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Original article

Vitamin D deficiency in non-alcoholic fatty liver disease: The chicken or the egg?

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SUMMARY

Background & aims: Serum vitamin D concentration is reduced in patients with non-alcoholic fatty liver disease (NAFLD). Although the mechanism of vitamin D deficiency in liver disease is not fully understood, a few reports have suggested the beneficial effects of vitamin D supplements. The present study investigated changes in serum 25-hydroxy vitamin D level and clinical parameters after total calorie restriction with vitamin D intake reduction in NAFLD patients.

Methods: Newly diagnosed NAFLD patients with elevated aminotransferase levels were chosen for a calorie restriction and weight-reduction program. A total of 82 patients received nutritional education from nutritionists every 2 weeks for 2 months. Serum 25-hydroxy vitamin D level, amount of vitamin D intake, and physical activity were thoroughly investigated.

Results: The mean serum 25-hydroxy vitamin D concentration was 13.0 ng/ml. Twenty-nine patients (35.4%) had severe vitamin D deficiency. Patients with a 25-hydroxy vitamin D concentration <10 ng/ml had an increased risk of abdominal obesity (72.4% vs. 47.2%, $P = 0.023$) and a higher prevalence of metabolic syndrome (69% vs. 42.2%, $P = 0.015$) compared with patients with 25-hydroxy vitamin D levels >10 ng/ml. Although total energy and vitamin D intake were reduced during the program, serum 25-hydroxy vitamin D levels increased in patients with NAFLD ($P < 0.001$). Liver enzymes and metabolic parameters also improved, even as vitamin D intake decreased. Serum vitamin D concentration increased with body weight and intrahepatic fat reduction, independent of decreases in vitamin D intake.

Conclusions: Weight loss per increased serum vitamin D level without vitamin D supplementation and improved metabolic parameters in NAFLD.

1. Introduction

Vitamin D has a significant role in many crucial physiological processes, including insulin resistance, muscle contraction, immune function, and calcium and bone metabolism [1–3]. The prevalence of vitamin D deficiency ranges from 52 to 72%, as indicated by several National Health Nutrition Surveys involving different countries [4–6].

Recently, the role of serum vitamin D was emphasized in chronic liver diseases and non-alcoholic fatty liver disease (NAFLD) in particular. For instance, a population-based cohort study, consisting of 1081 participants, suggested that low serum vitamin D is closely related to NAFLD in patients with insulin resistance and diabetes, independent of abdominal visceral fat [7]. Another study compared 607 NAFLD patients with matched controls and found that low serum vitamin D concentrations were associated with NAFLD, and might have a role in the development and progression of NAFLD [8]. Dasarathy et al. evaluated 148 biopsy-proven NAFLD patients and found that serum vitamin D was negatively correlated not only with hepatic

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Significance of this study

What is already known about this subject?

- Serum vitamin D level is negatively correlated with obesity, insulin resistance, and metabolic syndrome.
- Low serum vitamin D concentration is associated with non-alcoholic fatty liver disease (NAFLD).
- Ultraviolet exposure and vitamin D intake are the main sources of vitamin D.

What are the new findings?

- Weight reduction without increasing vitamin D intake leads to increased serum vitamin D levels in NAFLD patients.
- Weight loss increases serum vitamin D levels and improves metabolic parameters in NAFLD, but the mechanisms remain unclear.

How might the findings impact clinical practice in the foreseeable future?

- Serum vitamin D level has a crucial role in NAFLD patients, but weight reduction is more effective compared to vitamin D supplementation in increasing serum vitamin D levels in NAFLD patients.

