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Review Article

ROLE OF CALCIUM IN OBESITY: DOES IT HELP?

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ABSTRACT

Calcium is a micronutrient that has recently gained a lot of importance in reference to regulation of body weight or body fat. The present review focuses at identifying statistically established relationships between calcium intake and obesity, and to identify plausible mechanisms for this relationship. For this purpose we selected cross-sectional studies and randomized controlled trials which have tried to study this association. Studies for which full paper could be obtained were included in the present review. There were mixed results on the possible association of Ca^{+2} and body weight. Further investigation, with large sample studies specifically powered to identify this relationship are still needed as not all the experts are in compliance with the suggested association.

Key Words: *Calcium, Obesity, Body Weight, Body Fat, Fat Oxidation*

INTRODUCTION

Overweight and obesity are increasing worldwide at an alarming rate. In 2008, more than 1.4 billion adults, 20 and older, were overweight. Of these overweight adults, over 200 million men and nearly 300 million women were obese. Overall, more than 10% of the world's adult population was obese (WHO, 2013). Recently calcium has gained a lot of importance in playing an important role in regulation of obesity. Davies *et al.,* (2000) found that about 3% of the variability in BMI could be attributed to calcium intake differences. Heaney (2003) revaluated the data behind the publication of Davies *et al.,* (2000) estimated that by increasing calcium intake the prevalence of obesity can be reduced by 60-80%.

The present review aims at exploring the literature evidence for establishing a role between dietary calcium intake and obesity. We have also tried to identify plausible mechanisms that might play a role in regulating body weight or body fat.

Calcium and Obesity: Supporting Evidence from Scientific Literature

A cross – sectional study enrolled total 35 (21 male, 14 female) non-obese, healthy adults. Daily (24h) energy expenditure (EE) and macronutrient oxidation using whole –room indirect calorimetry; habitual Ca^{+2} intake estimated from analysis of a 4-day food records; acute Ca^{+2} intake estimated from measured food intake during a 24-h stay in a room calorimeter. Acute Ca^{+2} intake ($mg.kcal^{-1}$) was positively related with fat oxidation over 24h ($r=0.08$, $p= 0.03$), during sleep ($r=0.36$, $p=0.04$) and during light physical activity ($r= 0.32$, $p=0.07$) (Melanson *et al.,* 2003).

In a cross-sectional study 301 healthy 63 old men with different degrees of fasting insulin concentrations, were enrolled. Under reporters (URs) and non-under-reporters (non-URs) were identified. Sagittal abdominal obesity (SAD), dietary intake assessed by a 7-day food registration, and the fatty acid composition in serum phospholipids (PL) and adipose tissue (AT) were measured. The intake of dietary fat was inversely correlated with saggital abdominal obesity in the URs ($r=0.36$. $p= 0.001$). The intake of calcium was inversely correlated with saggital abdominal obesity in both groups (Rosell *et al.,* 2004).

