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Role of Vitamin D in Obesity

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ABSTRACT

Hypovitaminosis D and obesity represent global public health problems. Plasma concentrations of 25 (OH) D are more strongly correlated with visceral adipose tissue than subcutaneous fat, suggesting a link between vitamin D levels, insulin resistance and cardiometabolic risk, particularly in younger subjects. Various studies have shown that obesity is an important risk factor for vitamin D deficiency and how adiposity has a determining role in the serum level of vitamin D. The association between these two factors is complex and the multiple studies carried out to clarify this association have not provided univocal indications. Some hypotheses propose that the deficiency of vitamin D may remain a cause of obesity. However, the possible pathophysiological mechanisms do not exclude a multifactorial origin, thus supporting the importance of supplementing vitamin D in obese patients. Since adipose tissue is a major reserve of vitamin D, its role in the regulation of adipogenesis, insulin sensitivity, and in the reduction of cytokine release and adipose tissue inflammation has been demonstrated. Moreover, studies on the vascular effect of vitamin D have been carried out. This review attempts to summarize the current understanding regarding the causes of the reduced vitamin D levels in obese patients, the effects of vitamin D supplementation in these individuals, and the prevention of the complications associated to obesity such as the chronic inflammatory state and vascular complications which predispose to cardiovascular risk.

Keywords
Obesity; Vitamin D; Adipose tissue inflammation, Vascular dysfunction

INTRODUCTION

In the last decade, vitamin D [25 (OH) D] (VD), an important regulator of phosphorous and calcium metabolism, has been correlated to numerous metabolic, immunological, and neoplastic diseases. The association with obesity is highly relevant on a public health perspective, given its association with the metabolic syndrome, insulin resistance and cardiovascular disorders (CVD) [1, 2, 3,4,5,6,7]. Vitamin D precursor and metabolites are reported in Table 1.
Numerous studies have established a relationship between VD and body weight. There are two different types of adipose tissue, subcutaneous and visceral adipose tissue, which possess different endocrine-metabolic characteristics. Adipose tissue (AT) appears to be negatively associated with plasma levels of 25 hydroxy-vitamin D [25 (OH) D], the inactive form of the vitamin [8-15]. Various hypotheses have been proposed to account for the reduced VD levels in

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obesity, ranging from reduced exposure to sunlight to increased renal production of 1,25 di-hydroxyvitamin D [1,25 (OH) 2D] and the active form 1,25-dihydroxycholecalciferol (1,25-$(OH)_2D_3$) with a consequent negative feedback on the liver synthesis of 25 (OH) D. Moreover, an enhanced metabolic clearance and/or increased absorption of VD via the adipose tissue would account for a low bioavailability of 25 (OH) D in the circulation in obesity. Of note, body mass index (BMI) and adiposity may also exert negative effects on therapy, again with conflicting data [16-21].

Recent data have shown a negative link between serum levels of 25 (OH) D and insulin resistance, establishing a link with the metabolic syndrome [22,23]. This association is consistent with the evidence that higher VD levels are an separate predictor of improved beta cell function in the pancreas and that hypovitaminosis D is linked to reduced beta cell function, increased risk of insulin resistance and MS. [23].

Various studies performed demonstrated that visceral fat has a greater endocrine activity and is more strongly associated to insulin resistance, thereby predisposing to the MS [24]. The mechanisms which are involved in the onset of insulin resistance include increased lipolytic activity and the stimulation of pro-inflammatory cytokines including interleukin 6, Tumor Necrosis Factor α, C reactive protein), which trigger a pro-inflammatory, prothrombotic and vasoconstrictor state directly related to visceral obesity. Since cardiovascular disease is highly associated with obesity, a direct effect of VD could improve the vascular function and prevent adverse cardiovascular events. Because adipose tissue is a major reserve of vitamin D, its role in the regulation of adipogenesis, insulin sensitivity, and in the reduction of cytokine release and adipose tissue inflammation has been proved. [25-35].

In a large cohort of obese subjects treated with bariatric surgery, the vitamin status post-operatively can be influenced by the weight loss per se, and by variations in the absorption conditions. Guidelines developed by the American Association of Clinical Endocrinologists (AACE), Obesity Society (TOS) and American Society for Metabolic & Bariatric Surgery (ASMBS), which were updated in 2013, endorse great amounts of cholecalciferol, with at least 3000 IU per day for patients undergoing a sleeve gastrectomy and 50,000 IU 1-3 times a week in patients treated with malabsorptive surgical procedures, with further endorsement of a systematic follow-up, aimed at maintaining an optimal vitamin status over time [36].

This review will summarize the contemporary literature regarding the causes of reduced 25 (OH) D concentrations in obese subjects, the possible utilities of vitamin D supplementation in these subjects, and the prevention of the complications associated with obesity.

MECHANISMS OF REDUCTION OF VITAMIN D IN OBESITY

After exposure to solar radiation, the growth in concentrations of 25 (OH) vitamin D is 53% inferior in obese subjects compared to normal weight, regardless of the amount of the obtainable skin precursor. Vitamin D bioavailability would be reduced due to extreme sequestration in abundant adipose tissue since vitamin D is a fat-soluble vitamin [37]. In addition, the excessive stimulation of 1α-hydroxylase in adipocytes of obese subjects would regulate the local use of 25 (OH) vitamin D, which would elucidate a reduction in the circulating share related to the subcutaneous fat mass. Therefore, the adipose mass, would not limit itself to inactively store 25 (OH) vitamin D, rather, it would dynamically control the enzymes that metabolize it [38].

Numerous epidemiological trials, including the National Health and Nutrition Examination Survey (NHANES) III, Framingham study, and other clinical trials discovery augmented prevalence of hypovitaminosis D as BMI increases, precisely a decrease in the concentration of

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25 (OH) vitamin D corresponded to 0.74 nmol / l (0.28 ng / ml) or to 1.15% for each increase in BMI of 1Kg / m^2. Commonly, in the obese population, the prevalence of hypovitaminosis D is estimated to be between 21% and 90%, with average concentrations of 25 (OH) vitamin D around half the values found in normal weight subjects. In a recent meta-analysis, the occurrence of hypovitaminosis D in obese subjects resulted 35% higher than the normal weight and 24% higher than overweight patients independently of age, latitude, cut-offs used to describe the vitamin status and from the socio-economic development index of the analyzed geographical area [39]. The prevalence of hypovitaminosis D detected at pre-operative assessment in obese subjects undergoing bariatric surgery is attested to be between 23.7% and 92% with large variability, depending on several interfering factors. One of the largest studies reported in the literature, which refers to 232 patients with severe obesity, puts hypovitaminosis D in first place in order of incidence among micronutrient deficits [40].

Currently, volume dilution of VD is considered to be the most plausible system postulated to underly the negative association between concentrations of VD in the plasma and BMI. According to this hypothesis, both obese and non-obese individuals present comparable whole-body stores of VD. However, in obese individuals, VD is dispersed into a greater AT mass, leading to a reduction of serum VD concentrations [41]. In a study in women, levels of VD in different biological specimens including plasma, visceral, and panniculus AT were compared between obese and normal weight participants. The results showed similar concentrations and distribution patterns of VD between the two groups and provided evidence that the AT could play a role as a pool for VD [42]. If volumetric distribution has an imperative aspect in lowering VD in obesity, weight loss could potentially improve VD plasma concentration. However, various data examining weight reduction have showed contradictory findings, with some authors reporting enhanced 25 (OH) D serum levels [43,44] while others showing no significant changes. For example, Mason et al. [45] reported considerable augmentation in 25 (OH) D serum concentration after weight loss in obese postmenopausal women who performed a 12-month weight-reducing plan based on caloric restriction and physical activity.

