KAMIŃSKA, Weronika, BOBRZYK, Adrian, ŁYKO, Grzegorz, ANTOS, Maria, BATOR, Piotr, WAWRYSZUK, Angelika, RUMIAN, Maciej, MAKOWSKA, Weronika, RACHWAŁ, Krystian and KOSEL, Alicja. Supplementation of vitamin D in children with obesity and vitamin D deficiency - review of outcomes in terms of obesity parameters and comorbidities. Journal of Education, Health and Sport. 2023;44(1):322-332. eISSN 2391-8306. http://dx.doi.org/10.12775/JEHS.2023.44.01.021
https://apcz.umk.pl/JEHS/article/view/45295
https://zenodo.org/record/8265199

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 17.07.2023 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).
Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 17.07.2023 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159.
Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 21.07.2023. Revised:10.08.2023. Accepted: 18.08.2023. Published: 21.08.2023.

SUPPLEMENTATION OF VITAMIN D IN CHILDREN WITH OBESITY AND VITAMIN D DEFICIENCY - REVIEW OF OUTCOMES IN TERMS OF OBESITY PARAMETERS AND COMORBIDITIES

1. **Weronika KAMIŃSKA*** [1] weronika.kaminska1999@gmail.com

ORCID: 0009-0006-5893-6268

2. **Adrian BOBRZYK** [1] adrianbobrzyk@gmail.com

ORCID: 0009-0001-8154-1954

3. **Grzegorz ŁYKO** [1] grzeg.ly@gmail.com

ORCID: 0009-0005-8118-6779

4. **Maria ANTOS** [2] maria.antos@hotmail.com

ORCID: 0009-0000-6085-3652

5. **Piotr BATOR** [1] piotrbator9@icloud.com

ORCID: 0009-0009-3300-0078

6. **Angelika WAWRYSZUK** [2] angelawawryszuk@gmail.com

ORCID: 0000-0003-3880-2730

7. **Maciej RUMIAN** [2] rumni1998@interia.pl

ORCID: 0009-0009-0652-3201

8. **Weronika MAKOWSKA** [3] weronika.mak@gmail.com

ORCID:0009-0006-8960-6659

9. **Krystian RACHWAŁ** [1] kryrach@interia.pl

ORCID: 0009-0002-2527-6110

10. **Alicja KOSEL** [2] alicjakosel@gmail.com

ORCID: 0009-0008-2200-2580

[1] Faculty of Medical Sciences in Katowice, Medical University of Silesia, Medyków 18, 40-752 Katowice, Poland

[2] Collegium Medicum, Jan Kochanowski University, IX Wieków Kielc 19A, 25-317 Kielce, Poland

[3] Faculty of Medical Sciences in Zabrze, Medical University of Silesia, plac Traugutta 2, 41-800 Zabrze, Poland

*Author to whom correspondence should be addressed

Abstract:

In recent years, vitamin D deficiency and obesity in paediatric population have reached epidemic levels worldwide as crucial health concerns with far-reaching consequences. There has been a substantial growth in studies dedicated to these two public health issues over the last years. Numerous studies have confirmed that excess body weight has negative impact on vitamin D metabolism, leading to a higher risk of low levels of this essential vitamin, among individuals who are overweight or obese. Vitamin D deficiency may play a role in the development of obesity-related conditions as insulin resistance, type two diabetes, NAFLD and cardiovascular disease due to anti-inflammatory properties, impact on the endocrine system and metabolic functions of this vital nutrient. Vitamin D supplementation seems to be a beneficial addition to pharmacology and lifestyle changes during obesity treatment.

Keywords: children, obesity, vitamin D, vitamin D deficiency

Introduction and purpose:

In the past years the childhood obesity has grown to become a worldwide medical issue [1]. It is known that overweight in childhood and adolescence is an important risk factor for obesity in adulthood, as well as for the development of comorbidities. The factor contributing to obesity in children is a positive energy balance due to caloric intake in excess of caloric expenditure combined with a genetic predisposition for weight gain. The increasing prevalence of childhood obesity is associated with emergence of comorbidities previously considered to be diseases found mostly in adults, including type 2 diabetes mellitus [2], hypertension [3], non-alcoholic fatty liver disease [4], obstructive sleep apnoea [5], and dyslipidaemia [6].

