Helicobacter pylori and Osteoporotic Fractures

Subjects: Others

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Osteoporosis (OP) and osteoporotic fractures (OFs) are common multifactorial and heterogenic disorders of increasing incidence. Helicobacter pylori (H.p.) colonizes the stomach approximately in half of the world's population, causes gastroduodenal diseases and is prevalent in numerous extra-digestive diseases known to be associated with OP/OF. The studies regarding relationship between H.p. infection (HPI) and OP/OFs are inconsistent. The current review summarizes the relevant literature on the potential role of HPI in OP, falls and OFs and highlights the reasons for controversies in the publications. In the first section, after a brief overview of HPI biological features, we analyze the studies evaluating the association of HPI and bone status. The second part includes data on the prevalence of OP/OFs in HPI-induced gastroduodenal diseases (peptic ulcer, chronic/atrophic gastritis, and cancer) and the effects of acid-suppressive drugs. In the next section, we discuss the possible contribution of HPI-associated extra-digestive diseases and medications to OP/OF, focusing on conditions affecting both bone homeostasis and predisposing to falls. In the last section, we describe clinical implications of accumulated data on HPI as a co-factor of OP/OF and present a feasible 5-step algorithm for OP/OF risk assessment and management in regard to HPI, emphasizing the importance of an integrative (but differentiated) holistic approach. Increased awareness about the consequences of HPI linked to OP/OF can aid early detection and management. Further research on HPI – OP/OF relationship is needed to close current knowledge gaps and improve clinical management of both OP/OF and HPI-related disorders.

Keywords: Helicobacter pylori infection ; Osteoporosis ; Fractures ; Falls ; Medications ; Management.

1. Introduction

Both *Helicobacter pylori* (*H.p*.) infection (HPI) and osteoporotic fractures (OFs) constitute major challenges for public health systems globally due to huge clinical and economic burdens. Accumulating evidence suggests that in health and disease stomach and gut directly and indirectly via multiple neurohormonal pathways regulate the musculoskeletal and other systems by controlling appetite, food intake, absorption of nutrients and energy balance [1][2][3][4][5][6][7]. These physiological relationships (including the gut/stomach–bone axis) may be affected by HPI. HPI is associated with numerous diseases in and outside the stomach, many of which have the potential to influence bone and muscle status, predispose to falls and, consequently, contribute to OFs. As *H.p*. colonizes the human stomach in over 50% of the world's population [8][9][10][11] and HPI frequently coexists with OP/OF, deeper understanding the relationships among HPI-related diseases, the skeleton and falls becomes highly important; it may help to improve the preventive and therapeutic strategies for OFs. However, only a small number of studies have examined the association between HPI and bone status and the results have been controversial [12][13][14]. Although conventional wisdom suggests that in clinical practice the two main components of OFs—OP and falls—need to be integrated and viewed under complementary angles, the possible contribution of HPI-associated diseases to falls has not been addressed in the literature systematically.

2. HPI-Induced Upper Gut Diseases and Osteoporotic Fractures

2.1. Peptic Ulcer Disease

HPI is responsible for 95% of duodenal ulcers and 85% of gastric ulcers which usually arise at the junction of the antral and corpus mucosa. At least eight studies showed that PUD is an independent risk factor (RF) for OF [15][16][17][18][19][20][21][22]. History of PUD has been found to be associated with an increased risk of osteoporotic thoracic vertebral fracture in a large population sample of Finnish men (*n* = 30,000) but not in the women [16]. In a Polish study of 240 females [17], women with PUD (*n* = 143, mean age 60.3 years) not using hormone replacement therapy (HRT) had lower BMD in all studied regions as compared to controls without PUD (*n* = 120, mean age 58.4 years); moreover, among HRT users, the BMD in lumbar vertebrae and Ward's triangle was also significantly lower in women with PUD, whereas calcium intake was similar in both groups. Two reports from USA demonstrated an association between PUD and periprosthetic fractures after total hip replacement (*n* = 14,065; hazard ratio (HR) 1.5, 95% CI 1.1–2.2) [19] and total knee arthroplasty (*n* = 17,633;

