Cardiovascular Disease & Vitamin D

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***Abstract*— Vitamin D is an essential nutrient that is involved in many physiological functions of the human body, such as immunological function, bone health, calcium metabolism, and cell growth and differentiation. Although exposure to sunlight is the primary source, some foods and supplements can also provide it. Heart disease, stroke, and other cardiovascular illnesses (CVDs) may be at risk due to vitamin D deficiency (VDD). Low blood vitamin D levels have been associated with a higher risk of CVD development. It is unclear, nevertheless, if vitamin D levels are the primary cause or effect of these disorders. More study is needed to fully understand the relationship between vitamin D and cardiovascular health, even though some studies suggest that taking vitamin D supplements may lower the risk of CVD. Our goal in this study was to compile the data that is now available to support the link between vitamin D and cardiovascular diseases and anesthetic considerations.**

***Index Terms*— vitamin D insufficiency, cardiovascular disorders, supplementation, and anesthetic concerns**

I. BACKGROUND INFORMATION AND INTRODUCTION

One of the fat-soluble vitamins that is essential to several bodily physiological functions is vitamin D (VD)(1). By encouraging the absorption of calcium and phosphorus from the diet, which are critical for bone growth and development, it is best known for its function in preserving bone health(2). In addition, VD plays a role in the regulation of the immune system, the development and differentiation of cells, the function of muscles, and cardiovascular health(3). VD can be obtained from specific foods and supplements and is created in the skin as a result of sun exposure(4). Ergocalciferol (D2) and cholecalciferol (D3) are the two main forms of VD(5). While vitamin D3 is created in the skin in reaction to sunshine and is found in animal-based sources like egg yolks and fatty fish, vitamin D2 is mostly found in plant-based sources like mushrooms(6). VD deficiency (VDD) is uncommon in healthy people who get enough sun exposure and eat a balanced diet, but it can happen to those who don't get enough sunshine, have darker skin, or have certain medical conditions that impact how VD is metabolized(7). VDD is associated with an increased risk of a number of illnesses, such as cardiovascular disease (CVD), autoimmune diseases, and bone abnormalities(8). Therefore, it is crucial that people maintain adequate levels of vitamin D through the consumption of a varied and balanced diet, moderate sun exposure, and, in certain situations, VD supplements(9). However, consuming too much VD before beginning any supplement can have negative health implications(10). Recently, there has been an increase in interest in the potential contribution of VD to CVD prevention(11)

II. REVIEW

VD metabolism and physiology

Following ingestion, VD is converted into chylomicrons, which are subsequently taken up by the lymphatic system and released into the bloodstream(12). Vitamin D2 binds to albumin and a VD-binding protein (VDBP) during digestion(13). After being transported to the liver, vitamin-D-25-hydroxylase converts VD into 25(OH)D(14). It is converted into 1,25(OH)2D in the kidney by 25-hydroxyvitamin D-1α(15). After dissociating from VDBP in the blood, 1,25(OH)2D attaches to the intracellular nuclear VD receptor (VDR) to perform a number of physiological actions while preserving its own levels(16). In the epidermis, keratinocytes express 25-hydroxylase (CYP27A1), 1,25-hydroxycholecalciferol, and 1α-hydroxylase (CYP27B1), despite the fact that 1,25-hydroxycholecalciferol and 25-hydroxycholecalciferol are mostly generated in the kidneys and liver, respectively(1). However, because the skin is the target tissue, the skin's capacity to synthesis 1,25(OH)2 D3 is uncommon(2). Consequently, VD promotes keratinocyte

differentiation through its intricate relationship with calcium(3). VDR is present in every cell in the human body, although its concentrations are highest in cells involved in calcium homeostasis(4) . Additionally, a number of cells carry out the 25(OH)D1 alpha-hydroxylase activity (CYP27B1), which permits the kidneys to eliminate 1,25(OH)2D(5). Certain factors, such as the stage of cell growth and provocative signaling molecules, influence the enzyme in various tissues(6). Additionally, 1,25(OH)2D can be broken down by the extra-renal tissues(7). Via both genomic and nongenomic mechanisms, 1,25(OH)2D's activation of VDR results in significant physiologic activations within these organs(8). It is well known that VD has strong immunomodulatory properties and strengthens the immune system(8). The cardiovascular system contains many of the components linked to VD, indicating that it is important for cardiovascular health(9). VD's extraskeletal functions are currently being assessed as potential targets to reduce the risk of death, autoimmune and other illnesses, neurocognitive impairment, and cancer. Still, more investigation is needed(10).

