






# Vitamin D Deficiency Association with Comorbid Diseases in Palestine: “A Cross-Sectional Observation Study”

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**Background:** Vitamin D deficiency (VDD) is a global health concern. This study aimed to determine the prevalence of vitamin D deficiency and its associated comorbidities in Palestine, such as diabetes mellitus, hypertension, hyperlipidemia, and cardiovascular and autoimmune diseases.

**Methods:** A retrospective, descriptive study retrieved medical data from the Nat Health insurance processor database from 2014 to 2020. Patient information included age, sex, vitamin D laboratory order, symptoms, and comorbidities. This study included patients prescribed vitamin D at a dose of 50000IU for vitamin D deficiency confirmed by a serum vitamin D laboratory test. The collected data were analyzed using IBM SPSS. In addition, a chi-square test was conducted to assess the association between vitamin D deficiency, symptoms, and comorbidities.

**Results:** Data of 3011 patients were collected; 639 patients were diagnosed with osteoporosis, and 39 patients prescribed vitamin D without a laboratory test were excluded. Approximately, 1837 (78%) participants had vitamin D deficiency. A total of 1330 women (81.3%) were significantly more likely to have vitamin D deficiency than males, 507 (72.7%;  $P < 0.001$ ). Joint pain, back pain, and cervicgia were significantly associated with vitamin D deficiency ( $P < 0.001$ ). Asymptomatic participants (2.1%) were significantly less likely to have vitamin D deficiency than symptomatic participants (9.5%,  $p < 0.001$ ). Hypothyroidism is significantly associated with vitamin D deficiency ( $p = 0.048$ ).

**Conclusion:** In this retrospective study, the prevalence of vitamin D was high and alarming. There was a significant association between VDD, patients who presented with back pain, arthritis, and cervicgia symptoms, and patients diagnosed with hypothyroidism. Therefore, health initiative programs are warranted to increase awareness regarding screening, prevention, and treatment. Further studies are needed to confirm the relationship between vitamin D supplementation and the reduced risk of comorbid diseases.

**Keywords:** vitamin D deficiency, vitamin D deficiency treatment, comorbid disease, vitamin D supplement

## Introduction

Vitamin D is a fat-soluble vitamin with two primary forms, vitamin D<sub>2</sub> and D<sub>3</sub>, which differ only in their side-chain structure. Vitamin D significantly affects skeletal and neuromuscular health by regulating calcium and phosphorus absorption. It is also essential for developing bones, teeth, and muscles. It also helps improve resistance and protection against various diseases and conditions.<sup>1</sup>

The primary source of vitamin D is sunlight, which synthesizes cholecalciferol using ultraviolet (UV) light. Other sources rich in vitamin D include animal products such as fatty fish.<sup>2</sup> Time of exposure to the sun (during the mid-day, our skin produces more vitamin D), skin color (darker skin produces less vitamin D than pale skin), and the amount of skin exposed to sunlight (the more skin exposed, the more vitamin D produced) are factors influencing vitamin D synthesis.<sup>3</sup> Some studies

have not recommended using ultraviolet light to treat vitamin D deficiency because of its carcinogenic effects on the skin.<sup>4</sup> However, many supplements produce a sufficient amount of vitamin D.<sup>5</sup>

Several environmental and lifestyle risk factors have been associated with vitamin D deficiency. The most common ones are inadequate sunlight exposure or sunscreen use, inadequate dietary intake of food rich in vitamin D3, age, obesity, burns, pregnancy, skin pigmentation, and clothing style; all of which affect vitamin D levels.<sup>6</sup>

Recently, vitamin D deficiency has been considered a global health problem affecting approximately 50% of the worldwide population.<sup>7</sup> It exacerbates many illnesses, such as diabetes mellitus, cardiovascular diseases, autoimmune diseases, osteoporosis, and cancer. In addition, vitamin D deficiency is associated with adverse clinical outcomes like gingival inflammation and impaired bone growth.<sup>7,8</sup>

