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High parathyroid hormone level as a marker of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis: A systematic review and meta-analysis

Aunchalee Jaroenlapnopparat [a,b], Thanitsara Rittiphairoj [c], Natapat Chaisidhivej [d], Bradley Walker [a,b], Nipith Charoenngam [a,b,e,*]

[a] Department of Medicine, Mount Auburn Hospital/Beth Israel Lahey Health, Cambridge, MA, USA
[b] Department of Medicine, Harvard Medical School, Boston, MA, USA
[c] Harvard T.H. Chan School of Public Health, Boston, MA, USA
[d] Department of Medicine, Einstein Medical Center Philadelphia, Philadelphia, PA, USA
[e] Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

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ABSTRACT

Background and aims: Studies have suggested that high parathyroid hormone (PTH) was associated with non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), although the results from existing studies are inconsistent. Using systematic review and meta-analysis, we aimed to determine the association of PTH with NAFLD and NASH.

Methods: Potentially eligible studies were identified from Embase and Medline databases from using search strategy consisting of terms for "NAFLD/NASH", and "PTH". Eligible study must consist of one group of patients with NAFLD/NASH and another group without NAFLD/NASH. The study must provide mean ± SD PTH in both groups. We extracted such data to calculate mean difference (MD). Pooled MD was then calculated by combining MDs of each study using random-effects model. Funnel plot was used to assess for the presence of publication bias.

Results: A total of 388 articles were identified. After systematic review, 12 studies fulfilled the eligibility criteria and were included into the meta-analysis. The meta-analysis of 10 studies revealed the significant association between high PTH and NAFLD, with the pooled MD of 5.479 (95%CI 0.947–10.011, I^2 82.4%). The funnel plot was symmetric and did not suggest publication bias. The meta-analysis of 4 studies revealed the non-significant association between high PTH and NASH, with the pooled MD of 11.955 (95%CI -4.703 – 28.614, I^2 81.0%).

Conclusions: High PTH level is significantly associated with NAFLD and can be used as a marker of NAFLD. However, high PTH level is non-significantly associated with NASH. Further studies are needed to increase the sample size and eliminate the confounding factors.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of hepatic disease ranging from liver steatosis and steatohepatitis to potential end-stage liver fibrosis and cirrhosis. This condition is the most common etiology of chronic liver disease with a prevalence as high as 24% of the world population [1]. In the US, it is estimated that 80 million individuals are affected with this disease, costing approximately $103 billion in healthcare costs annually [2,3]. Nonalcoholic steatohepatitis (NASH) exhibits a lower prevalence estimated at approximately 1–6.5% [4]. Despite this relatively lower prevalence, NASH remains the second most common indication for liver transplant [5]. The major risk factors associated with NAFLD and NASH are obesity, insulin resistance and dyslipidemia [6]. In addition, multiple studies have attempted to identify novel biomarkers for diagnosis and risk stratification of NAFLD and NASH. These include adipokines (*e.g.*, leptin, adiponectin, tumor necrosis factor-alpha), molecules involved lipid pathways (*e.g.*, apolipoprotein A1, apolipoprotein B, free fatty acid) and oxidative stress markers (*e.g.*, cytochrome p450 2E1 expression) among others [7].

Parathyroid hormone (PTH) is a polypeptide hormone responsible

* Corresponding author. 330 Mt Auburn St, Cambridge, MA 02138, USA
E-mail address: nipith.charoenngam@gmail.com (N. Charoenngam).

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for maintaining calcium and phosphate homeostasis by inducing bone resorption, urinary phosphate excretion and 1,25-dihydroxyvitamin D production in the kidneys [8]. In addition, PTH was found to be associated with metabolic syndrome in US adults. The finding could possibly be explained by the association of high PTH level with hypertension, insulin resistance and dyslipidemia reported in observational studies [9, 10]. It also is known that vitamin D is associated with NAFLD due to involvement in multiple mechanisms including insulin resistance, adipose tissue inflammation, liver inflammation and fibrosis [11]. Given that PTH is inversely associated with vitamin D in calcium homeostasis, it could therefore be a mediator or a marker in the pathogenesis of NAFLD.

Interestingly, multiple studies have indicated that high levels of PTH were associated presence of NAFLD and NASH, suggesting that PTH may be another biomarker of NAFLD and NASH. Nevertheless, the results from existing studies are somewhat inconsistent [12–23]. The purpose of this systematic review and meta-analysis is to investigate the potential association between PTH levels and NAFLD/NASH development by identifying all available records and summarizing their results together.

2. Methods

2.1. Search strategy

Two investigators (AJ, NC) independently searched records indexed in Embase and Medline from inception to November 2021. The search strategy included terms related to "Parathyroid hormone", "Nonalcoholic fatty liver disease" and "Nonalcoholic steatohepatitis", as shown in Supplemental material 1. The PRISMA guideline for systematic review was followed, as indicated in Supplemental material 2. No language restriction was applied.

2.2. Eligibility criteria

Eligible study must be case-control study that consists of cases with NAFLD/NASH and controls without NAFLD/NASH. Then, the study must report estimates and variance of serum PTH levels of each group. Two investigators (AJ, NC) independently reviewed the titles and abstracts of retrieved records. Records that clearly did not fulfill the eligibility criteria based on type of article, study design or outcome of interest were excluded at this stage. Then, three investigators (AJ, TR, NC) independently evaluated full text of the remaining records to their final eligibility. The quality of each included study was assessed using the Newcastle-Ottawa quality assessment scale for case-control study, which was performed by two investigators (AJ, TR) [24]. Different opinion in the eligibility and quality assessment of the records were resolved by discussion with the senior investigator (NC).

