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Invited Article

The Institute of Medicine, the Food and Drug Administration, and the calcium conundrum

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Abstract

In the present article we aim to bring forward the apparent disconnect between two US government-sponsored entities – the Institute of Medicine (IOM) and the Food and Drug Administration (FDA) – regarding the safe upper limit of Ca intake.

In light of the 2011 US Congress-appointed IOM report indicating an upper limit of elemental Ca intake of 2000–2500 mg/d in adults (based on age group), it is perplexing that the FDA has not yet required a change on the labelling of over-the-counter Ca-containing antacids, some of which indicate an upper limit of elemental Ca intake of 2800–3000 mg/d. Even more concerning is that Ca intake is rarely from supplementation in isolation. National Health and Nutrition Examination Survey (NHANES) data from 2003–2006 indicate that mean dietary Ca intakes for males ranged from 871 to 1266 mg/d and for females from 748 to 968 mg/d depending on the age group. The estimated total Ca (diet + supplements) intake exceeded the upper limit in 5 % of the population older than 50 years. Furthermore, NHANES data from 1999–2000 indicate that when Ca is taken as part of an antacid preparation, patients often fail to report this as Ca intake. Thus, individuals taking the maximum allowable dose of supplemental Ca as antacids are at high risk for complications associated with excess Ca intake.

Our hope is that by describing Ca homeostasis and highlighting the risks and dangers of Ca overload, the FDA will align its recommendation with the IOM and solve the current Ca conundrum in the USA for the sake of patient safety.

Keywords
Calcium
Upper limit
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The Institute of Medicine (IOM) published a report in 1997 indicating 2500 mg Ca as the daily maximum intake for adults; it revised its position in 2011 to reflect a better understanding of the risks and benefits of high Ca intake as it relates to age[1,2]. The IOM now recommends a daily maximum Ca intake of 3000 mg for 9–18 years old, 2500 mg for children less than 8 years old and adults 19–50 years old, and 2000 mg for the remainder of the population (i.e. over age 50 years)[2]. These recommendations include enteral intake from all sources (i.e. dietary and supplementary). The Food and Drug Administration (FDA), however, continues to allow upwards of 3000 mg elemental Ca (corresponding to 10–15 tablets of $CaCO_3$) daily for use as an antacid (we are not including Ca citrate in our discussion given that it is not marketed for antacid use). Our hope is that by describing Ca homeostasis and highlighting the risks and dangers of Ca overload, the FDA will align its recommendations with the IOM and solve the current Ca conundrum in the USA.

Ca is an essential mineral with various activities in the human body (neuromuscular, musculoskeletal and coagulation). Ca absorption via the gastrointestinal tract occurs through three mechanisms, the first two of these being regulated by the active form of vitamin D: regulated transcellular active transport, regulated paracellular passive transport and unregulated paracellular passive transport. Five per cent of daily Ca intake is absorbed via the latter process and occurs irrespective of Ca and vitamin D levels in the body. While of little consequence under normal Ca intake, Ca absorption via this latter pathway can lead to hypercalcaemia under conditions of high intake. Gastric acidity in combination with the type of Ca salt also plays a role in absorption. As an example, unlike Ca citrate whose absorption is not affected by gastric acidity, 17 % of $CaCO_3$ is absorbed in an acidic environment as opposed to 1 % at higher gastric pH values[3].

Ca excretion is handled by both the gastrointestinal tract and the kidneys. Approximately 100–200 mg Ca/d is

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secreted (and then excreted) gastrointestinally, while 8000–10 000 mg Ca/d is filtered at the glomerulus. The proximal tubule, in Na-dependent passive manner, reabsorbs about 65 % of Ca; any stimulus promoting Na retention (i.e. activation of angiotensin II) will increase Ca reabsorption in this segment. Roughly 20 % is reabsorbed paracellularly via the paracellin-1 channel in the loop of Henle – reabsorption in this area can be inhibited via direct paracellin mutations or through loss of the voltage gradient created through the ROM-K channel (this will promote enhanced Ca excretion); and approximately 10 % is reabsorbed in the distal convoluted tubule (thiazide diuretics and alkalaemia can augment Ca reabsorption in this segment)[3].

