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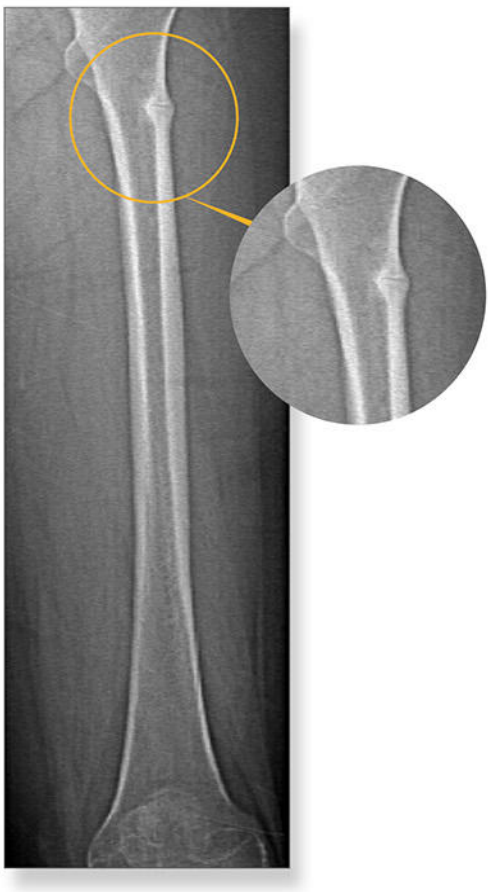

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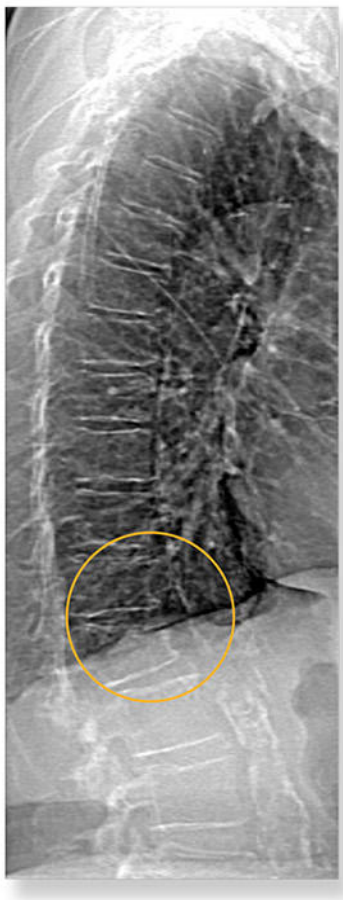

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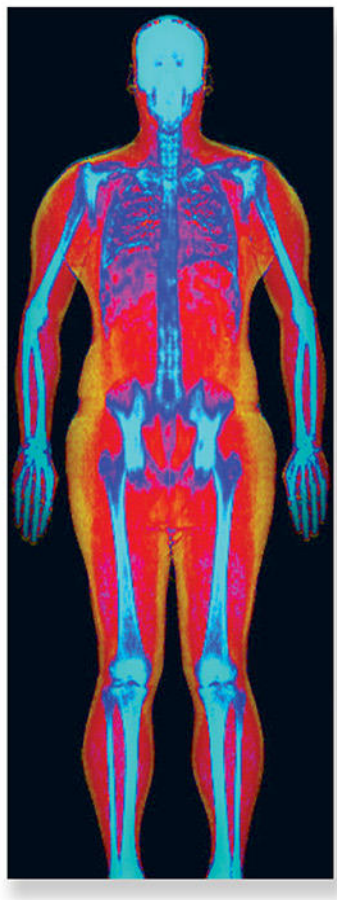

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SHORT REPORT

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Adverse Events From Calcium Supplementation: Relationship to Errors in Myocardial Infarction Self-Reporting in Randomized Controlled Trials of Calcium Supplementation

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ABSTRACT

The clinical effects of calcium supplements on adverse events reporting have not been well described. This study reviews randomized controlled trial (RCT) evidence of adverse events to clarify the epidemiology of these events. The hypothesis that patient self-report of myocardial infarction (MI) is increased in individuals receiving calcium supplementation is because of an increase in non-MI events incorrectly perceived by the patient as being because of MI, is examined. In seven RCTs summary self-reported gastrointestinal (GI) adverse event rates were more common in participants receiving calcium. These were described as constipation, excessive abdominal cramping, bloating, upper GI events, GI disease, GI symptoms, and severe diarrhoea or abdominal pain (calcium 14.1%, placebo 10.0%), relative risk (RR) 1.43 95% confidence interval (CI) 1.28 to 1.59, $p < 0.001$. Adjudicated functional GI hospitalizations in one study were calcium 6.8%, placebo 3.6% (RR 1.92, 95% CI 1.21–3.05, $p = 0.006$). Direct comparison of self-reported and adjudicated MI events in the two trials of dietary calcium supplementation showed self-reported MI rates of 3.6% in the calcium group and 2.1% in the placebo group. After adjudication the MI rates were 2.4% in the calcium group and 1.6% in the placebo group (RR 1.45, 95% CI 0.88–2.45, $p = 0.145$). These data support the hypothesis that calcium tablets increase the incidence of adverse GI events, which may account for an increase in self-reported MI in calcium treated patients but not controls. © 2012 American Society for Bone and Mineral Research.