Vitamin D is important regulator of calcium and phosphorus metabolism. Apart from its role in maintaining physiological condition of skeleton health, the results of previous studies have suggested that it also regulates influences glucose metabolism, hormone secretion and supports immune system functions [7-9]. Vitamin D deficiency is common health issue worldwide, especially in paediatric population [10]. Insufficient blood concentrations of vitamin D in childhood is associated with impaired bone mineralization but also with many other conditions, including increased risk of cardiovascular disease

and metabolic disorders like insulin resistance, impaired glucose tolerance or type 2 diabetes [11,12].

Obese children are particularly prone to low blood concentrations of vitamin D (25(OH)D). The relationship between this hypovitaminosis and obesity has been widely studied in the general population [13,14]. Vitamin D deficiency and excess body fat have mutual negative effects, resulting from metabolic processes that generate accumulation of inactive forms and decreased vit D bioavailability, in addition to decreased tissue secretion and sensitivity to insulin. There is no consensus as to why vitamin D levels are lower in obese individuals. The main hypothesis may be the impaired absorption of vitamin D, which is fat soluble, by the excessive adipose tissue. Moreover, it could be related to reduced sun exposure because of less outdoor activities and incorrect eating habits practising by obese children [15].

The aim of this review is to assess the impact of vitamin D supplementation in obese children with deficiency of this vitamin on the parameters of obesity and its complications.

Description of state of knowledge:

Obesity parameters

Currently, in the paediatric population, the use of body mass index (BMI) is recommended to assess the degree of overweight and obesity. A child or adolescent with a BMI percentile between the 85th and 94th is considered overweight, while above the 95th percentile is considered obese. Determining the body weight, waist circumference and skin fold thickness also can be helpful to establish the degree of the problem.

Some studies shows that vitamin D supplementation may lead to modest reductions in body weight and body fat in obese children and adolescents, although the evidence is mixed. A triple-blind randomized controlled trial published in 2020 in BMC Pediatrics indicated that high dose of vitamin D (50,000 IU weekly) connected with dietary and physical modification during 24 weeks of treatment helps to improve anthropometric and body composition parameters in obese Sri Lankan children with vitamin D deficiency compared with low-dose and placebo group [16].

In another similar study published in 2020 different conclusion was established. The reduction in the level of BMI was not statistically significant between study and placebo group but in this trial the weekly dose of vitamin D was lower than in previous cited study [17].

These results may suggest that supplementation higher doses of vitamin D can act synergistically with dietary changes and physical activity to reduce obesity parameters in vitamin D deficient and obese individuals. Nevertheless, more randomized controlled trials are needed to determine the benefits of vitamin D supplementation in this group.

Insulin resistance and impaired glucose metabolism

Obesity, particularly the accumulation of visceral fat, is strongly associated with development of insulin resistance, characterized by a diminished response of cells in the

body to the effects of insulin, leading to inadequate glucose uptake. Both excess body weight and insulin resistance are major risk factor for developing type 2 diabetes [18].

The most common methods for assessment of carbohydrate metabolism in paediatric and adult population include biochemical parameters like fasting plasma glucose (FPG), haemoglobin A1c (HgbA1c) and serum insulin. The oral glucose tolerance test (OGTT) is also commonly used to indicate conditions such as impaired glucose tolerance or diabetes. The state of insulin resistance (IR) in studies is most often calculated using the homeostasis model assessment (HOMA-IR) [19,20].

Several studies indicated the correlations between low levels of vitamin D, insulin resistance and impaired glucose metabolism in obese children. [21,22]. In addition, a meta-analyse published in 2021 demonstrated a positive effect of vitamin D supplementation on lowering fasting glucose and triglycerides [23]. What is more, in randomized controlled trial from 2020 vitamin D3 supplementation led to reductions in fasting plasma glucose concentration and enhancement in insulin sensitivity in children with overweight or obesity [24].

The most probably clarification for this correlation is thesis where vitamin D may directly stimulate the secretion of insulin from pancreatic beta cells, but also enhance the sensitivity of insulin receptors in peripheral tissues [25,26]. Furthermore, vitamin D deficiency has been shown to increase inflammation in the body, which is a key factor in the development of insulin resistance [27,28]

These results submit that maintaining adequate vitamin D levels may be important for preventing or managing insulin resistance or even type 2 diabetes in this population.

Non-alcoholic fatty liver disease

NAFLD is a condition characterized by the accumulation of excess fat in the hepatic cells, which can progress to more severe forms of liver diseases. It is caused by different factors than alcohol consumption. Furthermore, this disease is commonly associated with excess body weight, insulin resistance and metabolic syndrome. Obesity is one of the most considerable risk factors for the development and progression of NAFLD. Studies have consistently exhibited that individuals who are overweight or obese are more likely to develop NAFLD compared to people with a normal weight in paediatric as well as in adult population [29,30].

