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Circulating vitamin D_3 levels and risk of non-alcoholic fatty liver disease: is there a connection?

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Vitamin D_3 deficiency has been associated with the co-existence of many non-skeletal chronic pathologies (including obesity, type 2 diabetes, cardiovascular disease, several types of tumours and non-alcoholic fatty liver disease), suggesting the possibility that this vitamin can have multiple and beneficial pleiotropic effects in extra-skeletal contexts, thanks to the ubiquitous distribution of its specific receptor [1-5].

Non-alcoholic fatty liver disease (NAFLD) is one of these extra-skeletal chronic pathologies associated with low circulating vitamin D_3 levels. This disease has been the focus of significant scientific research, especially in the last 6-7 years [6].

NAFLD includes a broad spectrum of liver pathologies characterised by an accumulation of triglycerides in the liver in subjects without excessive alcohol consumption. The range of these pathologies includes simple steatosis and non-alcoholic steatohepatitis (NASH), which can lead to cirrhosis and even to hepatocellular carcinoma [7]. Today, NAFLD represents the most common form of chronic liver disease in western countries: it is estimated that it is present in roughly 25-30% of the general adult population [8,9]. Globally, its prevalence is progressively increasing in many parts of the world, similar to what has been observed for the incidence of obesity and type 2 diabetes, two metabolic pathologies with which NAFLD is closely connected, as they represent the most important risk factors for the disease [9,10].

The natural onset and progression of NAFLD toward its most advanced histological stages is explained by several risk factors (genetic, epigenetic, environmental and clinical) which take into account a broad range of pathological phenotypes resulting from it and for which different individual therapeutic approaches may be necessary [7]. This characteristic distinguishes NAFLD from other chronic liver diseases, in which the aetiological agent is well defined (as in the liver pathology caused by alcohol abuse or viral hepatitis), or for which there exists a specific pharmacological treatment (as in the case of viral and autoimmune hepatitis). The increasing importance of NAFLD from clinical and public health points of view is also determined by the fact that this pathology is not only linked to an increased risk of progression toward NASH and cirrhosis but that it is also frequently correlated to an increased risk of developing significant extrahepatic complications, including cardiovascular disease (which represents the main cause of death in this population of patients), chronic kidney disease, type 2 diabetes and the development of some types of tumours (especially colorectal, pancreas and breast cancers) [7,11]. For these reasons, from a clinical point of view it is particularly important to know the natural evolution of NAFLD and to identify the main risk factors which can modify its progression toward hepatic and extrahepatic complications.

Many epidemiological studies of the last 6-7 years have shown that patients with NAFLD have significantly lower circulating 25-hydroxyvitamin D_3 levels compared to control populations without fatty liver disease; these studies have further correlated low vitamin D_3 levels with greater histological severity of NAFLD, independently of the coexistence of obesity, diabetes and other typical features of metabolic syndrome [6,12]. Although the aetiopathogenetic mechanisms which can explain this association are still not completely clear, it has been hypothesised that vitamin D_3 can play an important hepatoprotective role. Findings from both experimental and