2.3. Data extraction

Data from each eligible record were extracted using the standardized data collection form, which contained the following information: last name of the first author, country of the study, number of participants (cases and controls), diagnosis of NAFLD and/or NASH, measurement of PTH, mean age of the participants, percentage of female participants and effect estimate along with its standard errors.

2.4. Statistical analysis

Mean serum PTH and standard errors of cases with NAFLD/NASH and controls were extracted from each study and the weighted mean difference (WMD) was calculated. Pooled WMD was then calculated by combining WMDs of each study using random-effects model. The heterogeneity of the WMDs across the eligible studies was calculated using the Q statistic, which is complimented with I^2 statistics. A value of I^2 of 0–25%, 26–50%, 51–75%, 76–100% indicates insignificant, low, moderate and high statistical heterogeneity, respectively [25]. Visualization of funnel plot was used for assessment of presence of publication bias. All analyses were performed using the StataMP15.

3. Results

3.1. Search results

A total of 420 records were identified from the electronic search. After removal of 32 duplicates, 388 records underwent title and abstract review. A total of 338 records were excluded at this stage as they clearly did not fulfill the eligibility criteria based on type of article, study design and outcome of interest, leaving 50 records for full text review. A total of 38 records were further excluded at this stage since they did not report the outcome of interest. Finally, a total of 12 studies fulfilled the eligibility criteria and were included into the meta-analysis [12–23]. Among them, ten studies reported the association between serum PTH level and NAFLD [12–21], while four studies reported the association between serum PTH level and NASH [15,17,22,23]. Fig. 1 summarizes the literature search and review process of this study. The characteristics of all eligible studies reporting the association of PTH with NAFLD and NASH were summarized in Table 1 and Table 2, respectively.

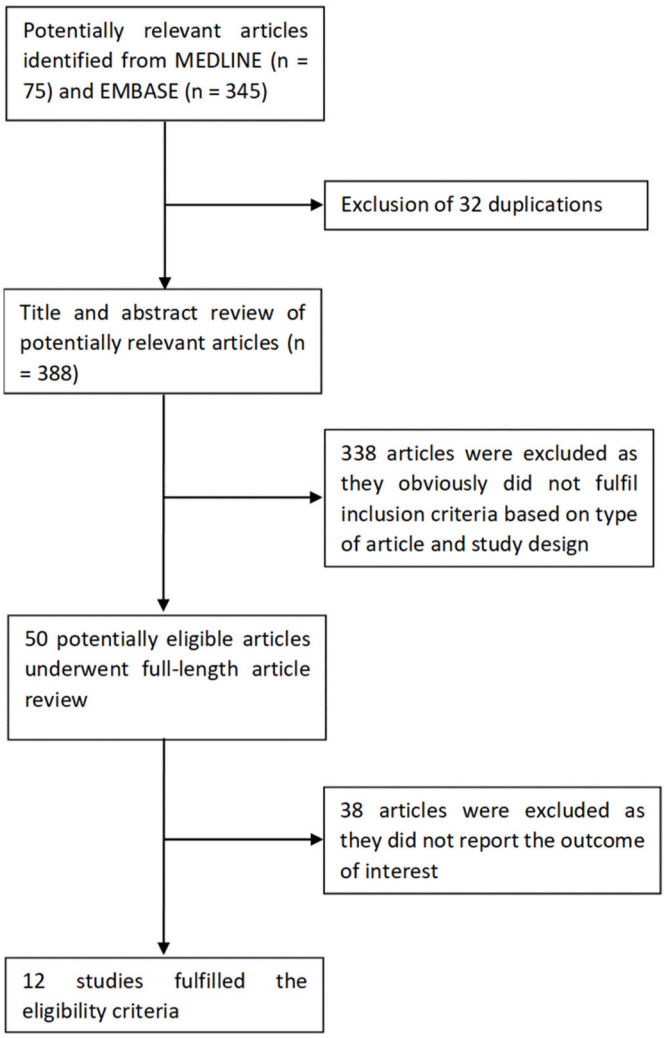

Fig. 1. Literature review and study selection process.

Table 1
Main characteristics of case-control studies investigating the association between non-alcoholic fatty liver disease and parathyroid hormone level included in the meta-analysis.

