OnLine Journal of Biological Sciences

Research Article

Exploring the Role of Vitamin B12 as an Anti-atherogenic and Anti-inflammatory Agent in Apparently Healthy Adults With Hypovitaminosis D

Shravan Ajith Panchwadkar, Sudha Kuthethur, Sowndarya Kollampare and Neelam Manjunath Pawar

Department of Biochemistry, Kasturba Medical College Mangalore, Manipal Academy of Higher Education, Manipal, India

Article history
Received: 16-10-2024
Revised: 01-01-2025
Accepted: 07-04-2025

Corresponding Author:
Sudha Kuthethur
Department of Biochemistry,
Kasturba Medical College
Mangalore, Manipal Academy of
Higher Education, Manipal, India
Email: sudha.k@manipal.edu

Abstract: Vitamin B12 deficiency is associated with metabolic changes like methyl malonic acidemia and hyperhomocystinemia eventually leading to atherosclerosis. Dyslipidemia and vitamin D (vit D) deficiency are independent risk factors of CVD. This study aims to explore the interrelationship between inflammatory markers, adverse lipid profile and vitamin B12 in hypovitaminosis D. Since, atherosclerosis is an inflammatory condition we have investigated CRP and NLR as inflammatory markers along with lipid profile parameters and atherogenic indices in apparently healthy individuals with vitamin D deficiency. 90 apparently healthy subjects aged between 25-55 years were divided into 3 groups of 30 members each, as vit D sufficient (vit D $\geq$ 30 ng/ml), insufficient (vit D = 21-29 ng/ml) and deficient groups (vit D $\leq$ 20 ng/ml). Deficient group was further divided into moderately and severely deficient (vit D less than 20 and 10 ng/ml) groups respectively. Fasting lipid profile was estimated spectrophotometrically. Plasma vit D and B12 were determined by ECLIA. CRP was assayed by ELISA. Neutrophil Lymphocyte Ratio (NLR) was calculated manually. Vitamin B12 was significantly lower in vit D deficient group compared to insufficient ($p<0.01$) and sufficient groups ($p<0.001$). TC/HDL was significantly higher in insufficient group ($p<0.01$) compared to sufficient group. Further, both the atherogenic indices, TC/HDL and non -HDL increased drastically in severely deficient group where vitamin B12 was the least. Inflammatory markers CRP and NLR showed profound increase with vitamin B12 deficiency. The proposed mechanisms that underlie an abnormal lipid profile in vitamin B12 deficiency include increase in methyl malonyl CoA which inhibits oxidation of fatty acid and contributes to lipogenesis. Hyperhomocysteinemia interferes in VLDL secretion leading to dyslipidemia. Further, vitamin D modulates the expression of enzymes involved in homocysteine metabolism. While Vitamin B12 attenuates the expression of inflammatory cytokines, homocysteine induces the same. The observed abnormal lipid profile and elevated inflammatory markers in groups with lower vitamin B12 suggests its potential role in inflammatory reactions that precede subclinical atherosclerosis in hypovitaminosis D. The study also highlights synergistic action of both the vitamins in cardio protection which has not been previously reported.

Keywords: Atherosclerosis, Inflammation, Vitamin B12, Vitamin D

Introduction

Atherosclerosis is a chronic, dynamic, inflammatory process driven by several risk factors. Vitamin D (vit D) deficiency is a nontraditional risk factor that has gained worldwide attention as it has a potential role in the prevention of cardiac diseases (Haider *et al.*, 2023). Preclinical studies have shown a direct role of vitamin D in the regulation of endothelial dysfunction, platelet aggregation, and have confirmed its relationship with hypertension, coronary artery disease, and heart failure (Nardin *et al.*, 2024). Calcitriol exhibits an anti-inflammatory role by inhibition of vascular smooth muscle cell proliferation, coagulation, and regulation of