KEY WORDS: CALCIUM SUPPLEMENTATION; GASTROINTESTINAL DISORDERS; MYOCARDIAL INFARCTION; REPORTING BIAS

Introduction

In randomized controlled trials (RCTs) of calcium supplementation an increase in minor self-reported adverse events are frequently reported but have not been collected together. Self-reported myocardial infarction (MI) is an outcome variable that has been demonstrated to be inaccurate.[1–5] Patient confusion regarding the final diagnosis is not surprising, especially if the patients are admitted to coronary care units. Heckbert et al.[5] identified a self-reported false positive rate for MI of 32% in the Women's Health Initiative, while Colditz et al.[1] found that 32% of participants in the Nurses Health Study were incorrect in their belief that they had sustained an MI. Fruergaard et al.[2] reported that 41% of patients admitted to a Coronary Care Unit (CCU) were considered not to have sustained an acute MI, whereas 11% of total admissions to the CCU were finally classified as because of gastrointestinal (GI) disease.

In this study the incidence of patient report of adverse events concentrating on symptoms that could reasonably misinterpreted as MI is reported in patients in RCTs of calcium supplements and placebo. In addition, a comparison of self-reported and adjudicated MI is presented.

Materials and Methods

Seven studies used in the Bolland et al.[6] meta-analyses published self-reported GI.[7–14] Self-reported GI events included the terms, constipation,[11–13] excessive abdominal cramping, bloating, upper GI events,[7] GI disease,[8] GI symptoms,[10] severe diarrhea, or abdominal pain.[9]

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For one study, data on adjudicated hospitalizations for GI disorders were available using the Western Australian Data Linkage System.[12,15] The principal hospitalization discharge code was considered the adjudicated cause of the event; codes included were abdominal pain (ICD-9-CM codes 789 and ICD-10-AM codes R10), indigestion (ICD-9-CM codes 536.8 and ICD-10-AM codes K30), and constipation (ICD-9-CM codes 564.0 and ICD-10-AM codes K59.0). The Western Australian Data Linkage System (WADLS) is a comprehensive, population-based linkage system that connects nearly 40 years of data from over 30 health-related datasets of residents of Western Australia coded using ICD codes and includes the coded discharge diagnosis data of all hospitalizations, both in public and private hospitals.[16]

Patient self-reported and adjudicated MI were available for comparison from two similar RCTs of calcium supplementation: Prince et al.[12] and Bolland et al.[17] Ascertainment of adjudicated events independent of patient report was achieved by using medical records in Bolland et al.[17] and WADLS in Prince et al.[12] Differences in MI and functional GI events were assessed by a chi-squared test. Results are presented as relative risk (RR) plus 95% confidence intervals (CI). All tests reported probability using the two tailed method, $p \leq 0.05$ was considered significant. The data was analyzed using PASW (version 18; SPSS Inc., Chicago, IL, USA).

Results

Figure 1, shows a Forest plot of the comparison of published self-reported adverse GI events in participants receiving calcium compared with placebo in seven RCTs. The data demonstrates an increased pooled RR for GI adverse events in the calcium-treated patients compared with the placebo-treated patients of 1.43 (1.28–1.59), $p < 0.001$. Overall, 506 of 5046 (10.0%) of patients receiving placebo reported adverse GI events compared with 716 of 5082 (14.1%) of patients receiving calcium tablets. There was no relationship to the calcium salt formulation or dose. Further evaluation of individual studies revealed evidence that both upper and lower GI system events were increased in participants receiving calcium.

Data on adjudicated hospital admissions for GI complaints derived from hospital discharge summary were increased in the calcium-treated patients with a total of 50 (6.8%) patients with any GI complaint (29 acute abdominal pain, 8 indigestion, and 15 constipation hospitalizations) compared with placebo 26 (3.6%) patients with any GI complaints (16 acute abdominal pain, 3 indigestion, and 8 constipation hospitalizations), RR 1.92 (1.21–3.05), $p = 0.006$. In particular, acute abdominal pain incidence was 4.0% over the 5 years of the study in calcium-treated patients compared with 2.2% in placebo patients. Total event categories are less than the sum of the individual groups because some individuals sustained more than one disorder.

In Table 1 the combined self-reported and adjudicated data available from the Bolland et al.[17] and Prince et al.[12] studies are presented. These data demonstrate an excess of self-reported MIs in the calcium treated patients RR 1.69 (1.09–2.61), $p = 0.020$. However, after adjudication, more events were found to be incorrectly classified in the calcium group than the placebo resulting in a RR of misreported MI of 2.44 (1.02–5.87), $p = 0.046$, while the rate of adjudicated MI was not increased in the calcium-treated patients compared with placebo RR 1.45 (0.88–2.45), $p = 0.145$. Specific reasons for incorrect self-reported MI in calcium-treated patients in Prince et al.[12] included one case of unspecified lower abdominal pain, one case of kidney stones, one case of chronic obstructive pulmonary disease, one case of unspecified oesophageal haemorrhage, one with no corresponding hospital admissions, and two cases of unstable angina. Specific reasons for incorrect self-reported MI in placebo-treated patients included three cases of unstable angina.