An observational study of 83,779 women aged > 20 years from the Nurses' Health Study demonstrated a strong relationship between vitamin D deficiency and an increased risk of type 2 diabetes. Also, it suggests that a daily intake of vitamin D and calcium can reduce the risk by 33%.<sup>9</sup> Another study shows that normalizing vitamin D levels reduce the risk of type-2 diabetes by 55%.<sup>10</sup> Vitamin D supplementation can reduce the risk of developing type-1 and type-2 diabetes and improve metabolic control; however, the exact mechanism is poorly understood; vitamin D might enhance the release and synthesis of insulin from pancreatic  $\beta$ -cells, which contain vitamin D receptor VDRs.<sup>11,12</sup> A cohort study in Finland included 10,821 children in the first year of life about doses of vitamin D supplementation and suspected rickets found that children who took vitamin D supplementations were less likely to develop type-1 diabetes by almost 80%.<sup>13</sup> Therefore, children need to take vitamin D supplements during their first year of life to prevent the development of type 1 diabetes.

Hypertension is a chronic silent killer disease caused by many risk factors, including age, race, obesity, smoking, and vitamin D deficiency. Low plasma vitamin D concentration is associated with an increased risk of hypertension.<sup>14</sup> One of the most critical factors for the development of hypertension is the inappropriate activation of the renin-angiotensin-aldosterone system (RAAS). Vitamin D plays a significant role in regulating RAAS molecular levels in humans and animals.<sup>14</sup> In 2013, a study was conducted with 283,537 participants to determine the association between vitamin D levels and the risk of hypertension. They found that for every 10ng/mL increment in vitamin D levels, there was a 12% decrease in the risk of hypertension. They also observed that vitamin D causes a 30% decrease in the danger of developing hypertension.<sup>15</sup>

Several studies have reported an association between vitamin D deficiency and autoimmune disease. However, the relationship between vitamin D deficiency and hypothyroidism remains unclear. Some studies have reported that the significant vitamin D deficiency in autoimmune thyroid disease patients suggests that vitamin D is involved in the pathogenesis of autoimmune thyroid disease and advises using vitamin D supplements.<sup>16</sup> Also, low vitamin D levels are expected in asthmatic patients and are associated with uncontrolled asthma.<sup>17</sup> A meta-analysis study done in 2019 studied the relationship between vitamin D and asthma control and showed the efficacy of vitamin D supplementation in reducing asthma exacerbation rates.<sup>18</sup>

Reviews and studies have linked vitamin D deficiency with COVID-19 disease (SARS-COV-19).<sup>19,20</sup> They supported vitamin D activity in reducing the risk of covid-19 infection and deaths documented. The benefit of vitamin D in covid-19 patients is due to its suggested mechanisms of action, such as maintaining cell junctions and enhancing cell immunity by reducing cytokine storms with affected interferon- $\gamma$  and tumor necrotic factor  $\alpha$ . Hypovitaminosis C stimulates the renin-angiotensin system (RAS); activation leads to chronic cardiovascular disease, reduces lung function, and increases the comorbidity risk of covid-19.<sup>21,22</sup>

The Palestinian population is more vulnerable to vitamin D deficiency due to economic and complex politics.<sup>23</sup> Based on the world food program, 50% of the population suffers from more than one micronutrient deficiency, particularly female adolescents in Gaza, where 72% are deficient in vitamin D, and 64% are deficient in vitamin A.<sup>24</sup> A study by Al-Azhar University in the Gaza Strip to determine the risk factors associated with vitamin D insufficiency among adolescents concluded that vitamin D deficiency is challenging to detect quickly, an epidemic problem among children in the Gaza Strip. However, the study revealed some modifiable risk factors related to vitamin D deficiency, including consuming unhealthy food without sufficient amounts of vitamin D, such as milk and fish, maximum exposure to sunlight in addition to covering the body during exposure to sunlight, and lack of knowledge of the importance of vitamin D.<sup>25</sup>

This study aimed to determine the association between vitamin D deficiency and sociodemographic factors, other comorbid diseases, and symptoms in Palestine and to make recommendations based on screening and prevention findings.