Serum levels of clinically approved markers of hepatic steatosis include biochemical parameters like aspartate-aminotransferase (AST), alanine-aminotransferase (ALT) and glutamate-pyruvate-transaminase (GGT). Moreover, ultrasound scan (USS), liver biopsies and magnetic resonance imaging (MRI) are commonly used to assess the severity of NAFLD [31].

Study published in Journal of Gastroenterology and Hepatology in 2014 showed noticeable association between low serum 25-hydroxyvitamin D concentration and NAFLD in adolescents, regardless of insulin resistance and obesity [32]. A meta-analysis from 2019 also indicated this correlation [33]. Presumably, deficiency in vitamin D may contribute to the development or progression of NAFLD through impact this vitamin on

insulin sensitivity and inflammatory processes, which are important factors in the pathogenesis of hepatic steatosis [34].

Moreover, the results of a randomized controlled trial on adults with NAFLD and vitamin D deficiency demonstrated a significant reduction in serum ALT and an increase in beneficial adiponectin levels after 6 months of lifestyle modification and vitamin D supply compared to control group (only with lifestyle modification) [35].

Therefore, vitamin D supplementation seems to have potential benefits in treatment of non-alcoholic fatty liver disease in children. However, the studies have mainly shown associations, but not necessarily a direct cause-and-effect relationship and long-term efficacy of intervention with vitamin D in treatment NAFLD in this population. In this subject more randomized-controlled trials on children and adolescent are needed to better assess the effectiveness of vitamin D supplementation of therapy in NAFLD.

Cardiovascular diseases

Another metabolic dysfunction observed in obesity includes dyslipidaemia which is abnormal lipid profile characterized by elevated levels of triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) with small dense low-density lipoprotein-cholesterol (sdLDL-C) and decreased levels of high-density lipoprotein cholesterol (HDL-C). What is more, obese and overweight individuals are more prone to develop hypertension, marked by persistently elevated systolic blood pressure above 140 mmHg and/or diastolic blood pressure above 90 mm Hg. These lipid and vascular abnormalities contribute to an increased risk of cardiovascular diseases, including atherosclerosis, coronary artery disease and stroke [36,37].

Several studies have indicated a potential link between low serum 25-hydroxyvitamin D level and higher risk of cardiovascular diseases, but the exact mechanisms of the relationship are still not fully understood [38-40]. One of proposed explanation is the role of vitamin D in suppressing of renin production which is a key component of the renin-angiotensin-aldosterone system. Thus, adequate level of this vitamin may potentially reduce blood pressure and the risk of hypertension [41]. It is also suggested that vitamin D due to its numerous receptors, including in liver and adipose tissue may influence lipid metabolism by regulating the expression of genes involved in cholesterol metabolism [42]. Furthermore, vitamin D and its anti-inflammatory properties may modulate the immune response, potentially reducing inflammation and protecting against damage in the vascular wall [43,44].

Nevertheless, studies directly examining the effects of vitamin D supplementation on markers of cardiometabolic risk in paediatric population with obesity have yielded inconsistent results. A meta-analysis published in 2021 have established that vitamin D supplementation ≥200,000 IU demonstrated a positive impact on reducing fasting glucose and triglycerides levels. Nonetheless, there was no significant effect observed on other cardiometabolic risk factors, such as HDL-C, LDL-C, TC, blood pressure, and waist circumferences [23]. Another meta-analysis of randomized controlled trials from 2022 has shown similarly, no significant improvement in cardiometabolic and bone-metabolic indicators after vitamin D intervention. However, the authors suggest that vitamin D

supplementation at higher daily doses, (>4000 IU per day), may have the potential to decrease CRP (C-reactive protein) levels, increase HDL levels and improve insulin sensitivity in overweight or obese children [45].

These results provide a thesis that maintaining sufficient vitamin D levels may have potential, modest benefits for cardiovascular health in paediatric patients with obesity. Importantly, further research, including clinical trials, are needed to better understand the relationship between vitamin D levels and cardiovascular diseases and to determine whether vitamin D supplementation can effectively reduce the risk of cardiovascular diseases.

