Journal of Health Informatics in Developing Countries
http://www.jhidc.org/
Vol. 16 No. 1, 2022

Submitted: Jan 25th, 2022 Accepted: March 10th, 2022

Role of Vitamin-D supplementation in the eradication of H-Pylori: Findings from a systematic review

Mohammed Abdulla Banama [1]*, Rawan Khalid Alasiri [1]

[1] *Rashid Hospital, Dubai Health Authority, Dubai, United Arab Emirates.*

Abstract

Background: H-pylori is a major public health problem that leads to a plethora of gastrointestinal problems. Treatment of Helicobacter Pylori has been found to reduce the burden of chronic gastritis and peptic ulcers. The role of Vitamin-D in the eradication of H-pylori has been investigated in numerous observational and experimental studies. We conducted this systematic review to review and synthesize the findings on the role of Vitamin-D in eradicating H-pylori infection from the human body.

Methods: This review systematically synthesizes the evidence from published research studies conducted between 2010 and 2022. The review was conducted by using an updated PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist. An electronic systematic literature search was carried out using PubMed and CINAHL (Cumulative Index to Nursing and Allied Health Literature). The primary outcome was the eradication of H-pylori from the stomach of the human body. Whereas the primary exposure or intervention serum vitamin-D levels.

Results: Ten articles were incorporated into the review. The findings from all studies revealed a positive role of serum vitamin-D in the eradication of H-pylori infection. Levels of Vit-D were inversely associated with H-pylori infection ($P<0.001$). The rate of eradication was 70 to 77.5% among study participants. Mean levels of Vitamin-D were significantly higher in the successful treatment group than in the failure group ($P<0.0001$).

Conclusion: The current review findings demonstrated a positive role of serum vitamin-D levels in the eradication of H-pylori infection with consistent findings across the studies. Future studies are recommended to conduct randomized controlled trials to assess the efficacy of vitamin-D supplementation in the eradication of H-pylori and various mechanisms by which vitamin D plays such an important role.

Keywords: Vitamin-D; helicobacter-Pylori; Eradication; Systematic review.

*Mohammed Abdulla Banama - Rashid Hospital, Dubai Health Authority, Dubai, United Arab Emirates; Email: Mabanama@dha.gov.ae. Orcid.org/0000-0002-4841-7644 .

1. Introduction

Helicobacter Pylori is one of the gram-negative bacteria that colonizes the stomach of human beings[1, 2]. Previously, H-pylori was considered an extracellular organism. However, researchers have recognized that it may be an intracellular microbe because the evidence suggests that during colonization of H-pylori, it gets invaded into phagocytes and epithelial cells[3-5]. The prevalence of helicobacter pylori is higher ranging from 25% if industrialized countries to 90% in low and middle countries[2, 6]. Numerous diseases such as gastritis, stomach ulcers, gastric cancer, and mucosa-associated lymphoid tissue lymphoma are caused by Helicobacter Pylori infection[7].

To prevent these adverse consequences, it is vital to eradicate Helicobacter Pylori from the human body[8]. Treatment of Helicobacter Pylori has been found to reduce the burden of chronic gastritis and peptic ulcers[8, 9]. Consequently, the same treatment can also be proven beneficial in the eradication of Helicobacter Pylori, thereby preventing the development of cancers[10]. However, inadequate prescription and use of antibiotics can lead to high resistance, thereby difficulty in treating this infection. Multiple factors influence the successful eradication of Helicobacter Pylori from the human body[11]. For example, resistance to antibiotics, the genetic profile of the patient, virulence of Helicobacter Pylori, and immunity of an individual plays a vital role in eradicating Helicobacter Pylori from the body[11].

In addition, the research has provided clues that vitamins such as vitamin E, C, and Vitamin D also play a role in the eradication of Helicobacter Pylori (H-pylori). Vitamin D’s role in eradicating H-pylori has been investigated in numerous observational and experimental studies in human beings[12, 13]. However, the findings are not synthesized collectively by including more recent literature to provide updated evidence on the role of vitamin D in eradicating H-pylori from the human body. Hence, we aimed to conduct this systematic review to review and synthesize the findings on the role of Vitamin-D in eradicating H-pylori infection from the human body. The findings of this review will provide insights into the importance of vit-D usage for the patients affected with H-Pylori infection. These findings will provide guidelines for clinicians to use vitamin-D in eradicating H-Pylori from the body.

2. Material and Methods

This systematic review focused on assessing the role of serum vitamin-D levels and eradication of H-pylori infection from the human body. This review was conducted by using an updated PRISMA guidelines for reporting the systematic review.

2.1 Eligibility Criteria

The review was undertaken to systematically synthesize the evidence from published research studies conducted between 2010 and 2022. A study was considered eligible for inclusion if it was primarily a research article on assessing the association between vitamin-D levels and H-pylori infection and published in the English language in a peer-reviewed local or international journal from 2010 to 2022.

