

Vitamin D and obesity in adults: a pathophysiological and clinical update

Abstract

Vitamin D deficiency has become an increasing focus of clinical interest, especially in understanding its associations with obesity in adults. The pathological associations linking the two appear to demonstrate complex cellular inflammatory, hormonal and genetic pathways. Enhanced understanding at both microcellular and clinical levels will help clarify the role of obesity in the development of vitamin D deficiency.

Key words: Vitamin D; Deficiency; Obesity; Metabolism; Adipocyte; Pathogenesis

Submitted 20 September 2019; accepted following double blind peer review: 5 November 2019

Julien Feghaly¹

Paul Johnson²

Atul Kalhan³

Author details can be found at the end of this article

Correspondence to:

Julien Feghaly; julien.feghaly@health.slu.edu

The aetiopathogenesis of vitamin D deficiency is multifactorial, including factors such as malnourishment (diet poor in oily fish, red meat, cheese and egg yolk), malabsorption (as a result of coeliac disease, cystic fibrosis, inflammatory bowel disease, or post-small bowel resection), and exposure to sunlight. This is further influenced by ethnicity, skin colour, geographical location, season of the year and age. Recently, there has been increased interest in the reported role of obesity in adults as a contributor to vitamin D deficiency. The pathogenesis of vitamin D deficiency in obese individuals has been linked to genetics, nutritional deficiencies, poor eating behaviour, and cellular build-up of vitamin D within the adipose tissue (Earthman et al, 2012; Galunska et al, 2016; Bouillon and Bikle, 2019).

Adipose tissue as an endocrine organ

Historically, adipose tissue has been considered a major site of energy storage. There is growing evidence for the central role played by adipose tissue as an important endocrine organ involved in regulation of nutrient homeostasis (Yadav et al, 2013). Adipose tissue releases cytokines that play a key role in maintaining physiological functions such as blood pressure regulation, and lipid and carbohydrate metabolism. These cytokines include leptin, adiponectin, visfatin, resistin, tumour necrosis factor- α (TNF- α), interleukin (IL-6), and angiotensinogen.

Adiponectin

Adiponectin, a collagen-like plasma protein expressed in adipose tissue, is thought to play an important role in the modulation of glucose and lipid metabolism in insulin-sensitive tissues by upregulating insulin signalling and increasing metabolism of fatty acids (Yadav et al, 2013). Expression of adiponectin is reduced with lower concentrations of 25-hydroxyvitamin D (25(OH)D). This may have imparted an evolutionary advantage of 'saving' fatty acid reserves during winter months when 25(OH)D concentrations are at their lowest. In obesity-linked insulin resistance, both adiponectin and adiponectin receptors are downregulated and 25(OH)D concentrations are lower. Adiponectin further induces various anti-inflammatory cytokines, such as interleukin-10, which are thought to be involved in protecting damaged vascular walls against the progression of atherosclerotic disease (Matsuzawa, 2008). Furthermore, adiponectin secretion is reduced by TNF- α and this may account for the decrease in levels of adiponectin with increase in the adiposity (Chandran et al, 2003).

Leptin

Leptin is a hormone derived mainly from adipose tissue (Myers et al, 2008) and to a lesser extent from the stomach epithelium, intestine, placenta, skeletal muscle, mammary

How to cite this article:

Feghaly J, Johnson P, Kalhan A. Vitamin D and obesity in adults: a pathophysiological and clinical update. *Br J Hosp Med*. 2020;81(1):1–5. <https://doi.org/10.12968/hmed.2019.0291>

epithelium and brain. Leptin acts to inhibit appetite and stimulate thermogenesis. When leptin concentrations rise fatty acid oxidation is increased and blood glucose levels decrease. Most obese individuals have a degree of leptin resistance, which leads to increased appetite and further weight gain despite higher concentrations of leptin (Yadav et al, 2013).

Cytokines

Macrophages are the primary mediators of the innate immune response. Macrophages comprise 5–10% of the immune cells within adipose tissue, but weight gain increases macrophage infiltration by up to 60%, resulting in increased release of pro-inflammatory cytokines creating a chronic low grade inflammatory state (Eder et al, 2009). These cytokines include TNF- α , IL-6 and C-reactive protein (Tzanavari et al, 2010; Ramdas and Jella, 2016). IL-6, a major regulator of the acute phase reaction, appears to have a cachectogenic role at the level of the hypothalamus where it acts as an endocrine mediator inducing insulin resistance and dyslipidaemia (Eder et al, 2009). Interestingly, IL-6 appears to worsen insulin resistance in liver and adipose tissue yet improves the insulin sensitivity of muscle tissue by increasing islet glucagon-like peptide 1 production (El-Kadre and Tinoco, 2013).