	Bhatt et al. [18]	Catena et al. [19]	Li et al. [22]
Country	India	Italy	China
Year of publication	2013	2013	2013
Total number of participants	Cases: 162 Controls: 173	Cases: 27 Controls: 41	Cases: 378 Controls: 870
Recruitment of participants	Cases: Cases were patients with NAFLD and BMI $\geq$23 kg/m^2 recruited from Fortis Hospital or All India Institute of Medical Sciences, New Delhi, India from May 2007 to January 2012. Controls: Controls were patient without NAFLD who had BMI $\geq$23 kg/m^2 recruited from the same clinical sites during the same period. Cases and controls were matched by age. Patients with T2D, CVD, other liver diseases, severe organ damage, HIV infection, pregnancy and lactation, or any pro-inflammatory state were excluded from the study	Cases: Cases were patients with NAFLD recruited from hospital-based specialized hypertension outpatient clinics from early spring to mid-autumn of 2012–2013. Controls: Controls were patients without NAFLD recruited from the same clinical sites during the same period. Patients with history of diabetes, obesity, moderate to severe hyperlipidemia, positive HBsAg or HCV, alcohol intake >20 g/day, smoking, using hepatosteatogenic drugs, cardiopulmonary, renal, and hepatic disease were excluded from the study	Cases: Cases were patients with NAFLD recruited from employees of a factory in Dali, Yunnan, China from May to July 2010. Controls: Controls were patients without NAFLD recruited from the same site during the same period. Subjects with alcohol intake of $\geq$140 g/week in men and $\geq$70 g/week in women, hepatitis B and C infection were excluded from the study.
Diagnosis of NAFLD	Based on liver ultrasonography and alcohol intake of <20 g/day	Based on liver ultrasonography	Based on liver ultrasonography
Measurement of PTH concentration	Electrochemiluminescence assay	Chemiluminescence technology	Chemiluminescence technology
Average age of participants (years)	Cases: 38 Controls: 37	Cases: 50 Controls: 41	Cases: 51 Controls: 49
Percentage of female	Cases: 20% Controls: 37%	Cases: 48% Controls: 59%	Cases: 31% Controls: 51%
BMI of the participants (**kg/m^2**)	Cases: 28.1 $\pm$ 3.2 (mean $\pm$ SD) Controls: 26.8 $\pm$ 3.2 (mean $\pm$ SD)	Cases: 26.6 $\pm$ 2.5 (mean $\pm$ SD) Controls: 24.3 $\pm$ 2.9 (mean $\pm$ SD)	Cases: 26.3 $\pm$ 2.9 (mean $\pm$ SD) Controls: 22.3 $\pm$ 2.9 (mean $\pm$ SD)
HOMA-IR of the participants	Cases: 2.5 $\pm$ 0.98 (mean $\pm$ SD) Controls: 1.6 $\pm$ 0.8 (mean $\pm$ SD)	Cases: 3.4 $\pm$ 0.6 (mean $\pm$ SD) Controls: 1.6 $\pm$ 0.7 (mean $\pm$ SD)	N/A
25-hydroxyvitamin D, calcium, phosphorus levels of the participants	25-hydroxyvitamin D levels Cases: 19.4 $\pm$ 8.5 ng/mL (mean $\pm$ SD) Controls: 27.8 $\pm$ 9.4 ng/mL (mean $\pm$ SD) Calcium levels Cases: 9.7 $\pm$ 0.1 mg/dL (mean $\pm$ SD) Controls: 9.6 $\pm$ 0.3 mg/dL (mean $\pm$ SD)	25-hydroxyvitamin D levels Cases: 20.4 $\pm$ 9.1 ng/mL (mean $\pm$ SD) Controls: 19.8 $\pm$ 10.1 ng/mL (mean $\pm$ SD) Calcium levels Cases: 9.3 $\pm$ 0.3 mg/dL (mean $\pm$ SD) Controls: 9.4 $\pm$ 0.4 mg/dL (mean $\pm$ SD) Phosphorus levels Cases: 3.2 $\pm$ 0.3 mg/dL (mean $\pm$ SD) Controls: 3.4 $\pm$ 0.3 mg/dL (mean $\pm$ SD)	25-hydroxyvitamin D levels Cases: 22.1 $\pm$ 8.1 ng/mL (mean $\pm$ SD) Controls: 22.8 $\pm$ 8.4 ng/mL (mean $\pm$ SD)
Newcastle-Ottawa score	Selection: 3 Comparability: 1 Exposure: 3	Selection: 3 Comparability: 1 Exposure: 3	Selection: 4 Comparability: 1 Exposure: 3

	Pirgon et al. [25]	Yildiz et al. [27]	Sezer et al. [26]
Country	Turkey	Turkey	Turkey
Year of publication	2013	2014	2016
Total number of participants	Cases: 45 Controls: 42	Cases: 58 Controls: 43	Cases: 58 Controls: 53
Recruitment of participants	Cases: Cases were patients with NAFLD recruited from obese children admitted to Pediatric Endocrine Unit during December 2010–February 2011. Controls: Controls were patient without NAFLD recruited from obese children from the same clinical sites during the same period. Patients with diabetes, took a medication or had condition known to influence vitamin D status, insulin action, or insulin secretion were excluded from the study	Cases: Cases were patients with hepatosteatosis recruited from obese children who were evaluated at general pediatric clinic during June 2012–February 2013 Controls: Controls were patients without hepatosteatosis recruited from obese children from the same clinical sites during the same period.	Cases: Cases were patients with hepatosteatosis recruited from children age 7–18 who came for evaluation of obesity at outpatient clinics of Pediatric Gastroenterology and Pediatric Endocrinology at the Kecioren Training and Research Hospital, Ankara, Turkey Controls: Controls were patients without hepatosteatosis recruited from children from the same clinical sites during the same period. Patients with a history of systemic diseases such as cardiovascular disease, diabetes, inflammatory bowel disease, primary hyperparathyroidism, Cushing syndrome, hypothyroidism, other liver diseases, and family history of hereditary hyperlipidemia were excluded from the study
Diagnosis of NAFLD	Based on liver ultrasonography with high ALT >40 U/L, and no other chronic liver conditions	Based on liver ultrasonography	Based on liver ultrasonography
Measurement of PTH concentration	Auto-analyzer	Not described	Architect c16000 system (Abbot Diagnostics, IL, USA)
Average age of participants (years)	Cases: 13 Controls: 13	Cases: 12 Controls: 11	Cases: 13 Controls: 13
Percentage of female	Cases: 53% Controls: 52%	Cases: 38% Controls: 56%	Cases: 45% Controls: 72%
BMI of the participants (**kg/m^2**)	Cases: 28.7 $\pm$ 4.7 (mean $\pm$ SD) Controls: 28.4 $\pm$ 3.6 (mean $\pm$ SD)	Controls: 29.3 $\pm$ 4.4 (mean $\pm$ SD) Cases: 30.9 $\pm$ 3.9 (mean $\pm$ SD)	Cases: 28.7 $\pm$ 4.3 (mean $\pm$ SD) Controls: 27.3 $\pm$ 3.3 (mean $\pm$ SD)