Table 1: Studies supporting anti-obesity effect of calcium

S.No.	Reference	Study Design	Sample Size and Characteristics	Intervention	Conclusion
1.	(Melanson *et al.*, 2003)	Cross-sectional	N=35, (21 =M; 14=F), Age = 31±6y; BMI =23.7 ±2.9kg/m^2	A balanced diet comprising 30% energy fat. 15% energy protein, 55% energy carbohydrate. Subjects selected their food.	High acute calcium intake is associated with higher rates of whole body fat oxidation.
2.	(Rosell *et al.*, 2004)	Cross-sectional	N=301, Healthy 63 year old men. BMI = 25.9 ± 3.1 kg/m^2	7 day food record (Calcium intake 1.0g/day)	Intake of calcium was inversely correlated with sagittal abdominal adiposity.
3.	(Teegarden *et al.*, 2008)	Randomized placebo control	N=24, Overweight women, Age =22.2 ± 3.1y, BMI=27.7 ± 1.8	Three groups- Control (n=9, Ca =497±58mg/d), Calcium (n=6, Ca =414±71mg/d), Dairy (n=9, Ca=1273± 167mg/d)	Calcium intake increases fat oxidation but does not change total energy expenditure.
4.	(Shahar *et al.*, 2007)	Randomized clinical trial	N=259, Diabetic Patients, Age=55y, BMI> 31kg/m^2	3 groups Mixed Glycemic Index Carbohydrate diet (Ca = 672.7± 433.5 mg/d) Low-glycemic index diet (Ca =573.8±348.2mg/d) Modified Mediterranean diet (Ca= 569.0±293.3mg/d)	A diet rich in dairy calcium intake enhances weight reduction in Type 2 diabetic patents.
5.	(Jacqmain *et al.*, 2003)	Cross-sectional	N=470 (M=235, F=235), Age = 40.9y, BMI =28.09 kg/m^2	Intervention 24 weeks Group A (Ca = <600mg/d) Group B (Ca = 600-1000mg/d) Group C (> 1000mg/d)	A low daily calcium intake is associated with greater adiposity, particularly in women.
6.	(Zemel *et al.*, 2004)	Randomized placebo control	N=32 (M=5, F=27) Age = 49 ± 6, BMI = 34.9 ± 4.3 kg/m^2	Intervention 24 weeks Group A (Ca=430mg/d) Group B (Ca=1256±134mg/d) Group C (Ca=1137±164 mg/d)	Increasing dietary calcium significantly augmented weight and fat loss secondary to caloric restriction and increased the percentage of fat lost from the trunk region.
7.	(Jacobsen *et al.*, 2005)	Randomized cross over study	N=10 (M=2, F=8) Age = 24.2 ± 2, BMI=26.5±2	Low Ca/ NP=474mg/d High Ca/NP =1735 mg/d High Ca/ HP =1869mg/d	A short term increase in dietary calcium intake, together with a normal protein intake, increased fecal fat and energy excretion by ~350Kj/d.

One intervention study included a prescribed 500kcal deficit diet in a randomized placebo-controlled calcium or dairy product intervention employing twenty four 18 to 31 year old (22.2 ± 3.1 years); overweight women (75.5 ± 9.6 kg). Subjects were randomized into 3 intervention groups: i) Placebo (< 800mg/d calcium intake) ii) 900mg/d calcium supplement iii) 3 servings of dairy products/ day to achieve and additional 900mg/d. Thermic effect of a meal (TEM), fat oxidation and total energy expenditure (TEE) were measured. There were no group effects observed in change in TEE, however, a group effect was observed for fat oxidation after adjusting for fat free mass (p =0.02). The treatment effect was due to an increase in fat oxidation in the calcium supplemented group of 1.5± 0.6g/h (p=0.02). The results of this study suggest that calcium intake, but not dairy intake, increases fat oxidation during a weight loss trial (Teegarden *et al.,* 2008). An ancillary study of a 6-month randomized clinical trial assessing the effect of three iso-caloric diets in type 2 diabetic patients: 1) mixed glycemic index carbohydrate diet, 2) low-glycemic index diet and 3) modified Mediterranean diet. A total of 259 diabetic patients were recruited. Among the high tertile of dairy calcium intake, the odds ratio for weight loss of more than 8% was 2.4, p=0.04, compared to the first tertile, after controlling non-dairy calcium intake , diet type and the change in energy intake from baseline. This study suggests that high dairy calcium intake leads to greater weight reduction (Shahar *et al.,* 2007).

Jacqmain *et al.,* (2003) studied the association between the daily calcium intake and body composition in a cross-sectional study in adults from phase-2 of the Quebec Family Study. Total of 470 subjects participated in the study (235 male, 235 female). Subjects were divided into 3 groups on the basis of their daily calcium intake: groups A (<600mg), group B (600-1000mg) and group C (> 1000mg). The results suggested that a low daily calcium intake is associated with greater adiposity, particularly in women. Zemel *et al.,* (2004) conducted a study to determine the effects of increasing dietary calcium intake in the phase of caloric restriction in humans. A randomized control trial was performed on 32 obese adults. Participants were maintained for 24 weeks on balanced deficit diets (500kcal/d deficit) and randomized to a standard diet (400 to 500 mg of dietary calcium /d supplemented with placebo), a high- calcium diets (standard diet supplemented with 800mg/d) or high dairy diet (1200 to 1300 mg of dietary calcium /d supplemented with placebo). Participants on standard diet lost 6.4 ± 2.5% of their body weight, which was increased by 26% (to 8.6 ±1.1%) on the high-calcium diet and 70% (to 10.9 ± 1.6%) of body weight, on the high- dairy diet (p<0.01). Fat loss was similarly augmented by the high calcium and high dairy diets by 34% and 64% respectively (p< 0.01). Moreover, fat loss from the trunk region represented 19.0±7.9% of total fat loss on the low-calcium diet and this fraction was increased to 50.1 ± 6.4% and 66.2 ±3.0% on the high- calcium and high dairy diets, respectively (p<0.001).