Possible mechanisms linking vitamin D and adipocytes

Several pathways have been proposed linking vitamin D deficiency and obesity. Obesity has been linked to reduced activity of the CYP2R1 gene, decreasing production of 25-hydroxylase, which forms the 25(OH)D that is needed as a substrate for all further activation of vitamin D. Expression of CYP2R1 mRNA in the liver has been demonstrated to be markedly lower (about 40%) in the livers of obese mice compared with normal mice. Other genes associated with regulation of vitamin D metabolism were not changed by diet-induced obesity, such as 25-hydroxylases (CYP27A1, CYP3A4) and the catabolic enzyme CYP24A1 (Bouillon and Bikle, 2019).

Vitamin D receptor, a member of the nuclear receptor super-family, plays a key role in adipogenesis (Kong and Li, 2006). Vitamin D receptor-regulated gene expression inhibited the early stage of adipocytes differentiation in the 3T3-L1 (pre-adipocyte cell line) model (Blumberg et al, 2006). Over-expression of the vitamin D receptor in adipose tissue increases adipose mass and reduces energy metabolism (Wong et al, 2011), while the absence of vitamin D receptor reduces plasma lipid concentrations because this leads to a state of increased energy expenditure (Narvaez et al, 2009). Vitamin D upregulates leptin in vitamin D receptor (-,-) mice, but the exact mechanism remains unclear (Kong et al, 2013).

Vitamin D and obesity: clinical correlates

An association between obesity and low vitamin D status (serum or plasma 25(OH)D concentration) is evident (Galunska et al, 2016; Bouillon and Bikle, 2019) although there are limited data to establish a causal relationship. Cross-sectional and prospective human studies have suggested beneficial effects of vitamin D status for reducing visceral fat mass (Hao et al, 2014), although randomised controlled trials of vitamin D supplementation have shown mixed evidence (Rosenblum et al, 2012; Wamberg et al, 2013). A systematic review suggested that altered vitamin D physiology and parathyroid physiology in obese individuals contributes to low 25(OH)D concentrations (Earthman et al, 2012), while an alternate mechanism suggested decreased 25(OH)D bioavailability as a result of increased adipocyte uptake (Wortsman et al, 2000). In a study that used a bi-directional genetic approach, a higher body mass index led to lower vitamin D concentrations. However, the effect of lower 25(OH)D concentrations leading to a higher body mass index was minimal (Vimaleswaran et al, 2013).

Further studies went on to determine similar associations despite lack of causation. Up to 68.9% of patients presenting for bariatric surgery were found to have low 25(OH)

Key points

- An association of vitamin D deficiency and obesity in adults exists, although an exact mechanism linking them is yet to be determined.
- Vitamin D deficiency is correlated with increased body mass index.
- Modulation of the CYP2R1 and vitamin D receptor genes by obesity appear likely to have key roles in the understanding of how obesity affects vitamin D status.

D concentrations (≤ 19.9 ng/ml), which was inversely associated with body mass index when body mass index was >50 kg/m² (Aridi et al, 2016). A study examining various anthropometric variables and vitamin D status in school children determined that only body mass index and weight independently influence 25(OH)D concentrations, suggesting that it is the amount of visceral rather than the subcutaneous adipose tissue which determines the serum concentrations of 25(OH)D in children (Rodríguez-Rodríguez et al, 2010). Analogous studies also found that children with low 25(OH)D concentrations were more likely to have higher total adiposity, metabolic syndrome and hypertension (Pacífico et al, 2011), further indicating an inverse relationship whereby as obesity increased, 25(OH)D concentrations decreased (Galunska et al, 2016).

In clinical trials, vitamin D supplementation has been demonstrated to decrease C-reactive protein and IL-6 levels, although TNF- α concentrations remained unchanged suggesting that the restoration of vitamin D could play a role in decreasing circulating levels of inflammatory markers (Meireles et al, 2016). Furthermore, improved vitamin D status could improve insulin resistance (von Hurst et al, 2010), as postulated by the measurement of a lower leptin:adiponectin ratio which is used as a clinical tool for the assessment of insulin resistance (Belenchia et al, 2013). However, other studies opposed these correlations, determining no significant influence on inflammatory biomarker levels and plasma adipokine concentrations in obese and overweight subjects following vitamin D supplementation (Dinca et al, 2016; Jamka et al, 2016), with the possible exception of IL-6 (Waterhouse et al, 2015).