steatosis and inflammation, but also with visceral and abdominal fat [9]. Furthermore, a case–control study showed that NAFLD patients had low serum vitamin D due to inadequate vitamin D and calcium intake [10]. A recent meta-analysis of 17 cross-sectional studies also showed that serum 25-hydroxy vitamin D (25(OH)D) level had an association with fatty liver disease [11]. There has not been a randomized controlled study until now, although there have been several studies that have described an association between plasma vitamin D levels and insulin resistance; however, none of these studies has shown a causal relationship. Moreover, a recent study assessing the amount of liver fat by proton magnetic resonance spectroscopy (^{1}H-MRS) showed that plasma 25(OH)D levels were not associated with insulin resistance and intrahepatic fat accumulation. Although there are several studies clearly indicating decreased serum vitamin D in patients with NAFLD, the mechanism is poorly understood. Serum vitamin D is either synthesized by ultraviolet (UV) rays in the skin or taken orally. Vitamin D3 (cholecalciferol) in blood is transformed into 25-hydroxy vitamin D via the liver. It remains unclear whether the low vitamin D concentration associated with NAFLD is the result of decreased dietary intake, decreased sun exposure, or decreased conversion of 25(OH)D because of parenchymal liver disease. Since NAFLD is a consequence of nutritional over-intake, it remains highly controversial whether or not vitamin D intake is reduced in NAFLD patients [12]. There is a lack of international research validating the routine screening of vitamin D deficiency and the effects of supplementation. Moreover, there is no evidence suggesting that NAFLD patients experience less sun exposure compared with non-NAFLD obese patients.

Therefore, the aim of the present study was to investigate the effects of a hypocaloric diet without vitamin D supplementation on plasma vitamin D levels, metabolic parameters, and liver fat accumulation.

2. Methods

2.1. Patient selection

Patients who presented with elevated liver enzymes and newly diagnosed NAFLD via abdominal computed tomography (CT) were selectively enrolled. Eligible patients had an alcohol consumption of <140 g/week for men and <70 g/week for women. The exclusion criteria were as follows: patients previously participating in a nutrition program for NAFLD or obesity; patients who took medications known to induce fatty liver (e.g., Chinese herbal medications, steroids, amiodarone) within the last month; serum creatinine >1.5 mg/dl or chronic renal disease; patients with hepatitis B, hepatitis C and autoimmune hepatitis; and patients who received medication to control blood glucose, blood pressure, or lipid lowering agent. From the 90 patients who had received nutritional education, a total of 82 patients with adequate meal-log records were eligible for serum 25-hydroxy vitamin D analysis.

2.2. Definition of terminology

Elevated liver enzymes were defined as aspartate transaminase (AST) or alanine transaminase (ALT) > 40 IU/l. A CT scanner was used to determine the fat content of the liver and to diagnose fatty liver. Liver Hounsfield units (HU) and liver-to-spleen HU ratio were evaluated in CT images prior to contrast enhancement. Fatty liver was defined as <1.0 HU of liver-to-spleen ratio. The CT used for research was a 32-channel multi-detector (Siemens, Forchheim, Germany). The average HUs within 12 regions of interest in the liver were used to determine the overall liver HU. Serum 25-hydroxy vitamin D levels were measured by radioimmunoassay (DiaSorin, Stillwater, MN, USA). The participants were categorized into two groups according to serum vitamin D levels: <10.0 ng/ml, and >10.0 ng/ml. Metabolic syndrome was defined, as suggested by the Asia-Pacific guidelines, by the presence of three or more of the following: (1) central obesity (waist circumference > 80 cm in women, >90 cm in men); (2) abnormal blood pressure (systolic > 130 mmHg or diastolic > 85 mmHg); (3) abnormal triglycerides (>150 mg/dl); (4) low HDL cholesterol (<50 mg/dl); and (5) abnormal fasting glucose (>100 mg/dl) [13].

2.3. Study design

This study was a subgroup analysis of a larger study: 'A randomized study to compare the impact of low-carbohydrate and low-fat diet education on hepatic fat in non-alcoholic fatty liver disease' (KCT0000970; https://cris.nih.go.kr/cris/index.jsp). The characteristics of the main study were as follows: 110 NAFLD patients were randomly allocated to the low-fat diet education (55 subjects) group or the low-carbohydrate education (55 subjects) group. Randomization was stratified according to BMI. There were no differences in basic characteristics, including age, sex, BMI, biochemical parameters, and serum 25-hydroxy vitamin D level. The dietary criteria for the low-carbohydrate diet group were as follows: consuming approximately 25 kcal/kg of ideal body weight to reduce weight, and consuming 50–60% carbohydrates, 20–25% proteins, and 20–25% fats. The dietary criteria for the low-fat diet group were as follows: taking about 25 kcal/kg according to ideal body weight to reduce weight, and consuming 60–70% carbohydrates, 15–20% proteins, and 15–20% fats. A professional nutritionist provided nutritional education every 2 weeks from the day of consent for 8 weeks. All participants were recommended to consume 25 kcal/kg of their ideal body weight in an effort to reduce