HR 1.87, 95% CI 1.28–2.75) [18]. In the Japanese study (*n* = 200, 105 women), multivariate analysis revealed that PUD (OR 4.98; 95% CI 1.51–16.45), along with HPI (OR 5.33; 95% CI 1.73–16.42) as well as common RFs (age, female gender, BMI), was independently related to OP [15]. A population-based study from Taiwan [20], which included 27,132 patients (aged ≥18 years) diagnosed with PUD and 27,132 randomly selected subjects (age- and gender-matched) without PUD, found that the OP risk (adjusted for covariates) was 1.85 times greater in the PUD group (13.99 vs. 5.80 per 1000 person-years). The highest risk was observed one year after PUD diagnosis (HR 63.4, 95% CI 28.2–142.7); use of a PPI significantly increased the OP risk (HR 1.17, 95% CI 1.03–1.34). Consistent with these data are results from two most recent large South Korean studies [21][22]. In the first prospective study (*n* = 10,030), PUD patients demonstrated a significantly higher OP risk (men: HR 1.72, 95% CI 1.02–2.92; women: HR 1.62, 95% CI 1.20–2.18); OP developed in 29.9% women and 11.1% men with PUD vs. 16.5% and 4.8% in controls, respectively [21]. The second report [22], based on analysis of 50,002 patients with PUD and equal number of controls matched by age, gender, past medical history, income and residence region, found increased risk of OP in PUD regardless of gender (adjusted HR 1.36, 95% CI 1.33–1.40). In contrast, a retrospective cross-sectional study from China (*n* = 867, with PUD 351 patient) reported that PUD was significantly associated with decreased BMD only in univariate analysis (OR 1.37, 95% CI 1.03–1.82) [23]. Lastly, in a cohort of patients operated for PUD between 1956 and 1985 (pre-HPI era) and followed for 30 years, the risk of OF was significantly (and independently of surgical procedure type) increased showing a standardized incidence ratio of 2.5 for the proximal femur, 4.7 for vertebra and 2.2 for the distal forearm [24].

Although these reports, as any observational study, cannot indicate causality, the relationship between PUD and fragility fractures is suggested. It appears that PUD may approximately double the risk of OP/OF.

2.2. Chronic/Atrophic Gastritis

It is well established that HPI is responsible for the majority (>90%) of chronic/atrophic gastritis [25][26] and plays an important role in the initiation of autoimmune atrophic gastritis [26][27][28]; the latter occurs in 2% of the general population with a higher prevalence in older (>60 years) females [29]. CagA+ *H.p.*, especially the East-Asian type, compared to the CagA− type induces more severe gastritis and mucosal atrophy and is more closely associated with gastric cancer [30]. Simultaneous presence of the CagA and other virulence factors (VacA, Helicobacter cysteine-rich protein C and the chaperonin Gro) increases the risk of chronic atrophic gastritis (a precursor lesion to gastric cancer) 18-fold [31].