Alternatively, low concentrations of VD in obese patients may be related to reduced dermal synthesis. Wortsman et al. [41] showed that cutaneous VD production of healthy and obese subjects did not show significant differences, despite obese patients presented decreased elevation of amounts of 25 (OH) D in blood post-irradiation and oral prescription of VD with respect to control group.

Gene expression analysis of VD metabolizing enzymes was performed both in lean and obese subjects to gain more insights into the low serum level of VD and its association with obesity. AT is not only a storage site for fat-soluble nutrients but seems to be important in the regulation of the metabolizing enzymes, and downregulating the cytochrome P450 2J2 gene, which encodes for the enzyme 25-hydroxylase, and downregulating cytochrome P450 27B1 expression, which encodes enzyme 1a-hydroxylase, in the panniculus AT of the obese versus control subjects [46,48]. There was no significant change in the regulation of cytochrome P450 24A1 which is implicated in the inactivation of calcitriol [1,25(OH)2D] (a bioactive form) between obese and lean individuals from this study. Interestingly, experimental evidence supports the hypothesis that VD itself could be implicated in the pathophysiology of obesity. An increased level of PTH secondary to hypovitaminosis D could stimulate lipid anabolism by increasing the Ca2+ flowing into the adipose tissue [49]. In addition, Blumberg et al. [50] demonstrated that in 3T3-L1 preadipocytes treatment with VD inhibits the adipogenesis by the downregulation of the transcription factor C/EBPbeta. In addition, 1,25(OH)D has been shown to activate the WNT/beta catenin pathway, which results in blocking of adipogenesis [51].

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Insulin release and peripheral insulin effects are calcium-mediated mechanisms that rely on the activation of calcium-dependent protein kinase C (PKC). VD participates in the activation of PKC by regulating intracellular Ca2+ concentrations. Furthermore, VD exerts positive control on the expression of insulin receptors in peripheral myocytes and prevents systemic inflammation by controlling the expression of certain cytokines. Upregulation of leptin and IL-6 in states of chronic low-grade inflammation associated with obesity-related hepatic steatosis interferes with 25 (OH) D actions by downregulating VD receptors (VDR) [52,53,54]. A key feature of obesity is adipocytes hypertrophy with an expanded adipose tissue size. Adipocyte hypertrophy is linked with insulin-resistance onset [55,56], enhanced release of leptin and pro-inflammation cytokines (IL-6, IL-8, TNFα), and reduced production of insulin-sensitizing adipocytokines including adiponectin and IL-10 [57,58, 59, 60, 61, 62].

Obesity-associated insulin resistance also has a fundamental role in the propagation of inflammation in the AT, leading to the upregulation of pro-inflammation cytokines including TNF-α, IL-6, and IL-1-β as reported in figure 1 [63]. These mediators activate a pro-inflammatory signaling cascade mediated by Jan N-terminal kinase-1 (JNK1) and Inhibit kappa-B-kinaseβ (IKK-β). Both JNK1 and the beta subunit of IKK-β are crucial in the onset of insulin resistance by downregulating the insulin receptor via phosphorylation of serine residues. Furthermore, IKK-β phosphorylates the inhibitor of nuclear factor kappa-B (NF-kB), promoting nuclear translocation and DNA binding, thereby promoting the secretion of inflammatory mediators including TNF-α. [64]. Several in vitro experiments have demonstrated that VD is able to counteract obesity-related chronic inflammation both by inhibiting proinflammatory cytokines IL-1β, IL-6, IL-8, IL-12 [53] and by decreasing inflammation in visceral AT (63, 64). Furthermore, vitamin D (1,25(OH)D2)may exert anti-inflammatory activity by regulating NF-kB, the key transcription factor in TNF-alpha activation. [65,66,67,68,69].

Recently, it was proposed that vitamin D and its receptor may further be implicated in the mechanisms that regulate the storage of fat in various tissues of the body. Hence, they may be an essential mediator of metabolic disease, with functions in regulating the accumulation of fat and the inflammatory response. Particularly, the vitamin D receptor expression in the liver and visceral adipose tissue is closely connected with the occurrence of hepatic steatosis, inflammation and dysfunction of adipose tissue. Moreover, vitamin D supplementation resulted in an improvement of the inflammatory state as reported by a significant reduction of the C-reactive protein. In addition, hypovitaminosis D is associated with low levels of leptin, a hormone produced in fat cells associated with satiety when they are saturated with fat. Leptin depletion associated with vitamin D deficiency can contribute to increased hunger by inducing hyperphagic attitudes [70,71,72].

The expression of different adipokines were investigated in experimental models of murine 3T3-L1 cells, stimulated with lipopolysaccharide (LPS) , which showed an increase in expression of inflammatory cytokines. The role of calcitriol (1.25 [OH] 2D3) in the physiology and pathophysiology of the adipocyte was evaluated, particularly, in the modulation of the inflammation of the AT. Therefore, transcriptional and morphological effects of both 1,25 [OH] 2D3 and the precursor cholecalciferol (D3) on 3T3-L1 adipocytes, were investigated showing anti-inflammatory properties, with a reduction in IL-6, TNF-α and an increase in IL-10 [73].

Likewise, a prominent diminution in IL-6 expression correlated with a reduction in NF-κB activation in human adipocytes harvested from bone marrow-derived human mesenchymal

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stromal cells (hMSCs) differentiated into adipocytes and primary adipocytes from human biopsies stimulated with LPS and treated with $1,25(OH)_2$ D_3 was detected [74]
Also, the treatment with $1,25(OH)_2$ D_3 was able to counteract the TNF-α-induced inflammation in 3T3-L1 adipocytes by the dephosphorylation of mitogen activated protein kinase p38 and downregulating the NF-κB activity [75],
Human adipocytes incubated with IL-1β and treated with $1,25(OH)_2D_3$ displayed a significant reduction in the expression of the mRNA for pro-inflammatory cytokines such as IL-6, IL-8 and MCP-1 [76]. Taketogether, these findings showed the linking between VD and the low-grade inflammation state associated to obesity which could predispose to high cardiovascular risk highlighting the potential role of VD in preventing these conditions.

VITAMIN D AND OBESITY-RELATED VASCULAR DYSFUNCTION

The accumulation of visceral AT in obesity contributes to a condition of chronic low-grade inflammation, thereby, stimulating insulin resistance and obesity-related complications, including hypertension, the MS, (T2DM) and cardiovascular disorders (CVD) [77, 78,79,80]. Insulin contributes to arterial homeostasis through endothelial nitric oxide (eNOS or NOS-3) activation and release of nitric oxide (NO), a mechanism dependent on the PI3K/Akt signaling pathway. Obesity-related insulin resistance impairs the PI3K/Akt pathway, leading to NO deficiency, endothelial dysfunction, and increased susceptibility to the development of hypertension and atherothrombosis [81,82]. An evidence proposed that VD and VDRs could perform a crucial attribute in the regulation of NO synthesis through eNOS action. Knock-out mice of endothelial VDR expression present a lowered bioavailability of NO due to downregulation of endothelial NOS (eNOS) [83].
Knock-out of endothelial-specific VDR demonstrated decreased eNOS expression and reduced ACh induced dilatation [83]. Furthermore, VDR activation promotes eNOS activity through its effects on intracellular calcium, with increased NO biosynthesis and improved vasodilation [83]. Reduced levels of VD showed negative effects on endothelial function due to a reduction in flow mediated dilatation, a marker of endothelial damage and predictor of adverse CVD (figure 2) [84]. While VD appears to exert potentially protective endothelial actions [85], VD supplementation on vascular function is controversial and remains to be elucidated [86]. In ex-vivo experiments, VD supplementation improved flow-induced dilatation, acetylcholine-induced dilatation, and NO production in isolated arteries harvested from AT during bariatric surgery. Moreover, VD-mediated improvements were greater in visceral AT than in subcutaneous AT vessels [87]. VD could elicit protective action counter to endothelial dysfunction, high blood pressure and CVD by the control of inflammation and hypoxic signaling in perivascular AT [88]. Recently, Ionica et al. demonstrated that administration with active VD in vitro counteracted oxidative stress in both AT and mesenteric arteries of obese patients exposed to a state of subclinical inflammation. Moreover, an improvement of vascular reactivity assessment in terms of lowered contractility and improved endothelium-mediated dilation was also demonstrated [89]. Obesity diminishes the vaso-protective properties of VD by decreasing its bioavailability and augmenting oxidative stress. Paschou et al. proposed that VD could prevent further macrophage recruitment in obesity-related atherosclerotic plaques by decreasing vascular inflammation by inhibiting nuclear factor kappa B and counteracting the oxidative stress state [90].
The vascular effects of VD were evaluated in rodent models of hypertension. Treatment with VD reduced blood pressure, whereas VD deficiency promoted the activation of the RAAS system [91] and macrophage Endoplasmic Reticulum stress. Of note, VD supplementation in obese and

