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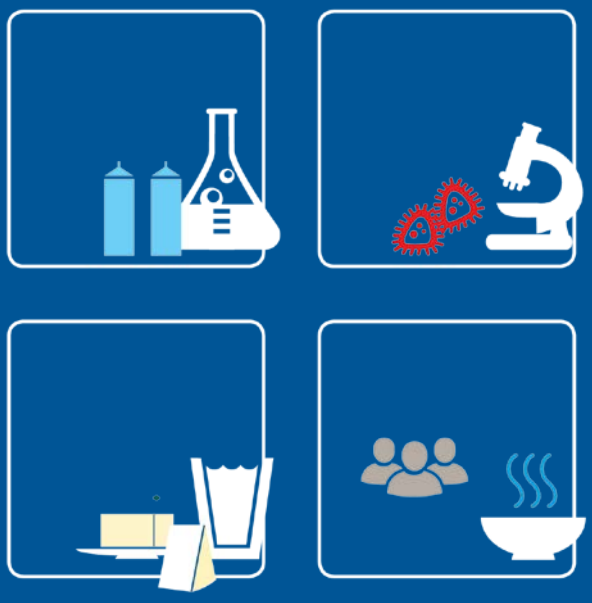

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Final report for "Calcium in dairy products in the prevention of obesity"

Kalcium i mejeriprodukter til forebyggelse af overvægt

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Dansk sammendrag

Data fra befolkningsundersøgelser tyder på, at et højt indtag af kalcium kan reducerer kropsvægten og/eller fedt massen, men de underliggende mekanismer er ikke klarlagt. Det primære formål med dette projekt var, at identificerer mekanismer hvorved kalcium (især fra mejeriprodukter) kan påvirke energibalancen hos mennesker. Endvidere at undersøge kalciums indvirkning på fedt og kolesterol niveauet i blod. Hovedresultatet er, at et øget indtag af kalcium fører til en øget fekal fedt- og energiudskillelse. Effekten vurderes at være tilstrækkelig til at kunne fører til (lille) negativ energibalance. Det er dog vigtigt at understrege, at dette er påvist i kontrollerede kort-tidsstudier og der er behov for lang-tidsstudier for at fastslå effekten. Flere faktorer synes at have betydning inklusiv kalciumkilde, den matrix kalcium indtages i, dosis mv. Resultaterne fra projektet viser endvidere, at kalcium delvis kan modvirke mættet fedts negative effekt på fedt og kolesterol niveauet i blod. Den gavnlige effekt kan kun delvis forklares ved den reducerede fedtfordøjelse, og det tyder på, at der er andre endnu ikke identificere mekanismer involveret.

Background

The prevalence of overweight and obesity in the Western world is increasing and it is now categorized as an epidemic by the World Health Organization (WHO) (1). Obesity poses a major risk for development of complicating diseases, including type 2 diabetes mellitus, hypertension, cardiovascular disease (CVD), and certain forms of cancer (2-9). Until recently the primary dietary focus concerning energy balance has been on macronutrient composition, but it is becoming clear that some non-caloric nutrients may exert an effect on energy balance. Calcium has been suggested to be one of these nutrients.

The first indication that dietary calcium intake is inversely related to body weight was reported in the mid-1980s based on data from the first National Health and Nutritional Examination Survey in USA (NHANES I) (10). However, at that time there was no plausible biological explanation for this association and it was relegated to the status of a chance association. In 2000 Zemel et al. and Davies et al. published data supporting results found by McCarron et al. fifteen years earlier and

the first plausible mechanisms were proposed (11;12). Since then the effect of dietary calcium intake on body fat mass and body weight has attracted a lot of attention and several observational studies addressing this topic have been reported (13-14). The overall picture emerging from these observational studies is that dietary calcium intake is inversely associated with body fat mass and body weight (14).

In 2003 another interesting observation was made by Jacqmain et al. (15). They found that dietary calcium intake among participants in the Québec Family Study was inversely associated with body fat mass, total cholesterol concentration and low density lipoprotein (LDL) cholesterol concentration. Subjects with high dietary calcium intake had lower total cholesterol and LDL cholesterol concentrations than subjects with a low dietary calcium intake, and therefore presumably a lower risk of developing CVD (15). However, to assess whether these associations are causal, it is necessary to perform human intervention studies and to find plausible mechanisms to explain how calcium may influence energy balance and blood lipoprotein metabolism.