Two publications by a Brazilian group reported that in postmenopausal women neither HPI, no atrophic chronic gastritis were associated with BMD or OP [32][33]. No association between HPI-induced chronic gastritis and OP was also observed in an Iranian study [34]. In contrast, a Norwegian study [35] found that, in patients with chronic atrophic gastritis, compared to sex- and age-matched controls, bone formation markers (OC, sclerostin, OPG and OPG/RANKL ratio) were lower and the incidence of OP was higher (the latter abnormality only in males). In older Korean women, presence of atrophic gastritis was significantly linked to OP after adjusting for seven variables including age, BMI, metabolic and lifestyle variables (OR 1.89, 95% CI 1.15–3.11) [36]. Similarly, Japanese men with HPI-induced atrophic gastritis (defined by serum pepsinogen I and pepsinogen II levels) demonstrated an increased risk of low trabecular bone density (OR 1.83, 95% CI 1.04–3.2) [37]. In a small Norwegian study (*n* = 17 patients, 41 controls), subjects with chronic atrophic gastritis, compared to controls, have: decreased circulating levels of OC (bone formation marker), sclerostin (an inhibitor of bone formation), osteoprotegerin (OPG) and OPG/RANKL ratio; unaffected levels of P1NP (bone formation marker) and bCTX (bone resorption marker); and (in males only) lower lumbar BMD and increased frequency of osteopenia and OP. No difference in bone quality assessed by microidentation was found [35]. These features were interpreted as suggestive of decreased bone formation and higher bone resorption in patients with chronic atrophic gastritis. A study from Germany reported that OP development was associated with gastritis/duodenitis (OR 1.14; $p = 0.045$) and PPI use [38]. A retrospective cohort study of Korean premenopausal women in their 40s (*n* = 983) who had undergone a 48-month follow-up assessment of BMD of L1–4 showed that atrophic gastritis (diagnosed by gastroduodenoscopy) was significantly associated with bone loss (adjusted for confounding factors); patients with persistent atrophic gastritis exhibited a greater decrease in BMD and the prolonged duration of the disease correlated positively with the amount of BMD reduction [39]. Atrophic gastritis and CagA seropositivity were associated with lower hemoglobin levels, and anemia was 2.6-times (in women) and 1.5-times (in men) more common among persons with atrophic gastritis [40]. Severe hypochlorhydria or achlorhydria were found in 44% of patients with idiopathic iron deficient anemia and in 1.8% among healthy controls [41].

Molecular mimicry between *H.p.* antigens and gastric H/K-ATPase has been proposed as a mechanism responsible for the association between HPI and development of chronic atrophic autoimmune gastritis [25][28][42][43][44][45]. In 20–30% of patients with HPI, autoantibodies to the H/K-ATPase were identified. In this organ-specific autoimmune disorder, autoantibodies to gastric parietal cells (in 90% of patients) and intrinsic factor (in 70% of patients) cause gastric gland atrophy, achlorhydria and hypergastrinemia (which induces hyperplasia of the ECL cells) resulting in vitamin B12 and iron malabsorption/deficiency and leading to megaloblastic/pernicious anemia and/or iron-deficient anemia, respectively [46][47]

[48][49][50][51]. The disease is clinically heterogeneous and may have an asymptomatic course. An inverse correlation between *H.p.* density and vitamin B12 levels has been shown [52]. Low serum B12 levels affect DNA synthesis, an important factor for bone remodeling. Vitamin B12 (and other B vitamins—B2, B6 and folate—linked to homocysteine metabolism) is regarded an essential factor for bone health [23][53][54][55][56][57][58][59][60][61][62]. Vitamin B12 deficiency was reported to have an increased fracture risk: 1.7- to [63] 1.9-fold [64] for hip fracture, 1.8-fold for vertebral fracture [64] and 2.9-fold for distal forearm fracture [64]. Peripheral neuropathy, occurring in vitamin B12 deficient patients [65], undoubtedly, increases risk of falls. Reversal of severe OP associated with pernicious anemia has been demonstrated after vitamin B12 replacement combined with etidronate (an antiresorptive bisphosphonate) therapy [66]. Repletion of B12 resulted in an 80% reduction in hip fracture risk among stroke patients [56]. However, recent trials and a meta-analysis did not show a preventive effect of treatment with vitamin B12 and folic acid on fracture risk [67]. Daily supplementation with B vitamins did not affect markers of bone turnover and did not reduce fracture risk in middle-aged and older women at high risk of cardiovascular disease [68]. Interestingly, a significantly increased hip fracture risk persists years after correction the vitamin B12 deficiency, indicating the independent pathophysiological importance of chronic atrophic gastritis and achlorhydria [63]. Chronic atrophic autoimmune gastritis is associated with multiple other nutritional deficiencies, including calcium, vitamins D, C and folic acid, each of which may affect the skeletal, nervous and hematological systems [50][58][69]. In addition, autoimmune gastritis clusters with autoimmune thyroiditis and type 1 diabetes mellitus [26][28], conditions linked to OP/OF. Iron deficiency with or without anemia has also been recognized as a RF for OP/OFs in many [70][71][72][73][74][75][76][77] but not all [78][79] studies (the topic is discussed in following sections).