Summary

In conclusion, maintaining an adequate level of vitamin D seems to have a beneficial impact on preventing and supporting the treatment of obesity-related diseases. Therefore, vitamin D supplementation has the potential as an promising addition in the obesity treatment in children with a deficiency of this vitamin. However, it is important to notice that the most crucial strategy in managing obesity and its comorbidities is weight loss through dietary changes and physical activity. Medications and supplements should only support this process. Nevertheless, additional research is necessary to establish the precise role of vitamin D in pathogenesis of obesity-related diseases in children and to determine optimal doses of vitamin D in this population.

Supplementary Materials: They have not been provided.
Author Contributions: WK: conceptualization, literature review, writing - original draft preparation; AB and MA: literature review, writing - review and editing. PB, GŁ, MR, AW, KR, AK and WM: writing - review and editing. All authors have read and agreed to the published version of the manuscript.
Funding Statement: this research received no external funding. Institutional Review.
Board Statement: Not applicable.
Informed Consent Statement: Not applicable.
Data Availability Statement: Not applicable.
Conflicts of Interest: the authors declare no conflict of interest.

List of references

1. Ng M., Fleming T., Robinson M., Thomson B., Graetz N., Margono C., Mullany E.C., Biryukov S., Abbafati C., Abera S.F., et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: A systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384:766–781. doi: 10.1016/S0140-6736(14)60460-8.

2. He QX, Zhao L, Tong JS, Liang XY, Li RN, Zhang P, Liang XH. The impact of obesity epidemic on type 2 diabetes in children and adolescents: A systematic review and meta-analysis. Prim Care Diabetes. 2022 Dec;16(6):736-744. doi: 10.1016/j.pcd.2022.09.006. Epub 2022 Sep 30. PMID: 36184528.

3. Fan, Jingwen et al. “Birth weight, childhood obesity and risk of hypertension: a Mendelian randomization study.” Journal of hypertension vol. 39,9 (2021): 1876-1883. doi:10.1097/HJH.0000000000002871

4. Liu, Jiaye et al. “Estimating Global Prevalence of Metabolic Dysfunction-Associated Fatty Liver Disease in Overweight or Obese Children and Adolescents: Systematic Review and Meta-Analysis.” International journal of public health vol. 66 1604371. 6 Oct. 2021, doi:10.3389/ijph.2021.1604371

5. Gulotta G, Iannella G, Vicini C, et al. Risk factors for obstructive sleep apnea syndrome in children: state of the art. Int J Environ Res Public Health. 2019;16(18):3235. doi: 10.3390/ijerph16183235

6. Umer A, Kelley GA, Cottrell LE, Giacobbi P Jr, Innes KE, Lilly CL. Childhood obesity and adult cardiovascular disease risk factors: a systematic review with meta-analysis. BMC Public Health. 2017;17:683. doi: 10.1186/s12889-017-4691-z [PMC free article] [PubMed] [CrossRef] [Google Scholar]

7. Bouillon, Roger et al. “Vitamin D and human health: lessons from vitamin D receptor null mice.” Endocrine reviews vol. 29,6 (2008): 726-76. doi:10.1210/er.2008-0004

8. Lips, P. “Vitamin D physiology.” Progress in biophysics and molecular biology vol. 92,1 (2006): 4-8. doi:10.1016/j.pbiomolbio.2006.02.016

9. Hattangdi-Haridas, Sonal R et al. “Vitamin D Deficiency and Effects of Vitamin D Supplementation on Disease Severity in Patients with Atopic Dermatitis: A Systematic Review and Meta-Analysis in Adults and Children.” Nutrients vol. 11,8 1854. 9 Aug. 2019, doi:10.3390/nu11081854

10. Saintonge, Sandy et al. “Implications of a new definition of vitamin D deficiency in a multiracial us adolescent population: the National Health and Nutrition Examination Survey III.” Pediatrics vol. 123,3 (2009): 797-803. doi:10.1542/peds.2008-1195

11. Wimalawansa, Sunil J. “Associations of vitamin D with insulin resistance, obesity, type 2 diabetes, and metabolic syndrome.” The Journal of steroid biochemistry and molecular biology vol. 175 (2018): 177-189. doi:10.1016/j.jsbmb.2016.09.017

12. Holick, Michael F. “Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease.” The American journal of clinical nutrition vol. 80,6 Suppl (2004): 1678S-88S. doi:10.1093/ajcn/80.6.1678S

13. Fiamenghi, Verônica Indicatti, and Elza Daniel de Mello. “Vitamin D deficiency in children and adolescents with obesity: a meta-analysis.” Jornal de pediatria vol. 97,3 (2021): 273-279. doi:10.1016/j.jped.2020.08.006

14. Malden S, Gillespie J, Hughes A, Gibson AM, Farooq A, Martin A, Summerbell C, Reilly JJ. Obesity in young children and its relationship with diagnosis of asthma, vitamin D deficiency, iron deficiency, specific allergies and flat-footedness: A systematic review and meta-analysis. Obes Rev. 2021 Mar;22(3):e13129. doi: 10.1111/obr.13129. Epub 2020 Aug 18. PMID: 32808447; PMCID: PMC7611974.