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Table 1 (*continued*)

	Pirgon et al. [25]	Yildiz et al. [27]	Sezer et al. [26]
HOMA-IR of the participants	Cases: 7.01 ± 2.10 (mean ± SD) Controls: 2.38 ± 0.79 (mean ± SD)	Cases: 5.3 ± 4.4 (mean ± SD) Controls: 3.6 ± 2.4 (mean ± SD)	Cases: 4.8 ± 3.0 (mean ± SD) Controls: 4.0 ± 2.5 (mean ± SD)
25-hydroxyvitamin D, calcium, phosphorus levels of the participants	25-hydroxyvitamin D levels Cases: 29.5 ± 18.4 ng/mL (mean ± SD) Controls: 41.0 ± 17.9 ng/mL (mean ± SD) Calcium levels Cases: 9.85 ± 0.25 mg/dL (mean ± SD) Controls: 9.7 ± 0.03 mg/dL (mean ± SD) Phosphorus levels Cases: 4.5 ± 0.4 mg/dL (mean ± SD) Controls: 4.4 ± 0.5 mg/dL (mean ± SD)	25-hydroxyvitamin D levels Cases: 12.6 (9.3–18.1) ng/mL (median, IQR) Controls: 16.4 (12.4–24.8) ng/mL (median, IQR) Calcium levels Controls: 9.8 ± 0.4 mg/dL (mean ± SD) Cases: 9.9 ± 0.4 mg/dL (mean ± SD) Phosphorus levels Controls: 4.7 ± 0.6 mg/dL (mean ± SD) Cases: 4.7 ± 0.6 mg/dL (mean ± SD)	25-hydroxyvitamin D levels Cases: 16.6 ± 6.2 pg/mL (mean ± SD) Controls: 14.6 ± 7.0 pg/mL (mean ± SD) Calcium levels Cases: 10.1 ± 0.4 mg/dL (mean ± SD) Controls: 10.0 ± 0.3 mg/dL (mean ± SD) Phosphorus levels Cases: 4.5 ± 0.6 mg/dL (mean ± SD) Controls: 4.5 ± 0.6 mg/dL (mean ± SD)
Newcastle-Ottawa score	Selection: 3 Comparability: 1 Exposure: 3	Selection: 3 Comparability: 1 Exposure: 3	Selection: 3 Comparability: 1 Exposure: 3