Using the PICO framework, the eligibility criteria were grouped into four categories: population, intervention, comparison, and outcome[14]. The population for the current review was people diagnosed with H-pylori infection. The exposure or intervention for this review was the levels of Vitamin D in the blood. The primary outcome was the eradication of H-pylori as tested by stool or blood test and endoscopy wherever applicable. Lastly, the comparison or control group relied mainly on how authors had categorized subjects with sufficient or insufficient vitamin-D levels.

2.2 Information sources and search strategy

An electronic systematic literature search was carried out using the above-mentioned eligibility criteria. Two large electronic databases, including PubMed and CINAHL (Cumulative Index to Nursing and Allied Health Literature), were used for the current systematic review. These databases were explored using a detailed search strategy, including search terms or combinations. Besides, within these databases, the reference lists of the included records were also searched to identify relevant articles.

The research articles were searched using a combination of search terms set out for the defined research question. Three major concepts were defined, including serum Vitamin-D concentrations, H-pylori, and eradication. This was followed by combining the major concepts using combinations (AND, OR) germane to the research question. Moreover, truncation (*) was used to identify additional research articles with the same root word. Additionally, indexed keywords in the Medical Subject Headings (MeSH) were used to ensure uniform search terms.

As an example, to capture relevant articles in each database, the following simple search terms were used:

Example: (Serum vitamin D*) AND (H-pylori" OR "Helicobacter-Pylori") AND (Eradication)

2.3 Study selection

A citation management system (Endnote software) was used to manage records exported from all the electronic databases. After making groups in the Endnote software by the name of the database (PubMed or CINAHL), the duplicates were removed from the endnote file from both databases. This was followed by screening the unique studies obtained from both databases. In the first step, all the studies were screened by study titles using the Endnote software. Study abstracts then screened the shortlisted studies. Lastly, the full text of selected studies was retrieved and screened against the eligibility criteria. The PRISMA flow diagram was used to report the study selection process (Figure 1).

2.4 Data collection process

A customized data extraction sheet was filed for the eligible studies with full-text articles. The parameters included in the data extraction form included the author’s name, publication year, country of study, study population, sample size, study design, the age and gender distribution of the study participants, intervention, or exposure based on levels of vitamin D, a method to assess H-pylori, standard triple or quadruple therapy type and key findings,

2.5 Synthesis of the study findings

First, the findings of the review were synthesized narratively. Initially, a descriptive analysis of all the final included studies was performed to record their main characteristics such as the title of the article, author, publication year, country of study, date of extraction, reviewer name, purpose/aim of the study, study type, study population, sample size, study design, key findings, and conclusion of authors. First, each included study was read and reviewed multiple times to extract data and retrieve relevant information based on the above-mentioned parameters. This was followed by summarizing the findings in tabular form.

3. Results

A total of 1099 records were identified in two databases (PubMed and CINAHL). After removing 108 duplicates, the remaining 991 unique studies were left whose titles and abstracts were screened. During this process of reviewing abstracts and titles, 605 abstracts and titles were found to be irrelevant and not related to the topic of interest at all. Hence, we had 386 remaining studies, of which 362 did not meet the eligibility criteria. Consequently, 24 abstracts were thoroughly read and reviewed for eligibility, and we found ten full-text articles that were incorporated into the review, as shown in Figure 1.

3.1.Study characteristics

Studies were conducted in different countries across the globe, and articles were found both from developed and developing countries. More specifically, we had three studies from China (n=3), and one each from Italy, the USA (United States of America), Pakistan, Lebanon, Egypt, Israel, and Turkey as shown in Table 1. Regarding the year of publication, almost half of the studies (n=4) were recently published in 2022 and 2021, followed by two studies being published in 2019 and 2018. One study was published in 2017, and another was in 2012. Overall, the sample size of the included studies ranged between 150 to 150,483 study participants. Regarding the gender distribution of the participants, the findings revealed that both males and females participated in the respective studies. However, there was no equal proportion of males and females; rather, the proportion varied across the studies (Table 1).