With regards to mechanisms, it has been proposed that calcium affects both sides of the energy equation, i.e. both energy intake and energy utilization. The mechanisms proposed for affecting energy intake include decreased digestibility of fat and decreased food intake, whereas the mechanisms proposed for affecting energy utilization include decreased *de novo* lipogenesis and increased lipolysis.

Aim

The primary aim of the present project was to identify mechanisms by which dietary calcium intake may affect energy balance in humans. The main focus was on calcium from dairy products. A secondary aim was to examine whether dietary calcium intake affects lipid profile.

The project consisted of three human intervention studies (study I-III). In addition a systematic review with a meta-analysis was included in the project (study IV). The papers that emerged from the studies are included in appendices I-II and IV. Study III has not been published yet (paper will

be forward when published, preliminary results are presented in appendix III). For a detailed description of the studies please see the papers.

Results

Fecal fat excretion

Our studies clearly show that dairy calcium decreases fat digestibility (measured as an increase in faecal fat and energy excretion – study II), and that dairy calcium reduces lipid response after a high fat meal (study I). Others have found that calcium *per se* decreases fat digestibility. The effect is most likely due to formation of insoluble calcium-fatty acid soaps and formation of hydrophobic aggregations with phosphor, bile acids, fatty acids and other hydrophobic components. The effect seems to depend on several factors, including source of calcium, matrix in which calcium is provided, dietary protein intake, dose of calcium, habitual calcium intake etc. The most important criterion is that calcium and fat must be present in the intestine at the same time. As a part of the project we performed a systematic review of the literature to identify all the randomized controlled trails (RCTs) in healthy humans examining the effect of dietary calcium (dairy or supplement) on fat digestibility (measured as faecal fat excretion) (study IV). Based on these studies we performed a meta-analysis, which showed that increased calcium intake results in an increased excretion of faecal fat (Standardised Mean Differences (SMD) of 0.99) (95% CI: 0.63-1.34; $p<0.0001$), which we estimate to correspond to an increased faecal fat excretion of ~2g/day. However, there was moderate heterogeneity ($I2=49.5\%$), which suggests that the outcome of this meta-analysis is confounded by study characteristics such as differences in study design, calcium sources, matrix in which calcium is provided etc. In contrast the studies using dairy calcium showed homogeneity ($I2=0\%$). Based on these studies we estimated that an increase in dairy calcium intake of ~1200 mg/day produced an increase in faecal fat excretion of 5.2 g/day (198 kJ), at least in subjects with a low habitual calcium intake. An effect of this size is sufficient to affect energy balance. Assuming no change in dietary energy intake it corresponds to a change in body weight of -2.2 kg/year. However, it has to be emphasized that the majority of the RCTs were strictly controlled, short-term intervention studies and there is therefore a need for long-term studies in free living subjects in order to establish effectiveness. We have collected fecal samples

from study III and calcium as well as energy and fat content will be measured on these samples to provide us with information on long-term effect.

Appetite regulation

Dietary calcium has also been proposed to affect appetite regulation. This has only been addressed in a few studies and the hypothesis that a low dietary calcium intake leads to a high food intake is mostly based on speculation. In study I we found no indication that a high intake of dairy calcium or supplementary calcium had any effect on short-term appetite regulation. Others have suggested that increased dietary calcium may affect long-term appetite regulation by decreasing fat intake in subjects with low habitual calcium intake, but this has only been shown in a very small study and no plausible mechanisms have been proposed. Thus, based on the available data it is questionable whether dietary calcium affects food intake.

Energy expenditure and lipid oxidation

Based on *in vitro* studies and animal studies increased dietary calcium intake has been proposed to affect energy utilization by inhibiting *de novo* lipogenesis and stimulating lipolysis and thermogenesis, and thereby increasing energy expenditure and lipid oxidation. Preliminary studies from study III show no significant effect of a high dairy intake on basal metabolic rate (BMR). However, a significant lower respiration quotient (RQ) was found in the high dairy group compared to the low dairy group (when adjusting for baseline RQ) which may indicate a higher lipid oxidation (appendix III). However, RQ has to be corrected for protein oxidation before a final conclusion can be drawn. In agreement with our results, high dietary calcium intake has been shown to increase lipid oxidation in a few studies (16-19), whereas no studies have found an effect on energy expenditure in humans (20-23).