the renin-angiotensin system (Cosentino *et al.*, 2021). Several studies have implicated hyperhomocystinemia as an additional risk factor for Cardiovascular Disease (CVD). Vitamin B12 acts as a coenzyme of methionine synthase which forms methionine from homocysteine. Therefore, vitamin B12 deficiency interferes with this reaction and leads to hyperhomocysteinemia a pathology characterized by proinflammatory, cytotoxic, and proatherogenic consequences (Şener *et al.*, 2019). Vit D is known to modulate the gene expression of enzymes involved in homocysteine metabolism (Lee *et al.*, 2024). Hypocalcaemia secondary to vitamin D deficiency is suspected to adversely affect calcium-dependent vitamin B12 absorption (Muralidharan *et al.*, 2024). Thus, there exists a complex relationship between these two vitamins. Vitamin B12 deficiency appears to be a neglected topic of public health that needs more attention. Hence this study attempts to establish the antiatherogenic and anti-inflammatory role of vitamin B12 in vitamin D deficiency. Several observational studies have linked the anti-inflammatory effects of vitamin D to the prevention of atherosclerosis (Khanolkar *et al.*, 2023; Saghir Afifeh *et al.*, 2021). Therefore, addressing the deficiency of vitamin D and ensuring sufficient levels is crucial in preventing subclinical atherosclerosis. Since atherosclerosis is an inflammatory condition we have investigated CRP and NLR as inflammatory markers along with lipid profile and atherogenic indices (TC/HDL and non-HDL) in apparently healthy individuals with vitamin D deficiency. To the best of our knowledge, this is the first study to explore the synergistic role of vitamin D and B12 in cardio protection.

Materials and Methods

This prospective cross-sectional study was conducted after obtaining approval from the Institutional Ethics Committee (IEC KMC MLR08/2023/354). Written consent was obtained from all the participants of the study. The study population included 90 healthy subjects aged between 25 and 55 years of both genders. The study subjects were divided into three groups based on serum vit D levels:

- Group I (Vit D sufficient) = 30 subjects (vit D $\geq$ 30 ng/mL)
- Group II (Vit D insufficient) = 30 subjects (vit D = 21-29 ng/mL)
- Group III (Vit D deficient) = 30 subjects (vit D $\leq$ 20 ng/mL)
- Group III was further divided into,
- Group IIIa (moderately deficient) = 16 subjects (vit D 10-19 ng/mL)
- Group IIIb (severely deficient) = 14 subjects (vit D < 10 ng/mL) as per Gani & How (2015)

Patients with diabetes mellitus, systemic illness, kidney disease, and subjects on vitamin supplements at the time of blood collection were excluded from the study.

Fasting blood samples were collected in heparin vacuum tubes and centrifuged for 10 min at 3000g; separated plasma was stored at -80 °C and used for biochemical investigations. Lipid Profile was determined by spectrophotometric assays in a semi-analyzer (Almas *et al.*, 2022; Koh *et al.*, 2022., Malik and Pundir, 2002). Atherogenic indicators like non-HDL cholesterol and Total cholesterol/HDL were calculated manually. Vit D and vitamin B12 were estimated by ECLIA in Roche Cobas Pro fully automated analyser (Jiang *et al.*, 202; Ranjan *et al.*, 2020). Neutrophil-Lymphocyte Ratio was calculated from total blood count obtained from Sysmex automated haematology analyser and C - reactive protein was determined by sandwich ELISA (Ghule *et al.*, 2021).

A statistical package SPSS version 29 was used for the data analysis. Data was analyzed using a one-way ANOVA test and inter-group comparison was done by post hoc Tukey's test. The difference of $p<0.05$ was considered significant.

Results

Demographic and baseline data of the study groups are depicted in Table (1). Vitamin B12 levels steadily declined from vit D sufficient to insufficient to deficient groups. Vitamin B12 was significantly lower in vit D-deficient group compared to the insufficient ($p<0.01$) and sufficient group ($p<0.001$) (Table 2).

Table 1: Demographic and baseline data of the study population (mean ± SEM)

	Group I	Group II	Group IIIa	Group IIIb	p value
Age (range)	28-54	26-54	25-50	25-54	NS
Male: Female	13:17	14:16	9:06	7:08	NS
Vitamin D (ng/ml)	40.52±1.65	24.04±0.62	13.38 ± 0.74	6.98±0.43	0.001
Creatinine (mg/dl)	0.89±0.05	0.95±0.14	1.29±0.45	1.03±0.76	NS

NS – Not Significant

Table 2: Comparison of atherogenic profile among the 3 groups (Mean ± SEM)