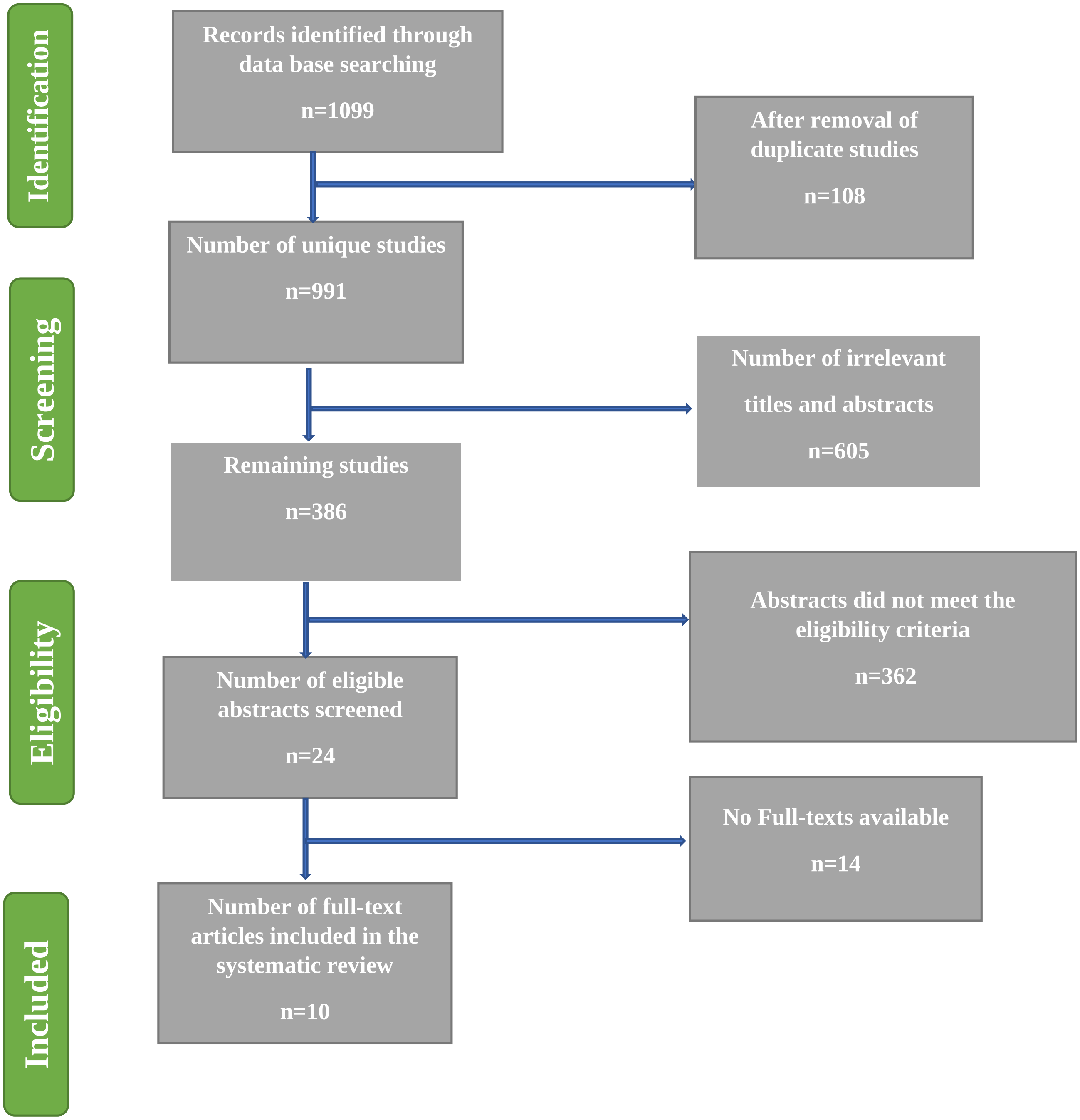

Figure 1: Flow chart summarizing the identification and selection of papers for systematic review

Overall, the proportion of males was found to be higher than the proportion of females, and it ranged from 36.7% to 80%, whereas the proportion of females ranged from 20% to 63.6%. With respect to the type of study, there were mixed study designs. For example, two studies were retrospective, three were follow-up studies, three were cross-sectional, and one was a case-control study. The mean age of the participants ranged from 41.55 to 59 years. However, the minimum age of the patients was 20, and the maximum was 80 years. Almost all studies mentioned how they assessed the patients for H-pylori infection. The methods to assess H-pylori included urea breath, stool, and endoscopy (Table 2). The majority of the studies used cut-offs of serum vitamin D levels as <20ng/ml for lower levels, except two studies used <10 and one used <30 as the cut-off of low serum Vitamin D levels, as shown in table 2. In addition, 70% of studies mentioned the type of triple or quadruple therapy given to patients as a standard therapy to treat H-pylori infection (Table 2).

Table 1: Characteristics of the eligible studies on the association between serum vit-D levels and H-pylori eradication (n=10)

Author	Year	Country	Study Design	Sample Size	Mean Age±SD	Gender
Antico et al[15]	2012	Italy	Case-control study	36,733	37–80 years	M=80% F=20%
Yildirim et al[16]	2017	Turkey	Follow-up study	220	47.4±14.1	M=57% F=43%
Shahawy et al[17]	2018	Egypt	Follow-up study	150	59.52±15.05	M=60.5% F=40%
Assaad et al[18]	2018	Lebanon.	Cross-sectional study	294	40.55 ± 14.11	M=36.7% F=63.3%
Han et al[19]	2019	China	Multicenter observational prospective cohort	496	47.6±11.4	M=51.5% F=48.5%
Huang et al[20]	2019	China	Retrospective study	160	55.42 ± 11.19	M=47.5% F=52.5%
Gao et al[21]	2020	China	Cross-sectional study	6896	12.25 months (7 to 19.7)	M=56.5% F=43.4%
Shafir et al[22]	2021	Israel	Retrospective study	150,483	41.55±15.05	M=50.5% F=49.5%
Magsi et al[23]	2021	Pakistan	Follow-up study	150	18 to 60 years	M=48.85% F=51.5%
Kuang et al[24]	2022	USA	NHANES data	3512	20 to 80 years	M=48.9% F=51.05%