Several studies have linked Ca overload to decreased gastrointestinal motility (thereby leading to constipation, ileus or perforation), vascular and soft tissue calcification, prostate cancer, interactions with other mineral absorption (such as Fe and Zn) and milk alkali syndrome (leading to nephrocalcinosis and nephrolithiasis)[2]. The increased risk of nephrolithiasis, as demonstrated by the 2006 Women's Health Initiative publication by Jackson *et al.*, is largely responsible for the IOM's 2011 revisions regarding Ca intake. This was a large cohort study of 36 282 postmenopausal women aged 50 to 75 years who, in addition to pre-study Ca and vitamin D intake of 1100 mg and 9·125 μg (365 IU) daily, respectively, at study entry, were randomized to receive 1000 mg elemental Ca and 10 μg (400 IU) vitamin D *v.* placebo. Thus, the study group totalled 2100 mg Ca/d and 19·125 μg vitamin D (765 IU)/d. With an intention to treat analysis, the study reported a hazard ratio of 1·17 (95 % CI 1·02, 1·34) for nephrolithiasis in the intervention group with a number needed to harm of 273 and with no statistically significant benefits of the additional Ca to fracture prevention[4].

National Health and Nutrition Examination Survey data from 2003–2006 indicate that mean dietary Ca intakes for males ranged from 871 to 1266 mg/d and for females from 748 to 968 mg/d depending on the age group[5]. In addition, 43 % of the US population over the age of 1 year and about 62 % of adults over 70 years of age used supplemental Ca[5]. Five per cent of the population older than 50 years took more than the recommended upper limit of Ca through diet and supplements[5]. The above data may be an underestimation in patients taking over-the-counter Ca-containing antacids since Ca intake as a part of an antacid preparation is often not recognized and reported by patients as Ca intake[6].

$CaCO_3$ is very commonly used as an antacid for gastro-oesophageal reflux disease (GERD), which is highly prevalent in the USA. In 2005 Yuen *et al.* published a study indicating that among 1172 study subjects 34·6 % experienced GERD symptoms at least monthly, 26·2 % at least weekly, 8·2 % at least daily and that 44·1 % reported they would rather take antacids than visit/call a doctor if they had symptoms[7]. $CaCO_3$ works by neutralizing gastric acid and hence increasing the gastric pH. When ingested on an empty stomach the duration of action is just 20 to 60 min. Acid-neutralizing capacity (ANC) of $CaCO_3$ is 58 meq per 15 ml (or about 1200 mg). Prior studies showed that antacids at the dose of about 100–300 meq ANC/d (about 2000–6200 mg $CaCO_3$/d) have a similar effect as H2 antagonists for the treatment of peptic ulcer and non-ulcer dyspepsia but had no role in erosive oesophagitis healing. For symptomatic relief in peptic ulcer disease, most studies found antacids equivalent to placebo. For relief of GERD symptoms, two studies found antacids at a dose of 560–592 meq ANC/d (about 11 500–12 200 mg $CaCO_3$/d) superior to placebo[8]. Hence a patient is likely to take high doses of the Ca-based antacid for relief and, as noted above, may not appreciate the excessive enteral intake of Ca. Several cases of Ca-related disease have been reported with the use of $CaCO_3$ exceeding 3000 mg daily, especially in those with impaired renal function[2]. We recently managed a patient who developed milk alkali syndrome after taking 2500 mg $CaCO_3$/d for just a week.

Ca-containing antacids continue to have a role in symptom relief of minor GERD episodes, but proton-pump inhibitors are a better choice for severe symptoms. Hence, the FDA-regulated maximum allowable dose of $CaCO_3$ as an antacid should be no more than the IOM-recommended maximum allowable dose as a dietary supplement; any more than this increases the likelihood of adverse effects. Additionally, we recommend that labelling on over-the-counter Ca preparations (either as a supplement or as an antacid) indicate maximum allowable Ca for all purposes. In light of the above, we find it perplexing the FDA has not yet mandated a labelling change on over-the-counter Ca-containing antacids as some of these products still indicate an upper limit for elemental Ca intake of 2800–3000 mg daily irrespective of the age group or dietary Ca intake. We contend that while Ca-containing antacids are generally well tolerated, these preparations, when taken in excess, can lead to serious complications and that current FDA regulations are lacking in appropriate customer warnings for these products. Hence, we recommend that the FDA considers the IOM's recommendation and requires that manufacturers revise dosing recommendations and daily maximums for over-the-counter Ca-containing antacids; failure to do so will not only put the public's health at risk, but it will continue to highlight the Ca conundrum existing in this country.

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