Conclusions

Emerging evidence based on epidemiological studies, cohort analysis and systematic reviews suggests that reduced vitamin D status is common in obese adults and is usually inversely associated with measures of adiposity, although an exact mechanism linking them is yet to be elucidated. The strongest evidence suggesting that vitamin D status correlates inversely with body mass index comes from epidemiological studies. It is hard to distinguish whether this is a cause or effect relationship. Multiple confounding factors such as sedentary lifestyle, relative lack of sun exposure, dietary choices, race, and ethnic origin can also potentially dampen the strengthen of this association. Ongoing molecular level research on the CYP2R1 gene, vitamin D receptor, adipogenesis and adiopolysis will help improve our understanding the mechanisms linking lowering of serum 25(OH) vitamin D concentrations with increased obesity.

Author details

¹ Department of Internal Medicine, St. Louis University Hospital, St. Louis, Missouri, USA

² University of Nicosia Medical School, Nicosia, Cyprus

³ Department of Endocrinology, Royal Glamorgan Hospital, Rhondda Cynon Taf, Wales

Conflicts of interest

The authors declare no conflicts of interest..

References

- Aridi HD, Alami RS, Fouani T, Shamseddine G, Tamim H, Safadi B. Prevalence of vitamin D deficiency in adults presenting for bariatric surgery in Lebanon. *Surg Obes Relat Dis*. 2016;12(2):405–411. <https://doi.org/10.1016/j.soard.2015.09.022>
- Belenchia AM, Tosh AK, Hillman LS, Peterson CA. Correcting vitamin D insufficiency improves insulin sensitivity in obese adolescents: a randomized controlled trial. *Am J Clin Nutr*. 2013;97(4):774–781. <https://doi.org/10.3945/ajcn.112.050013>
- Blumberg JM, Tzameli I, Astapova I, Lam FS, Flier JS, Hollenberg AN. Complex role of the vitamin D receptor and its ligand in adipogenesis in 3T3-L1 cells. *J Biol Chem*. 2006;281(16):11205–11213. <https://doi.org/10.1074/jbc.M510343200>
- Bouillon R, Bikle D. Vitamin D metabolism revised: fall of dogmas. *J Bone Miner Res*. 2019;jbmr.3884. <https://doi.org/10.1002/jbmr.3884>
- Chandran M, Phillips SA, Ciaraldi T, Henry RR. Adiponectin: more than just another fat cell hormone? *Diabetes Care*. 2003;26(8):2442–2450. <https://doi.org/10.2337/diacare.26.8.2442>
- Dinca M, Serban MC, Sahebkar A et al; for Lipid Blood Pressure Meta-analysis Collaboration LBPMC Group. Does vitamin D supplementation alter plasma adipokines concentrations? A systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res*. 2016;107:360–371. <https://doi.org/10.1016/j.phrs.2016.03.035>
- Earthman CP, Beckman LM, Masodkar K, Sibley SD. The link between obesity and low circulating 25-hydroxyvitamin D concentrations: considerations and implications. *Int J Obes*. 2012;36(3):387–396. <https://doi.org/10.1038/ijo.2011.119>
- Eder K, Baffy N, Falus A, Fulop AK. The major inflammatory mediator interleukin-6 and obesity. *Inflamm Res*. 2009;58(11):727–736. <https://doi.org/10.1007/s00011-009-0060-4>
- El-Kadre LJ, Tinoco ACA. Interleukin-6 and obesity. *Curr Opin Clin Nutr Metab Care*. 2013;16(5):1. <https://doi.org/10.1097/MCO.0b013e32836410e6>
- Galunska B, Gerova D, Galcheva S, Iotova V, Veeramachaneni R, Indurkar PS. Association between vitamin D status and obesity in Bulgarian pre-pubertal children: a pilot study. *International Journal of Research in Medical Sciences*. 2016;4(2):361–368. <https://doi.org/10.18203/2320-6012.ijrms20160284>
- Hao Y, Ma X, Shen Y et al. Associations of serum 25-hydroxyvitamin D3 levels with visceral adipose tissue in Chinese men with normal glucose tolerance. *PLoS One*. 2014;9(1):e86773. <https://doi.org/10.1371/journal.pone.0086773>
- Jamka M, Woźniewicz M, Walkowiak J, Bogdański P, Jeszka J, Stelmach-Mardas M. The effect of vitamin D supplementation on selected inflammatory biomarkers in obese and overweight subjects: a systematic review with meta-analysis. *Eur J Nutr*. 2016;55(6):2163–2176. <https://doi.org/10.1007/s00394-015-1089-5>
- Kong J, Chen Y, Zhu G, Zhao Q, Li YC. 1,25-Dihydroxyvitamin D3 upregulates leptin expression in mouse adipose tissue. *J Endocrinol*. 2013;216(2):265–271. <https://doi.org/10.1530/JOE-12-0344>
- Kong J, Li YC. Molecular mechanism of 1,25-dihydroxyvitamin D3 inhibition of adipogenesis in 3T3-L1 cells. *Am J Physiol Endocrinol Metab*. 2006;290(5):E916–E924. <https://doi.org/10.1152/ajpendo.00410.2005>
- Matsuzawa Y. The role of fat topology in the risk of disease. *Int J Obes*. 2008;32(S7) Suppl 7:S83–S92. <https://doi.org/10.1038/ijo.2008.243>
- Meireles MS, Kamimura MA, Dalboni MA, Giffoni de Carvalho JT, Aoike DT, Cuppari L. Effect of cholecalciferol on vitamin D-regulatory proteins in monocytes and on inflammatory markers in dialysis patients: A randomized controlled trial. *Clin Nutr*. 2016;35(6):1251–1258. <https://doi.org/10.1016/j.clnu.2016.04.014>
- Myers MG, Cowley MA, Münzberg H. Mechanisms of leptin action and leptin resistance. *Annu Rev Physiol*. 2008;70(1):537–556. <https://doi.org/10.1146/annurev.physiol.70.113006.100707>
- Narvaez CJ, Matthews D, Broun E, Chan M, Welsh J. Lean phenotype and resistance to diet-induced obesity in vitamin D receptor knockout mice correlates with induction of uncoupling protein-1 in white adipose tissue. *Endocrinology*. 2009;150(2):651–661. <https://doi.org/10.1210/en.2008-1118>
- Pacifico L, Anania C, Osborn JF, Ferraro F, Bonci E, Olivero E, Chiesa C. Low 25(OH)D3 levels are associated with total adiposity, metabolic syndrome, and hypertension in Caucasian children and adolescents. *Eur J Endocrinol*. 2011;165(4):603–611. <https://doi.org/10.1530/EJE-11-0545>
- Ramdas J, Jella V. Elevated C reactive protein levels in obese individuals with metabolic syndromes. *Int J Adv Med*. 2016;3(2):162–165. <https://doi.org/10.18203/2349-3933.ijam20160909>
- Rodríguez-Rodríguez E, Navia-Lombán B, López-Sobaler AM, Ortega RM. Associations between abdominal fat and body mass index on vitamin D status in a group of Spanish schoolchildren. *Eur J Clin Nutr*. 2010;64(5):461–467. <https://doi.org/10.1038/ejcn.2010.26>