3.2.Key findings on the role of serum Vit-D levels in the eradication of H-Pylori infection

Table 2 summarizes key findings of results on the role of serum Vit-D levels in eradicating H-Pylori infection extracted from the eligible studies. For example, Antico et al. conducted a case-control study on 36,733 participants in Italy in 2012[15]. The authors found a positive effect of vitamin D in eradicating H-pylori infection[15]. More precisely, the authors reported that the mean level of vitamin D in patients with autoimmune gastritis was 9.8 ± 5.6 ng/mL (95% confidence interval (CI): 8.4–11.2), 11.1 ± 8.4 (CI 7.5–14.7) in H. pylori gastritis patients, 22.2 ± 13.5 (CI 18.6–25.8) in nonspecific lymphocytic gastritis patients, 21.3 ± 12.2 (CI 19.7–22.9) in healthy participants, and 21.8 ± 13.1 (CI 21.7–21.9) in the 36,384 outpatients[15]. Further, the same study demonstrated that levels of Vitamin D in patients with autoimmune gastritis were significantly lower than in patients with nonspecific gastritis and H-pylori gastritis patients[15].

Similarly, Yildirim et al. undertook a study in Turkey on 220 study participants[16]. The author's findings were consistent with the findings by Antico et al. [15]. The authors found that Vitamin-D deficiency prevalence was 30.5%[16]. In addition, the eradication was found to be successful in 77.2% of the patients[16]. Mean levels of Vitamin D were significantly higher in the successful treatment group (19.03 ±8.13) than failure group (9.13 ±4.7) (P=0.001) [16]. Likewise, after one year, Shahawy et al. carried out a follow-up study in Egypt on 150 patients and had analogous findings to the above-mentioned two studies[17]. The authors reported that eradication was found to be successful in 70% of the patients. In addition, the mean levels of Vitamin D were significantly higher in the successful treatment group (27.41 ± 7.1) than in the failure group (14.7 ± 4.5) (P<0.001) [17].

In 2018, another study was conducted by Asaad et al. in Lebanon on 294 patients, and it was a cross-sectional study[18]. The authors found that H-pylori prevalence was 52.4% in their study sample, and the prevalence of H-pylori was higher among patients with lower levels of Vitamin D (OR = 29.14; CI = 11.77-72.13) with significant results[18]. These findings imply that there is an inverse association between levels of Vitamin D and H-pylori infection[18]. One year later, Han et al. undertook a multi-center observational prospective cohort study in China on 496 patients[19]. The findings of the study showed that vitamin D levels in serum were significantly lower in H. pylori-positive (17.0 ± 6.9 ng/mL) than H. pylori-negative group vs [19.2 ± 8.0 ng/mL, P= 0.000) [19]. In addition, the rate of eradication significantly differed between patients with serum vitamin D levels of <10 ng/mL and≥10 ng/mL (71.7% vs 87.3%,P= 0.005) [19]. Also, high Vit- D level ≥10 ng/mL was protective and helpful in eradication of H-Pylori (odds ratio 0.381, 95% CI (0.183-0.791,P= 0.010) [19].

Huang et al. undertook a study in 2019 on 160 patients in China and found similar results to other studies mentioned above[20]. The authors found that the eradication rate was 77.5% in the study participants[20]. Patients in the eradication failure group had lower levels of Vit-D (15.09 ± 7.72 ng/ml) than patients in the success group (19.87 ± 6.35 ng/ml). P-value: 0.004. The Odds ratio (OR) for eradication failure in individuals with lower Vit-D levels than those with higher Vit-D levels were 1.489 (95%, confidence interval (CI): 1.046–2.121) [20]. Gao et al. studied 6896 patients in China by performing a cross-sectional study[21]. The findings revealed that the prevalence of Vit-D deficiency in H-pylori positive patients was 20.7%, and it was 12.1% in H-pylori negative patients (p-value<0.001) [21]. Patients with H-pylori positive status were 2.06 times more likely to be vitamin-D deficient than those with H-pylori negative status (Odds ratio (OR): 2.06; 95% CI: 1.77, 2.38) after adjusting for other factors [21].

