytes (63, 64), thereby increasing vitamin D status and enhancing calcium absorption. Similarly, more research with a range of BMIs, durations and dosages of supplementation would allow for an appropriate supplementation protocol to be established for individuals, based on BMI if it is evidenced that this also plays a role. Acute calcium intake also increased fat oxidation. Although, this area is still relatively poorly researched, with only three studies (with eight outcomes) included in the analyses from two independent laboratories. This lack of data is evident in the wider confidence intervals compared to the chronic analysis, and the result that removal of any single outcome (apart from two) resulted in a non-significant effect,

substantiating the need for more data in order to gain more robust conclusions.

However heterogeneity, risk of bias and funnel plots were relatively similar to the chronic studies. In order to be more confident in this conclusion it is suggested that further work is undertaken to demonstrate that these results can be replicated in multiple independent laboratories under double-blind conditions.

In conclusion, chronic (>7 d) high-calcium (~1300 vs. ~488 mg d⁻¹) intake increases fat oxidation, which may contribute to the fat loss benefits of a high-calcium, energy restricted diet. The effect is most profound in individuals with a low habitual calcium intake, and may be more effective under energy restriction. Acute calcium supplementation (in a single meal) also appears to increase fat oxidation, however further work is required to substantiate this.

Conflict of Interest statement

None of the authors had a personal or financial conflict of interest.

Acknowledgements

JTG and EJS designed the study. JTG and PLSR collected and prepared the data. JTG analyzed the data. JTG wrote the manuscript and PLSR and EJS reviewed the manuscript.

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Table and figure legends:

Table 1. Characteristics of chronic studies included in the analyses
BMI, body mass index; M, male; F, female; CN, control; Ca^{2+} , calcium; DA, dairy; PL, placebo; FO, fat oxidation.

Table 2. Characteristics of acute studies included in the analyses
BMI, body mass index; M, male; F, female; CN, control; Ca^{2+} , calcium; DA, dairy; FO, fat oxidation.

Figure 1. Process of study selection

Figure 2. Effects of chronic high-calcium intake on fat oxidation; every square represents the subgroup's SMD with 95% confidence intervals (CI) indicated by horizontal lines; square sizes are proportional to the weighting of the study. Ca^{2+} , calcium; DA, dairy.

Figure 3. Effects of acute high-calcium intake on fat oxidation; every square represents the subgroup's SMD with 95% confidence intervals (CI) indicated by horizontal lines; square sizes are proportional to the weighting of the study. Ca^{2+} , calcium; DA, dairy.

Figure 4. Risk of bias across expressed as a percentage across all studies on chronic (A) and acute (B) calcium intake. White, grey and black bars indicate low, unclear and high risk of bias, respectively.

Figure 5. Funnel plots of the standardized mean differences (SMD) versus the standard errors of the SMDs for chronic (A) and acute (B) high-calcium intake for fat oxidation. The broken line indicates the weighted mean SMD.