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overweight patients displayed a significant reduction in urinary isoprostane, a biomarker of oxidative stress [92].
The correlation between plasma 25 (OH) D and CRP was evaluated in the Rotterdam Study, which showed that serum VD was negatively correlated with CRP [93]. In another study, it was found that VD could counteract the effects of inflammation in subjects affected by type 2 diabetes mellitus (T2DM) through several mechanisms, involving the protection from cytokine-induced beta cells apoptosis [94]. Of note, VD deficiency in obesity leads to an increase of HOMA values, an index of insulin resistance, and dyslipidemia, whereas vitamin D3 supplementation improved both insulin sensitivity and lipid profile in obese and overweight subjects [95,96]. Finally, VD supplementation in T2DM patients significantly reduced levels of inflammatory biomarker including CRP and TNF-alpha, and of leptin [97].

CLINICAL TRIALS OF VITAMIN D SUPPLEMENTATION IN OBESITY

During the last decades, clinical trials have investigated the impacts of VD supplementation in obesity. VD deficiency is a relatively common finding in obese subjects who are indicated for bariatric surgery. Surgical procedures have become the most utilized and effective treatment for obesity; however, bariatric surgery interferes with VD absorption and may lead to hypertension, insulin resistance or obesity [98,99,100]. Shaharki et al. conducted a single blinded clinical trial to assess the implications of VD supplementation prior to surgery on 100 patients referred to a bariatric surgery center for obesity in Iran. The study showed that 7-week supplementation with 50,000 units of vitamin D3 administered once a week leads to increased VD levels, potentially reducing the surgical risk [101].
The metabolic effects of VD administration in obese individuals have been evaluated in an interventional study by Safarpour et.al. In this study, 90 obese patients with T2DM and VD deficiency were designated to VD supplementation or to placebo for eight weeks. Blood levels of circulating SIRT1 [102] and Irisin [103] were significantly increased in the VD treated cohort and have shown an improvement of the insulin resistance [104]. The effectiveness of VD on SIRT1 blood levels in obese patients should be further evaluated by larger studies with a longer follow-up since other clinical trials fail to show this [105].
Moreover, the VD supplementation in an obese/overweight population of African Americans showed a significant effect on the levels of long-chain ceramides [106] which are known to affect sphingolipids metabolism, whose role in inflammatory diseases as well as in cancer have been described [107].
Vitamin D level corrections may also have an impact on obesity-related insulin resistance and cardiovascular diseases. This is highlighted by a clinical study conducted on 225 overweight or obese adolescents with vitamin D deficiency. Subjects were divided into 3 groups receiving vitamin D supplements at different dosages for 6 months. Vitamin D administration did not show a significant benefit in many vascular indices such as arterial stiffness or endothelial function, however, demonstrated an improvement in insulin resistance and decreased blood pressure, suggesting a beneficial role for its use in obese subjects who are prone to cardiovascular events [108]. Since the metabolic syndrome is frequently correlated to obesity, the clinical utilities of VD administration were also studied in this context. Indeed, vitamin D administration through a national Vitamin D project significantly reduced metabolic syndrome among a large population of Saudi Arabian adolescents, leading to the suggestion of introducing fortified foods to enhance the vitamin D levels in the whole Saudi Arabia population, where VD deficiency is relatively common due to a lack of sun exposure [109]. In a recent trial with vitamin D administration in

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overweight/obese Asian Indian women, with a condition of pre-diabetes and vitamin D-deficiency, a relevant reduction in fasting blood glucose was shown, as well as glycated hemoglobin (HbA1c) parameters, and subcutaneous fat the thoracic and abdominal region [110-112]. Recently, in a blinded, randomized controlled trial including 306 obesity subjects, the group having been casually assigned to receive fortified low-fat yogurt, contained 1500 IU Nano encapsulated vitamin D_3 per 150 g/d, presented an improvement of metabolic parameters and insulin resistance index compared to placebo [113]. The treatment with cholecalciferol in combination with a weight loss plan considerably resulted in improvements of insulin sensitivity in healthy participants with obesity meaning that this approach could be useful in the management of the obesity-associated insulin resistance [114,115].

CONCLUSION

Despite the evidence of detrimental effects of VD deficiency in obesity, the clinical impact of VD supplementation is still controversial due to conflicting results reported by clinical studies [116,117]. Many of the studies performed so far are conducted on small study populations and this may effect on the strength of the results that can sometimes fail in reaching statistical significance. Moreover, the follow-up of the patients from these studies are carried on for short periods, usually for a few weeks, or for a maximum of a few months, which may not be enough to capture more permanent metabolic modifications introduced by a long-term supplementation of vitamin D. Various studies are needed to better elucidate the actual role of VD deficiency in the development of the obesity and related vascular complications, and to clarify the effect of VD supplementation. Currently, weight loss treatment represents the only strategy to lead to an improvement of VD insufficiency and to prevent the insulin resistance onset, dyslipidemia and hypertension associated to the obesity-related metabolic syndrome. Taken together, vitamin D supplementation could be a beneficial therapeutic strategy to improve VD deficiency in obese subjects as well as in patients undergoing bariatric surgery in the post-operative window or in individuals with VD insufficiency after a weight loss program. More studies are required to better elucidate the possible role of VD deficiency in the development of the obesity and its vascular complications, and to clarify the effect of VD supplementation.

Name	Clinical practice	Abbreviation	Function
7-dehydrocholestrol	Pro-vitamin D_3	7DHC	Membrane lipid molecule
Cholecalciferol	Pre-vitamin D_3		Inactive form of vitamin D_3
Ergocalciferol	Pre-vitamin D_2		Vitamin D_2
Calcidiol	25-hydroxyvitamin D	25(OH)D	vitamin D status in the body
Calcitriol	1,25-Dihydroxyvitamin D	1,25(OH)D_2	Active form of vitamin D

Table1. Vitamin D precursors and metabolites.

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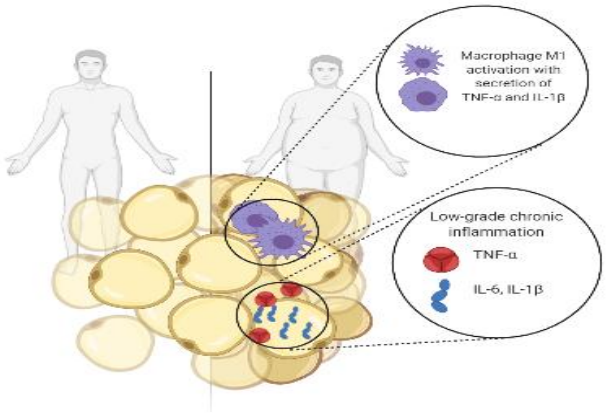

Figure 1. Adipose tissue inflammatory network in obese patients

Adipose tissue in obese undergoes a state of chronic low-grade inflammation. This is due to a complex cytokines network that promotes a pro-inflammatory environment. Cytokines involved are TNF-α, IL-1β and IL-6. The effect on the reshaping of the cellular signaling network is also responsible for the migration of macrophages and their polarization towards the pro-inflammatory M1 phenotype. Picture created with Biorender.com.