	Group I (Sufficient)	Group II (Insufficient)	Group III (Deficient)
N	30	30	30
Vit D (ng/ml)	40.52±1.65	24.04±0.62[a]	10.28±4.04[#]
Vit B12 (pg/ml)	457±63.05	421.73±52.14	350.88±63.11[# a]
TG (mg/dl)	112.76±6.88	128.13±11.92	132.96±12.24
TC (mg/dl)	194.64±9.77	183.28±8.14	192±11.16
HDL (mg/dl)	61.19±4.99	64.15±3.71	54.13±3.98
TC/HDL	3.09±0.29	3.99±0.19*	3.59±0.27
LDL (mg/dl)	107.90±9.57	123.53±7	122.51±10.35
VLDL (mg/dl)	22.55 1.38	28.11±3.24	29.52±4.22
Non-HDL (mg/dl)	119.12±7.80	130.81±11.08	140.5±9.8[$]

N = Number of subjects; [#] p <0.001 Significantly different from sufficient group; [a] p<0.01 Significantly different from insufficient group; [*] p<0.04 Significantly different from sufficient group; [$] p<0.05 Significantly different from sufficient group

Further, there was a notable decline in vitamin B12 in the severely deficient group compared to the moderately deficient group ($p<0.01$). Table (3) an apparent increase in triglyceride values was observed in groups II and III compared to group I. Atherogenic lipids VLDL and LDL also showed a similar trend. Although total cholesterol remained constant between the groups, HDL was the lowest in vit D-deficient group and decreased further in the severely deficient group ($p = 0.01$). Moreover, atherogenic indices (TC/HDL) were significantly higher in the insufficient group ($p = 0.004$) and non-HDL cholesterol was significantly higher in the vitamin D deficient group compared to vit D sufficient group ($p = 0.05$). Both TC/HDL and non-HDL increased drastically in the severely deficient group compared to the moderately deficient group where vitamin B12 was the least (Table 3).

There was a steep increase in plasma CRP in vit D deficient group ($p = 0.04$) compared to the sufficient group and the increase was profound in the severely deficient group ($p = 0.05$). (Table 4) However, an increase in NLR was statistically insignificant in groups with vit D deficiency (Table 5).

Table 3: Comparison of atherogenic markers within Vitamin D deficient group III (IIIA and IIIB)

	Group IIIa (Deficient) Vit D (10-19 ng/mL) n = 16	Group IIIb (Severely deficient) Vit D (<10 ng/mL) n = 14	p value
Vit.D (ng/ml)	13.38±0.74	6.98±0.43	<0.001
Vit-B12 (pg/ml)	401.5±34.30	273±57.34	<0.01
TG (mg/dl)	125.45±20.58	140.97±13.06	NS
TC (mg/dl)	183.56±12.82	201.01±18.78	NS
HDL (mg/dl)	73.21±7.71	48.37±4.45	0.01
TC/HDL	2.89±0.32	4.34±0.34	0.004
LDL (mg/dl)	110.02±13.37	134.12±15.43	NS
VLDL (mg/dl)	30.76±7.92	28.20±2.61	NS
Non HDL (mg/dl)	110.35±13.90	152.64±16.03	0.05

N = Number of subjects; NS = Not significant

Table 4: Comparison of inflammatory markers among the 3 groups (Mean ±SEM)

	Group I (Sufficient group)	Group II (Insufficient group)	Group III (Deficient group)
Vit D (ng/ml)	40.52±1.65	24.04±0.62[a]	10.28±4.04[#]
CRP	1.55±0.02	3.32±0.03	4.72±0.03*
Vit-B12 (pg/ml)	457±63.05	421.73±52.14	350.88±63.11[# a]
NLR	1.71±0.11	2.29±0.48	2.28±0.29

[#] p <0.001 Significantly different from sufficient group; [a] p<0.01 Significantly different from insufficient group; [*] p<0.04 Significantly different from sufficient group

Table 5: Comparison of inflammatory markers based on Vitamin D deficient levels (Mean ± SEM)

	Group IIIA (Moderately deficient) Vit D (10-19 ng/ml)	Group IIIB (Severely deficient) Vit D (<10 ng/ml)	p value
Vit.D (ng/ml)	13.38±0.74	6.98±0.43	<0.001
Vit-B12 (pg/ml)	401.5±34.30	273±57.34	<0.01
NLR	2.49±0.59	2.16±0.33	NS
CRP	3.86±0.02	5.58±0.09	<0.05