	Muhsen et al. [24]	Mantovani et al. [23]	He et al. [20]
Country	Saudi Arabia	Italy	China
Year of publication	2018	2018	2018
Total number of participants	Cases: 11 Controls: 82	Cases: 52 Controls: 15	Cases: 209 Controls: 122
Recruitment of participants	Cases: Cases were patients with NAFLD and minimum duration of 5 years of cirrhosis recruited from patients who underwent pretransplant assessment in 2014–1015 at King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia Controls: Controls were patient without cirrhosis recruited from family medicine clinic at the same clinical site Patients were age and gender matched Patients with primary bone disease, evidence of secondary causes of osteoporosis other than chronic liver disease, malignancy, cardiopulmonary disease, end stage renal failure, systemic use of steroid, autoimmune hepatitis, alcoholic liver disease, and metabolic liver diseases such as Wilson disease were excluded from the study	Cases: Cases were patients with hepatic steatosis recruited from white post-menopausal women with T2D who attended diabetes outpatient service from October to December 2017 Controls: Controls were patients without hepatic steatosis recruited from white post-menopausal women with T2D from the same clinical sites during the same period. Patient with alcohol consumption more than 20 g/day, known causes of chronic liver disease, cirrhosis of any etiology, end stage renal disease, overt thyroid disease, treatment with hormone replacement therapy or steroids were excluded from the study	Cases: Cases were patients with NAFLD with T2D who were admitted to the Department of Endocrinology and Metabolism of Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China during March 2015 to December 2016 Controls: Controls were patients without NAFLD who had T2D recruited from the same clinical sites during the same period. Patients with T1D, gestational diabetes, other specific types of diabetes, weekly alcohol intake ≥140 g for men, ≥70 g for women, viral hepatitis, autoimmune liver disease, renal dysfunction, hypo/hyperthyroidism, acute infection, severe cardiovascular disease, severe cerebrovascular disease, malignant, using drugs known to influence vitamin D metabolism, and psychiatric diseases were excluded from the study
Diagnosis of NAFLD	Not described Cirrhosis confirmed by minimum of two of the followings: imaging (ultrasound or CT abdomen), liver biopsy, fibroscan	Based on liver ultrasonography and liver stiffness measurement by fibroscan	Based on liver ultrasonography
Measurement of PTH concentration	Electrochemiluminescence assay	Immuno-chemiluminescent technology	Not described
Average age of participants (years)	Cases: No information Controls: 57	Cases: 71 Controls: 77	Cases: 57 Controls: 59
Percentage of female	Cases: No information Controls: 34%	Cases: 100% Controls: 100%	Cases: 52% Controls: 46%
BMI of the participants **(kg/m^2)**	N/A	Cases: 29.6 ± 5.0 (mean ± SD) Controls: 27.1 ± 5.0 (mean ± SD)	Cases: 26.8 ± 3.0 (mean ± SD) Controls: 23.3 ± 2.5 (mean ± SD)
HOMA-IR of the participants	N/A	Cases: 2.3 (1.3–4.1) (median, IQR) Controls: 1.1 (0.7–1.9) (median, IQR)	Cases: 1.7 ± 0.7 (mean ± SD) Controls: 1.2 ± 0.6 (mean ± SD)
25-hydroxyvitamin D, calcium, phosphorus levels of the participants	25-hydroxyvitamin D levels Cases: 20.3 (95%CI, 14.2–26.5) ng/mL Controls: 16.4 (95%CI, 7.0–25.8) ng/mL Calcium levels Cases: 9.2 (95%CI, 8.8–9.7) mg/dL Controls: 9.5 (95%CI, 9.2–9.7) mg/dL Phosphorus levels Cases: 3.1 (95%CI, 2.8–3.5) mg/dL Controls: 3.47 (95%CI, 3.1–3.9) mg/dL	25-hydroxyvitamin D levels Cases: 31.9 ± 13.4 ng/mL (mean ± SD) Controls: 32.9 ± 8.8 ng/mL (mean ± SD) Calcium levels Cases: 9.6 ± 0.4 mg/dL (mean ± SD) Controls: 9.2 ± 0.4 mg/dL (mean ± SD) Phosphorus levels Cases: 3.4 ± 0.3 mg/dL (mean ± SD) Controls: 3.4 ± 0.3 mg/dL (mean ± SD)	25-hydroxyvitamin D levels Cases: 16.4 (12.7–21.4) ng/mL (median, IQR) Controls: 19.6 (13.8–26.3) ng/mL (median, IQR) Calcium levels Cases: 9.4 ± 0.4 mg/dL (mean ± SD) Controls: 9.3 ± 0.4 mg/dL (mean ± SD) Phosphorus levels Cases: 4.0 ± 0.5 mg/dL (mean ± SD) Controls: 3.9 ± 0.6 mg/dL (mean ± SD)
Newcastle-Ottawa score	Selection: 2 Comparability: 1 Exposure: 3	Selection: 3 Comparability: 1 Exposure: 3	Selection: 3 Comparability: 1 Exposure: 3

	Jamialahmadi et al. [21]
Country	Iran
Year of publication	2021
Total number of participants	Cases: 51 Controls: 39
Recruitment of participants	Cases: Cases were patients with positive liver histology for hepatic steatosis recruited from patients with BMI over 40 kg/m^2 or over 35 with more than 2 comorbidities who referred to Imam reza outpatient clinic during December 2016 to September 2017

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Table 1 (*continued*)

	Jamialahmadi et al. [21]
	Controls: Controls were patients with negative histology for hepatic steatosis recruited from the same clinical site during the same duration Patients with alcohol intake over 30 g/day in males, 20 g/day in females, positive HbsAg or HCV antibody, and drug-induced liver injury were excluded from the study
Diagnosis of NAFLD	2D-SWE and liver biopsy
Measurement of PTH concentration	Not described
Average age of participants (years)	39
Percentage of female	80%
BMI of the participants **(kg/m^2)**	Total: 45.5 ± 6.3 (mean ± SD)
HOMA-IR of the participants	Total: 6.3 ± 6.8 (mean ± SD)
25-hydroxyvitamin D, calcium, phosphates levels of the participants	N/A
Newcastle-Ottawa score	Selection: 3 Comparability: 1 Exposure: 3

Abbreviation: 2D-SWE: Two-dimensional shear wave elastography; ALT: Alanine Aminotransferase; BMI: Body Mass Index; CT: Computerized Tomography; CVD: Cerebrovascular Disease; HBsAg: Hepatitis b Antigen; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; HOMA-IR: The Homeostasis Model Assessment-estimated Insulin Resistance; N/A: Not Available; NAFLD: Nonalcoholic Fatty Liver Disease; PTH: Parathyroid hormone; T2DM: Type 2 Diabetes Mellitus; T1D: Type 1 Diabetes Mellitus; USA: United States of America.

3.2. Association between serum parathyroid hormone level and nonalcoholic fatty liver disease

The meta-analysis of 10 studies consisting of 1051 NAFLD patients and 1510 controls [12–21] revealed that high PTH level was associated with presence of NAFLD, with the pooled WMD of 5.479 (95%CI 0.947–10.011). This meta-analysis had high statistical heterogeneity with I^2 of 82.4%. The forest plot of this meta-analysis is shown in Fig. 2.

3.3. Association between serum parathyroid hormone level and nonalcoholic steatohepatitis

The meta-analysis of 4 studies consisting of 99 patients with NASH and 143 controls [15,17,22,23] revealed the non-significant association between high PTH level and presence of NASH, with the pooled WMD of 11.955 (95%CI -4.703 – 28.614). This meta-analysis had high statistical heterogeneity with I^2 of 81.0%. The forest plot of this meta-analysis is shown in Fig. 3.

