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Review Article

Helicobacter Pylori and Bone Health in Children

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Abstract

Helicobacter pylori (HP) is a gram-negative pathogen, widespread throughout the world and has infected more than 50% of the global population. Developing countries, most people contract in early childhood. HP may be the cause of stomach cancer, gastritis and ulcers of the stomach and duodenum. Gastric acid secretion is reduced and the natural stomach functions are affected. Several studies have been made on growth and appetite changes and nutrient absorption. As HP in childhood may affect the absorption of some nutrients and vitamins, sometimes be subsequent growth retardation in the paediatric age group. It has been shown that the absorption of iron and vitamin B12 is disrupted by HP infection. Bone health is very important in childhood and is affected by several factors such as nutrition, lifestyle and genetics. Bone metabolism in childhood is different from in adulthood as during childhood, the skeletal structure is continually growing and continually renewing. For healthy bone mineralisation is necessary to sufficient calcium intake and optimal Vitamin D source. All of these elements have a separate effect on bone health. All childhood infections affect growth and development. Previous studies have shown that height and other stages of development are negatively affected by HP. However, none of these studies have any data related to the effect on the bone health of children. However, a few studies which have shown that elderly who are HP (+) at risk of osteoporosis. The aim of this review was to evaluate related to HP and bone health in children.

Keywords: *Helicobacter pylori; Children; Bone; İnfection*

Introduction

Helicobacter pylori (HP) is one of the most widespread chronic bacterial infections throughout the world and is estimated to have infected approximately half of the global population [1-3]. However, the worldwide distribution of the prevalence of HP is not homogenous [4,5]. In recent decades the infection prevalence in western countries has shown a decrease [6,7]. While HP is seen in developing countries at over 80%, this rate is 20 - 80% in developed countries. Low socio-economic conditions are a risk factor. The infection is spread by human to human contact. Although HP is so widespread, clinical symptoms only occur in only 10 - 20% of HP (+) individuals [1-3]. When HPI is contracted in the early years (almost always before 10 years old) and is not treated with antibiotics, it generally continues to be present in the stomach throughout life [4].

In many cases where HP has colonised the stomach and in some children infected with HP, the clinical table may occur in the form of gastritis, stomach and duodenal ulcers and other gastrointestinl diseases [5,8]. As in gastritis, these symptoms are explained with the T helper 1 response of the immune system [9,10]. It has been recently understood that there is a relationship between HP and the devel-

opment of non-gastric diseases such as iron deficiency anaemia, chronic idiopathic thrombocytopenic purpura, growth retardation and diabetes mellitus [11]. HPI may lead to systemic effects as a result of local infection [12]. HP infection is a chronic process where infection on a chronic base creates chronic inflammatory effects in both the stomach and other non-gastric systems [13-15]. As HP in childhood may affect the absorption of some nutrients and vitamins, there may sometimes be subsequent growth retardation in the paediatric age group [16-18].

Bone health is very important in childhood and is affected by several factors such as nutrition, lifestyle and genetics [19]. Bone metabolism in childhood is different from in adulthood as during childhood, the skeletal structure is continually growing and at the same time continually renewing [20-22]. In terms of bone health, bone mineralisation disorders are a significant health problem in both adults and children. Osteoporosis is a systemic bone disease which occurs with low bone mass and defects in the bone micro-architecture. Bone fragility increases and as a result, there is an increased risk of fracture [23]. Osteoporosis which affects bone health is encountered from childhood onwards as a significant cause of morbidity and mortality. Although the etiology is not fully known, several local and systemic diseases or sometimes the treatment of these diseases affects bone tissue [23,24]. For healthy bone mineralisation in all age groups, sufficient calcium intake and absorption is necessary together with an optimal source of vitamin D [20-22]. Peak bone mass is reached in early adulthood and this defines the lifelong resistance to osteoporosis [22].

The effect of HP infection on bone

During HP infection,levels of tumour necrosis factor-alpha, and cytokines such as interleukine-1 and interleukine-6 increase [25]. As the increase in these factors has been shown to contribute to osteoporosis, it is therefore thought that individuals with HP infection are at increased risk of osteoporosis. A limited number of studies have evaluated bone tissue associated with HP, which is very often seen in childhood in the form of chronic infection. In one study evaluating HP, 41 HP (+) children were examined in respect of biochemical changes in bone metabolism [26]. A comparison was made with HP (-) children in respect of levels of serum intact parathyroid hormone, ß-collagen I carboxy terminal telopeptide, total alkaline phosphatase (ALP), bone-specific ALP, N-terminal cross-links of human procollagen type I, N-mid-osteocalcin, calcium, phosphate, ferritin, and estradiol and no difference was determined. In the results of that study, only the vitamin B12 level was found to be lower in the HP (+) group than in the HP(-) group [26].

