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Review Article

Nutritional Deficiencies Associated with Gastroesophageal Reflux Disease (GERD) in Elderly/Older Adults

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ABSTRACT

Introduction: Gastroesophageal reflux disease (GERD) is the most common upper gastrointestinal disorder encountered in the elderly patient. GERD is one of the highly prevalent diseases seen in the clinical practice. In the elderly population, few studies have addressed the prevalence of GERD. It is estimated that 20-30% of the US population experience weekly symptoms of GERD, and two out of five people experience heartburn or acid regurgitation at least once a month.

Methods: To ensure peer-review articles were used, the search engine, PubMed was utilized along with medical reference-related websites and US Department websites as well as professional organizations. Some medications used by older adults may promote acid reflux, prescription treatments include proton pump inhibitors (PPIs), coating agents, H2 blockers and over-the-counter medications that contain antacids or decreased dosages of the prescription strength H2 blockers and PPIs**.**

Discussion: Decreased stomach acidity could be responsible for risk of nutrient deficiencies including vitamin B12 (cobalamin), vitamin C (ascorbate), calcium, iron and magnesium deficiencies or medications that are used to alleviate the symptoms of GERD may also be responsible for increasing the risk for deficiencies.

The purpose of this review is to demonstrate and provide reasons why regular assessment, screening, testing, and/or clinically evaluating nutritional deficiencies common in older adults and relating to physical pathogenesis and/or drug treatments of GERD, should be added to the GERD treatment protocol for older adults.

Introduction

According to the Merck Manual (2020), Gastroesophageal Reflux Disease (GERD) is the "incompetence of the lower esophageal sphincter [which] allows reflux of gastric contents into the esophagus". Reflux that occurs over a prolonged period of time leads to complications including inflammation of the esophagus (esophagitis), abnormal scarring, and stricture, and is also associated with throat, vocal irritation, or respiratory complications [1, 2]. Mild or new cases of GERD respond well to diet and lifestyles changes without medications; however, more serious GERD cases may require intensive therapies, medications and/or surgical interventions that can interfere with nutrient absorption, transport and/or utilization [2, 3].

GERD is the most common upper gastrointestinal disorder encountered in the elderly patient. GERD is one of the highly prevalent diseases seen in the clinical practice [4]. In the elderly population, few studies have addressed the prevalence of GERD. Additionally, most studies assess regurgitation and heartburn as symptoms and some of the other symptoms such as chest pain, cough, laryngitis are not assessed [5]. In 2014, GERD prevalence was 18.1-27.8% in North America, 8.8-25.9% in Europe, 2.5-7.8% in East Asia, 8.7-33.1% in the Middle East, 11.6% in Australia, and 23.0% in South America [6]. It is estimated that 20-30% of the US population experience weekly symptoms of GERD, and

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two out of five people experience heartburn or acid regurgitation at least once a month [6-8]. In 2015, one large-scale study (n=71k), found that GERD is more common in whites than in Asians, and they found no relationship between age and the risk for GERD [9]. There is an increased prevalence of gastritis and complications in the elderly [10]. According to the 2017 United States (US) Census, there are 49.3 million free living people over the age of 65 living in the US. This is 15.4% of the population. If we consider those aged 55 and greater, this number is 28.3% [11]. If the studies above are accurate, it is likely that almost 30% of US older adults may experience GERD symptoms.

The purpose of this review is to demonstrate and provide reasons why regular assessment, screening, testing, and/or clinically evaluating nutritional deficiencies common for older adults and relating to physical pathogenesis and/or drug treatments of GERD, should be added to the GERD treatment protocol for older adults in accordance with the Dietary Reference Intake (DRI) as a Special Consideration.

Materials and Methods for Selection

To ensure peer-review articles were used, the search engine, PubMed was utilized [12]. The keywords included Gastroesophageal Reflux Disease, GERD, gastritis, gastroenterology, proton pump inhibitors (PPIs), GERD treatment, nutritional deficiencies, vitamin B12, vitamin C, vitamin D, iron (Fe), calcium (Ca), magnesium (Mg), older American, older adult, aged, elderly, as well as combinations of keywords. References associated with the articles were also examined to determine additional information, and review articles were utilized if the author/reviewer(s) came to original conclusions based on the studies cited in their review(s). Medical reference-related websites, health professional organizations, and US Department websites such as the Merck Manual Professional Version, emedicine Health American Gastroenterological Association website, US Census, and others were also utilized [1-3, 11].