In 2021, two authors conducted studies in Israel and Pakistan[22, 23]. Shafir et al. conducted a Retrospective study on 150,483 in Israel and found comparable results. The authors found that levels of Vit-D were inversely associated with H-pylori infection (P<0.001) [22]. Moreover, the eradication was found to be successful in 70% of the patients[22]. In addition, the odds of positive H-Pylori were higher among patients with sufficient vitamin-D levels than Vitamin-D deficient group by 31% (OR 1.31, 99% CI 1.22-1.4). Mean levels of Vitamin D were significantly higher in the successful treatment group (19.34 ± 9.55) than in the failure group (18.64 ± 9.61) (P<0.001) [22]. Similarly, Magsi et al. found analogous results while studying 150 patients in Pakistan [9]. The authors found that the eradication was found to be successful in 71.8% of the patients [9]. Mean levels of Vitamin D were significantly higher in the successful treatment group (31.01 ± 7.8 ng/mL) than in the failure group (18.9 ± 5.6 ng/mL;) (P<0.0001) [9]. Recently in 2022, Kuang et al. published data from the NHANES (National Health and Nutrition Examination Survey) in the USA, and the data were from 3512 study participants aged 20 to 80 years[24]. Overall, the authors found no significant relationship between Vit-D and H-Pylori infection in the general population[24]. However, in non-Hispanic whites (OR=1.02, 95% CI: 1.00 to 1.03), other races (OR=1.08, 95% CI: 1.01 to 1.06), and people born in other countries (OR=1.09, 95% CI: 1.04 to 1.15), lower serum Vit-D levels were associated with higher odds of H-pylori infection[24].

Table (2) Summary of key findings of results on the role of serum Vit-D levels in the eradication of H-Pylori infection extracted from the eligible studies (n=10)

Author	Year	Intervention or Exposure group	Control/unexposed groups	Treatment regiment of H-Pylori	Methods to test H-pylori	Key findings
Antico et al[15]	2012	Mean levels were calculated	Mean levels were calculated	NA	NR	- Mean level of vitamin D in patients with autoimmune gastritis was 9.8 ± 5.6 ng/mL (95% CI: 8.4–11.2), 11.1 ± 8.4 (CI 7.5–14.7) in H. pylori gastritis patients, 22.2 ± 13.5 (CI 18.6–25.8) in nonspecific lymphocytic gastritis patients, 21.3 ± 12.2 (CI 19.7–22.9) in healthy participants, and

						21.8 ± 13.1 (CI 21.7–21.9) in the 36,384 outpatients. - Levels of Vitamin D in patients with autoimmune gastritis were significantly lower than in patients with nonspecific gastritis and H-pylori gastritis patients.
Yildirim et al[16]	2017	Serum levels of 25-hydroxy-vitamin D (25(OH)D) ≥ 10ng/ml	Serum levels of 25-hydroxy-vitamin D (25(OH)D) <10ng/ml	Bismuth-containing quadruple therapy for 14 days for all patients	14C-urea breath test- four weeks after therapy	-Eradication was found to be successful in 77.2% of the patients. -Mean levels of Vitamin D were significantly higher in the successful treatment group (19.03 ±8.13) than failure group(9.13 ±4.7) (P=0.001). -Vitamin-D deficiency prevalence was 30.5%.
Shahawy et al[17]	2018	Serum levels of 25-hydroxy-vitamin D (25(OH)D) ≥ 20ng/ml	Serum levels of 25-hydroxy-vitamin D (25(OH)D) <20ng/ml	Clarithromycin-based triple therapy for 14 days	Stool antigen test- four weeks after therapy	-Eradication was found to be successful in 70% of the patients. -Mean levels of Vitamin D were significantly higher in the successful treatment group (27.41 ± 7.1) than failure group (14.7 ± 4.5) (P<0.001).
Assaad et al[18]	2018	Serum levels of 25-hydroxy-vitamin D (25(OH)D) ≥ 20ng/ml	Serum levels of 25-hydroxy-vitamin D (25(OH)D) > 20 nanog/L	NA	Biopsy of gastric tissue via upper GI endoscopy	-H-pylori prevalence was 52.4% -The prevalence was higher among patients with lower levels of Vitamin D (OR = 29.14; CI = 11.77-72.13)
Han et al[19]	2019	Serum levels of 25-hydroxy-vitamin D (25(OH)D) ≥ 10ng/ml	Serum levels of 25-hydroxy-vitamin D (25(OH)D) <10ng/ml	1000 mg amoxicillin, 40 mg esomeprazole, and 220 mg colloidal bismuth tartrate capsule twice daily: 14days	C-urea breath tes	- Vitamin D levels in serum were significantly lower in H. pylori positive (17.0 ± 6.9 ng/mL) than H. pylori negative group vs [19.2 ± 8.0 ng/mL,P= 0.000). - The rate of eradication significantly differed between patients with serum vitamin D levels of <10 ng/mL and≥10 ng/mL (71.7% vs 87.3%, P= 0.005). -High vit- D level ≥10 ng/mL was protective and helpful in eradication of H-Pylori (odds ratio 0.381, 95% CI (0.183-0.791, P= 0.010)
Huang et al[20]	2019	Serum levels of 25-hydroxy-vitamin D (25(OH)D) ≥ 30ng/ml	Serum levels of 25-hydroxy-vitamin D (25(OH)D) <20ng/ml	Amoxicillin 2000 mg/day, clarithromycin 1000 mg/day, esomeprazole 40 mg/day with bismuth potassium	urea breath tests	_ The rate of eradication was 77.5% in the study participants. -Patients in eradication failure group had lower levels of Vit-D (15.09 ± 7.72 ng/ml) than patients with success group