Body weight

In study III an increase in intake of dairy products combined with a strict controlled energy restricted diet was not found to affect changes in body weight or composition during 24 weeks compared to a similar diet with a very low amount of dairy products. However, as mention above

not all measurements from this study is available jet (including some of the compliances measurements) and therefore the results must be considered preliminary. In contrast to the results from our study a recently published meta-analyses concludes that inclusion of dairy products in energy-restricted weight loss diets significantly affects weight (-1.11 kg ;95% CI:-1.75,-0.47, P=0.001), body fat mass(-1.29 kg ;95% CI:-1.98,-0.6, P=0.001), lean body mass (2.43 cm; 95% CI:3.42,1.44, P=0.001) compared with an energy-restricted weight loos diet with a low intake of dairy products (24). There are several possible explanations for this discrepancy. As described above protein seems to interfere with the effect of calcium on fat digestibility. Although we aimed at a protein intake at 18E% the mean protein intake in study III were higher in both groups. In agreement other studies with a protein intake above 20E% we have not been able to show beneficial effects of a high dairy/calcium intake (25-26) whereas the mean protein intake in several of the studies showing a beneficial effect has been below 20E% (27-28). According to the latest nation-wide survey of dietary habits in Denmark only 10% of the adults in Denmark have a mean protein intake of 17E% or above (29). Secondly subjects included in the study all had a low intake of dairy products at baseline. In the high dairy group subjects were instructed to increase their dairy intake considerable while subjects in the low dairy group were instructed to maintain their low intake. Although this were combined with instructions on how to control calorie intake in both groups it is possible that the high dairy group have increased the calorie intake at least for the first weeks due to the incorporation of dairy products in the diet. An increase in energy intake with no change in body weight or composition has been shown in studies where subjects have been instructed to increase dairy products consumption with no energy restriction (30). Although it did not reached significance the low dairy group decreased their mean energy intake ~400 kJ/day more than the high dairy group which may suggest that a larger study might have shown statistically significant results on energy intake.

Blood lipid profile

Several studies indicate that whole fat milk and other full fat dairy products may not affect blood lipid profile adversely, as would be predicted from fat content and composition, and some studies even indicate that intake of dairy products, especially low-fat products, has a beneficial effect on lipid profile. Results from study I and II indicate that this is due, at least in part, to the high content

of calcium in dairy products. The beneficial effect of calcium is partly explained by the decrease in fat digestibility produced by calcium, but it is likely that other mechanisms are also involved. Data from RCTs examining the effect of supplementary calcium on lipid profile are conflicting, which is most probably due to differences in study characteristics, including time of ingestion of the supplement and the matrix in which calcium are provided (31-38). However, it is obvious that any dietary intervention with a beneficial effect on lipid profile, and thereby on the risk of CVD, will be of importance both to the population and the individual. More research is needed to establish whether dietary calcium has a beneficial effect on lipid profile and how to optimize any effect.

Industry and societal results

The findings from the present project have attracted considerable public interest, as well as from both the national and the global dairy industry, and have resulted in several new collaborations with both industrial partners and other national and international research groups. Two new research projects have been planned and funded in collaboration with industrial partners , one with the Danish Dairy Industry: “The effect of protein and calcium on blood lipid profile” (~5 mill DKK;); and one with the Global Dairy Platform: and “The effect of cheese on blood lipid profile and energy balance” (~7 mill DKK).

Research education

The project has resulted in one Ph.D. In addition 3 master theses and 1 bachelor thesis have been based on data from the project.

Collaboration, including cross-institutional, interdisciplinary and international cooperation

Collaboration with industry: Arla Foods Ingredients amba, Pharma Vinci A/S

Collaboration with international research groups: Nutrition and Toxicology Research Institute, University of Maastricht, Holland; Division of Endocrinology, Metabolism, and Diabetes, university of Colorado, Denvor, USA; Division of Kinesiology (PEPS), Department of Social and Preventive Medicine, Laval University, Québec, Canada.

Other: The Dutch Dairy Association, The Danish Dairy Research Foundation, Global Dairy Platform

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