Importantly, pharmacologic HPI eradication results in gradual and significant improvement in chronic atrophic gastritis [80][81][82]. On the other hand, when interpreting the studies on HPI-induced chronic/atrophic corpus gastritis, it has to be kept in mind that with progression of the severity and extension of atrophic lesions *H.p.* is spontaneously eradicated [44][83][84].

In conclusion, findings in patients with HPI-induced (especially with cagA+ strains) chronic/atrophic gastritis suggest that gastric corpus structural and functional (e.g., hypoacidity, hormonal disbalance, etc.) changes and associated nutritional deficiencies may negatively affect bone metabolism, neuromuscular and a wide range of other functions predisposing to OP, falls and OFs.

2.3. Gastric Cancer

HPI is an important determinant of neoplastic gastric lesions classified by WHO/IARC [85] as class 1 human carcinogen for non-cardia gastric adenocarcinomas [86][87][88]. HPI increases the cancer risk 5.8–7.9-fold [86][89], and the risk is 2–3-times higher in subjects infected with cagA+ strains [87][90][91][92].

According to most but not all studies [93][94], gastric cancer survivors who underwent gastrectomy, compared to the general population [95][96][97][98][99][100][101][102][103][104][105] or age- and sex-matched healthy controls [106][107][108][109], have significantly lower BMD, higher prevalence of osteopenia/OP (38.3% [97] to 55% [104]) and higher fracture rates (approximately 40% [97][101][106]). Bone loss (although of a lesser degree) was also reported in gastric cancer survivors after endoscopic tumor resection undertaken in early stage [103]. In South Korea, nationwide cohort study of cancer survivors who underwent gastrectomy (n = 133,179 matched to non-cancer controls, 1:1) demonstrated an increased risk of fractures (HR 1.61; 95% CI 1.53–1.70), which was higher in patients after total gastrectomy (HR 2.18; 95% CI 1.96–2.44) and adjuvant chemotherapy (HR 2.01; 95% CI 1.81–2.23); the elevated OF risk was significantly associated with anemia [109]. In a report from Japan, the adjusted hazard ratio for OF in men after gastrectomy (n = 132) was 2.55 (95% CI 1.17–5.55) and 3.56 (95% CI 1.33–9.52) in those who survived >20 years [110].

A considerable amount of OFs after gastrectomy occurs in the early postoperative period [101][104]. Bone remodeling imbalance with disproportionately increased bone resorption [98][100], decreased BMD [111] and higher fracture rates [101] were often observed during the first postoperative year. Altered bone metabolism was reflected by increased serum concentrations of bone resorption markers (C-terminal telopeptides of type I collagen, deoxypyridinoline and pyridinoline) [100], elevated serum PTH and alkaline phosphatase (ALP) levels [98][111] and associated with vitamin D deficiency [111][112][113][114][115]. Some researchers, however, observed no changes in BMD, a slight elevation of OC and only minor increase in PTH levels after total gastrectomy [93]. The causes of OP and subsequent fractures in patients with gastric cancer are multifactorial. Malabsorption (especially of calcium, phosphate, iron, proteins, vitamins B12 and D), malnutrition, weight loss, use of certain medications (e.g., fluorouracil and cisplatin which induce apoptosis of osteoblasts and increase osteoclast activity [116][117][118], hormones, radiotherapy, comorbidities, physical inactivity, old age and smoking–all were documented as factors contributing to bone loss and OFs in gastric cancer patients [99][101][103][104][115][118][119].

It is well established that HPI eradication reduces the incidence of gastric cancer [120][121][122][123] and favors regression of the low-grade B-cell gastric MALT [124].