In another study ten subjects participated in a randomized crossover study of three iso-caloric 1 week diets with low: low calcium and normal protein (LC/NP: 500mg calcium, 15% of energy (E% from protein), high calcium and normal protein (HC/NP: 1800mg calcium, 15% E protein) high calcium and high protein (HC/HP: 1800mg calcium, 23E% protein). The calcium intake had no effect on 24-h EE or fat oxidation, but fecal fat excretion increased ~2.5 fold during the HC/NP diet compared with the LC/NP and the HC/HP diets (1045 vs. 684 and 668Kj/ d; p<0.05). A short-term increase in dietary calcium intake with a normal protein intake, increased fecal fat and energy excretion by ~350 kj/ day (Jacobsen *et al.,* 2005).

Calcium and Obesity: Contraindicating Evidence from Scientific Literature

Bowen *et al.,* (2005) have shown in their trial that in an energy restriction phase the mean calcium intake by dairy protein (DP) group was 2371±45mg/d and by mixed protein (MP) group was 509 ± 24mg/d. Total weight loss reported in males in DP group is -9.4kg±1.3 and MP group is -12±1.5kg. For the females these values were -9.4±1.0 kg and -7.8±06. Hence, they concluded that calcium or dairy source of protein does not affect weight reduction. A recent randomized trial has observed three groups: Dairy, Calcium and Placebo for 12 weeks. Respective, mean calcium intakes for the three groups were: 1244.8±108.0, 1035.1±72.3 and 449.0±69.7 mg/d. The dairy group consumed 19% energy from protein whereas calcium group and placebo had 17.4% and 16.7% energy from protein. Mean net weight loss

(Δwt) for the three groups was 4.3, 3.4 and 3.2 kg. Body fat% loss was recorded to be 3.5% for dairy group, 1.6% in calcium group and 2.1% in placebo. This suggests that dairy source of protein and calcium is more effective than other sources. Calcium alone might not be an effective measure to control obesity (Smilowitz *et al.*, 2011).

Table 2: Studies contraindicating anti-obesity effect of calcium

S.No.	Reference	Study Design	Sample Size and Characteristics	Intervention	Conclusion
1	(Bowen, Noakes, and Clifton, 2005)	Randomized, parallel study	N=50 (M=20, F=30), Age= 20-65 y, BMI = 27-40kg/m^2	Intervention = 12 weeks + 4 weeks follow up Dairy protein group M (Ca = 899±120mg/day) F (Ca= 787±57 mg/day) Mixed protein group M (Ca=935±139 mg/d) F (Ca=737±80 mg/d)	Increased dietary calcium in an energy restricted, high protein diet does not affect weight loss or body composition.
2	(Smilowitz *et al.*, 2011)	Randomized placebo control	N=105, Age =18-35 y, BMI= 25-34.9kg/m^2	3 groups Dairy (n=22, Ca=1244.8±108.0 mg/d) Calcium (n=16, Ca= 1035.1±72.3mg/d) Placebo (n=23, Ca =449± 69.7mg/d)	Dietary fat and not calcium supplementation or dairy product consumption is associated with changes in anthropometrics.
3	(Yanovski *et al.*, 2009)	Randomized Trial	N=340, Age = 38.8±10.5y, BMI=25 to < 30 kg/m^2	Calcium Group (n=170, Ca = 1500mg/d) Placebo (n=170)	Dietary supplementation with elemental calcium, 1500mg/d, for 2 years had no statistically or clinically significant effects on weight in overweight and obese adults.
4	(Shapses Heshka, and Heymsfield, 2004)	Data from 3 separate randomized double blind, placebo controlled trial	N=100, Premenopausal and postmenopausal women	Calcium group (Ca = 1607±215) Placebo group (Ca= 587.67±225.33)	Calcium supplementation did not significantly affect amount of weight or fat lost by women on moderately restricted diet.