## Methods

### Data Collection and Study Design

This retrospective, descriptive cross-sectional study was conducted by retrieving medical data from Nat Health, a major health insurance claim processor in Palestine, from 2014 to 2020 for all patients prescribed vitamin D or screened for vitamin D deficiency. Patient information was extracted, including age, sex, laboratory orders, complaints of symptoms, and comorbidities. The study included all patients prescribed vitamin D at a dose of 50000IU for vitamin D deficiency confirmed by a serum vitamin D laboratory test. Patients diagnosed with osteoporosis and with incomplete information were excluded. The cutoff point for vitamin D was determined based on the Endocrine Society Clinical Practice Guidelines: normal >30ng/mL, insufficient 21–29ng/mL, and deficient <20ng/mL.<sup>26</sup>

The endocrine society clinical practice guidelines for the treatment of vitamin D deficiency are as follows: for an infant from 0–1 year, patients are treated with 2000 IU/d of vitamin D or 50,000 IU once weekly for six weeks to reach normal levels of 25(OH)D, then followed by maintenance dose therapy 400–1000IU/d. Children from 1–18 years were treated with 2000 IU/d or 50000IU of vitamin D once weekly, both regimens for at least six weeks to achieve an average level, followed by maintenance dose therapy of 600–1000 IU/d. Finally, adult patients were treated with 50,000 units of vitamin D weekly for eight weeks to achieve an average level, followed by maintenance dose therapy of 1500\_2000IU/d.<sup>26</sup>

### Statistical Analysis

Data from 3011 patients were collected; 639 patients were diagnosed with osteoporosis, and 39 patients prescribed vitamin D without a laboratory test were excluded. The total sample size was 2333 individuals. All patients prescribed vitamin D at a dose of 50000IU after the confirmed vitamin D level laboratory test were classified as having vitamin D deficiency.

Descriptive statistics were performed to present quantitative data as frequencies and percentages, including patient demographics, comorbidities, vitamin D dosage, and symptoms. In addition, chi-square tests with a 95% confidence interval were conducted to assess the associations between vitamin D deficiency, patient demographics, and comorbidities. Then, a third chi-square test with a 95% confidence interval was performed to assess the association between patient symptoms and vitamin D deficiency. The collected data were analyzed using IBM SPSS version 22.

### Ethical Consideration

Ethical approval for the study was obtained from the ethical committee of Birzeit University (approval reference number BZUPNH2104). The requirement for informed consent from each participant was waived because this was an observational, retrospective study. The patients were anonymized, and their information was nonidentifiable. The study complied with the ethical guidelines of the Declaration of Helsinki and patient data.

## Results

Of the 2333 patients included in the study, 1636 (70.1%) were females, and approximately half of the patients, 1092 (46.8%), were aged 21–40. A total of 1837 (78.7%) patients were classified as having vitamin D deficiency and were prescribed vitamin D 50000IU (Table 1).

Regarding comorbidities, (64.1%) of patients were healthy. One-fifth of the patients (20.8%) had hypertension, (12.7%) were diabetic patients, and (12%) had high cholesterol levels, whereas only (1.6%) had asthma, and (2%) had ASCVD (Figure 1).

Figure 2 shows the patients' symptoms. The most common symptom was joint pain (23.3%), followed by arthritis (14.8%). Only 0.6% of patients had headaches.

Bivariate analysis revealed that 1330 women (81.3%) were significantly more likely to have vitamin D deficiency than males, 507 (72.7%;  $P < 0.001$ ). Additionally, 99 (32.4%) younger individuals aged  $\leq 20$  years were significantly less likely to have vitamin D deficiency than those aged  $> 20$  years ( $p < 0.001$ ) (Table 2).