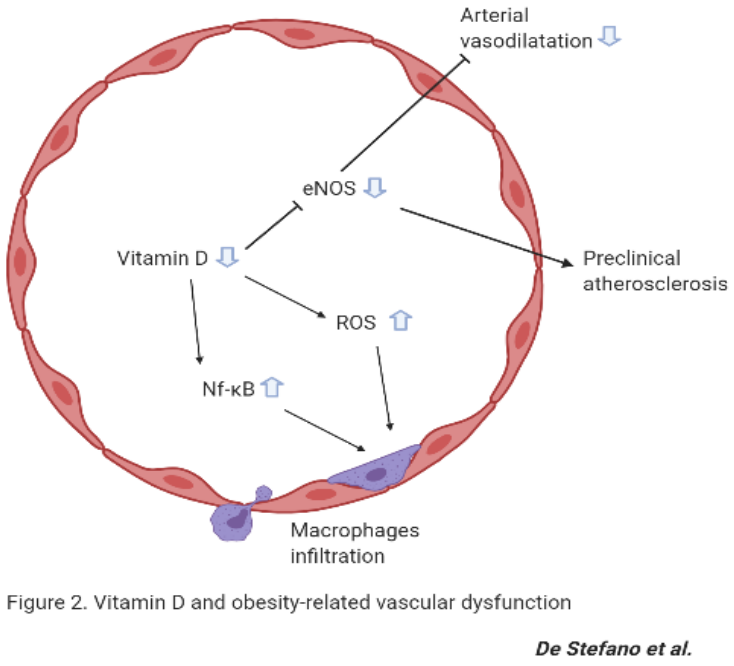

Figure 2. Vitamin D and obesity-related vascular dysfunctions

Low levels of VD in obese subjects have a direct impact on endothelial function and correlate with the insurgence of cardiovascular events in this population. Reduced VD impairs the activity of endothelial nitric oxide synthetase (eNOS) therefore reducing nitric oxide production

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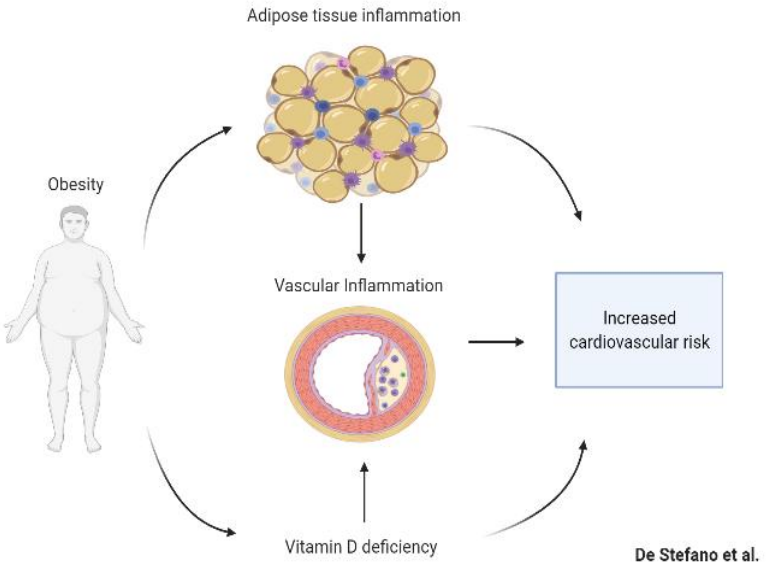
impairing endothelial relaxation and promoting the insurgence of vascular dysfunction. eNOS reduction also promotes the insurgence of pre-clinical atherosclerosis. Moreover, VD reduction does not counteract reactive oxidative species (ROS) production, and induces the pro-inflammatory pathway mediated by the activation of the transcription factor Nf-κB. ROS accumulation and Nf-κB activation synergistically promote macrophages infiltration and M1 polarization. Picture created with Biorender.com.

Graphical abstract



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REFERENCES

1. Holick, M.F.; Vitamin D deficiency. N Engl J Med 2007, 357, 266-281.
2. Candi, E.; Tesauro, M.; Cardillo, C.; Lena, A.M.; Schinzari, F.; Rodia, G.: Sica, G.; Gentileschi,P.; Rovella, V.; Annicchiarico-Petruzzelli, M.; et al. Metabolic profiling of visceral adipose tissue from obese subjects with or without metabolic syndrome. Biochem J 2018,15,1019-1035.
3. Piro, M.C.; Tesauro, M.; Lena, A.M.; Gentileschi, P., Sica, G.; Rodia, G.; Annicchiarico-Petruzzelli, M.; Rovella, V.; Cardillo, C.; Melino, G. et al. Free-amino acid metabolic profiling of visceral adipose tissue from obese subjects. Amino Acids 2020,52,1125–1137.
4. Formica, V.; Luccchett,i J.; Cunningham, D.; Smyth, E.C.; Ferroni, P.; Nardecchia, A.; Tesauro, M.; Cereda, V.; Guadagni, F.; Roselli, M. Systemic inflammation, as measured

by the neutrophil/lymphocyte ratio, may have differential prognostic impact before and during treatment with fluorouracil, irinotecan and bevacizumab in metastatic colorectal cancer patients. Med Oncol 2014, 31,166.