2.4. Gastroesophageal Reflux Disease (GERD)

HPI does not influence the function of the lower esophageal sphincter, the motility of the esophagus and the esophageal acid exposure. HPI might protect the distal esophagus (possibly an evolutionary adaptation [9]) by causing atrophy of the fundal gastric glands and hypochlorhydria, especially in subjects with cagA+, vacA+ strains and pro-inflammatory genotypes (IL-1β and IL-1RN) [125][126][127][128][129][130]. Many studies, as would be expected, reported an inverse association between HPI-induced corpus gastritis and GERD, its severity, prevalence of Barrett's esophagus (BO) and esophageal adenocarcinoma [9][38][131][132][133][134][135][136][137][138][139]. The strongest relationship was observed in East Asian populations [130][138]. A meta-analysis of 72 studies (84,717 patients with BO and 390,749 controls) found that HPI reduces the risk of BO by 32% (OR 0.68, 95% CI 0.58–0.79) [138]. Six meta-analyses on association of HPI and esophageal adenocarcinoma indicated an inverse relationship [139], whereas a recent meta-analysis (35 studies including 345,886 patients) did not find such association, except the Middle East data [140]. Other researchers concluded that presence of HPI might aggravate GERD [141], or, at least, is not "protective" against GERD, as the incidence of GERD and its sequelae in patients with HPI is higher than that after eradication of the infection [142][143], HPI eradication improves GERD symptoms and esophagitis [144][145][146][147][148] and does not increase the risk of BO [149][150][151]. Meta-analyses on effect of eradication HPI produced, however, inconsistent results [130]: a significantly higher risk of developing de novo GERD was demonstrated in Asian studies [152], but not in Western ones [153][154][155]. In a recent retrospective large cohort study from US (*n* = 36,803 patients with HPI), rates of esophageal and proximal gastric cancers 5, 10 and 15 years after treatment/eradication of HPI were low—0.15%, 0.26% and 0.34%, respectively [156]. In the interpretation of the data on the relationship between HPI and GERD the type and location of HPI-induced gastritis should be taken into account. As the level of gastric acid secretion is the main pathophysiological factor in GERD, chronic atrophic corpus gastritis causing hypo-/achlorhydria may exert a "protective" effect, while antrum gastritis with hyperchlorhydria can play an opposite role, and, not unexpectedly, HPI eradication may differently affect outcomes.

Several studies reported an association between GERD and vertebral fractures or kyphosis [157][158][159]. The most recent publications, however, did not confirm that GERD and decreased BMD are linked [23], neither that the incidence of OFs is higher among subjects with BO [160] (Kumar S 2017). As in the total population, older age, female gender and a higher comorbidity index were the independent risk factors for OFs in patients with BO. In the BO cohort, PPI therapy even prolonged and in high-doses, was not associated with increased fracture risk (HR 0.89; 95% CI 0.12–6.55), although a predisposition (numerically but non-significantly) for osteoporotic hip and vertebral fractures was observed [160].

The Maastricht IV/Florence Consensus Report on the management of HPI acknowledges that GERD is less common amongst those who are infected, but concludes that eradication of H.p. does not influence the severity of GERD [161]. In patients with GERD, according to Italian guidelines [162] and other recommendations [148], HPI can be eradicated.

3. Conclusions

In this study, we attempt to illuminate the existing clinical information on links between HPI and OP/OFs and, the complexity and interdependence of HPI–host interactions. The available evidence indicates that diseases and disorders induced by HPI (especially with virulent strains (cagA+) may contribute directly and indirectly to the development and progression of OP, falls and OFs. Despite remaining gaps in knowledge (the underlying mechanisms have not been definitely proven), there is considerable amount of data to suggest that predictive, preventive and therapeutic strategies for OP/OFs should assume HPI-related pathologies as potential pathophysiological co-factors and concentrate on individualized management of their effects on both bone health and falls. In patients with HPI-associated diseases and disorders bone status and risk for falls and fractures should be assessed, whereas in individuals with risk or presence of OP/OF the HPI status needs to be investigated and appropriate treatment prescribed. A five-step algorithm to provide guidance on assessment of the possible contribution of HPI to OP/OF is presented; its clinical effectiveness needs to be validated. Further well-designed prospective studies are warranted to provide a deeper understanding of the HPI–OP/OFs axis and develop personalized preventive and curative therapies.

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