Results

I Medications

Medications typically used by older Americans may promote acid reflux include anticholinergics, calcium channel blockers, theophylline, tricyclic antidepressants, and sedatives as well as nonsteroidal anti-inflammatory drugs, steroids, iron sulfate, antibiotics, and potassium chloride tablets [5]. Prescription treatments for GERD usually include proton pump inhibitors (PPIs) such as omeprazole/Prilosec, lansoprazole/Prevacid, pantoprazole/Protonix, or esomeprazole/Nexium and/or coating agents (sucralfate/Carafate) which coat membranes and provide a barrier to the gastric secretions [1, 3, 13, 14]. Promotility drugs (metoclopramide/Reglan/Clopra/Maxolon and bethanechol/ Duvoid/ Urabeth/ Urecholine) also may be prescribed, which tighten the lower esophageal sphincter and promote rapid gastric emptying [1, 3, 13, 14]. Over-the-counter medications commonly used to treat GERD symptoms include antacids (Gaviscon, Maalox, Mylanta, and Tums), histamine-2 receptor blockers (H2 blockers) (cimetidine/ Tagamet, famotidine/ Pepcid, ranitidine/Zantac and nizatidine/Axid) [3, 14]. Most, if not all of the medications listed above have side effects which also might lead to vitamin and mineral deficiencies.

II Side Effects of Medications Used to Treat GERD

Antacids may have side effects such as diarrhea or constipation and the side effects for prokinetics are nausea, diarrhea, fatigue, depression, anxiety, or delayed physical movements. Diarrhea and nausea decrease the ability of nutrients to be absorbed, while fatigue, depression and movement restriction can lead to decreased food intake [15]. The side effects of histamine H2-receptor antagonists (H2 blockers) and PPIs are rare, but can include headaches (Famotidine, Cimetidine, and Ranitidine), diarrhea, dizziness, rash, and gynecomastia (Cimetidine) and the side effects of PPIs are headache, diarrhea, constipation, nausea, and/or itching [16, 17].

III Possible Mechanisms for Nutritional Deficiencies Associated with GERD

H2 blockers and PPIs both work by decreasing the production of hydrochloric acid (HCl) in the stomach [16, 17]. PPIs are the preferred treatment of upper gastrointestinal disorders and have been associated with an increased risk of vitamin B12 (cobalamin), vitamin C (ascorbate), calcium, iron and magnesium deficiencies or altered nutrient metabolism [15, 18]. An acidic stomach environment and pepsin are required for protein digestion. HCl denatures the protein which sequentially, unfolds/uncoils the protein for eventual cleaving by proteases and this uncoiling also releases bound/enclosed vitamins and minerals. Additionally, low pH is needed for production of proteases. Low pH in the stomach activates pepsinogen to pepsin, which cleaves peptide bonds at the aromatic (cyclic) amino acids [19].

Vitamin B12 is one of these enclosed vitamins. After release of B12 from the protein, it binds to transcobalamin-1 (haptocorrin/R-factor) and released by trypsin (which also requires an acidic environment to form) and then binds to gastric intrinsic factor (IF). Then, this B12-IF complex binds to a receptor located in the ileum for absorption [19, 20]. Vitamin B12 deficiency is estimated to affect 10-15% of those over 60 years of age, and according to the US National Institute of Health, between 10-30% of older Americans may be unable to absorb vitamin B12 normally [21, 22]. Therefore, a supplement of B12 may be needed to bypass the intestinal absorptive process intra-nasally, intramuscularly, or sublingually. Oral vitamin B12 supplements should not be affected by PPIs, as supplemental forms are not protein-bound; thus, gastric HCl and pepsin are not required for B12 supplement absorption. It has been suggested that additional B12 supplementation is not needed, unless blood biomarkers and clinical symptoms indicate a vitamin B12 deficiency. However, until clinical trials have been completed (several are ongoing), it is recommended to assess vitamin B12 status before and during a PPI regimen [23]. Vitamin B12 deficiency, if left untreated, may cause irreversible neurological damage and macrocytic anemia [22].