As shown in Table 3, there was a significant association between vitamin D deficiency and hypothyroidism ( $p = 0.048$ ), and (86.1%) of the patients with hypothyroidism had vitamin D deficiency. In comparison (78.4%) of the others

**Table 1** Participant Characteristics (N = 2333)

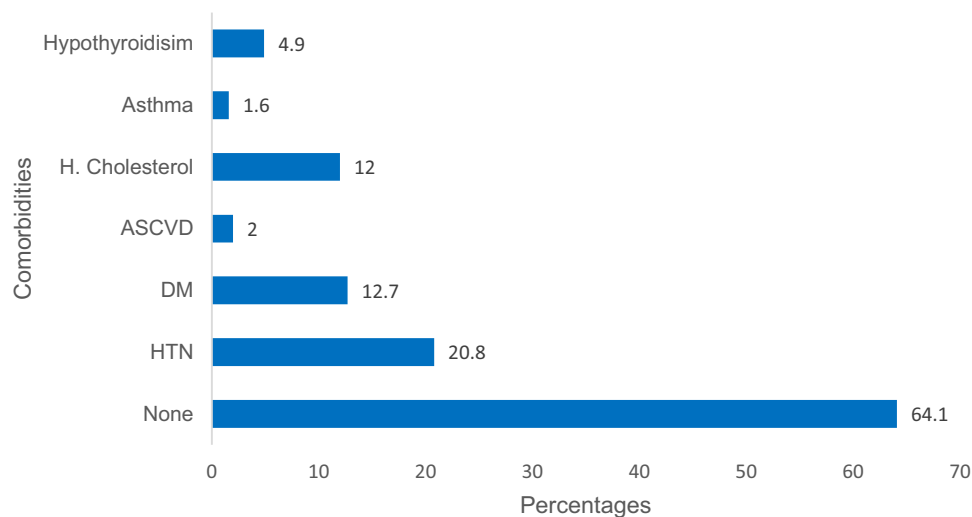
Category	Subcategory	n (%)
Gender	Male	697 (29.9)
	Female	1636 (70.1)
Age (years)	0–20	306 (13.1)
	21–40	1092 (46.8)
	41–60	788 (33.8)
	>60	147 (6.3)
Vitamin D deficiency	Yes	1837 (78.7)
Prescribed Vitamin D dose	200 IU	160 (6.9)
	0.25 mcg	81 (3.5)
	2000 IU	137 (5.9)
	5000 IU	59 (2.5)
	15,000 IU	59 (2.5)
	50,000 IU	1837 (78.7)

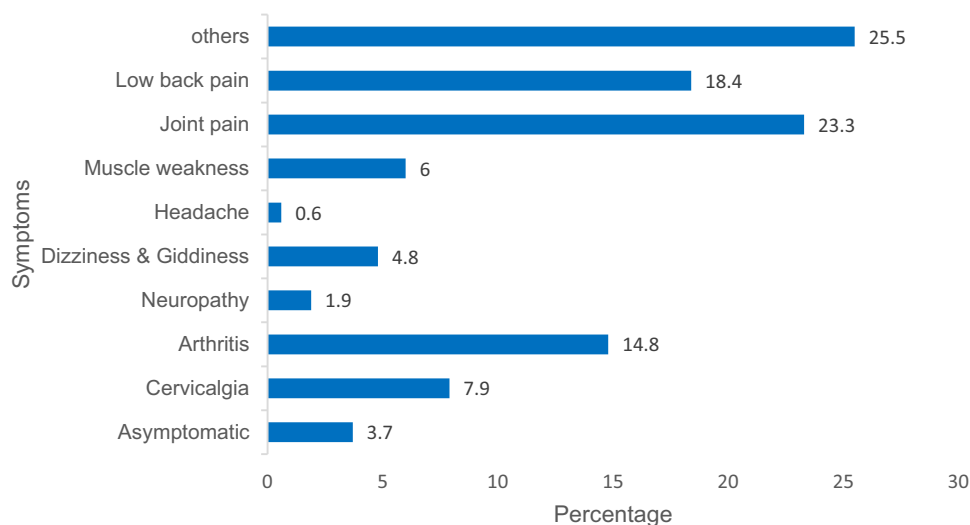
had vitamin D deficiency without hypothyroidism. However, no significant association was observed between other comorbidities and the probability of vitamin D deficiency.

Table 4 shows that asymptomatic participants (2.1%) were significantly less likely to have vitamin D deficiency than symptomatic participants (9.5%;  $p < 0.001$ ). Respondents with vitamin D deficiency were more likely to complain of cervicalgia (9.2%), lower back pain (21%), and joint pain (25.7%) ( $P$ -value  $< 0.001$ ). Add that (16.1%) complained of arthritis ( $p = 0.001$ ).

