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REVIEW ARTICLE

Hypochlorhydric stomach: a risk condition for calcium malabsorption and osteoporosis?

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Abstract

Malabsorption of dietary calcium is a cause of osteoporosis. Dissolution of calcium salts (e.g. calcium carbonate) in the stomach is one step in the proper active and passive absorption of calcium as a calcium ion (Ca^{2+}) in the proximal small intestine. Stomach acid markedly increases dissolution and ionization of poorly soluble calcium salts. If acid is not properly secreted, calcium salts are minimally dissolved (ionized) and, subsequently, may not be properly and effectively absorbed. Atrophic gastritis, gastric surgery, and high-dose, long-term use of antisecretory drugs markedly reduce acid secretion and may, therefore, be risk conditions for malabsorption of dietary and supplementary calcium, and may thereby increase the risk of osteoporosis in the long term.

Key Words: *Achlorhydria, atrophic gastritis, calcium carbonate, calcium salt, hypochlorhydria, malabsorption, osteoporosis, proton-pump inhibitor, stomach acid*

Introduction

Malabsorption of dietary calcium is a risk factor for osteoporosis. Acid induces dissolution of the calcium in the stomach as a calcium ion (Ca^{2+}). If the stomach does not secrete acid, calcium salts may not be effectively dissolved and ionized, and may be poorly absorbed in the proximal small intestine. There are three major conditions that significantly decrease acid secretion in human beings. These are the use of potent acid inhibitors in high doses, resections and bypasses of the stomach, including bariatric surgery, and the development of atrophic gastritis in the gastric corpus and fundus. All result in a decrease in gastric acid secretion and may thereby influence calcium homeostasis in the longer term.

In the normal stomach, the "acid machine" converts poorly soluble calcium salts (including calcium carbonate) to calcium chloride ($CaCl_2$) which easily dissociates to Ca ion (Ca^{2+}) and is, thereby, highly water-soluble, even in the pH-neutral milieu of the gut. However, some reports and opinions have also been published which dispute the significance of stomach acid for calcium absorption and emphasize that the *in vitro* water solubility of calcium salts is not associated with their *in vivo* absorbability [1–3]. This may certainly be true in subjects with a healthy stomach and normal acid secretion. However, in subjects with an hypochlorhydric stomach, and with failure of the "gastric acid machine", this may no longer be the case. Most studies on the absorption of calcium salts have been done in subjects or animals with normal acid secretion. Very little is known about the absorbability of micronutrients, including calcium, in subjects with a permanently acid-free or hypochlorhydric stomach.

Active and passive absorption of dietary calcium

In addition to gastric acid, the bioavailability of dietary calcium salts depends on several factors, including the physiological function of the stomach and intestine, levels of vitamin D in the tissues and circulation, diet and the chemical structure and quantity of the calcium compounds ingested [4–12]. Active vitamin D-promoted transcellular absorption of

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calcium ion in the duodenum and proximal small intestine is obviously the most important physiological pathway for absorption of the calcium, although passive paracellular and transepithelial absorptions of calcium by vesicles and diacytosis of soluble complexes of calcium with tissue or food-derived proteins may also occur, even in the colon [7,8,12–18].

The net absorption of calcium is certainly the sum of the active and passive absorptions, the latter being proportional to the gradient of the calcium concentration between the gut lumen and circulation, and possibly being prominent when active absorption is saturated or impaired. The transit time of the dietary bolus in the small intestine is up to 1–3 h, during which most of the active and passive absorption will obviously occur. This time window is relatively short and may require optimal physiological conditions, e.g. effective ionization of the calcium compounds ingested, for both active and passive absorption phenomena. Regarding the passive absorptions, it is conceivable that these pathways also require the dissolution and ionization of calcium salts, and that the calcium salts are minimally absorbed as whole molecules neither passively nor actively, e.g. as carbonate salts.