Discussion

Calcium therapy increases patient self-report and adjudicated hospitalization rate of functional GI events. The substantial increase in GI adverse events, which on occasion results in hospitalization, is not currently identified in prescribing guidelines for calcium supplementation and should be included in the differential diagnosis of GI disorders. The potential mechanism of these adverse effects on the GI tract is unknown. In view of the recognized high error rate in the self-report of MI and the effect of calcium supplementation to increase functional GI disorders, which may be mistaken for MI, self-reported MI should not be used as a primary outcome variable in RCTs of calcium supplementation.

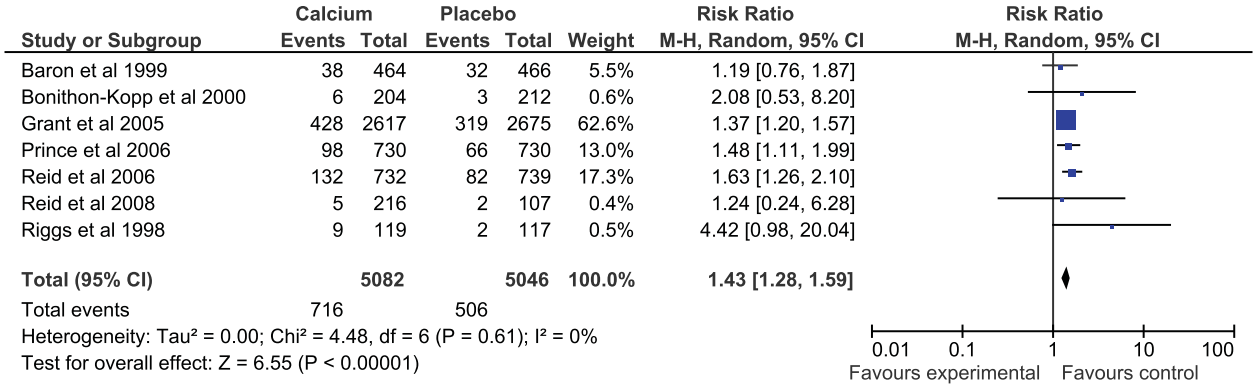

Fig. 1. Random effects model of calcium supplementation on the risk for GI complaints compared with placebo. For Grant et al. (2005), events were reported in those who received calcium (calcium and calcium + Vit D cf. placebo and Vit D only).

Table 1. Self-Reported and Adjudicated Myocardial Infarction by Treatment Group

	Calcium	Placebo	*p* value[a]
Self-reported myocardial infarction			
Prince et al., 2006	21/730 (2.9)	17/730 (2.3)	0.512
Bolland et al., 2008	31/732 (4.2)	14/739 (1.9)	0.011
Total	52/1462 (3.6)	31/1469 (2.1)	0.020
Self-reported—adjudicated myocardial infarction			
Prince et al., 2006	14/730 (1.9)	14/730 (1.9)	1.000
Bolland et al., 2008	21/732 (2.9)	10/739 (1.4)	0.048
Total	35/1462 (2.4)	24/1469 (1.6)	0.145
Self-reported—nonverified myocardial infarction			
Prince et al., 2006	7/730 (1.0)	3/730 (0.4)	0.218
Bolland et al., 2008	10/732 (1.4)	4/739 (0.5)	0.116
Total	17/1462 (1.2)	7/1469 (0.5)	0.046

Results are number (%) for the first event only.
[a]Calcium group compared with placebo group by chi-squared test.

These findings are relevant to identification of MI events from patient self-report. In the Bolland et al.[17] study MI events were increased in the calcium supplementation group before and after adjudication but not when combined with the Prince et al.[12] analysis. Although there was a significant increase in misreported MI in the calcium supplementation group in the combined analysis this was of marginal statistical significance. These data raise the possibility that ascertainment bias may have been present in studies using self-reported events that have found an association between calcium medication and MI.[6,17,18] In conclusion, the combined data support the hypothesis that calcium supplements increase functional GI events, which may be mistaken by participants as MI leading to reporting bias in studies of calcium supplementation.

Disclosures

All authors state that they have no conflicts of interest.

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Authors' roles: Study design: JRL, KZ, and RLP. Data collection: JRL, KZ, and RLP. Data analysis: JRL and RLP. Data interpretation: JRL, KZ, and RLP. Drafting manuscript: JRL, KZ, and RLP. Revising manuscript content: JRL, KZ, and RLP. Approving final version of manuscript: JRL, KZ, and RLP. JRL takes responsibility for the integrity of the data analysis.

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