## Discussion

This study aimed to evaluate the prevalence of vitamin D deficiency and its association with patients' characteristics, health status, and symptoms. In this study, a high prevalence of vitamin D was observed; more than three-fourths of the

**Figure 1** Participants' health status and comorbidities.



**Figure 2** Participants' symptoms.

participants were prescribed 50000 IU vitamin D for VDD. The results showed that females were significantly more likely to have vitamin D deficiency than males for several reasons not addressed in this study because of multiple constraints, such as lifestyle dressing, feeding, and time exposure to the sun. A similar finding in a regional study in Jordan and Bahrain, VDD was higher in females, especially women whose dress style covered most of the body, reducing the skin's exposure to the Sun.<sup>27,28</sup> On the other hand, a study that analyzed the effect of gender on vitamin D status in a large cohort of morbidly obese Norwegian patients revealed that vitamin D deficiency was more prevalent in men than in women, 56% versus 47% ( $P < 0.001$ ).<sup>12,29</sup>

Age is a confirmed risk factor for hypovitaminosis D because of reduced skin efficacy to synthesize vitamins or inadequate vitamin intake. Furthermore, advanced age is a risk factor for Vitamin D deficiency and has been associated with an increased risk of falls and fractures.<sup>26</sup> No significant relationship was observed between the risk of vitamin D deficiency and age  $\leq 20$  years. The results showed that the highest percentage of adult patients aged 21–60 years had a vitamin D deficiency. A retrospective study in Turkey found that the highest prevalence of vitamin D deficiency occurred among individuals aged 20–30 years. The authors suggest that older adults may be taking supplements.<sup>30</sup> The Endocrine Society recommends checking Vitamin D levels in patients who are of advanced age with a history of fall or non-traumatic fracture, malabsorption, and use of anticonvulsants, glucocorticoids, antifungals, cholestyramine, or HIV antivirals.<sup>26</sup>

Vitamin D deficiency can be asymptomatic; it can also cause symptoms such as Low Back Pain, Headache, Joint Pain, Dizziness & Giddiness, muscle weakness, cervicalgia neuropathy, and arthritis; these symptoms were an indication

**Table 2** Associations Between Demographics and Vitamin D Deficiency

Comorbidity		Vitamin D Deficiency		P-value
		Yes	No	
Gender	Male	507 (72.7)	190 (27.3)	<0.001
	Female	1330 (81.3)	306 (18.7)	
Age	0–20	99 (32.4)	207 (67.6)	<0.001
	21–40	967 (88.6)	125 (11.4)	
	41–60	667 (84.6)	121 (15.4)	
	>60	104 (70.7)	43 (29.3)	

**Table 3** Associations Between Vitamin D Deficiency and Comorbidities

Comorbidity		Vitamin D Deficiency		P-value
		Yes	No	
None	Yes	1160 (77.5)	336 (22.5)	0.058
	No	677 (80.9)	160 (19.1)	
HTN	Yes	381 (78.6)	104 (21.4)	0.912
	No	1456 (78.8)	392 (21.2)	
DM	Yes	234 (79.1)	62 (20.9)	0.888
	No	1603 (78.7)	434 (21.3)	
ASCVD	Yes	37 (78.7)	10 (21.3)	0.998
	No	1800 (78.7)	486 (21.3)	
H. Cholesterol	Yes	232 (83.2)	47 (16.8)	0.055
	No	1605 (78.1)	449 (21.9)	
Asthma	Yes	29 (78.4)	8 (21.6)	0.957
	No	1808 (78.7)	488 (21.3)	
Hypothyroidism	Yes	99 (86.1)	16 (13.9)	0.048
	No	1738 (78.4)	480 (21.6)	

by treating physicians to order vitamin d level testing. The study found that VDD's most common significant symptoms were cervicalgia, lower back pain, joint pain, and arthritis ( $p = 0.001$ ). For example, a meta-analysis that investigated the association between vitamin D levels and low back pain reported a strong association between vitamin D deficiency and LBP in younger women and those with severe vitamin deficiency.<sup>31</sup>