The complex cycle of active calcium absorption in the intestinal epithelial cells involves specific molecular mechanisms for binding of the calcium ion (Ca^{2+}) to carrier proteins and transmembrane channel molecules in the enterocytes, some of these protein bindings being vitamin D-dependent [13–17]. These absorption phenomena take place in the pH-neutral milieu of the intestinal epithelium, are no longer influenced by stomach acid, and are hence outside the scope of this review. Complex mechanisms also occur during the metabolism of calcium in bone tissues but these phenomena are also beyond the scope of this paper. We will focus on phenomena and mechanisms related to the influence of stomach acid on dissolution, ionization and absorption of the dietary calcium.

Solubility of calcium salts

Supplementary calcium is usually given as calcium carbonate tablets in most commercially available medications. At neutral pH, calcium carbonate is practically insoluble in water. Calcium ascorbate, calcium citrate, calcium lactate, and calcium gluconate dissolve somewhat better than carbonates and phosphates, whereas calcium oxalate is largely insoluble under any biological condition [7,8,19]. The maximal solubility of calcium citrate at room temperature and neutral pH is approximately 100 mg in 100 ml of water, which provides maximally 25 mg of elemental calcium (Ca^{2+}) dissolved in solution. Correspondingly, maximal dissolution of calcium carbonate at neutral pH provides much less than 10 mg of elemental calcium in 100 ml of aqueous solution. These solubilities cannot be improved by adding calcium salts to the solution. However, when hydrochloric acid is present or added, solubility is markedly improved.

Complete dissolution of calcium requires an equivalent amount of hydrochloric acid to be secreted into the gastric juice as calcium is ingested. For example, complete dissolution of a single 500-mg (approximately 5 mmoles) tablet of calcium carbonate into ionic form (Ca^{2+}) consumes 10 mmoles of hydrochloric acid (for the physiochemical background see: http://en.wikipedia.org/wiki/calcium_carbonate). This will provide 200 mg of elemental calcium in the gastric juice from 500 mg of calcium carbonate. Basal acid output in the healthy stomach is 0.2–5 mmol/h into approximately 100–200 ml of gastric juice. Postprandially, the peak and maximal acid outputs increase 10–20-fold for a short period of time.

In order to ensure the presence of maximal intragastric acidity, calcium carbonate tablets are recommended to be taken with food [4]. It is believed that the dissolution of calcium salts is better postprandially, when the acid output is maximal, than under fasting conditions. However, the use of proton-pump inhibitors (PPIs) or the presence of atrophic gastritis decrease both the basal and maximal outputs of acid, and will, therefore, diminish the quantity of acid available for dissociation of calcium salts postprandially. Furthermore, it is conceivable that the simultaneously ingested food also needs and consumes acid for various digestive processes in the postprandial phase, and that this acid is no longer available for dissolution of the calcium salts. In addition, acid may be needed and consumed in the postprandial phase for dissolution of many dietary micronutrients other than calcium, such as, for example, iron, magnesium and zinc.

The need for elemental calcium is ≥ 800 mg/day, the amount which has to be dissolved and ionized from the dietary calcium salts within a relatively short period of time (the normal stomach will empty within 1–2 h after ingestion of food). It may be estimated that the acid required for fully dissolution of 800 mg of elemental calcium from 2 g of calcium carbonate is about 40 mmoles of hydrochloric acid, which corresponds to the amount of acid secreted maximally in 1–2 h by a normal healthy stomach. Therefore, the quantity of acid needed is high, which may mean that acid secretion must be normal or nearly normal to ensure a physiologically effective dissolution of all nutrients ingested.

As a simplified summary, hydrochloric acid (the "stomach acid machine") ionizes calcium salts, e.g. calcium carbonate, to one Ca^{2+} ion and two Cl^- ions in the stomach, resulting in the production of water and CO_2, the latter being mostly exhaled in the breath. Small amounts of soluble bicarbonates may also be formed by the reaction of dissolved CO_2 with calcium carbonate. Thus, calcium chloride ($CaCl_2$) is formed, which is highly water-soluble in neutral and even in alkaline milieu. At pH 7, some 50–70 g of calcium chloride will be maximally dissolved and ionized into 100 ml of water, the pKa value of calcium chloride being above pH 7, indicating that the calcium is well ionized and soluble when transferred from the stomach acid to the small intestine as calcium chloride.