3.4. Evaluation for publication bias

Funnel plot was generated and used for assessment for publication bias. For the meta-analysis of association between PTH and NAFLD, the funnel plot was fairly symmetric, which was not suggestive of presence of publication bias (Fig. 4). Given that only four studies were eligible for the meta-analysis of association between PTH and NASH, publication bias cannot be evaluated with visualization of funnel plot.

4. Discussion

This is the first meta-analysis that demonstrates the association between PTH level and presence of NAFLD and NASH. The meta-analysis revealed that high PTH level was significantly associated with presence of NAFLD. We also found a trend towards association between high PTH level and NASH; however, statistical significance was not achieved, probably due to limited number of participants as only four studies were included in this meta-analysis.

The relationship between PTH levels and NAFLD/NASH is interesting. Although it was incidentally found in the past, our meta-analysis has confirmed this association. These findings may have clinical implications as they may suggest that high PTH level could be another biochemical marker of presence of NAFLD and possibly NASH. The goal for management of NAFLD is to prevent liver fibrosis by controlling risk factors such as obesity and insulin resistance. Non-invasive tests such as transient elastography, blood-based scores using aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet, albumin are currently use in real practice to monitor disease progression. Biomarkers such as cytokeratin (CK)-18 and fibroblast growth factor (FGF)-21 are being studied but not widely used due to availability [26,27]. PTH may be a good marker to be considered to combine in non-invasive blood-based scores for disease monitoring in the future.

Although the exact mechanism of the observation is still undetermined, there are potential pathologic mechanisms that could account for this. First, increased serum PTH may directly result in increased hepatic fatty acid accumulation. This notion is based on the observation that PTH modulates fatty acid metabolism primarily via inhibiting catecholamine-induced beta-oxidation and increasing intracellular calcium load in the adipocytes [28,29]. It is therefore possible that PTH may also induce hepatic lipogenesis, although the direct effect of PTH on the hepatic tissue is still to be further investigated.

The second potential mechanism is that PTH may exert indirect systemic effects in the peripheral tissues that can contribute to the development of fatty liver. PTH is shown to cause a decrease in glucose uptake within adipocytes, thereby inducing an insulin resistant state. It can also induce peripheral lipolysis by affecting protein kinase A-mediated phosphorylation of hormone-sensitive lipase [30]. These effects subsequently result in elevated plasma free fatty acids, which, in turn, promotes hepatic lipid accumulation [31]. Additionally, insulin resistance induced by high levels of PTH can also promote the development of hyperglycemia and hyperinsulinemia, both of which enhance de novo hepatic lipogenesis predisposing to NAFLD and NASH [32].

Recently, Yang et al. reported a new non-invasive model to predict fibrosis in NAFLD patients. PTH level significantly increased the predictability of the model. It is also interesting that vitamin D and calcium are not associated with fibrosis in this study, implying that PTH is an independent marker of NAFLD [33]. Nevertheless, this observation should be carefully interpreted since multiple factors could play a role in the relationship between PTH and NAFLD.

Aside from its role in regulation of fatty acid metabolism, high levels of PTH may reflect low levels of vitamin D, which have been shown to be associated with NAFLD and NASH in several observational studies [34,35]. This is believed to be due to the effects of vitamin D that improves insulin sensitivity and reduces the functionality of hepatic stellate cells and inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha [36–39]. The lack of these positive effects of vitamin D may therefore potentiate the metabolic disturbance and inflammatory process underlying NAFLD and NASH. Moreover, high PTH could also associated with high serum calcium, which was found to be associated with NAFLD. Although the mechanisms remain unclear, calcium has been reported to be related to metabolic syndrome and inflammation of

Table 2
Main characteristics of case-control studies investigating the association between non-alcoholic steatohepatitis and parathyroid hormone level included in the meta-analysis.