In another study conducted on an adult group (mean age 65 years), it was determined that category A positive HP males were at greater risk of osteoporosis and these individuals had lower levels of oestrogen. As a result of the study comparing 80 osteoporotic males with 160 control subjects , osteoporosis was seen to be more widespread in the males infected with category A positive HP strains [27]. A Japanese study of an elderly population (mean age 63 years) demonstrated a greater risk of osteoporosis in (HP+) individuals [12]. A similar study in Taiwan of an HP (+) elderly (mean age 77 years) population showed an increased risk of osteoporosis in females with upper gastro-intestinal disease [28].

Although several parameters were examined in the above-mentioned studies of both children and adults, the vitamin D level was not examined. An adequate vitamin D source together with a sufficient source of calcium is known to be important for the development of healthy bones [20-22]. However, to the best of our knowledge there are no studies in literature which have examined the level of vitamin D in HP (+) children.

The effect of HP on height development in childhood

One of the most important indicators of health, bone development and growth in childhood is the appropriate height for age and the normal continuation of this development during follow-up. In a scan of literature on this subject the most noteworthy studies were seen to be on the effect of HP infection on height and weight gain [29-31]. In paediatric studies, the effects of HP infection on the growth of children have been examined and discussed. It has been shown that acute or chronic infections can impair linear growth by negative effects on micro nutrient absorption, appetite and metabolism [32]. However, at the same time the growth rate in childhood is also defined by

factors such as diet, socio-economic status, other infections and genetics [33]. Therefore, there are some potential difficulties in accurately defining the effect of HP infection on growth. In this context, several population-based, cross-sectional and comparative studies have been made related to the height, weight or growth curve of HP (+) or (-) children [29,31,34,35]. The results of studies which have researched the effects of HP infection on growth are summarized in Table 1 [36].

Author	Age	Diagnostic test	Conclusion
Perri., *et al.* (1997)/Italy	3 - 14 yr	Urea breath test	HPI was associated with growth delay
Oderda., *et al.* (1998)/Italy	5 - 13 yr	Serology	No association with short stature
Quiñonez., *et al.* (1999)/Guatemala	5 - 10 yr	Serology	No association with height for age and nutritional status
Choe., *et al.* (2000)/Korea	10 - 15 yr	Serology	HPI was associated with delayed pubertal growth
Richter., *et al.* (2001)/Germany	5 - 7 yr	Urea breath test	HPI was associated with growth delay
Ertem., *et al*. (2002)/Turkey	3 - 12 yr	Urea breath test	HPI was associated with short stature
Sood., *et al*. (2005)/UK	Mean age 11.49 yr	Urea breath test	No association with height and weight z scores
Süoglu., *et al*. (2007)/Turkey	4 - 16 yr	Endoscopy	HPI and IDA had a significant effect on height z scores
Mohammad., *et al*. (2008)/Egypt	6 - 15 yr	Urea breath test	HPI affected both body weight and height
Soylu., *et al*. (2008)/Turkey	7 - 17 yr	Endoscopy	No association with anthropometry
Cherian., *et al*. (2009)/Australia	< 16 yr	Stool antigen	No association with BMI or other anthropometric measures
Gulcan., *et al*. (2010)/Turkey	6 - 15 yr	Serology,Endoscopy	RAP originating from HPIaffected both BMI and linear growth

Table 1: *Cross-sectional studies on the association between Helicobacter pylori infection and growth retardation. HPI: Helicobacter pylori infection; IDA: Iron deficiency anemia; RAP: Recurrent abdominal pain.*

In the evaluation of HP (+) children, studies in literature have been conducted more to examine height growth and weight gain. When comparisons have been made of appropriate height for age, which is an important indicator of bone health in childhood, it can be seen that different results have been obtained from studies in different countries [29,35,37].

Thomas., *et al*. conducted two consecutive studies on children in rural Gambia. The first study included 125 infants and the second, 65 children and those with HP (+) were determined by the urea breath test. According to the results of these studies, the children with early HP colonisation were determined in later childhood as shorter in comparison with their contemporaries. This growth retardation in childhood has been shown to be temporary and the difference has balanced out in later years [38].