5. Mammi C, Pastore D, Lombardo MF, Ferrelli F, Caprio M, Consoli C, Tesauro, M.; Gatta, L.; Fini, M.; Federici, M., et al. Sildenafil Reduces Insulin-Resistance in Human Endothelial Cells. PLoS ONE 2011,6,e14542
6. Biancone, L.; Onali, S.; Calabrese, E.; Petruzziello, C.; Zorzi, F.; Condino, G.; Sica G.S.; Pallone, F. Non-invasive techniques for assessing postoperative recurrence in Crohn's disease, Dig Liver Dis 2008, 40,S265-S270,
7. Bellia, A.; Rizza, S.; Galli, A.; Fabiano, R.; Donadel, G.; Lombardo, M.F.; Cardillo, C.; Sbraccia, P.; Tesauro, M.; Lauro, D. Early vascular and metabolic effects of rosuvastatin compared with simvastatin in patients with type 2 diabetes. Atherosclerosis 2010, 210, 199-201.
8. Forouhi, N.G.; Luan, J.; Cooper, A.; Boucher, B.J.; Wareham, N.J. Baseline serum 25-hydroxy vitamin d is predictive of future glycemic status and insulin resistance: the Medical Research Council Ely Prospective Study 1990-2000.Diabetes. 2008,57,2619-2625.
9. Lappe, J.M.; Travers-Gustafson, D.; Davies, K.M.; Recker, R.R.; Neaney, R.P. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Clin Nutr 2007 ,85,1586-1591
10. Arunabh, S.; Pollack, S.; Yeh, J.; Aloia, J.F. Body fat content and 25-hydroxyvitamin D levels in healthy women. J Clin Endocrinol Metab 2003, 88, 157-161.
11. Alemzadeh, R.; Kichler, J.; Babar, G.; Calhoun, M. Hypovitaminosis D in obese children and adolescents: relationships with adiposity, insulin sensitivity, ethnicity and season. Metabolism 2008, 57,183-191
12. Botella-Carretero, J.I.; Alvarez-Blasco, F.; Villafruela, J.J.; Balsa, JA, Vazquez, C.; EscobarMorreale, H.F. Vitamin D deficiency is associated with the metabolic syndrome in morbidly obesity. Clin Nutr, 2007 26,573-580.
13. Ernst, B.; Thurnheer, M.; Schmid, S.M.; Wilms, B.; Schultes, B. Seasonal variation in the deficiency of 25-hydroxyvitamin D3 in mildly to extremely obese subjects. Obes Surg 2009, 19, 180-183.
14. Snijder, M.B.; Vab Dam, R.M.; Visser, M.; Deeg, D.J.; Dekker, J.M.; Bouter, L.M.; Seideli, J.M.; Lips, P. Adiposity in relation to vitamin D status and parathyroid hormone levels: a population based study in older men and women. J Clin Endocrinol Metab 2005, 90, 4119-4123.
15 Rueda, S.; Fernandez-Fernandez, C.; Romero, F.; Martinez de Osab ,J.; Vidal, J. Vitamin D, PTH, and the metabolic syndrome in severly obese subjects. Obes Surg 2008 ,18, 151-154.
16. Bolland, M.J.; Grey, A.B.; Ames, R.W.; Mason, B.H.; Horne, A.M.; Gamble, G.D.; and Reid, I.R. The effect of seasonal variation of 25-hydroxyvitamin D and fat mass on a diagnosis of vitamin D sufficiency. An J Clin Nutr 2007,86, 959-964.
17 Bluma, M.; Dolnikowski, G.; Seyoum, E.; Harris, S.S.; Booth, S.L.; Peterson, J.; Saltzman, E.; Dawson-Hughes, B. Vitamin D3 in fat tissue. Endocr 2008,33,90-94.
18. Blum, M.; Dallal, G.E.; Dawsonj-Hughes, B. Body size and serum 25 hydroxyvitamin D response to oral supplements in healthy older aduls. J Am Coll Nutr 2008, 27,274-279.

19. Lee, P.; Greenfield, J.R.; Seibel, M.J.; Eisman, J.A.; Center J.R. Adequacy of vitamin D replacement in severe deficiency is dependent on body mass index. Am J Med 2009, 122,1056-1060
20. Forsythe, L.K.; Livingstone, M.B.; Barnes, M.S; Horigan, G.; McSorley, E.M.: Bonham, M.P.; Magee, P.J.; Hill, T.R.; Lucey, A.J.; Cashman, K.D.; et al. Effect of adiposity on vitamin D status and the 25-hydroxycholecalciferol response to supplementation in healthy young and older Irish adults. Br J Nutr 2011, 107, 126-134.
21. Canto-Costa, M.H.; Kunii, I.; Hauache, O.M. Body fat and cholecaciferol supplementation in elderly homebound individuals. Braz J Med Biol Res 2006, 39, 91-98
22. Nelson, M.L.; Blum, J.M.; Hollis, B.W.; Rosen, C.; Sullivan, S.S. Supplements of 20 mcr/d cholecalciferol optimized serum 25-hydroxyvitamin D concentrations in 80% of premenopausal women in winter. J Nutr 2009,139, 540-546
23. Mc Gill, A.T.; Stewart, J.M.; Lithander, F.; Poppit, C.; Poppit, S.D. Relationships of low serum vitamin D3 with anthropometry and markers of the metabolic syndrome and diabetes in overweight obesity. Nutr J 2008, 7, 1-5.
24. Tesauro, M.; Schinzari, F.; Rovella, V.; Melina, D.; Mores, N.; Barini, A.; Mettimano, M.; Lauro, D.; Iantorno, M.; Quon, M.J. Tumor necrosis factor-alpha antagonism improves vasodilation during hyperinsulinemia in metabolic syndrome. Diabetes Care 2008, 31,1439-1441.
25. Chiu, K.C; Chu, A.; Go, V.L.; Saad, M.F. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. Am J Clin Nutr 2004, 79, 820–825.
26. Liu, S.; Song, Y.; Ford, E.S.; Manson, J.E.; Buring, J.E.; Ridker, P.M. Dietary calcium, vitamin D, and the prevalence of metabolic syndrome in middle aged and older US women. Diabetes Care 2005,28,2926–2932
27. Salekzamani, S.; Neyestani, T.R.; Alavi-Majd, H.; Houshiarrad, A.; Kalayi, A.; Shariatzadeh, N.; Gharavi, A. Is vitamin D status a determining factor for metabolic syndrome? A case-control study. Diabetes Metab Syndr Obes 2011,4,205-212.
28. Kayaniyil, S.; Retnakaran, R.; Harris, S.B.; Vieth, R.; Knight, J.A.; Gerstein, H.C.; Perkins, B.A.; Zinman, B.; Hanley, A.J. Prospective associations of vitamin D with β-cell function and glycemia: the Prospective Metabolism and Islet cell Evaluation (PROMISE) cohort study. Diabetes 2011, 60,2947-2953.
29. Kohrt, W.M. Abdominal obesity and associated cardiovascular comorbilities in the elderly. Coron Artery Dis 1998,9,489-494.
30. Bonora, E.; Del Prato, S.; Bonadonna, R.C.; Total body fat content and fat topography are associated differently with in vivo glucose metabolism in non-obese and obese non-diabetic woman. Diabetes 1992,41,1151-1159.
31. Patel, P., Abate, N. Body fat distribution and insulin resistance. Nutrients 2013, 5, 2019–2027.
32. Després, J., Lemieux, I. Abdominal obesity and metabolic syndrome. Nature 2006,444, 881–887.
33. Despres, J.P.; Lemieux, I.; Bergeron, J.; Pibarot, P.; Mathieu, P.; Larose, E.; Rodes-Cabau, J.; Bertrand, O.F.; Poirier, P. Abdominal Obesity and the metabolic syndrome: contribution to global cardiometabolic risckArterosclerThrombVasc Biol 2008, 28,1039-1049.
34. Mathieu, P.; Poirier, P.; Pibarot. P.; Lemieux, I.; Despres, J.P. Visceral obesity: the link among inflammation, hypertension and cardiovascular disease. Hypertension 2009, 53,577-584.