- Rosenblum JL, Castro VM, Moore CE, Kaplan LM. Calcium and vitamin D supplementation is associated with decreased abdominal visceral adipose tissue in overweight and obese adults. *Am J Clin Nutr*. 2012;95(1):101–108. <https://doi.org/10.3945/ajcn.111.019489>
- Tzanavari T, Giannogonas P, Karalis KP. TNF- α and obesity. *Curr Dir Autoimmun*. 2010;11:145–156. <https://doi.org/10.1159/000289203>
- Vimalleswaran KS, Berry DJ, Lu C et al; Genetic Investigation of Anthropometric Traits-GIANT Consortium. Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomization analysis of multiple cohorts. *PLoS Med*. 2013;10(2):e1001383. <https://doi.org/10.1371/journal.pmed.1001383>
- von Hurst PR, Stonehouse W, Coad J. Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient – a randomised, placebo-controlled trial. *Br J Nutr*. 2010;103(4):549–555. <https://doi.org/10.1017/S0007114509992017>
- Wamberg L, Kampmann U, Stødkilde-Jørgensen H, Rejnmark L, Pedersen SB, Richelsen B. Effects of vitamin D supplementation on body fat accumulation, inflammation, and metabolic risk factors in obese adults with low vitamin D levels— results from a randomized trial. *Eur J Intern Med*. 2013;24(7):644–649. <https://doi.org/10.1016/j.ejim.2013.03.005>
- Waterhouse M, Tran B, Ebeling PR et al. Effect of vitamin D supplementation on selected inflammatory biomarkers in older adults: a secondary analysis of data from a randomised, placebo-controlled trial. *Br J Nutr*. 2015;114(5):693–699. <https://doi.org/10.1017/S0007114515002366>
- Wong KE, Kong J, Zhang W et al. Targeted expression of human vitamin D receptor in adipocytes decreases energy expenditure and induces obesity in mice. *J Biol Chem*. 2011;286(39):33804–33810. <https://doi.org/10.1074/jbc.M111.257568>
- Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr*. 2000;72(3):690–693. <https://doi.org/10.1093/ajcn/72.3.690>
- Yadav A, Kataria MA, Saini V, Yadav A. Role of leptin and adiponectin in insulin resistance. *Clin Chim Acta*. 2013;417:80–84. <https://doi.org/10.1016/j.cca.2012.12.007>