	Diez Rodriguez et al. [29]	Ghoghaei et al. [28]	Mantovani et al. [23]
Country	Spain	Iran	Italy
Year of publication	2014	2015	2018
Total number of participants	Cases: 18 Controls: 63	Cases: 20 Controls: 26	Cases: 10 Controls: 15
Recruitment of participants	Cases: Cases were patients who had positive liver histology for NASH recruited from patients who underwent bariatric surgery at third level hospital from June 2008 to March 2013 Controls: Controls were patient with who had negative liver histology for NASH recruited from family medicine clinic at the same clinical site	Cases: Cases were patients who had positive NASH from liver histology recruited from patients who underwent bariatric surgery at Erfan Hospital, Tehran, Iran from December 2009 to March 2011 Controls: Controls were patient with who had negative NASH from liver histology recruited from family medicine clinic at the same clinical site	Cases: Cases were patients with hepatic steatosis and significant fibrosis recruited from white post-menopausal women with T2D who attended diabetes outpatient service from October to December 2017 Controls: Controls were patients without hepatic steatosis and significant fibrosis recruited from white post-menopausal women with T2D from the same clinical sites during the same period.
	Patients with primary hyperparathyroidism, renal disease, alcohol intake over 20 g/day, other causes of liver disease such as HBV, HCV, autoimmune hepatitis, hemochromatosis, steatosis inducing drugs were excluded from the study	Patient with alcohol consumption more than 200 g/week, known causes of chronic liver disease (such as wilson's disease, hemochromatosis, etc.), positive viral hepatitis or HIV, positive ANA, impaired renal function, taking steatosis inducing drugs, taking drugs affecting calcium and vitamin D metabolism were excluded from the study	Patient with alcohol consumption more than 20 g/day, known causes of chronic liver disease, cirrhosis of any etiology, end stage renal disease, overt thyroid disease, treatment with hormone replacement therapy or steroids were excluded from the study
Diagnosis of NASH	Liver biopsy	Liver biopsy	Based on liver ultrasonography and fibroscan
Measurement of PTH concentration	Immunochemiluminescence	ELISA method	Not described
Average age of participants (years)	44	Cases: 39 Controls: 36	Cases: 72 Controls: 77
Percentage of female	73%	Cases: 81% Controls: 65%	Cases: 100% Controls: 100%
BMI of the participants **(kg/m^2)**	Total: 46.9	Cases: 44.3 ± 5.8 (mean ± SD) Controls: 45.2 ± 9.0 (mean ± SD)	Cases: 29.6 ± 4.0 (mean ± SD) Controls: 27.1 ± 5.0 (mean ± SD)
HOMA-IR of the participants	N/A	N/A	Cases: 3.8 (1.8–8.3) (median, IQR) Controls: 1.1 (0.7–1.9) (median, IQR)
25-hydroxyvitamin D, calcium, phosphorus levels of the participants	25-hydroxyvitamin D levels Cases: 22.6 ± 16.0 ng/mL (mean ± SD) Controls: 26.8 ± 20.5 ng/mL (mean ± SD)	25-hydroxyvitamin D levels Cases: 14.1 ± 13.5 ng/mL (mean ± SD) Controls: 8.7 ± 5.6 ng/mL (mean ± SD) Calcium levels Cases: 9.1 ± 0.5 mg/dL (mean ± SD) Controls: 9.2 ± 0.4 mg/dL (mean ± SD) Phosphorus levels Cases: 3.4 ± 0.5 mg/dL (mean ± SD) Controls: 3.2 ± 0.6 mg/dL (mean ± SD)	25-hydroxyvitamin D levels Cases: 22.2 ± 7.7 ng/mL (mean ± SD) Controls: 32.9 ± 8.8 ng/mL (mean ± SD) Calcium levels Cases: 2.3 ± 0.1 mg/dL (mean ± SD) Controls: 2.3 ± 0.1 mg/dL (mean ± SD) Phosphorus levels Cases: 1.1 ± 0.1 mg/dL (mean ± SD) Controls: 1.1 ± 0.2 mg/dL (mean ± SD)
Newcastle-Ottawa score	Selection: 3 Comparability: 1 Exposure: 3	Selection: 3 Comparability: 1 Exposure: 3	Selection: 3 Comparability: 1 Exposure: 2

	Jamialahmadi et al. [21]
Country	Saudi Arabia
Year of publication	2021
Total number of participants	Cases: 51 Controls: 39
Recruitment of participants	Cases: Cases were patients with positive liver histology for NASH recruited from patients with BMI over 40 kg/m^2 or over 35 with more than two comorbidities who referred to Imam Reza outpatient clinic during December 2016 to September 2017 Controls: Controls were patients with negative histology for NASH recruited from the same clinical site during the same duration Patients with alcohol intake over 30 g/day in males, 20 g/day in females, positive HbsAg or HCV antibody, and drug-induced liver injury were excluded from the study
Diagnosis of NASH	Two-dimensional shear wave elastography (2D-SWE) and liver biopsy
Measurement of PTH concentration	Not described
Average age of participants (years)	39
Percentage of female	80%
BMI of the participants **(kg/m^2)**	Total: 45.5 ± 6.3 (mean ± SD)
HOMA-IR of the participants	Total: 6.3 ± 6.8 (mean ± SD)
25-hydroxyvitamin D, calcium, phosphorus levels of the participants	N/A
Newcastle-Ottawa score	Selection: 3 Comparability: 1 Exposure: 3

Abbreviation: 2D-SWE: Two-dimensional shear wave elastography; ANA: Antinuclear antibody; BMI: Body Mass Index; ELISA: Enzyme-Linked Immunosorbent Assay; HBsAg: Hepatitis b Antigen; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; HOMA-IR: The Homeostasis Model Assessment-estimated Insulin Resistance; N/A: Not Available; NAFLD: Nonalcoholic Fatty Liver Disease; NASH: Nonalcoholic hepatosteatosis; T2D: Type 2 Diabetes Mellitus.