35. Mathieu, P.; Lemieux, I.; Despres, J.P. Obesity, inflammation and cardiovascular risk. Clinical Pharmacology & Therapeutics 2010, 87, 407–416.
36. Mechanick, J.I; Youdim, A.; Jones, D.B.; Garvey, W.T.; Hurley, D.L.; McMahon, M.M.; Heinberg, L.J; Kushner, R.; Adams, T.D.; Shikora, S. American Association of Clinical Endocrinologists; Obesity Society; American Society for Metabolic & Bariatric Surgery. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient--2013 update: cosponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery. Obesity 2013,21,S1-27.
37. Piccolo, B.D.; Hall, L.M.; Stephensen, C.B.; Gertz, E.R.; Van Loan, M.D. Circulating 25-Hydroxyvitamin D Concentrations in Overweight and Obese Adults Are Explained by Sun Exposure, Skin Reflectance, and Body Composition. Curr Dev Nutr. 2019, 27,3(7)
38. Li, J.; Byrne, M.E.; Chang, E.; Jiang, Y.; Donkin, S.S.; Buhman, K.K.; Burgess, J.R.; Teegarden, D.1alpha,25-Dihydroxyvitamin D hydroxylase in adipocytes. J Steroid Biochem Mol Biol 2008,112,122-126.
39. Pereira-Santos, M.; Costa, P.R.F.; Assis, A.M.O.; Santos, C.A.; Santos, D.B,; Obesity and vitamin D deficiency: a systematic review and meta-analysis. Obesity Rev 2015,16,341-349.
40. Ernst, B.; Thurnheer, M.; Schmid, S.M.; Schultes, B. Evidence for the necessity to systematically assess micronutrient status prior to bariatric surgery. Obes Surg 2009,19,66-73.
41. Wortsman, J.; Matsuoka, L.Y.; Chen, T.C.; Lu, Z.; Holick, M.F. Decreased bioavailability of vitamin D in obesity. Am. J. Clin. Nutr 2000, 72, 690–693.
42. Walsh, J.S.; Bowles, S.; Evans, A.L. Vitamin D in obesity. Curr. Opin. Endocrinol. Diabetes Obes. 2017, 24,389–394.
43. Carrelli, A.; Bucovsky, M.; Horst, R. Vitamin D storage in adipose tissue of obese and normal weight women. J. Bone Miner. Res. 2017, 32, 237–242.
44. Wamberg, L.; Christiansen, T.; Paulsen, S.K. Expression of vitamin D-metabolizing enzymes in human adipose tissue—the effect of obesity and diet-induced weight loss. Int. J. Obes. 2013, 37, 651–657.
45. Rock, C.L.; Emond, J.A.; Flatt, S.W.; Heath, D.D.; Karanja, N.; Pakiz, B.; Sherwood, N.E.; Thomson, C.A. Weight Loss Is Associated with Increased Serum 25-Hydroxyvitamin D in Overweight or Obese Women. Obesity 2012, 20, 2296–2301.
46. Mason, C.; Xiao, L.; Imayama, I.; Duggan, C.R.; Bain, C.; Foster-Schubert, K.E.; Kong, A.; Campbell, K.L.; Wang, C.-Y.; Neuhouser, M.L.; et al. Effects of weight loss on serum vitamin D in postmenopausal women12345. Am. J. Clin. Nutr 2011, 94, 95–103.
47. Ganglo, A.; Bergeron, J.; Lemieux, I.; Després, J.-P. Changes in circulating vitamin D levels with loss of adipose tissue. Curr. Opin. Clin. Nutr. Metab. Care 2016, 19, 464–470.
48. Costa, P.R.F.; Assis, A.M.O.; Santos, C.A.S.T.; Santos, D.B.; Pereira-Santos, M.; Pereira-Santos, M.; PereiraSantos, M. Obesity and vitamin D deficiency: A systematic review and meta-analysis. Obes. Rev 2015, 16,341–349.
49. Wood, R.J. Vitamin D and adipogenesis: Newmolecular insights. Nutr. Rev 2008, 66, 40–46
50. Blumberg, J.M.; Tzameli, I.; Astapova, I.; Lam, F.S.; Flier, J.S.; Hollenberg, A.N. Complex Role of the Vitamin D Receptor and Its Ligand in Adipogenesis in 3T3-L1 Cells. J. Boil. Chem 2006, 281, 11205–11213.

51. Lee, H.; Bae, S.; Yoon, Y. Anti-adipogenic effects of 1,25-dihydroxyvitamin D3 are mediated by the maintenance of the wingless-type MMTV integration site/β-catenin pathway. Int J Mol Med 2012, 30, 1219-1224.
52. Trexler AJ, Taraska JW. Regulation of insulin exocytosis by calcium-dependent protein kinase C in beta cells. Cell Calcium 2017,67,1-10.
53. Wright, D.C.; Hucker, K.A.; Holloszy, J.O.; Han, D.H. Ca2+ and AMPK both mediate stimulation of glucose transport by muscle contractions. Diabete 2004 53,330–335.
54. Vimaleswaran, K.S.; Berry, D.J.; Lu, C.; Tikkanen, E.; Pilz, S.; Hiraki, L.T.; et al. Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomization analysis of multiple cohorts. PLoS Med 2013, 10, e1001383.
55. Drincic, A.T.; Armas, L.A.; Van Diest, E.E.; Heaney, R.P. Volumetric dilution, rather than sequestration best explains the low vitamin D status of obesity. Obesity 2012, 20,1444–1448.
56. Longo, M.; Zatterale, F.; Naderi, J.; Parrillo, L.; Formisano, P.; Raciti, G.A.; Beguinot, F.; Miele, C. Adipose Tissue Dysfunction as Determinant of Obesity-Associated Metabolic Complications. Int J Mol Sci. 2019 ,20,2358.
57 Klöting, N.; Blüher, M. Adipocyte dysfunction, inflammation and metabolic syndrome. Rev EndocrMetabDisord. 2014,15, 277–287.
58. Klöting, N.; Fasshauer, M.; Dietrich, A.; Kovacs P.; Schön M.R.; Kern, M.; Stumvoll, M.; Blüher M. Insulin-sensitive obesity. Am J Physiol Endocrinol Metab 2010, 299, E506-515.
59. Mantzoros, C.S.; Magkos, F.; Brinkoetter M.; Sienkiewicz, E.; Dardeno, T.A.; Kim, S.Y.; et al. Leptin in human physiology and pathophysiology. Am J PhysiolEndocrinolMetab 2011, 301: E567–584.
60. Sundari, L. P. R.;, Bakta, M.; Astawa, N.M.; Adiatmika, P. G.; Arijana, G. K. N.; Tunas, K. The Effect of Vitamin D Administration on Leptin, Adiponectin and mRNA MCP-1 Levels in Adipose Tissue of Obese Female Wistar Rats. Curr Res Nutr Food Sci 2020, 8, 541-549.
61. Burhans, M.S.; Hagman, D.K.; Kuzma, J.N.; Schmidt, K.A.; Kratz, M. Contribution of Adipose Tissue Inflammation to the Development of Type 2 Diabetes Mellitus. Compr Physiol. 2018,9,1-58.
62. Arango Duque, G.; Descoteaux, A. Macrophage cytokines: involvement in immunity and infectious diseases. Front Immunol 2014,5,1-12.
63 Patel, P.S.; Buras, E.D.; Balasubramanyam, A. The role of the immune system in obesity and insulin resistance. J Obes 2013,2013,1-9.
64. Zakharova, I.; Klimov, L.; Kuryaninova, V.; Nikitina, I.; Malyavskaya, S.; Dolbnya, S.; Kasyanova A.; Atanesyan, R.; Stoyan, M.; Todieva, A. Vitamin D Insufficiency in Overweight and Obese Children and Adolescents. Front Endocrinol (Lausanne) 2019 10, 1-13.
65. Gil, Á.; Plaza-Diaz, J.; Mesa, M.D.; Vitamin D: Classic and Novel Actions. Ann NutrMetab 2018, 72,87-95.
66. Abbas, M.A. Physiological functions of Vitamin D in adipose tissue. J Steroid BiochemMol Biol 2017 165,369–381.
68. Roy, P.; Nadeau, M.; Valle, M.; Bellmann, K.; Marette, A.; Tchernof, A.; et al. Vitamin D reduces LPS-induced cytokine release in omental adipose tissue of women but not men. Steroids 2015 104,65–71.