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Conflict of interest
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in vitro studies have shown that vitamin D_3 is able to positively modulate insulin signalling (by improving insulin resistance at the muscular and hepatic levels), reduce the production of multiple prothrombotic, procoagulant and pro-oxidant factors and perform immunomodulatory actions, in addition to reducing the proliferation of fibroblasts and the production of collagen [6,12].
To date, however, the literature has not produced broad prospective cohort studies or ample randomised clinical trials which evaluate a possible correlation between circulating vitamin D_3 levels and risk of developing NAFLD; nor have researchers examined whether extended vitamin D_3 supplementation is able to reduce the risk of the development or progression of NAFLD/NASH (which is documented by means of a hepatic biopsy, the 'gold standard' for the diagnosis and staging of this liver pathology). Such data is clinically important so as to be able to confirm the biological plausibility and possible causal role of vitamin D_3 in the development and progression of NAFLD.
A recent observational study conducted by Kim et al. aimed to provide an answer to one of these specific points. The "Kangbuk Samsung Health Study", an interesting analysis of a broad cohort of Korean subjects [13], had two main objectives: (1) to determine if circulating baseline levels of 25-hydroxyvitamin D_3 could predict the risk of developing new incident forms of NAFLD and/or the probability of resolving known forms of NAFLD at follow-up; and (2) to examine the correlation of temporal variations of 25-hydroxyvitamin D_3 levels, measured at baseline and follow-up, with the probability of developing and/or resolving NAFLD [13].
With regard to the first objective (evaluation of the association between baseline vitamin D_3 levels and incidence of NAFLD), the authors screened a cohort of over 139,000 adult subjects (~44% males, average age 36.8 years, average BMI 22 kg/m^2) who had no history of alcohol abuse, NAFLD or other known liver pathologies [13]. These subjects were not selected on the basis of their baseline vitamin status: ~77% of the sample had baseline 25-hydroxyvitamin D_3 levels < 20 ng/mL. Circulating levels of 25-hydroxyvitamin D_3 were measured in all participants, and a liver ultrasound was performed at both baseline and follow-up.
In the first part of the study, as reported in Table I, the authors clearly showed the existence of an inverse relation between circulating 25-hydroxyvitamin D_3 levels and risk of developing NAFLD (upon performance of the liver ultrasound) during the follow-up period (median time of roughly four years). This risk was independent of multiple known risk factors and other possible confounding influences [13]. To examine the link between baseline circulating levels of 25-hydroxyvitamin D_3 and the probability of resolving known forms of NAFLD during follow-up, a sample of roughly 48,700 subjects affected by NAFLD at baseline was analysed. In this case – as summarised in Table II – the authors reported a positive correlation of dose-effect type between circulating levels of 25-hydroxyvitamin D_3 at baseline and the probability of observing resolution of NAFLD at follow-up [13].
In connection with the second objective of the study (examination of the correlation between temporal variations of vitamin D_3 levels and the probability of developing and/or resolving NAFLD), the authors found that an increase in circulating levels of 25-hydroxyvitamin D_3 – passing, that is, from insufficient baseline values (< 20 ng/mL) to adequate ones (≥ 20 ng/mL) at follow-up (median period of 1.8 years) – was associated with a significantly reduced risk of developing NAFLD (adjusted Hazard Ratio [HR] 0.87, 95% confidence interval [IC] 0.82-0.91) in subjects who did not have NAFLD at baseline; on the contrary, consistently adequate values of 25-hydroxyvitamin D_3, at both baseline and follow-up (≥ 20 ng/mL), were correlated to a greater probability of resolution of NAFLD (adjusted HR 1.10, 95% IC 1.02-1.20) in subjects with NAFLD at baseline [13].
The results of this broad prospective cohort study therefore suggest that maintaining sufficient levels of 25-hydroxyvitamin D_3 can constitute an efficient approach in the primary and secondary prevention of NAFLD [13]. Nonetheless, the observational design of this study does not allow us to posit any causal inference regarding the observed correlation between levels of 25-hydroxyvitamin D_3 and risk of NAFLD, although it is in line with the recent observations of a Mendelian randomisation study, conducted on three European populations, which found a significant inverse relation between genetically predicted levels of 25-hydroxyvitamin D_3 and risk of NAFLD [14]. Other crucial limitations of the study by Kim et al. [13] include the fact that

TABLE I.
Risk of developing NAFLD (at the liver ultrasound) at follow-up based on circulating levels of hydroxyvitamin D_3 in subjects without NAFLD at baseline (n = 139,599) (from Kim et al., 2022 [13], modified).

Baseline 25(OH)D, ng/mL	Persons-years	Incident cases of NAFLD (n)	HR (95% CI) adjusted for gender and age	HR (95% CI) adjusted for multiple confounding factors
< 10	114,688	4,310	1.00 (reference)	1.00 (reference)
10-19	343,137	16,487	0,95 (95% IC 0,92-0,99)	0,89 (95% IC 0,86-0,92)
20-29	102,627	5,740	0,91 (95% IC 0,88-0,95)	0,81 (95% IC 0,78-0,85)
≥ 30	20,569	994	0,76 (95% IC 0,71-0,82)	0,72 (95% IC 0,67-0,77)
P-value per trend			< 0.001	< 0.001

TABLE II.
Resolution of NAFLD (at liver ultrasound) at follow-up based on circulating levels of hydroxyvitamin D_3 in subjects with NAFLD at baseline (n = 48,702) (from Kim et al., 2022 [13], modified).