15. Yao Y, Zhu L, He L, Duan Y, Liang W, Nie Z, Jin Y, Wu X, Fang Y. A meta-analysis of the relationship between vitamin D deficiency and obesity. Int J Clin Exp Med. 2015 Sep 15;8(9):14977-84. PMID: 26628980; PMCID: PMC4658869.

16. Samaranayake, D B D L et al. “Vitamin D supplementation in obese Sri Lankan children: a randomized controlled trial.” BMC pediatrics vol. 20,1 426. 5 Sep. 2020, doi:10.1186/s12887-020-02329-w

17. Brzeziński, Michał et al. “Long-Term Effects of Vitamin D Supplementation in Obese Children During Integrated Weight-Loss Programme-A Double Blind Randomized Placebo-Controlled Trial.” Nutrients vol. 12,4 1093. 15 Apr. 2020, doi:10.3390/nu12041093

18. Valaiyapathi, Badhma et al. “Pathophysiology of Type 2 Diabetes in Children and Adolescents.” Current diabetes reviews vol. 16,3 (2020): 220-229. doi:10.2174/1573399814666180608074510

19. Henderson, M et al. “Measuring insulin sensitivity in youth: How do the different indices compare with the gold-standard method?.” Diabetes & metabolism vol. 37,1 (2011): 72-8. doi:10.1016/j.diabet.2010.06.008

20. González-González, José G et al. “HOMA-IR as a predictor of Health Outcomes in Patients with Metabolic Risk Factors: A Systematic Review and Meta-analysis.” High blood pressure & cardiovascular prevention : the official journal of the Italian Society of Hypertension vol. 29,6 (2022): 547-564. doi:10.1007/s40292-022-00542-5

21. Gün, Emrah et al. “Serum 25-hydroxyvitamin D is associated with insulin resistance independently of obesity in children ages 5-17.” Primary care diabetes vol. 14,6 (2020): 741-746. doi:10.1016/j.pcd.2020.06.006

22. Çığrı, Emrah, and Funda Çatan İnan. “The Relationship between Anthropometric Measurements and Vitamin D Levels and Insulin Resistance in Obese Children and Adolescents.” Children (Basel, Switzerland) vol. 9,12 1837. 27 Nov. 2022, doi:10.3390/children9121837

23. Cai, Bin et al. “Effect of vitamin D supplementation on markers of cardiometabolic risk in children and adolescents: A meta-analysis of randomized clinical trials.”

Nutrition, metabolism, and cardiovascular diseases : NMCD vol. 31,10 (2021): 2800-2814. doi:10.1016/j.numecd.2021.06.013

24. Rajakumar, Kumaravel et al. “Effect of vitamin D3 supplementation on vascular and metabolic health of vitamin D-deficient overweight and obese children: a randomized clinical trial.” The American journal of clinical nutrition vol. 111,4 (2020): 757-768. doi:10.1093/ajcn/nqz340

25. Alvarez, Jessica A, and Ambika Ashraf. “Role of vitamin d in insulin secretion and insulin sensitivity for glucose homeostasis.” International journal of endocrinology vol. 2010 (2010): 351385. doi:10.1155/2010/351385

26. Sergeev, Igor N. “1,25-Dihydroxyvitamin D3 and type 2 diabetes: Ca2+-dependent molecular mechanisms and the role of vitamin D status.” Hormone molecular biology and clinical investigation vol. 26,1 (2016): 61-5. doi:10.1515/hmbci-2015-0069

27. Clemente-Postigo, Mercedes et al. “Serum 25-hydroxyvitamin D and adipose tissue vitamin D receptor gene expression: relationship with obesity and type 2 diabetes.” The Journal of clinical endocrinology and metabolism vol. 100,4 (2015): E591-5. doi:10.1210/jc.2014-3016

28. Szymczak-Pajor, Izabela, and Agnieszka Śliwińska. “Analysis of Association between Vitamin D Deficiency and Insulin Resistance.” Nutrients vol. 11,4 794. 6 Apr. 2019, doi:10.3390/nu11040794