Most bone and joint specialists consider severe joint pain to be a strong indicator of vitamin D deficiency. These results are supported by other research findings where mild vitamin d deficiency was associated with knee joint pain and mild vitamin D deficiency.<sup>32</sup> Furthermore, an Indian study investigated the association between vitamin D levels and arthritis and reported that serum vitamin D levels were significantly lower in patients with arthritis than in healthy controls. The study concludes that vitamin D deficiency is one of the causes contributing to the worsening and raising the susceptibility of Arthritis due to vitamin D's immunomodulatory activity.<sup>33</sup> Other reported symptoms associated with a confirmed vitamin D deficiency include muscle weakness, neck pain (cervicalgia), and neuropathies were reported in this research. Vitamin D deficiency has also been linked to painful diabetic neuropathy. The vitamin D level was lower in painful diabetic neuropathy patients than in others.<sup>34</sup>

In addition, the results showed that a small percentage of patients (0.6%) with headaches had vitamin D deficiency. This finding is not supported by a preliminary study that reported vitamin D deficiency is common in patients with a cluster headache.<sup>35</sup> Moreover, several studies support the effectiveness of vitamin D in decreasing the severity and frequency of migraines and cluster headaches.<sup>36</sup> Although there are several causes of a headache, headaches in chronic form without a specific cause may be related to vitamin D deficiency due to the anti-inflammatory effect of vitamin D. However, the exact relationship is difficult to establish because of complex pathophysiology.

Approximately 3.7% of asymptomatic patients had vitamin D deficiency and were treated with vitamin D 50000 IU. However, the absence of symptoms does not imply a normal vitamin D level, and screening is not required.<sup>26</sup> For example, a similar cross-sectional study in Pakistan, to determine vitamin D status among healthy medical students, reported that Vitamin D deficiency is common among asymptomatic students, especially females, emphasizing the need to add Vitamin D supplementation in their routine diet.<sup>37</sup> The decision to perform routine screening of asymptomatic

**Table 4** Associations Between Vitamin D Deficiency and Symptoms They Suffered from (N = 2333)

Comorbidity		Vitamin D Deficiency		P-value
		Yes	No	
Asymptomatic	Yes	39 (2.1)	47 (9.5)	<0.001
	No	1798 (97.9)	449 (90.5)	
Cervicalgia	Yes	169 (9.2)	16 (3.2)	<0.001
	No	1668 (90.8)	480 (96.8)	
Arthritis	Yes	296 (16.1)	49 (9.9)	0.001
	No	1541 (83.9)	447 (90.1)	
Neuropathy	Yes	33 (1.8)	12 (2.4)	0.371
	No	1804 (98.2)	484 (97.6)	
Dizziness & Giddiness	Yes	94 (5.1)	17 (3.4)	0.117
	No	1743 (94.9)	479 (96.6)	
Headache	Yes	12 (0.7)	2 (0.4)	0.552
	No	1825 (99.3)	494 (99.6)	
Muscle weakness	Yes	114 (6.2)	26 (5.2)	0.423
	No	1723 (93.8)	470 (94.8)	
Joint pain	Yes	473 (25.7)	70 (14.1)	<0.001
	No	1364 (74.3)	426 (85.9)	
Low back pain	Yes	386 (21)	43 (8.7)	<0.001
	No	1451 (79)	453 (91.3)	
Others	Yes	378 (20.6)	218 (44)	<0.001
	No	1459 (79.4)	278 (56)	

**Note:** Vertigo, palpitations, spasm muscle, skin sensation disorders, chest pain, sciatica, shortness of breath, menstrual disorder, tremor, gastritis, trigger finger, syncope and collapse, cough, ulcerative colitis, nausea, abdominal pain, renal colic, irregular menstruation, salivary gland disorder, synovitis and tenosynovitis, urticaria, tinnitus, calcaneal, tachycardia, swelling limb, polymyositis.

patients remains controversial. The American Endocrine Society does not recommend routine Vitamin D screening unless the patient has certain risk factors and characteristics, including advanced age with a history of fall or non-traumatic fracture, malabsorption, and use of certain medications that lower vitamin D such as anticonvulsants, glucocorticoids, antifungals, cholestyramine, or HIV antivirals.<sup>26</sup> Screening is also recommended for pregnant or lactating women, people with dark skin tone, and for measurement are osteoporosis, osteomalacia, rickets, chronic kidney disease, liver failure, hyperparathyroidism, obesity, granulomatous disease, and lymphoma.