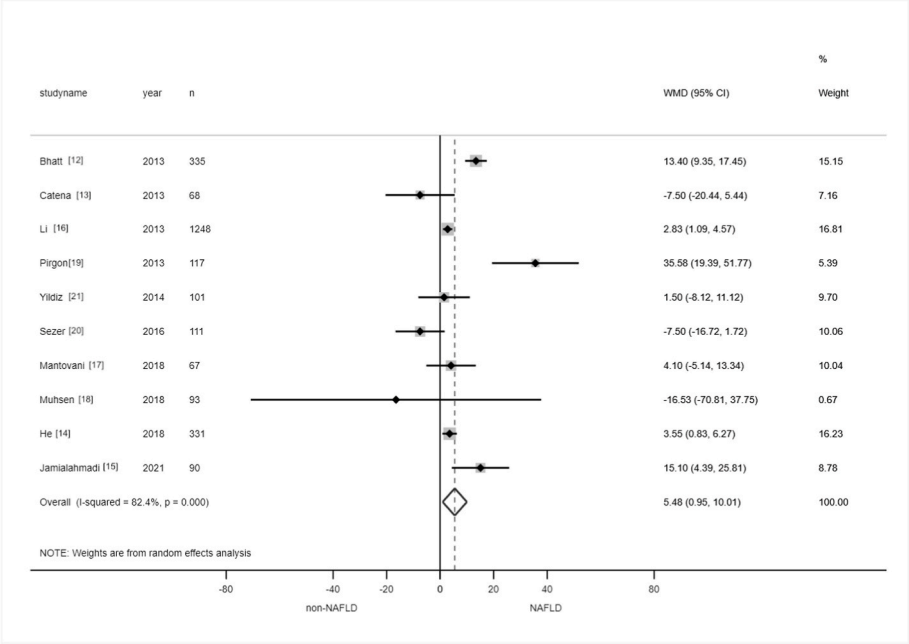

Fig. 2. Forest plot of meta-analysis of the association between serum parathyroid hormone level and nonalcoholic fatty liver disease
Abbreviation: WMD: Weighted Mean Difference.

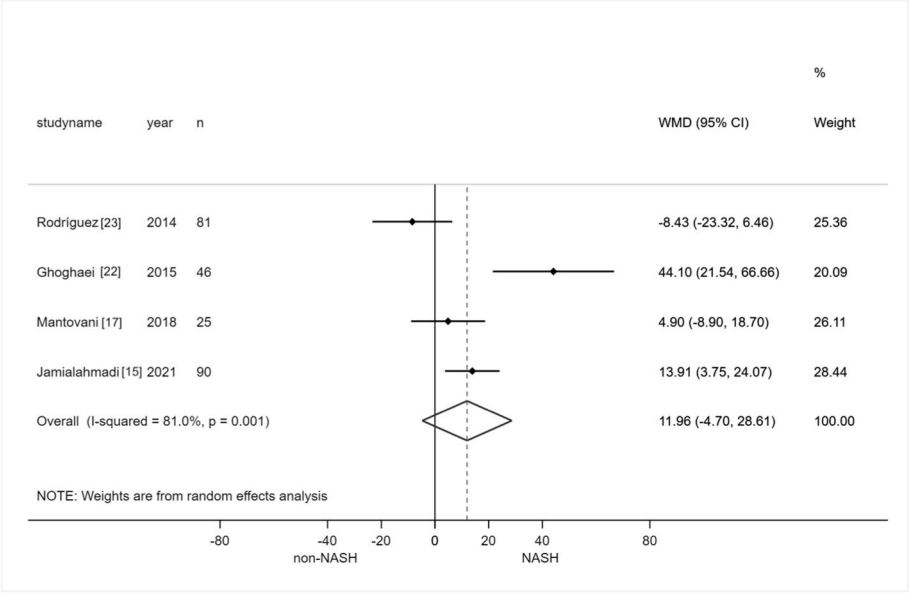

Fig. 3. Forest plot of meta-analysis of the association between serum parathyroid hormone level and nonalcoholic steatohepatitis
Abbreviation: WMD: Weighted Mean Difference.

the liver [40].

5. Limitations

This study has certain limitations that should be acknowledged. First, this is a systematic review and meta-analysis of observational studies and, therefore, the observed association may not be causal and could be a function of confounding effects as high PTH and NAFLD/NASH can be observed in patients with vitamin D derangement, obesity and cardiometabolic disorders. More data from previous studies are needed to perform subgroup analysis. Second, both meta-analyses of the association of PTH with NAFLD and NASH had high statistical heterogeneity. This is likely due to differences in study design, population and quality of the included studies. Third, the number of included studies as well as total number of participants in the meta-analysis of PTH and NASH are relatively small, which may compromise the statistical power of the analysis. This indicates the need for further study on this topic. Finally, the small number of included studies in meta-analysis could jeopardize the validity of the funnel plot for assessment of publication bias.

6. Conclusion

Our meta-analysis suggests that high PTH level can be a marker of NAFLD. High PTH level also tended to be associated with NASH,

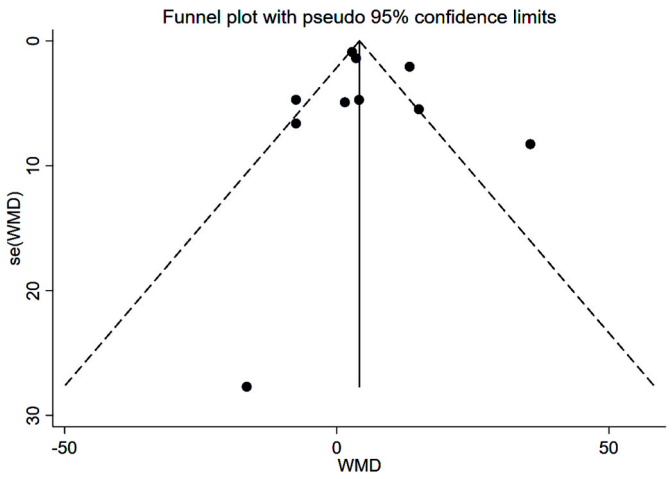

Fig. 4. Funnel plot of meta-analysis of the association between serum parathyroid hormone level and nonalcoholic fatty liver disease.

although statistical significance was not reached due to inadequate power.

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Authors' contributions

All authors had access to the data and a role in writing the manuscript.

Availability of data and material

All data and materials support the published claims and comply with field standards.

Conflict of interest/competing interest

All the authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2023.102827.

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