Vitamin C (ascorbic acid) and vitamin C containing fruits (such as citrus and tomato products) are avoided by some people due to concerns that it causes more acid and has been associated with nausea in some people. Additionally, PPIs generate an alkaline gastric environment – potentially decreasing vitamin C absorption [24]. However, it is currently not recommended to consume vitamin C supplements [25]. Dietary vitamin C aids in the absorption of iron (Fe) and magnesium (Mg) by the

reduction of ferric to ferrous iron, which is a requirement for the uptake of iron into the mucosal cells from the lumen [26]. Ascorbic acid facilitates iron absorption by forming a chelate with ferric iron at acid pH that remains soluble at the alkaline pH of the duodenum [27]. Fe absorption is dependent on vitamin C presence because dietary Fe is in an insoluble form (Fe3+). Fe3+ is then reduced by a reductase enzyme and dietary ascorbic acid, and subsequently absorbed [19]. If acid levels decrease and/or vitamin C intake is low, Fe absorption decreases [28].

Therefore, long term vitamin C and/or Fe insufficiency can potentially become Fe deficient when the person with GERD both avoids vitamin C containing foods and intakes PPIs or H2 blockers. Fe is needed for cellular respiration, cell growth and regulation, electron-transfer reactions and Fe controls gene expression, deficiency of iron can along with vitamin C, result in microcytic anemia. Long-term use (> 1 year) of PPIs has been reported to increase the risk of an iron deficiency; therefore, it is recommended to monitor iron deficiency symptoms during prolonged PPI regimens [29]. Interestingly, PPIs have been demonstrated to decrease iron absorption via inhibition of intestinal ferroportin by upregulating hepcidin [30]. Another consideration is that in a deficiency of both Fe and folate, the hematological changes will likely be unclear. Vitamin B12 deficiency may result in megaloblastic anemia and Fe anemia results in microcytic anemia, and so determination of the erythrocyte size may not be possible as a possible deficiency determination. Vitamin B12 deficiency results in the same hematological changes (megaloblastic anemia) as folate insufficiency/deficiency, because vitamin B12 deficiency can cause a secondary folate deficiency, and excess folate can mask a vitamin B12 deficiency [31].

Vitamin D levels are lower in persons with chronic atrophic gastritis, older adults that live in northern industrialized cities, and those with malabsorptive disorders or who are institutionalized with limited access to the outdoors [32-34]. The biosynthesis ability of vitamin D decreases with age, and adults over the age of 65 years produce 4 times less vitamin D than adults aged 20-30 years old [33]. Vitamin D is absorbed in the small intestine and the absorption site is located very close to the stomach in the small intestine. Vitamin D absorption requires the presence of stomach acid, bile, and pancreatic products, and dietary fat and vitamin D along with bile forms micelles in order to be efficiently absorbed [35]. We hypothesize that Ca levels may be directly affected too, since calcium uptake is about 90% controlled by vitamin D, and if vitamin D is not being absorbed, it follows that there will be less calcium absorbed. Nonetheless, prolonged use of PPIs has been associated with hip, wrist, and spinal fractures, which may indicate a lack of absorption of vitamin D and/or calcium [15]. More studies are needed to investigate our theory.

However, most studies suggest that PPIs likely do not affect vitamin D status [36].The major function of Mg is in bone formation and in ATP reactions [37]. Several articles report hypomagnesemia in long-term PPI treatment [38-41]. A recent meta-analysis article also reported that PPI use is associated with increased odds of hypomagnesemia, perhaps due to PPIs "aggravating" the *TRPM6*/*TRPM7* genes that may lead to decreased magnesium intestinal absorption [42]. The DRIs also suggest that Mg intake is low, absorption is decreased, and urinary Mg is increased in elderly people [37]. Therefore, the monitoring of serum magnesium levels should be considered in patients with chronic use of PPIs or GERD, since it is likely that there is a dose-response relationship [38, 42]. The current treatment for hypomagnesemia associated with PPIs is magnesium supplementation and discontinuation of the PPI. One article suggested discontinuation of PPI treatment as the most important treatment for hypomagnesemia [38].