In a study in Colombia by Bravo., *et al*. 347 healthy children aged between 12 - 60 months were observed from an anthropometric aspect for 2.5 years. Follow-up was made by examining height development once every 2 months and the urea breath test for HP was applied once every 4 months. As a result of this study, a decrease was determined in the growth rate of the HP (+) children of 0.042 ± 0.014 cm per month (approximately 0.5 cm per year) [39].

In the poor suburbs of Ecuador, Egrove et al evaluated a study group of 124 children with a mean age of 19 ± 9 months and according to the results, new and ongoing HP seriously retarded growth. Children with HP (+) were determined by examination of fecal antigens. The basic result of that study was that young children with new HP had a reduced linear growth rate compared to HP (-) children. The annual growth rate of children with new HP infection was determined to be negatively affected by 1 cm /year. This result shows an effect double that of the results of the study of children in Colombia (0.5 cm/year) [40].

In a study in Italy by Peri., *et al*. of children aged 3 - 14 years, HP was determined by the 13-C urea breath test and the hypothesis was proposed that HP infection was one of the environmental factors which could affect the development of children [30].

According to the results of a cross-sectional study including 3315 subjects in Turkey (scanning was made with the urea breath test), Ertem., *et al*. reported that retarded growth development was associated with HP [41]. In another study, two cohorts of school-age Andean children were followed up for approximately 4 years and at the age of 10.1 years the height of the HP (+) children was approximately 1.1 cm shorter than that of the HP (-) children [42].

Previous studies have been made examining the relationship between iron-deficiency anaemia and height for age in HP (+) children. In a study by Cho., *et al*. adolescents with iron deficiency anaemia associated with HP were evaluated and there was seen to be a negative effect on height development [16]. Suğoğlu., *et al*. obtained endoscopic biopsy material from a study group aged 4 - 16 years and according to z-scoring of height development, a negative effect was determined of the HP (+) children with iron deficiency anaemia compared to HP (-) children without iron deficiency anaemia [34].

Children who were always *H. pylori*-positive were 1.76 cm shorter by the end of the observation period than those who were always negative, and 1.45 cm shorter than those who cleared the infection, after adjustment for initial values and all other covariates [36].

HP and nutrition

Previous studies have shown that HP has an effect on nutrition [43]. In developing countries in particular, studies have found retarded development and malnutrition associated with HP infection [44,45] resulting in increased morbidity and mortality [46]. As a result of stomach acidity associated with HP in developing countries, there is a greater incidence of gardia, cholera, typhoid and non-typhoid salmonella and other infections. Associated with this condition, nutritional disorders, retarded development and sometimes more serious consequences are encountered [29,43]. Some studies have shown growth retardation in children with HP infection together with iron deficiency anaemia [47]. This has been seen to occur in infants [18,38,39] and school-age children [48]. However, the long-term effects of HP infection on weight and height are not fully known [31,49,50]. It is inevitable that all these conditions have a negative effect on bone health.

In studies of HP (+) individuals, especially where iron deficiency anaemia has developed [43,51] vitamin B12 absorption has been reduced [26] and pernicious anaemia has developed [52], it has been shown that β carotene levels were low [53] and there were effects on the vitamin E mucosal concentrations [54]. Although studies have been made related to folate and zinc, no data has been obtained that these vitamins were affected [55].

In other studies, the hormone ghrelin (a 28-amino acid peptide), which regulates appetite, has been shown to be affected by HP in the stomach [37]. There are also studies related to leptin, another hormone which affects appetite. In these studies results have been obtained showing that as a result of gastric damage associated with HP, there is an increase in leptin and gastrin levels, a reduction in the level of ghrelin and therefore appetite is affected and dyspeptic complaints develop [43]. These dyspeptic complaints result in a negative effect on nutrition in childhood and thus all the systems and especially bone health are affected negatively in children in their developmental phase.

In conclusion, it can be said from this review of literature that there are few studies which have evaluated the combination of bone health and HP infection in children. It can be seen that previous studies have focused more on examining the relationship between HP infection and height development. According to the results of those studies, decreased stomach acidity in the paediatric age group associated with HP infection causes dyspeptic complaints thus reducing appetite. In addition, the absorption of important substances such as iron and vitamin B12 is reduced due to HP infection. This has a negative effect, especially on height and other development stages in growing children. Although there have been no studies related to the negative effect of HP infection on bone health in children, there can be considered to be a potential risk. However, there are studies related to the development of osteoporosis associated with HP infection

in the elderly population. In accordance with these findings, there is a need for more extensive studies of bone health and HP infection in the paediatric age group.

Conflict of Interest

The authors have declared that there is no conflict of interest.

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