				citrate 440 mg/day: 14 days		(19.87 ± 6.35 ng/ml) P-value: 0.004 - The OR for eradication failure in individuals with lower vit-D levels than those with higher Vit-D levels were 1.489 (95%, CI: 1.046–2.121)
Gao et al[21]	2020	Serum levels of 25-hydroxy-vitamin D (25(OH)D) ≥ 20ng/ml	Serum levels of 25-hydroxy-vitamin D (25(OH)D) <20ng/ml	NR	Anti–H. pylori IgG	-The prevalence of vit-D deficiency in H-pylori positive patients was 20.7% and it was 12.1% in H-pylori negative patients (p-value<0.001). -Patients with H-pylori positive status were 2.06 times likely to be vit-D deficient than with H-pylori negative status (OR: 2.06; 95% CI: 1.77, 2.38) after adjusting for other factors.
Shafir et al[22]	2021	Serum levels of 25-hydroxy-vitamin D (25(OH)D) ≥ 20ng/ml	Serum levels of 25-hydroxy-vitamin D (25(OH)D) <20ng/ml	Clarithromycin-based triple therapy for 14 days	stool antigen tests or urea breath tests.	-Levels of Vit-D were inversely associated with H-pylori infection (P<0.001). -The odds of positive H-Pylori were higher among patients with sufficient vitamin-D levels than Vitamin-D deficient group by 31% (OR 1.31, 99% CI 1.22-1.4). -Eradication was found to be successful in 70% of the patients. -Mean levels of Vitamin D were significantly higher in the successful treatment group (19.34 ± 9.55) than in the failure group (18.64 ± 9.61) (P<0.001).
Magsi et al[23]	2021	Serum levels of 25-hydroxy-vitamin D (25(OH)D) ≥ 30ng/ml	Serum levels of 25-hydroxy-vitamin D (25(OH)D) <30ng/ml	First-line eradication therapy: omeprazole, amoxicillin, and clarithromycin for 14 days	Stool antigen tests	-Eradication was found to be successful in 71.8% of the patients. - Mean levels of Vitamin D were significantly higher in the successful treatment group (31.01 ± 7.8 ng/mL) than in the failure group (18.9 ± 5.6 ng/mL;) (P<0.0001).
Kuang et al[24]	2022	Serum levels of 25-hydroxy-vitamin D (25(OH)D) ≥ 20ng/ml	Serum levels of 25-hydroxy-vitamin D (25(OH)D) <20ng/ml	NR	H. pylori CagA antibody	-No significant relationship between Vit-D and H-Pylori infection in general population. -In non-hispanic whites (AOR=1.02, 95% CI: 1.00 to 1.03). other races (AOR=1.08, 95% CI: 1.01 to 1.06), and people born in other countries (AOR=1.09, 95% CI: 1.04 to 1.15) , lower serum Vit-D

						levels were associated with higher odds of H-pylori infection-

4. Discussion

This systematic review was undertaken to assess the relationship between serum vitamin-D levels and H-pylori eradication. In general, findings from all studies revealed a positive role of serum vitamin-D in the eradication of infection. The consistency across ten eligible studies demonstrated that vitamin D should be considered an essential vitamin that plays a key role in eradicating H-pylori infection. The authors of the included studies showed that patients with positive H-pylori infection had lower vitamin D levels than patients with negative H-pylori infection. In addition, the mean levels of vitamin D were found to be higher in patients with successful eradication of H-pylori than in those who were not successful with significant results. These findings provide a pathway for gastroenterologists and clinicians to be cognizant of the vitamin-D levels of patients while treating these patients in clinical settings.

The precise mechanisms through which vitamin D proves helpful in the eradication of infections from the body remain controversial. However, these findings can be explained by the antimicrobial activity of vitamin D in eradicating infectious diseases. For example, the role of this vitamin is well-known for the treatment of infections such as tuberculosis and staphylococcus aureus in the past[25, 26]. In addition, Vitamin D being a fat-soluble vitamin, primarily regulates calcium and phosphorus metabolism. Apart from its role in bone synthesis and regulation, Vitamin-D also targets immune cells such as monocytes, macrophages, lymphocytes, and dendritic cells. Therefore, this vitamin also has an immunomodulatory role[27]. The absence of vitamin D can lead to rising in immunity-related disorders, thereby can result in infectious diseases such as Helicobacter Pylori[27, 28].