Discussion

Likely, the deficiency risks are low in the general population, however, in elderly and malnourished patients, those on chronic hemodialysis and on concomitant PPI therapy (or on other stomach acidity-decreasing medications) are at risk for vitamin B12, vitamin C, vitamin D/calcium, iron and magnesium deficiencies. Presently, there are no recommendations for screening or supplementation of vitamins or minerals for older GERD therapy patients. The present recommendations for best practice are not specific to special populations, but there are Special Considerations (per the Dietary Reference Intakes (DRI)/ National Academy of Sciences (NAS)) for older adults in the US population for vitamins C, B12 and D, Fe, and Ca [1, 22, 25, 28, 31, 33]. Our recommendations for possible nutrient deficiency screenings are not in total conflict with the best practice advice of the American Gastroenterological Association concerning PPIs and GERD. We agree with "Best Practice Advice 8: Long-term PPI users should not routinely raise their intake of calcium, vitamin B12, or magnesium beyond the Dietary Reference Intake, Recommended Dietary Allowance (RDA) [43]. It is not necessary to increase any nutrient above the RDA, and this paper is not encouraging supplementation above RDA requirements. Best Practice and Advice 9 states that: "Long-term PPI users should not routinely screen or monitor bone mineral density, serum creatinine, magnesium, or vitamin B12" [43].

However, in the case for older adults, the screening for bone mineral density, creatine, and Mg are typically already done in conjunction with bone screening health, and vitamin B12 is screened for as an age-related deficiency due to decreased acid levels in older Americans [20, 25]. Possible deficiencies of vitamin B12, Ca, and vitamin D in older Americans (with or without GERD) are of concern in the US by the DRI/NAS [31, 44, 45]. Therefore, we suggest that physicians treating older adults for GERD/GERD symptoms can also utilize these tests for possible key nutrient deficiency screenings, and if needed, suggest vitamin B12 supplements or alternate forms of B12 (nasal, intra-muscular, or sublingual). Ca, Fe, and Mg levels are commonly obtained from blood laboratory chem panels and could be used to screen for possible deficiency risks. Additionally, routine 25-hydroxy vitamin D blood test levels could also be utilized and evaluated for possible changes during GERD treatment.

Conclusions and Suggestions for Health Professionals

Diet records of patients with GERD can be useful for discovering potential interventions (avoidance of eating/drinking before bedtime, removal of EtOH, caffeine, spicy or fried foods, chocolate, etc…from the diet), but due to the physiological processes and drug interactions/use associated with GERD, dietary intake alone may not be reflective of adequate nutrient status. In those persons that present symptoms or

clinical diagnosis of GERD, it is advisable to screen, assess, test for, or clinically evaluate nutritional deficiencies that could be related to both the physical pathogenesis which affect both the absorption and transport of nutrients due to prescription or over-the-counter drug use for GERD treatment and/or achlorhydria [46]. It is important to also reiterate that the documented prevalence of age-related nutrient deficiencies or risk for deficiencies in older adults warrants screening and/or assessment and should be done in accordance to the DRI/NAS recommendations as routine part of older adult care, especially if the patient has GERD or GERD-like symptoms.

Conflicts of Interest

None.

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Author Contributions

BBW wrote the first draft of the article and EF contributed to the editing and writing of the article.

Abbreviations

Ca: Calcium
DRI: Dietary Reference Intake
IF: Gastric intrinsic factor
GERD: Gastroesophageal reflux disease
H2 Blocker: Histamine H2-receptor antagonists
Fe: Iron
Mg: Magnesium
NAS: National Academy of Sciences
PPIs: Proton pump inhibitors
RDA: Recommended Dietary Allowance
US: United States

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