N = Number of samples; NS = Not significant

Discussion

A growing body of literature has linked hypovitaminosis D with dyslipidemia that leads to atherosclerosis and CVD. The results of the present study also corroborate this, where atherogenic lipids like triglycerides, VLDL, LDL, non non-HDL were higher in subjects with vit D insufficiency and deficiency. The expression of vit D receptors, enzyme 1-alpha hydroxylase that converts vit D to calcitriol, and angiotensin-converting enzyme on vascular endothelial cells, smooth muscle cells, and cardiomyocytes, points to the direct involvement of calcitriol in the prevention and progression of CVD (Thompson *et al.*, 2023). An earlier study on children reported a positive correlation between vitamin B12 and D (Konuksever *et al.*, 2022) which supports the findings of our research. In the current study, atherogenic indices TC/HDL and non-HDL were inversely associated with vitamin B12 deficiency. Low vitamin B12 was independently linked to aberrant lipid profiles and atherogenic indices in young Saudi women (Al-Musharaf *et al.*, 2020). Intake of vitamin B12 tablets improved lipid profiles and decreased the chances of CVD in the American population (Huang *et al.*, 2023). Wistar rats with low vitamin B12 produced offspring with increased adiposity and an adverse lipid profile (Qin *et al.*, 2022).

If vitamin B12 is the nutritional cause, mutations in the homocysteine methyl transferase gene may be a genetic cause of hyperhomocysteinemia. Further, Vit D modulates the expression of genes involved in homocysteine metabolism (Şener *et al.*, 2019). A consistent decrease of vitamin B12 in vit D insufficiency and deficiency observed in the current study directly points to the antiatherogenic and anti-inflammatory role of vitamin B12. Furthermore, vitamin B12 deficiency in hypovitaminosis D may aggravate the risk of the development of CVD in the study subjects. Vitamin B12 acts as a coenzyme of isomerase that forms succinyl-CoA from methylmalonyl-CoA. Vitamin B12 deficiency results in aggregation of methyl malonyl CoA which inhibits beta oxidation of fatty acid and lipolysis in the liver, thereby promoting lipogenesis. Other studies have proposed an independent role of vitamin B12 in CVD, possibly through gene expression of enzymes involved in

fatty acid metabolism and lipogenesis (Ge *et al.*, 2022; Mahalle *et al.*, 2013). Moreover, homocysteine interferes with the assembly/secretion of VLDL, leading to abnormal serum lipids (Obeid and Herrmann, 2009). These are the proposed mechanisms that underlie abnormal lipid profiles in vitamin B12 deficiency. Abnormal lipid profile may culminate in atherosclerosis which is a chronic inflammatory disorder involving metabolic and immune dysregulation. Proliferation of T-cells and transcription of inflammatory cytokines are inhibited by VDR signalling. Moreover, this signalling is inversely correlated to CRP (Olsen *et al.*, 2022; Harb *et al.*, 2020). Our study suggests that vitamin B12 deficiency is associated with metabolic dysfunction and inflammation in vit D deficiency.

Several earlier researchers have reported low inflammatory cytokines, IL6 and CRP in patients with higher levels of serum B12 (Domínguez-López *et al.*, 2024). This is in accordance with the results of our study where subjects with low vitamin B12 had high CRP and NLR. Likewise, in naturally aged mice, there was a reciprocal relation between serum vitamin B12 and IL-6 (Domínguez-López *et al.*, 2024). There is strong evidence to support the relationship between homocysteine and inflammation. Hyperhomocysteinemia stimulates pro-inflammatory signalling molecules like CRP in a number of inflammatory conditions, like type 1diabetes, rheumatoid arthritis, and angiographic coronary artery disease (Yao *et al.*, 2018). Moreover, vitamin B12 attenuates inflammation by modulating gene expression of proinflammatory cytokines in cultured T lymphocytes and adipocytes mainly through epigenetic alterations (Cassiano *et al.*, 2023). Neutrophil-lymphocyte ratio (NLR ratio) is another marker employed to represent inflammation, particularly in metabolic illnesses. A study by Baş *et al.*, linked vit D deficiency to higher NLR. Similarly, another experimental group lacking vitamin B12 had apparently higher NLR values than the control group (Caldiroli *et al.*, 2023). Higher serum levels of CRP and NLR observed in severe deficiency of both vit D and vitamin B12 definitely point to their anti-inflammatory action.