Another study revealed that the measured change in body weight among all participants who completed the 2-year trial was 1.31 kg ($p<0.001$ versus baseline weight); fat mass increased by 0.82 kg ($p=0.004$ vs. baseline fat mass). The study did not find any statistically or clinically significant between –group differences in weight reduction of calcium and placebo groups (Yanovski *et al.,* 2009). Shapses *et al.,* (2004) carried out a randomized trial on 100 women (post and pre-menopausal) who were obese or overweight. The subjects were divided into 2 groups: calcium supplement and placebo. Subjects in each group were again categorized as – Pre menopausal and Postmenopausal. There was no significant difference in body weight or fat mass change between the placebo and the calcium supplemented groups in the pooled analysis (adjusted mean ± SD, body weight, placebo – 6.2 ± 0.7 vs. Ca -7.0 ± 0.7 kg; fat mass, placebo -4.5 ± 0.6 vs. Ca – 5.5 ± 0.6kg).

Possible Mechanisms for Calcium Regulation of Body Weight

Calcium and Lipid Metabolism: Intracellular calcium ($[Ca^{+2}]_i$) plays a key role in metabolic derangements associated with obesity (Byyny *et al.,* 1992; Draznin *et al.,* 1988; Draznin *et al.,* 1987). Increasing $[Ca^{+2}]_i$, via stimulation of either receptor or voltage –mediated calcium channel has also been shown to stimulate the expression and activity of fatty acid synthase (FAS), a key enzyme in de novo lipogenesis, and inhibit basal and agonist-stimulated lipolysis in both human and murine adipocytes (Xue *et al.,* 1998; Jones *et al.,* 1996). Therefore, increasing $[Ca^{+2}]_i$ appears to promote triglyceride accumulation in adipocytes by exerting a coordinated control over lipogenesis and lipolysis, serving to simultaneously stimulate the former and suppress the latter, resulting in lipid filling and adipocyte hypertrophy (Shi *et al.,* 2000).

Suppression of 1, 25$(OH)_2$ D with high calcium diets would be anticipated to reduce adipocyte intracellular Ca^{+2} effect (Zemel, 2001). High calcium (1.2%) diets reduced lipogenesis by 51% and stimulated lipolysis, inhibit fatty acid synthase and activate lipolysis, thereby exerting an anti-obesity by three-to-five fold resulting in 26% to 39% reductions in body weight and adipose tissue mass (Zemel *et al.,* 2000). Davies *et al.,* (2000) concluded that a 1000mg/ day increase in calcium intake is associated with an 8kg reduction in body weight.

Increasing dietary calcium in the absence of energy restriction appears to result in a repartitioning of dietary energy from adipose tissue to lean body mass resulting in a net reduction in fat mass in both mice and humans (Zemel *et al.,* 2002; Zemel *et al.,* 2000).

Fecal Fat Loss: A total of 2200 mg/d dietary calcium intake resulted in an increase in fecal fat excretion from 6 to 13 % (Denke *et al.,* 1993). Another study revealed that calcium supplementation of chocolate increased fecal fat 2-fold (from 4.4 to 8.4 g/d; $P < 0.0001$) and reduced the absorption of cocoa butter by 13.0%. This was mainly due to an increase in the excretion of palmitic and stearic acids (3.4 g/d), which reduced the absorbable energy value of the chocolate by 9%. These results suggest that calcium supplementation can be used as a means of reducing the absorbable energy value of chocolate (Shahkhalili *et al.,* 2001).

Calcium and Glucose Metabolism: Hepatic glucose production (HGP) is crucial for glucose homeostasis. It was experimentally demonstrated that calcium sensing enzyme calcium calmodulin –dependent kinase II (CaMKII), is activated in a calcium and IP3R –dependent manner by c-AMP and glucagon in primary hepatic cells and by glucagon and fasting in vivo. Genetic deficiency or inhibition of CaMKII blocks nuclear translocation of FoxO1 by affecting its phosphorylation, impairs fasting – and glucagon /c-AMP induced glycogenolysis and gluconeogenesis, and lowers blood glucose levels, while constitutively active CaMKII has the opposite effects. Importantly, the suppressive effect of nuclear FoxO1, indicating that the effect of CaMKII deficiency requires nuclear exclusion of FoxO1. This same pathway is also involved in excessive HGP in the setting of obesity (Ozcan *et al.,* 2012)

CONCLUSION

The evidence from literature suggests that calcium supplementation or habitual calcium intake may prove to be an effective strategy for reduction of obesity. There is a need to understand the actual mechanism

involved in the effectiveness of dietary calcium on regulation of body fat or body weight. Studies specifically powered to understand the association between calcium intake and obesity needs to be conducted.

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