Baseline 25(OH)D, ng/mL	Persons-years	Cases with resolution of NAFLD (n)	HR (95% CI) adjusted for gender and age	HR (95% CI) adjusted for multiple confounding factors
< 10	25,318	1,819	1,00 (reference)	1.00 (reference)
10-19	118,651	8,202	1.12 (95% IC 1.06-1.18)	1.09 (95% IC 1.03-1.15)
20-29	41,262	2,929	1.17 (95% IC 1.10-1.24)	1.13 (95% IC 1.06-1.21)
≥ 30	6,140	499	1.23 (95% IC 1.12-1.36)	1.21 (95% IC 1.09-1.35)
P-value per trend			< 0.001	< 0.001

the NAFLD diagnosis was established by means of a liver ultrasound, which may not be sufficiently accurate to show the presence of a slightly fatty liver, and that the population of the study was made up exclusively of Korean subjects (therefore limiting the extendibility of these observations to different ethnicities).

In spite of these defects, the findings of this broad longitudinal study [13] convincingly demonstrate the need to conduct broad randomised clinical trials in the near future with an adequate treatment duration in order to evaluate the possible benefits of vitamin D_3 supplementation on the risk of the development and progression of NAFLD/NASH (studies in which these hepatic outcomes are examined by liver biopsies). In addition, such trials must also take into account the vitamin D status of the participants, given that it is reasonable to suppose the any benefits from high-dose vitamin D_3 supplementation on NAFLD/NASH can be greater in patients with vitamin D deficiency with respect to those with normal circulating vitamin D_3 levels.

References

1 Autier P, Boniol M, Pizot C, et al. Vitamin D status and ill health: a systematic review. Lancet Diabetes Endocrinol 2014;2:76-89. https://doi.org/10.1016/S2213-8587(13)70165-7

2 Targher G, Pichiri I, Lippi G. Vitamin D, thrombosis, and hemostasis: more than skin deep. Semin Thromb Hemost 2012;38:114-124. https://doi.org/10.1055/s-0031-1300957

3 Lips P, Eekhoff M, van Schoor N, et al. Vitamin D and type 2 diabetes. J Steroid Biochem Mol Biol 2017;173:280-285. https://doi.org/10.1016/j.jsbmb.2016.11.021

4 Zittermann A, Trummer C, Theiler-Schwetz V, et al. Vitamin D and cardiovascular disease: an updated narrative review. Int J Mol Sci 2021;22:2896. https://doi.org/10.3390/ijms22062896

5 Marquina C, Mousa A, Scragg R, et al. Vitamin D and cardiometabolic disorders: a review of current evidence, genetic determinants and pathomechanisms. Obes Rev 2019;20:262-277. https://doi.org/10.1111/obr.12793

6 Targher G, Scorletti E, Mantovani A, et al. Nonalcoholic fatty liver disease and reduced serum vitamin D_3 levels. Metab Syndr Relat Disord 2013;11:217-228. https://doi.org/10.1089/met.2013.0044

7 Mantovani A, Scorletti E, Mosca A, et al. Complications, morbidity and mortality of nonalcoholic fatty liver disease. Metabolism 2020;111S:154170. https://doi.org/10.1016/j.metabol.2020.154170

8 Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73-84. https://doi.org/10.1002/hep.28431

9 Le MH, Yeo YH, Li X, et al. 2019 Global NAFLD prevalence: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2021:S1542-3565(21)01280-5. https://doi.org/10.1016/j.cgh.2021.12.002

10 Estes C, Anstee QM, Arias-Loste MT, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. J Hepatol 2018;69:896-904. https://doi.org/10.1016/j.jhep.2018.05.036

11 Targher G, Tilg H, Byrne CD. Non-alcoholic fatty liver disease: a multisystem disease requiring a multidisciplinary and holistic approach. Lancet Gastroenterol Hepatol 2021;6:578-588. https://doi.org/10.1016/S2468-1253(21)00020-0

12 Zhang Z, Thorne JL, Moore JB. Vitamin D and nonalcoholic fatty liver disease. Curr Opin Clin Nutr Metab Care 2019;22:449-458. https://doi.org/10.1097/MCO.0000000000000605

13 Kim Y, Chang Y, Ryu S, et al. Resolution of, and risk of incident non-alcoholic fatty liver disease with changes in serum 25-hydroxy vitamin D status. J Clin Endocrinol Metab 2022;107;e3437-e3447. https://doi.org/10.1210/clinem/dgac255

14 Yuan S, Larsson SC. Inverse association between serum 25-hydroxyvitamin D and nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2022;S1542-3565(22)00075-1. https://doi.org/10.1016/j.cgh.2022.01.021

15 Lippi G, Targher G. Are we overrating the extra-skeletal benefits of oral vitamin D supplementation? Ann Transl Med 2019;7:499. https://doi.org/10.21037/atm.2019.08.93

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