Conclusion

On the whole, it can be concluded that vitamin B12 deficiency may be considered as another non-traditional factor that can be inflammatory and atherogenic in hypovitaminosis D patients. The study highlights the synergistic preventive role played by water and fat-soluble vitamins in inflammatory processes that precede atherosclerosis.

Limitations

Estimation of serum homocysteine and polymorphism studies of vitamin B12 intrinsic factor receptor and vitamin D receptor would have substantiated the association of both vitamins with abnormal lipid profiles in apparently healthy individuals.

Acknowledgment

We express our gratitude to the patients and authorities of the institution and the associated hospitals for permitting us to undertake this research project.

Funding Information

The authors have not received any financial support or funding to report.

Author's Contributions

Shravan Ajith Panchwadkar: Obtained the ethics approval with assistance from Sudha Kutherthur and performed analysis of parameters.

Sudha Kuthethur: Handled the conception and designed the study drafted the manuscript.

Sowndarya Kollampare: Contributed to the manuscript writing and approved the final version.

Neelam Manjunath Pawar: Performed statistical analysis. Contributed to the manuscript writing and approved the final version.

Ethics

The study was approved by the Institutional Ethics Committee (IEC KMC MLR08/2023/354).

Conflicts of Interest

There are no conflicts of interest.

References

Almas, T., Malik, J., Alsubai, A. K., Ehtesham, M., Laique, T., Ishaq, U., Mehmood, A., Jawad Zaidi , S. M., Hadeed , S., Huang , H., & Oruk, M. (2022). Effect of COVID-19 on lipid profile parameters and its correlation with acute phase reactants: A single-center retrospective analysis. *Annals of Medicine and Surgery*, *78*, 103856. https://doi.org/10.1016/j.amsu.2022.103856

Al-Musharaf, S., Aljuraiban, G. S., Danish Hussain, S., Alnaami, A. M., Saravanan, P., & Al-Daghri, N. (2020). Low Serum Vitamin B12 Levels Are Associated with Adverse Lipid Profiles in Apparently Healthy Young Saudi Women. In *Nutrients* (Vol. 12, Issue 8, p. 2395). https://doi.org/10.3390/nu12082395

Caldiroli, A., La Tegola, D., Affaticati, L. M., Manzo, F., Cella, F., Scalia, A., Capuzzi, E., Nicastro, M., Colmegn, F., & Buoli, M. (2023). Clinical and Peripheral Biomarkers in Female Patients Affected by Anorexia: Does the Neutrophil/Lymphocyte Ratio (NLR) Affect Severity? *Nutrients*, *15*(5), 1133. https://doi.org/10.3390/nu15051133

Cassiano, L. M. G., Cavalcante-Silva, V., Oliveira, M. S., Prado, B. V. O., Cardoso, C. G., Salim, A. C. M., Franco, G. R., D'Almeida, V., Francisco, S. C., & Coimbra, R. S. (2023). Vitamin B12 attenuates leukocyte inflammatory signature in COVID-19 via methyl-dependent changes in epigenetic markings. *Frontiers in Immunology*, *14*, 1048790. https://doi.org/10.3389/fimmu.2023.1048790

Cosentino, N., Campodonico, J., Milazzo, V., De Metrio, M., Brambilla, M., Camera, M., & Marenzi, G. (2021). Vitamin D and Cardiovascular Disease: Current Evidence and Future Perspectives. *Nutrients*, *13*(10), 3603. https://doi.org/10.3390/nu13103603

Domínguez-López, I., Kovatcheva, M., Casas, R., Toledo, E., Fitó, M., Ros, E., Estruch, R., Serrano, M., & Lamuela-Raventós, R. M. (2024). Higher circulating vitamin B12 is associated with lower levels of inflammatory markers in individuals at high cardiovascular risk and in naturally aged mice. *Journal of the Science of Food and Agriculture*, *104*(2), 875-882. https://doi.org/10.1002/jsfa.12976

Gani, L., & How, C. (2015). Vitamin D deficiency. *Singapore Medical Journal*, *56*(08), 433-437. https://doi.org/10.11622/smedj.2015119