The evidence suggests that the antimicrobial properties of vitamin D are mediated by the release of antimicrobial peptides such as DEFB4A (defensin beta 4A)/β-defensin 2 and cathelicidin antimicrobial peptides [29]. However, the evidence is not consistent regarding the mechanisms through which vitamin D shows its antimicrobial properties. For example, a study conducted on mice showed that cathelicidin antimicrobial peptides are not responsible for anti-H-pylori activities of vitamin-D in the stomachs of mice[30]. The same study also detected a lower expression of a gene named VDR (Vitamin D Receptor) in gastric epithelial cells and mice stomach tissues[30]. The study also showed that instead of VDR, the antimicrobial activity of vitamin-D is mediated through PDIA3 receptor[30]. On the contrary, the previous study found that cathelicidin antimicrobial peptides are the direct target genes of VDR[31]. Given these mixed findings, it is not clear how vitamin D plays a role in eradicating H-pylori from the body. These conflicting results provide some evidence about the mechanisms through which vitamin D may play a role. However, the inconsistency in findings may prevent researchers from making definite conclusions about the same. These inconsistent results warrant large longitudinal studies in human beings to understand the mechanisms by which vitamin-D plays a role in eradicating H-Pylori infection.

4.1. Strengths and Limitations

This is a unique review that assessed the effect of vitamin-D levels in eradicating H-pylori from the stomach of human bodies. Further, we used the PRISMA checklist to undertake this review and assessed the quality of the eligible studies. The findings of this review can provide a framework for clinicians, gastroenterologists, and policymakers to use the evidence on the importance of vitamin D in the treatment of H-pylori infection. In addition, our included studies were from both developed and developing countries, which provides us the confidence to generalize the review findings across high and low-middle income countries. Also, the study participants in different studies covered all population groups such as children and adults and even patients diagnosed with chronic diseases such as Diabetes Mellitus.

Despite these strengths, the findings need to be interpreted with caution due to some caveats associated with the individual studies. First, the majority of the studies did not select study participants randomly, which may limit the generalizability of the study findings to other populations outside the ones chosen from registries or cohorts. Second, due to the observational nature of study designs, the issue of unmeasured confounding can always persist. However, one may overcome this issue by having an explicit theory about the potential confounders and identifying confounders using some causal diagrams such as direct acyclic graphs. These graphs can help a researcher place a minimum set of variables that need to be adjusted as potential confounders, which may be highly correlated with unmeasured confounders. This way, unmeasured confounding can be addressed to a greater extent in observational studies. Further, included studies were conducted in high-income countries. Therefore, it may be challenging to extrapolate the findings to the low-middle income countries. Lastly, only ten studies were included in this review based on the eligibility criteria. Consequently, the findings should be interpreted with caution, and randomized controlled trials are warranted to make firm conclusions about the effectiveness of vitamin-D supplementation in the eradication of H-pylori.

Given the limitations of the existing review, more robust evidence in the form of meta-analysis or systematic reviews with more studies is warranted. However, the findings of the current review may help to learn about the importance of vitamin D in making a bigger difference for patients with H-pylori. These findings can provide a guideline to the researchers on the role of vitamin D in the management of H-pylori infections and recurrence.

5. Conclusion

H-pylori is a major public health problem that leads to many gastrointestinal problems. Hence, there should be some cost-effective approaches to overcome the burden and associated adverse consequences caused by H-Pylori. The current review findings demonstrated a positive role of serum vitamin-D levels in the eradication of H-pylori infection. In addition, the findings are consistent across the studies, which provide confidence about using vitamin D while managing the diagnosed patients with H-pylori. Vitamin D deficiency has been found to be related to multiple other health outcomes, and it seems that this deficiency is prevalent across the globe. Those who are deficient in vitamin D during the treatment of H-pylori can be provided with vitamin-D supplements, which are cost-effective and easily accessible in all countries. In addition, vitamin D does not produce additional risks or cause side effects which can prevent a clinician from prescribing this small but beneficial vitamin to the patients. Providing vitamin D to these patients can help them get rid of H-pylori and benefit from other health-related problems such as bone-related diseases and psychiatric disorders. Future studies are recommended to conduct large randomized controlled trials to assess vitamin-D supplementation’s efficacy in eradicating H-pylori. Also, research is required to understand various mechanisms by which vitamin D plays such an important role.

6. Declarations

6.1 Conflict of Interest Statement

The authors have no conflict of interests to declare.