69. Franzè, E.; Marafini, I.; De Simone, V.; Monteleone, I.; Caprioli, F.; Colantoni, A.; Ortenzi, A.; Crescenzi, F.; Izzo, R.; Sica, G.; et al. Interleukin-34 Induces Cc-chemokine Ligand 20 in Gut Epithelial Cells. J Crohns Colitis 2016,10,87-94.
70. Cimini, F.A.; Barchetta, I.; Carotti, S.; Bertoccini, L.; Baroni, M. G.; Vespasiani-Gentilucci, U.; Cavallo, M. G.; Morini, S. Relationship between adipose tissue dysfunction, vitamin D deficiency and the pathogenesis of non-alcoholic fatty liver disease. *Worl J Gastroenterol* 2017, *23*, 3407–3417.
71. Chen, N.; Wan Z.; Han SF.; Li BY.; Zhang ZL.; Qin, L.Q. Effect of vitamin D supplementation on the level of circulating high-sensitivity C-reactive protein: a meta-analysis of randomized controlled trials. Nutrients. 2014, 10, 2206-2016.
72. Mehmood, Z.H.; Papandreou, D. An Updated Mini Review of Vitamin D and Obesity: Adipogenesis and Inflammation State. Open Access Maced J Med Sci 2016,4,526-532.
73. Karkeni, E., Bonnet, L., Marcotorchino, J., Tourniaire, F., Astier, J., Ye, J., &Landrier, J. F. Vitamin D limits inflammation-linked microRNA expression in adipocytes in vitro and in vivo: A new mechanism for the regulation of inflammation by vitamin D. *Epigenetics 2018*, *13*,156–162.
74. Mutt, S.J.; Karhu, T,; Lehtonen, S,; Lehenkari, P.; Carlberg, C.; Saarnio, J.; Sebert, S.; Hyppönen, E.; Järvelin, M.R.; Herzig, K.H. Inhibition of cytokine secretion from adipocytes by 1,25-dihydroxyvitamin D_3 via the NF-κB pathway. FASEB J. 2012, 26,4400-4407.
75. Marcotorchino, J.; Gouranton, E.; Romier, B.; Tourniaire, F.; Astier, J.; Malezet, C.; Amiot, M.J.; Landrier, J.F. Vitamin D reduces the inflammatory response and restores glucose uptake in adipocytes. Mol Nutr Food Res 2012,56,1771-1782.
76. Zhu, J.; Bing, C.; Wilding, J. α,25$(OH)_2D_3$ attenuates IL-6 and IL-1β-mediated inflammatory responses in macrophage conditioned medium-stimulated human white preadipocytes by modulating p44/42 MAPK and NF-κB signaling pathways. DiabetolMetab Syndr 2019,11,9
77. Farhangi, M.A.; Mesgari-Abbasi, M.; Hajiluian, G.; Nameni, G.; Shahabi, P. Adipose tissue inflammation and oxidative stress: the ameliorative effects of vitamin D. Inflammation 2017 40, 1688–1697.
78. Mehmood, Z.H.; Papandreou, D. An Updated Mini Review of Vitamin D and Obesity: Adipogenesis and Inflammation State. Open Access Maced J Med Sci 2016 4,526-532
79. Chait A, den Hartigh LJ. Adipose Tissue Distribution, Inflammation and Its Metabolic Consequences, Including Diabetes and Cardiovascular Disease. Front Cardiovasc Med 2020,7,1-41.
80. Campia, U.; Tesauro, M.; Di Daniele, N.; Cardillo, C. The vascular endothelin system in obesity and type 2 diabetes: pathophysiology and therapeutic implications. Life Sci 2014 118,149-155.
81. Schinzari, F.; Iantorno, M.; Campia, U.; Mores, N.; Rovella, V.; Tesauro, M.; Di Daniele, N.; Cardillo C. Vasodilator responses and endothelin-dependent vasoconstriction in metabolically healthy obesity and the metabolic syndrome. Am J Physiol Endocrinol Metab 2015, 309, E787-792.
82. De Stefano, A.; Mannucci, L.; Massoud, R.; Bernardini, S.; Cortese C. Performance characteristics of lipoprotein-associated phospholipase A2 activity assay on the Dimension Vista analyser and preliminary study of a healthy Italian population. Biochem Med (Zagreb) 2017,27,1-10

83. Ni, W.; Watts, S.W.; Ng, M., Chen, S.; Glenn, D.J.; Gardner, D.G. Elimination of vitamin D receptor in vascular endothelial cells alters vascular function. Hypertension 2014,64,1290-1298.
84. Hashemi, S.M.; Mokhtari, S.M.; Sadeghi, M.; Foroozan, R.; Safari, M. Effect of vitamin D therapy on endothelial function in ischemic heart disease female patients with vitamin D deficiency or insufficiency: A primary report. ARYA Atheroscler 2015,11,54-59.
85. Kim, D.H.; Meza, C.A.; Clarke, H.; Kim, J.S.; Hickner, R.C. Vitamin D and Endothelial Function. Nutrients 2020,12,3-17.
86. Beveridge, L.A.; Khan, F.; Struthers, A.D.; Armitage, J.; Barchetta, I., Bressendorff, I., Cavallo, M.G., Clarke, R.; Dalan, R.; Dreyer, G.; et al. Effect of Vitamin D Supplementation on Markers of Vascular Function: A Systematic Review and Individual Participant Meta-Analysis. J Am Heart Assoc 2018, 7,1-20.
87. Mahmoud, A.M.; Szczurek, M.; Hassan, C.; Masrur, M.; Gangemi, A.; Phillips, S.A. Vitamin D Improves Nitric Oxide-Dependent Vasodilation in Adipose Tissue Arterioles from Bariatric Surgery Patients. Nutrients 2019,11,1-19.
88. Pelham, C.J; Drews, E.M.; Agrawal, D.K. Vitamin D controls resistance artery function through regulation of perivascular adipose tissue hypoxia and inflammation. J Mol Cell Cardiol 2016,98,1-10.
89. Ionica M, Aburel OM, Vaduva A, Petrus A, Rațiu S, Olariu S, Sturza A, Muntean DM. Vitamin D alleviates oxidative stress in adipose tissue and mesenteric vessels from obese patients with subclinical inflammation. Can J PhysiolPharmacol 2020,98,85-92.
90. Paschou, S.A.; Kosmopoulos, M.; Nikas, I.P.; Spartalis, M.; Kassi, E.; Goulis, D.G. Lambrinoudaki I, Siasos G. The Impact of Obesity on the Association between Vitamin D Deficiency and Cardiovascular Disease. Nutrients 2019, 11, 1-11.
91. Schinzari, F.; Tesauro, M.; Veneziani, A.; Mores, N.; Di Daniele, N.; Cardillo, C. Favorable Vascular Actions of Angiotensin-(1-7) in Human Obesity. Hypertension 2018,71,185-191.
92. Javanbakht, M.H.; Mohammady, H.; Fooladsaz, K.; Razzaghi, M.; Zarei, M.; Djalali, M. Are Serum Levels of F2-Isoprostane and Oxidized-LDL Related to Vitamin D Status in Type 2 Diabetic Patients? A Case-Control Study. Rep Biochem Mol Biol 2016,5,26-32.
93. Martins, D.; Meng, Y.X.; Tareen, N.; Artaza, J.; Lee, J.E.; Farodolu, C.; Gibbons, G.; Norris, K. The Effect of ShortTerm Vitamin D Supplementation on the Inflammatory and Oxidative Mediators of Arterial Stiffness. Health 2014 6,1503-1511.
94. Liefaard, M.C.; Ligthart, S.; Vitezova, A.; Hofman, A.; Uitterlinden, A.G.; Kiefte-de Jong, JC.; Franco, O.H.; Zillikens, M.C.; Dehghan, A. Vitamin D and C-Reactive Protein: A Mendelian Randomization Study. PLoS One 2015,10, e0131740.
95. Imga, N.N.; Karci, A.C.; Oztas, D.; Berker, D.; Guler, S. Effects of vitamin D supplementation on insulin resistance and dyslipidemia in overweight and obese premenopausal women. Arch Med Sci 2019 15,598-606.
96. Zakharova I, Klimov L, Kuryaninova V, Nikitina I, Malyavskaya S, Dolbnya S, Kasyanova A, Atanesyan R, Stoyan M, Todieva A.; et al. Vitamin D Insufficiency in Overweight and Obese Children and Adolescents. Front Endocrinol (Lausanne) 2019,10,1-13.
97. Mousa A, Naderpoor N, Teede H, Scragg R, de Courten B. Vitamin D supplementation for improvement of chronic low-grade inflammation in patients with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Nutr Rev 2018,76,380-394.