Ge, Y., Zadeh, M., & Mohamadzadeh, M. (2022). Vitamin B12 Regulates the Transcriptional, Metabolic, and Epigenetic Programing in Human Ileal Epithelial Cells. *Nutrients*, *14*(14), 2825. https://doi.org/10.3390/nu14142825

Ghule, A., Kamble, T. K., Talwar, D., Kumar, S., Acharya, S., Wanjari, A., Gaidhane, S. A., & Agrawal, S. (2021). Association of Serum High Sensitivity C-Reactive Protein With Pre-diabetes in Rural Population: A Two-Year Cross-Sectional Study. In *Cureus* (Vol. 13, Issue 10, p. e19088). https://doi.org/10.7759/cureus.19088

Haider, F., Ghafoor, H., Hassan, O. F., Farooqui, K., Bel Khair, A. O. M., & Shoaib, F. (2023). Vitamin D and Cardiovascular Diseases: An Update. *Cureus*, *15*(11), e49734. https://doi.org/10.7759/cureus.49734

Harb, Z., Deckert, V., Bressenot, A. M., Christov, C., Guéant-Rodriguez, R.-M., Raso, J., Alberto , J. M., Pais de Barros, J.-P., Umoret, R., Peyrin-Biroulet, L., Lagrost, L., Bronowicki, J.-P., & Guéant, J.-L. (2020). The deficit in folate and vitamin B12 triggers liver macrovesicular steatosis and inflammation in rats with dextran sodium sulfate-induced colitis. *The Journal of Nutritional Biochemistry*, *84*, 108415. https://doi.org/10.1016/j.jnutbio.2020.108415

Huang, J., Khatun, P., Xiong, Y., Liu, B., Zhao, Y., & Lyu, Q. (2023). Intakes of folate, vitamin B6, and vitamin B12 and cardiovascular disease risk: a national population-based cross-sectional study. In *Frontiers in Cardiovascular Medicine* (Vol. 10, p. 1237103). https://doi.org/10.3389/fcvm.2023.1237103

Jiang, W., Men, S., wen, X., Yuan, X., Pu, D., Liu, X., Jia, X., & Wang, C. (2020). A preliminary study for the establishment of a reference interval for vitamin B12 in China after performance verification of a second-generation ECLIA kit. In *Journal of Clinical Laboratory Analysis* (Vol. 34, Issue 5, p. e23165). https://doi.org/10.1002/jcla.23165

Khanolkar, S., Hirani, S., Mishra, A., Vardhan, S., Hirani, S., Prasad, R., & Wanjari, M. (2023). Exploring the Role of Vitamin D in Atherosclerosis and Its Impact on Cardiovascular Events: A Comprehensive Review. *Cureus*, *15*(7), e42470. https://doi.org/10.7759/cureus.42470

Koh, S. M., Chung, S. H., Yum, Y. J., Park, S. J., Joo, H. J., Kim, Y.-H., & Kim, E. J. (2022). Comparison of the effects of triglyceride variability and exposure estimate on clinical prognosis in diabetic patients. *Cardiovascular Diabetology*, *21*(1), 245. https://doi.org/10.1186/s12933-022-01681-8

Konuksever, D., & Yücel Karakaya, S. P. (2022). Evaluation of correlation between vitamin D with vitamin B12 and folate in children. In *Nutrition* (Vols. 99-100, p. 111683). https://doi.org/10.1016/j.nut.2022.111683

Lee, Y.-A., Kang, S.-G., Song, S.-W., & Kim, S.-H. (2024). Association between Homocysteine and Vitamin D Levels in Asymptomatic Korean Adults. *Nutrients*, *16*(8), 1155. https://doi.org/10.3390/nu16081155

Mahalle, N., Kulkarni, M. V., Garg, M. K., & Naik, S. S. (2013). Vitamin B12 deficiency and hyperhomocysteinemia as correlates of cardiovascular risk factors in Indian subjects with coronary artery disease. In *Journal of Cardiology* (Vol. 61, Issue 4, pp. 289-294). https://doi.org/10.1016/j.jjcc.2012.11.009

Malik, V., & Pundir, C. S. (2002). Determination of total cholesterol in serum by cholesterol esterase and cholesterol oxidase immobilized and co-immobilized on to arylamine glass. *Biotechnology and Applied Biochemistry*, *35*(3), 191-197. https://doi.org/10.1111/j.1470-8744.2002.tb01188.x