The reaction of hydrochloric acid with calcium salts is so basic a physiological phenomenon in the stomach that two British gastroenterologists have recently suggested a new breath test for non-invasive assay of gastric acid secretion. In the test, ^{13}C-labeled calcium carbonate is ingested, after which CO_2 in the breath is measured with mass spectrometry [20]. If the stomach is achlorhydric, no labeled CO_2 will appear in the breath.

Acid-inhibitory drugs

Acid-inhibitory drugs, PPIs in particular, decrease acid secretion significantly, as is well known. Long-term use of these drugs in high doses may raise the risks of calcium malabsorption and traumatic bone fractures slightly, but significantly, as was considered in two recent meta-analyses [21,22]. Notably, the use of PPIs in high doses for longer than 1 year has been reported to increase the incidences of hip or other osteoporotic fractures significantly in several large recent surveys from the USA and Europe [23–27].

Even relatively short exposures to PPIs may decrease the mineral density in human bone tissues and the absorption of calcium in the gut [28]. Ordinary doses (20 mg/day) of PPIs are reported to decrease bone mineral density after 18 months [29]. Correspondingly, high doses of PPI (60 mg/day) for even a few days were shown to decrease the absorption of calcium in some clinical experiments [30,31].

The mechanisms of PPI-induced decrease of bone mineral density have not been explicitly defined and are under discussion, but are more likely to be related to the acid-inhibitory capacity of these drugs than to possible actions of PPIs on bone cells [25]. Supporting this view, not only PPIs but also the long-term use of H_2-receptor antagonists result in a slight but significant reduction in bone mineral density, particularly in the elderly [32,33].

Atrophic gastritis

Atrophic gastritis (loss of normal glands in the mucosa) in the gastric corpus results in a permanently hypochlorhydric or achlorhydric stomach. Atrophic gastritis is a human, *in vivo* model of all disease conditions associated with a persistently low intragastric acidity. The significance of atrophic gastritis to the malabsorption of vitamins, micronutrients and medicines has, however, been surprisingly poorly studied. There have been few reports since the 1960s emphasizing the risk of malabsorption of calcium in patients with achlorhydria and atrophic stomach mucosa [12,34,35]. These reports suggest that bone density in the lumbar spine tends to decrease in patients with pernicious anemia (patients with pernicious anemia always have severe corpus atrophy and achlorhydric stomach), even though negative reports have also been published [1,2,36]. It is noteworthy that, in one published study, the decrease in bone mineral density was found to be linearly related to a decline in serum levels of pepsinogen I (PgI) [37]. PgI, a precursor of proteolytic pepsin enzyme in the gastric juice, is a serum biomarker of the structure and function of the oxyntic mucosa in the gastric corpus and fundus, its serum/plasma level tending to decrease linearly with increase in the grade of atrophy in the oxyntic mucosa.

In atrophic corpus gastritis, the normal acid-secreting oxyntic glands and parietal cells will gradually disappear over the course of years and decades, and will finally be lost completely. The stomach will first be hypochlorhydric and finally achlorhydric. Atrophic gastritis by itself is caused by *Helicobacter pylori* infection in most cases, or may also be autoimmune in origin. The decrease in capacity of the stomach mucosa to secrete acid is associated with increases in the grade of atrophy and in gland loss. In patients with atrophic gastritis even of a mild degree, both basal and maximal acid output (MAO) are reduced by 50% [38]. The MAO in subjects with mild atrophy is around 15 mmol/h on average, whereas in subjects with a healthy oxyntic mucosa this output is some 30–50 mmol/h [38].