29. Liu, Jiaye et al. “Estimating Global Prevalence of Metabolic Dysfunction-Associated Fatty Liver Disease in Overweight or Obese Children and Adolescents: Systematic Review and Meta-Analysis.” International journal of public health vol. 66 1604371. 6 Oct. 2021, doi:10.3389/ijph.2021.1604371

30. Quek, Jingxuan et al. “Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis.” The lancet. Gastroenterology & hepatology vol. 8,1 (2023): 20-30. doi:10.1016/S2468-1253(22)00317-X

31. Castera, Laurent et al. “Noninvasive Assessment of Liver Disease in Patients With Nonalcoholic Fatty Liver Disease.” Gastroenterology vol. 156,5 (2019): 1264-1281.e4. doi:10.1053/j.gastro.2018.12.036

32. Black, Lucinda J et al. “Low serum 25-hydroxyvitamin D concentrations associate with non-alcoholic fatty liver disease in adolescents independent of adiposity.” Journal of gastroenterology and hepatology vol. 29,6 (2014): 1215-22. doi:10.1111/jgh.12541

33. Zhu, Shanshan et al. “The Level of Vitamin D in Children and Adolescents with Nonalcoholic Fatty Liver Disease: A Meta-Analysis.” BioMed research international vol. 2019 7643542. 14 Jul. 2019, doi:10.1155/2019/7643542

34. Eliades, Myrto, and Elias Spyrou. “Vitamin D: a new player in non-alcoholic fatty liver disease?.” World journal of gastroenterology vol. 21,6 (2015): 1718-27. doi:10.3748/wjg.v21.i6.1718

35. Sakpal, Mallikarjun et al. “Vitamin D supplementation in patients with nonalcoholic fatty liver disease: A randomized controlled trial.” JGH open : an open access journal of gastroenterology and hepatology vol. 1,2 62-67. 12 Oct. 2017, doi:10.1002/jgh3.12010

36. Franssen, Remco et al. “Obesity and dyslipidemia.” The Medical clinics of North America vol. 95,5 (2011): 893-902. doi:10.1016/j.mcna.2011.06.003

37. Riaz, Haris et al. “Association Between Obesity and Cardiovascular Outcomes: A Systematic Review and Meta-analysis of Mendelian Randomization Studies.” JAMA network open vol. 1,7 e183788. 2 Nov. 2018, doi:10.1001/jamanetworkopen.2018.3788

38. Brøndum-Jacobsen, Peter et al. “25-hydroxyvitamin d levels and risk of ischemic heart disease, myocardial infarction, and early death: population-based study and meta-analyses of 18 and 17 studies.” Arteriosclerosis, thrombosis, and vascular biology vol. 32,11 (2012): 2794-802. doi:10.1161/ATVBAHA.112.248039

39. Parker, Johanna et al. “Levels of vitamin D and cardiometabolic disorders: systematic review and meta-analysis.” Maturitas vol. 65,3 (2010): 225-36. doi:10.1016/j.maturitas.2009.12.013

40. Barbalho, Sandra Maria et al. “Association between vitamin D status and metabolic syndrome risk factors.” Diabetes & metabolic syndrome vol. 12,4 (2018): 501-507. doi:10.1016/j.dsx.2018.03.011

41. Vaidya, Anand, and John P Forman. “Vitamin D and vascular disease: the current and future status of vitamin D therapy in hypertension and kidney disease.” Current hypertension reports vol. 14,2 (2012): 111-9. doi:10.1007/s11906-012-0248-9

42. Szymczak-Pajor, Izabela et al. “The Molecular Mechanisms by Which Vitamin D Prevents Insulin Resistance and Associated Disorders.” International journal of molecular sciences vol. 21,18 6644. 11 Sep. 2020, doi:10.3390/ijms21186644

43. Kassi, Eva et al. “Role of vitamin D in atherosclerosis.” Circulation vol. 128,23 (2013): 2517-31. doi:10.1161/CIRCULATIONAHA.113.002654

44. Surdu, Andrei Mihai et al. “Vitamin D and Its Role in the Lipid Metabolism and the Development of Atherosclerosis.” Biomedicines vol. 9,2 172. 9 Feb. 2021, doi:10.3390/biomedicines9020172

45. Gou, Hao et al. “Efficacy of vitamin D supplementation on child and adolescent overweight/obesity: a systematic review and meta-analysis of randomized controlled trials.” European journal of pediatrics vol. 182,1 (2023): 255-264. doi:10.1007/s00431-022-04673-8