Muralidharan, J., Romould, G. G., Kashyap, S., Pasanna, R., Sivadas, A., Sachdev, H. S., Kurpad, A. V., & Devi, S. (2024). Effect of calcium supplementation on reversing metformin-based inhibition of vitamin B12 bioavailability in healthy adults using a [13C] cyanocobalamin tracer - A pilot study. *Clinical Nutrition ESPEN*, *62*, 76-80. https://doi.org/10.1016/j.clnesp.2024.04.024

Nardin, M., Verdoia, M., Nardin, S., Cao, D., Chiarito, M., Kedhi, E., Galasso, G., Condorelli, G., & De Luca, G. (2024). Vitamin D and Cardiovascular Diseases: From Physiology to Pathophysiology and Outcomes. *Biomedicines*, *12*(4), 768. https://doi.org/10.3390/biomedicines12040768

Obeid, R., & Herrmann, W. (2009). Corrigendum to "Homocysteine and lipids: S-Adenosyl methionine as a key intermediate" [FEBS Lett. 583 (2009) 1215-1225]. *FEBS Letters*, *583*(18), 3107-3107. https://doi.org/10.1016/j.febslet.2009.08.028

Olsen, B., Bodea, J., Garcia, A., Beebe, K., Campbell, C., Schwalbach, C., Salzberg, D., Miller, H., Adams, R., Mirea, L., Castillo, P., Horn, B., Bansal, S., Mohanakumar, T., & Ngwube, A. (2022). Vitamin D Supplementation: Association With Serum Cytokines in Pediatric Hematopoietic Stem Cell Transplantation. *Frontiers in Pediatrics*, *10*, 913586. https://doi.org/10.3389/fped.2022.913586

Qin, S., Wang, Y., Li, L., Liu, J., Xiao, C., Duan, D., Hao, W., Qin, C., Chen, J., Yao, L., Zhang, R., You, J., Zheng, J.-S., Shen, E., & Wu, L. (2022). Early-life vitamin B12 orchestrates lipid peroxidation to ensure reproductive success via SBP-1/SREBP1 in Caenorhabditis elegans. In *Cell Reports* (Vol. 40, Issue 12, p. 111381). https://doi.org/10.1016/j.celrep.2022.111381

Ranjan, A., Sudha, K., Nandini, M., & Durgarao, Y. (2020). Novel evidence of relationship between serum vitamin B12 and folate with total vitamin D in subclinical hypothyroidism. *Biomedicine*, *40*(3), 278-280. https://doi.org/10.51248/.v40i3.7

Saghir Afifeh, A. M., Verdoia, M., Nardin, M., Negro, F., Viglione, F., Rolla, R., & De Luca, G. (2021). Determinants of vitamin D activation in patients with acute coronary syndromes and its correlation with inflammatory markers. *Nutrition, Metabolism and Cardiovascular Diseases*, *31*(1), 36-43. https://doi.org/10.1016/j.numecd.2020.09.021

Şener, Y. Z., Okşul, M., & Hekimsoy, V. (2019). Factors Related with Both Atherosclerosis and Homocysteine Levels. *Acta Cardiol Sin*, *35*(6), 662. https://doi.org/10.6515/ACS.201911_35(6).20190108C

Thompson, B., Waterhouse, M., English, D. R., McLeod, D. S., Armstrong, B. K., Baxter, C., Duarte Romero, B., Ebeling, P. R., Hartel, G., Kimlin, M. G., Rahman, S. T., van der Pols, J. C., Venn, A. J., Webb, P. M., Whiteman, D. C., & Neale, R. E. (2023). Vitamin D supplementation and major cardiovascular events: D-Health randomised controlled trial. In *BMJ* (Vol. 381, p. e075230). https://doi.org/10.1136/bmj-2023-075230

Yao, Y., Shang, M., Gao, L.-J., Zhao, J., Yang, X., Liu, T., Tang, R., Jiang, C., Long, D., Ning, M., Zhu, H., Lv, Q., Hu, R., Du, X., & Dong, J. (2018). Elevated homocysteine increases the risk of left atrial/left atrial appendage thrombus in non-valvular atrial fibrillation with low CHA2DS2-VASc score. *EP Europace*, *20*(7), 1093-1098. https://doi.org/10.1093/europace/eux189