The prevalence of atrophic gastritis tends to increase with age, and the disease is relatively common, even in developed countries [39,40]. Interestingly, the malabsorption of calcium is also considered to be age-related and increases in prevalence with age [41]. In Finland, 30–40% of elderly people have chronic gastritis (*H. pylori* infection) at present and it is estimated that approximately half of them will develop atrophic corpus gastritis of some grade during their lifetime, if the infection is not eradicated [40]. Some 2.5–5% of these people will have advanced

(moderate or severe) atrophic gastritis and a practically achlorhydric stomach in those aged over 50 years [40,42]. In Finland (total population 5.5 million) this means that 35,500–100,000 people may have a clinically significant hypochlorhydric or achlorhydric stomach due to atrophic gastritis, and may be at risk for malabsorption of all essential micronutrients, including calcium. It is noteworthy that these patients often remain undiagnosed, probably since they tend to be asymptomatic.

Gastric surgery

Although the mechanisms are poorly known, several clinical observations support the importance of the acid-secreting stomach for calcium homeostasis and bone health. Gastrectomy (including bariatric surgery) and surgical bypasses of the proximal jejunum are obvious risks for bone disease and calcium malabsorption in the longer term. Even partial gastrectomies (both Billroth I and Billroth II reconstructions) result in a decrease in bone mineral density in both clinical patients and animal experiments [43–46].

In rats, gastrectomy or fundectomy results in a decrease in blood calcium concentration in just 3 weeks, this decrease being rapid, severe and even fatal if the fundectomy is done in parathyreoidectomized rats [43]. There also are observations in clinical patients suggesting that the blood concentration of calcium will decrease in the long run after total gastrectomy [47,48], even though studies have also been published indicating that the gastrectomy does not influence blood levels of calcium in the short term [49,50].

What are the clinical considerations?

The calculations of the Osteoporosis Foundation in Finland show that approximately 400,000 persons have a decreased mineral bone density (www.osteoporoosiliitto.fi/). Annually, 30,000–40,000 patients in Finland have traumatic bone fractures related to low bone mineral density. Prescriptions for supplementary calcium in these patients may require examinations and even prior tests of gastric acid secretion and atrophic gastritis, considerations of the use of potent acid-inhibitory drugs, and some estimation of the capacity of the stomach to dissolve calcium salts. For the identification of patients with atrophic gastritis, such clinical examinations comprise gastroscopy with biopsy examination of the gastric corpus and fundus mucosa, or simple tests of the serum/plasma levels of stomach-specific biomarkers (PgI and PgII, amidated gastrin-17 and *H. pylori* antibodies) [42]. These biomarker panels are inexpensive and reliable new diagnostic alternatives and commercially available. For these tests, the blood sample can be taken even from the finger tip. Due to their extreme simplicity, these tests are very useful diagnostic tools for the identification and screening of subjects with atrophic gastritis and persistent stomach hypoacidity, even in primary care.

In the presence of a healthy stomach with a normally functioning "acid machine", absorption of supplementary calcium may not be a clinical problem, and all commercially available calcium salts are likely to be of equivalent bioavailability, even though only some 20% of the dietary calcium ingested as a supplement is normally absorbed [51,52].

On the other hand, in patients with an acid-free or hypoacid stomach, absorption problems may occur with most of the supplementary oral calcium salts. In these patients, to ensure maximal calcium ionization, the best option could be a prescription of the calcium salt as the most soluble compound available, with the addition of vitamin D, at small doses but given several times per day on an empty stomach, and with abundant water or acid juice, or as effervescent tablets. In hypochlorhydric subjects, this strategy may ascertain the best maximal quantity of ionized calcium in the maximal volume of gastric juice entering the small intestine daily from the stomach.

The absorption of calcium from natural foods, such as milk, beans, cheese and fish, may also be worth emphasizing, and worthy of therapeutic consideration in subjects with a hypochlorhydric stomach, even though the absorption of calcium from both food and dietary supplements is supposed to be similar [53]. Considering the best soluble calcium formulations, calcium chloride in the form of effervescent tablets, calcium ascorbate or calcium citrate are some available options [54]. However, new problems may also occur with some of them. For example, calcium ascorbate may be of limited applicability as a supplement in the long term and in high doses, due to risks of renal stones related to endogenous conversions of ascorbates to oxalates [55].

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