6.2 Funding Disclosure

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

7. References

1. Andersen, L.P., et al., Isolation of a "Helicobacter heilmanii"-like organism from the human stomach. Eur J Clin Microbiol Infect Dis, 1996. 15(1): p. 95-6.
2. Goh, K.L., et al., Epidemiology of Helicobacter pylori infection and public health implications. Helicobacter, 2011. 16 Suppl 1(0 1): p. 1-9.
3. Allen, L.A., L.S. Schlesinger, and B. Kang, Virulent strains of Helicobacter pylori demonstrate delayed phagocytosis and stimulate homotypic phagosome fusion in macrophages. J Exp Med, 2000. 191(1): p. 115-28.
4. Ozbek, A., et al., Can Helicobacter pylori invade human gastric mucosa?: an in vivo study using electron microscopy, immunohistochemical methods, and real-time polymerase chain reaction. J Clin Gastroenterol, 2010. 44(6): p. 416-22.
5. Chu, Y.T., et al., Invasion and multiplication of Helicobacter pylori in gastric epithelial cells and implications for antibiotic resistance. Infect Immun, 2010. 78(10): p. 4157-65.
6. Dunn, B.E., H. Cohen, and M.J. Blaser, Helicobacter pylori. Clin Microbiol Rev, 1997. 10(4): p. 720-41.
7. Perez-Perez, G.I., D. Rothenbacher, and H. Brenner, Epidemiology of Helicobacter pylori infection. Helicobacter, 2004. 9 Suppl 1: p. 1-6.
8. Malfertheiner, P., A. Link, and M. Selgrad, Helicobacter pylori: perspectives and time trends. Nat Rev Gastroenterol Hepatol, 2014. 11(10): p. 628-38.
9. Take, S., et al., The effect of eradicating helicobacter pylori on the development of gastric cancer in patients with peptic ulcer disease. Am J Gastroenterol, 2005. 100(5): p. 1037-42.
10. Mégraud, F. and P. Lehours, Helicobacter pylori and gastric cancer prevention is possible. Cancer Detect Prev, 2004. 28(6): p. 392-8.
11. Uotani, T., M. Miftahussurur, and Y. Yamaoka, Effect of bacterial and host factors on Helicobacter pylori eradication therapy. Expert Opin Ther Targets, 2015. 19(12): p. 1637-50.
12. Shatla, M.M., A.S. Faisal, and M.Z. El-Readi, Is Vitamin D Deficiency a Risk Factor for Helicobacter Pylori Eradication Failure? Clin Lab, 2021. 67(2).
13. Mut Surmeli, D., et al., Vitamin D deficiency and risk of Helicobacter pylori infection in older adults: a cross-sectional study. Aging Clin Exp Res, 2019. 31(7): p. 985-991.
14. Schardt, C., et al., Utilization of the PICO framework to improve searching PubMed for clinical questions. BMC medical informatics and decision making, 2007. 7(1): p. 1-6.
15. Antico, A., et al., Hypovitaminosis D as predisposing factor for atrophic type A gastritis: a case-

control study and review of the literature on the interaction of Vitamin D with the immune system. Clin Rev Allergy Immunol, 2012. 42(3): p. 355-64.
16. Yildirim, O., et al., The influence of vitamin D deficiency on eradication rates of Helicobacter pylori. Adv Clin Exp Med, 2017. 26(9): p. 1377-1381.
17. El Shahawy, M.S., et al., The effect of vitamin D deficiency on eradication rates of Helicobacter pylori infection. JGH Open, 2018. 2(6): p. 270-275.
18. Assaad, S., et al., Dietary habits and Helicobacter pylori infection: a cross sectional study at a Lebanese hospital. BMC gastroenterology, 2018. 18(1): p. 48-48.
19. Han, C., et al., Influence of serum vitamin D level on Helicobacter pylori eradication: A multi-center, observational, prospective and cohort study. Journal of digestive diseases, 2019. 20(8): p. 421-426.
20. Huang, B., et al., Effect of 25-hydroxyvitamin D on Helicobacter pylori eradication in patients with type 2 diabetes. Wiener klinische Wochenschrift, 2019. 131(3): p. 75-80.
21. Gao, T., et al., Association of Helicobacter pylori Infection with Vitamin D Deficiency in Infants and Toddlers. Am J Trop Med Hyg, 2020. 102(3): p. 541-546.
22. Shafrir, A., et al., The Association between Serum Vitamin D Levels and Helicobacter pylori Presence and Eradication. Nutrients, 2021. 13(1).
23. Magsi, I., et al., Response of Helicobacter Pylori Eradication Treatment in Patients With Normal and Below-Normal Serum Vitamin D Levels. Cureus, 2021. 13(4): p. e14777.
24. Kuang, W.M., et al., Association between serum vitamin D levels and Helicobacter pylori cytotoxic-associated gene A seropositivity: a cross-sectional study in US adults from NHANES III. BMJ Open, 2022. 12(4): p. e058164.
25. Campbell, G.R. and S.A. Spector, Vitamin D inhibits human immunodeficiency virus type 1 and Mycobacterium tuberculosis infection in macrophages through the induction of autophagy. PLoS Pathog, 2012. 8(5): p. e1002689.
26. Hewison, M., Antibacterial effects of vitamin D. Nat Rev Endocrinol, 2011. 7(6): p. 337-45.
27. Baeke, F., et al., Vitamin D: modulator of the immune system. Curr Opin Pharmacol, 2010. 10(4): p. 482-96.
28. Hong, J.Y., et al., Association between vitamin D deficiency and tuberculosis in a Korean population. Int J Tuberc Lung Dis, 2014. 18(1): p. 73-8.
29. Youssef, D.A., et al., Antimicrobial implications of vitamin D. Dermato-endocrinology, 2011. 3(4): p. 220-229.

30. Hu, W., et al., Vitamin D3 activates the autolysosomal degradation function against Helicobacter pylori through the PDIA3 receptor in gastric epithelial cells. Autophagy, 2019. 15(4): p. 707-725.
31. Gombart, A.F., N. Borregaard, and H.P. Koeffler, Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D3. Faseb j, 2005. 19(9): p. 1067-77.