98. Ding, L.; Fan, Y.; Li, H.; Zhang, Y.; Qi, D.; Tang, S.; Cui, J.; He, Q.; Zhuo, C.; Liu, M. Comparative Effectiveness of Bariatric Surgeries in Patients with Obesity and Type 2 Diabetes Mellitus: A Network Meta-Analysis of Randomized Controlled Trials. Obesity reviews : an official journal of the International Association for the Study of Obesity 2020, 21, 1-10.
99. Samson, R.; Ayinapudi, K.; le Jemtel, T. H.; Oparil, S. Obesity, Hypertension, and Bariatric Surgery. Current hypertension reports 2020, 22.
100 O'Kane, M.; Parretti, H. M.; Pinkney, J.; Welbourn, R.; Hughes, C. A.; Mok, J.; Walker, N.; Thomas, D.; Devin, J.; Coulman, K. British Obesity and Metabolic Surgery Society Guidelines on Perioperative and Postoperative Biochemical Monitoring and Micronutrient Replacement for Patients Undergoing Bariatric Surgery-2020 Update. Obesity reviews : an official journal of the International Association for the Study of Obesity 2020, 21, 1-23.
101. Sayadi Shahraki, M.; Khalili, N.; Yousefvand, S.; Sheikhbahaei, E.; Shahabi Shahmiri, S. Severe Obesity and Vitamin D Deficiency Treatment Options before Bariatric Surgery: A Randomized Clinical Trial. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery 2019, 15, 1604–1611.
102. Kosgei, V. J.; Coelho, D.; Guéant-Rodriguez, R.-M.; Guéant, J.-L. Sirt1-PPARS Cross-Talk in Complex Metabolic Diseases and Inherited Disorders of the One Carbon Metabolism. Cells 2020, 9.
103. Arhire, L. I.; Mihalache, L.; Covasa, M. Irisin: A Hope in Understanding and Managing Obesity and Metabolic Syndrome. Frontiers in endocrinology 2019, 10, 1-10.
104. Safarpour, P.; Daneshi-Maskooni, M.; Vafa, M.; Nourbakhsh, M.; Janani, L.; Maddah, M.; Amiri, F.-S.; Mohammadi, F.; Sadeghi, H. Vitamin D Supplementation Improves SIRT1, Irisin, and Glucose Indices in Overweight or Obese Type 2 Diabetic Patients: A Double-Blind Randomized Placebo-Controlled Clinical Trial. BMC family practice 2020, 21,2-10.
105. Aliashrafi, S.; Arefhosseini, S. R.-; Lotfi-Dizaji, L.; Ebrahimi-Mameghani, M. Effect of Vitamin D Supplementation in Combination with Weight Loss Diet on Lipid Profile and Sirtuin 1 in Obese Subjects with Vitamin D Deficiency: A Double Blind Randomized Clinical Trial. Health promotion perspectives 2019, 9, 263-269.
106. Chen, L.; Dong, Y.; Bhagatwala, J.; Raed, A.; Huang, Y.; Zhu, H. Vitamin D3 Supplementation Increases Long-Chain Ceramide Levels in Overweight/Obese African Americans: A Post-Hoc Analysis of a Randomized Controlled Trial. Nutrients 2020, 12,2-9.
107. Guitton, J.; Bandet, C. L.; Mariko, M. L.; Tan-Chen, S.; Bourron, O.; Benomar, Y.; Hajduch, E.; le Stunff, H. Sphingosine-1-Phosphate Metabolism in the Regulation of Obesity/Type 2 Diabetes. Cells 2020, 9,1-19.
108. Rajakumar, K.; Moore, C. G.; Khalid, A. T.; Vallejo, A. N.; Virji, M. A.; Holick, M. F.; Greenspan, S. L.; Arslanian, S.; Reis, S. E. 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 2020, 111, 757–768.
109. Al-Daghri, N. M.; Amer, O. E.; Khattak, M. N. K.; Sabico, S.; Ghouse Ahmed Ansari, M.; Al-Saleh, Y.; Aljohani, N.; Alfawaz, H.; Alokail, M. S. Effects of Different Vitamin D Supplementation Strategies in Reversing Metabolic Syndrome and Its Component Risk

Factors in Adolescents. The Journal of steroid biochemistry and molecular biology 2019, 191, 105378.

110. Bhatt, S.P.; Misra, A.; Pandey, R.M.; *et al.* Vitamin D Supplementation in Overweight/obese Asian Indian Women with Prediabetes Reduces Glycemic Measures and Truncal Subcutaneous Fat: A 78 Weeks Randomized Placebo-Controlled Trial (*PREVENT-WIN* Trial). *Sci Rep* 2020, 10, 220
111. Sica, G.S., Djapardy, V., Westaby, S., Maynard, N.D. Diagnosis and management of aortoesophageal fistula caused by a foreign body. Annals of Thoracic Surgery Volume 77, Issue 6, June 2004, Pages 2217-2218 ISSN: 00034975 DOI: 10.1016/j.athoracsur.2003.06.031 PubMed ID: 15172312
112. Sica, G.S., Iaculli, E., Biancone, L., di Carlo, S., Scaramuzzo, R., Fiorani, C., Gentileschi, P., Gaspari, A.L. Comparative study of laparoscopic vs open gastrectomy in gastric cancer management .World Journal of Gastroenterology Volume 17, Issue 41, 7 November 2011, Pages 4602-4606. ISSN: 10079327 DOI: 10.3748/wjg.v17.i41.4602 PubMed ID: 22147966
113. Sharifan, P.; Ziaee, A.; Darroudi, S.; Rezaie, M.; Safarian, M.; Eslami. S.; Khadem-Rezaiyan, M.; Tayefi, M.; Mohammadi, M.; Ghazizadeh H, Khorasanchi, Z.;. et al. Effect of low-fat dairy products fortified with 1500IU nano encapsulated vitamin D_3 on cardiometabolic indicators in adults with abdominal obesity: A total blinded randomized controlled trial. Curr Med Res Opin. 2021,12,1
114. EuroSurg Collaborative. EuroSurg: a new European student-driven research network in surgery. Colorectal Dis. 2016 Feb;18(2):214-5. doi:10.1111/codi.13260. PubMed PMID: 26748779.
115. Simone Sibio, A. Di Giorgio, S. D'Ugo,G. Palmieri, L. Cinelli, V. Formica, B. Sensi, G. Bagaglini, S. Di Carlo, V. Bellato, G. S. Sica. Histotype influences emergency presentation and prognosis in colon cancer surgery. Langenbeck's Archives of Surgery (2019) 404:841–851 https://doi.org/10.1007/s00423-019-01826-6
116. Cefalo, C.M.A.; Conte, C.; Sorice, GP.; Moffa, S.; Sun, V.A.; Cinti, F.; Salomone, E.; Muscogiuri, G.; et al. Effect of Vitamin D Supplementation on Obesity-Induced Insulin Resistance: A Double-Blind, Randomized, Placebo-Controlled Trial. Obesity 2018, 26,651-657
117. Palaniswamy, S.; Gill, D.; de Silva, N. M.; Lowry, E.; Jokelainen, J.; Karhu, T.; Mutt, S. J.; Dehghan, A.; Sliz, E.; Chasman, D. I.; Timonen, M.; Viinamäki, H.; Keinänen-Kiukaanniemi, S.; Hyppönen, E.; Herzig, K.-H.; Sebert, S.; Järvelin, M.-R. Could Vitamin D Reduce Obesity-Associated Inflammation? Observational and Mendelian Randomization Study. The American journal of clinical nutrition 2020,111, 1036–1047.