Approximately 80% of patients with diabetes in this study had vitamin D deficiency. Even though this finding was not significant other studies showed low vitamin D levels associated with worsening type II diabetes outcomes and complications.<sup>38</sup> In a similar study, more than 50% of type 2 diabetes patients had vitamin D deficiency.<sup>39</sup> In addition, vitamin D can potentially reduce the risk of type-2 diabetes when administered as a supplement.<sup>9</sup> On the other hand, in a recent trial, 4000 IU daily for 48 weeks (n = 127) did not improve diabetic control in patients with A1C  $\leq$ 7.5% controlled with lifestyle and metformin.<sup>40</sup>

Concerning hypertension, 78% of the participants with hypertension were deficient in vitamin D. However, this finding was not significant. Furthermore, in a meta-analysis, there was no increase in the risk of hypertension among elderly individuals with vitamin D deficiency. However, a strong association between low vitamin D levels and increased risk of hypertension was found in younger females.<sup>41</sup> Hypertension has been reported to be associated with low vitamin D levels and increased hypertension prevalence.<sup>42</sup> However, some studies suggest the opposite; they did not find an association between a low vitamin D concentration and a greater risk of hypertension.<sup>43</sup> Further studies are needed to confirm the association between vitamin D deficiency and hypertension; trials of vitamin D supplementation and a lower risk of hypertension are still debatable.

High cholesterol levels were not associated with VDD in this study, even though 83% of the participants with high cholesterol levels were vitamin D deficient. A cross-sectional study shows a strong relationship between vitamin D deficiency and serum lipid profile.<sup>44</sup> Furthermore, (75%) of the patients with cardiovascular disease were diagnosed with vitamin D deficiency. However, the association between vitamin D levels and cardiovascular disease (CVD) remains unclear. Some trials have not confirmed the effect of vitamin D supplementation in lowering the risk of CVD. A meta-analysis of 19 prospective studies concluded an inverse association between vitamin D concentration and risk of cardiovascular disease, a 52% risk increase for CVD in patients with low vitamin D.<sup>45</sup> Further studies are required to confirm this association.

Although the number of patients with asthma participating in our study was small (37 patients), the prevalence of vitamin D was 78%, with no significant associations compared with non-asthmatic patients. Never the less in, a retrospective analysis was conducted to see if there is a relationship between asthma and low vitamin D; the study concluded that vitamin D sufficiency is associated with decreased asthma exacerbation in adults.<sup>46</sup>

Vitamin D deficiency has been associated with autoimmune thyroid diseases, and impaired vitamin D signaling encourages thyroid tumorigenesis.<sup>47</sup> The highest proportion of comorbidities was hypothyroidism, and 88% of patients with hypothyroidism were vitamin D-deficient, with a significant relationship ( $p = 0.48$ ). A Saudi study conducted in 2013 found that vitamin D deficiency is significantly associated with the severity of hypothyroidism. In addition, they encourage the patients to take vitamin D supplementation and recommend that all patients with hypothyroidism be screened for vitamin D deficiency.<sup>16</sup>

## Limitations

This study had some limitations. First, a lack of appropriate documentation of vital information, such as a patient's weight and body mass index, to determine a relationship between obesity and vitamin D deficiency does not document vitamin D levels after a laboratory test.

## Conclusion

In this study, a high prevalence of vitamin D deficiency was observed. The study highlighted a significant link between vitamin D deficiency and symptoms, such as joint pain, low back pain, cervicalgia, and hypothyroidism. Further studies are needed to confirm the relationship between vitamin D supplementation and the reduced risk of comorbid diseases and to increase our understanding of the relationship between vitamin D, patient health status, comorbidities, and questions about adequate, optimal, and excessive vitamin D intake.

## Disclosure

The authors report no conflicts of interest in this work.

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