The recommended dietary allowances for vitamin D based on bone health (which covers the needs of 97.5% of the population) are 600 IU/d for people aged 1 to 70 and 800 IU/d for people over 70(11). This corresponds to a serum 25-hydroxyvitamin D level of 20 ng/mL or higher (≥50 nmol/L) under conditions of minimal sun exposure(12).

VD examination

The commonly recognized biological indicator of VD status is the plasma/serum level of 25(OH)D(13). Among a number of different metabolites, 25(OH)D has the longest half-life, ranging from two to three weeks, and indicates proper dietary VD status(14). 1,25(OH)2D has a half-life of only four hours, whereas vitamin D3 (cholecalciferol) has a half-life of twenty-four hours(15). While a negligible proportion is not bound (0.2% to 0.6% of 1,25(OH)2D and 0.02% to 0.05% of 25(OH)D), the enhanced percentage of 1,25(OH)2D and 25(OH)D bound to VDBP in circulation is 80% to 90%, while it is 10% to 20% for albumin(16). Two official reports from the US Endocrine Society and the Institute of Medicine state that there is no consensus regarding the optimal amounts of 25(OH)D(1). According to US Endocrine Society standards, a concentration of 25(OH)D above 30 ng/mL is appropriate, but the Institute of Medicine provides a cut-off value of 20 ng/mL(2). Serum 25(OH)D is tested using a variety of methods. Since liquid chromatography-tandem mass spectrometry can differentiate between 25(OH)D2 and 25(OH)D3, it is the gold standard(3). In addition to the enzyme-linked immunosorbent assay, two methods are widely used: radioimmunoassay and chemiluminescence(4). 400–1,000 IU per day is the recommended dietary intake(5). Due to its negligible affinity for VDBP, vitamin D2 (ergocalciferol) is the assumed dietary measure, as opposed to vitamin D3 (cholecalciferol)(6). Consequently, supplementation does not result in increased blood levels of VD serum(7)

III. THE CARDIOVASCULAR SYSTEM AND VD

VD's direct impacts on the cardiovascular system or its classic and developing cardiovascular risk variables can be used to quantify its effects on cardiovascular health(8). The VDR is expressed by fibroblasts, vascular endothelial and smooth muscle cells, and cardiomyocytes(9). These cells also contain 1α-hydroxylase, which aids in the synthesis of the active form of VD(10). Experimental models have shown that VD has a variety of cardiovascular effects, including antihypertrophic qualities, inhibition of cardiomyocyte proliferation, stimulation of smooth muscle cell proliferation, expression of endothelial growth factor, and inhibition of the renin-angiotensin-aldosterone system and natriuretic peptide emission(11). Angiotensin I expression and local angiotensin II production in the myocardium, kidney tissue, and renal arteries can be directly inhibited by activating VDR with calcitriol or its analogs(12). Additionally, it has been discovered that VD increases the production of angiotensin-converting enzyme-2, the enzyme responsible for converting angiotensin II into angiotensins 1–7(13). The antihypertensive, antifibrotic, and anti-inflammatory properties of angiotensin 1–7 are thereby enhanced as it further counteracts the high level of angiotensin II(14). Lastly, the immune cells that need VDR can directly affect the emissions of miR-106b-5p(15). By influencing juxtaglomerular cells, this may increase renin production, suggesting that inflammation plays a significant role in renin-driven hypertension(16). Furthermore, certain metalloproteinases and

metalloproteinase inhibitors that promote the development of heart failure are expressed in a manner that is regulated by VD(1). In addition to its direct effects, VD may also indirectly affect the cardiovascular system by influencing cardiovascular risk factors(2). Dyslipidemia, Type 2 Diabetes Mellitus, and hypertension are all linked to a VD deficit(3). Lastly, there is mounting evidence that it has anti-inflammatory properties by increasing interleukin-10 and inhibiting the activation of nuclear factor kappa B and tumor necrosis factor-alpha, all of which are known to be important causes of CVD(4). All things considered, these findings strongly suggest that VD plays a role in the onset and progression of CVD as well as its potential impact on both immediate and long-term cardiovascular outcomes(5)

IV. ATHEROSCLEROSIS

Hereditary and environmental factors interact to cause atherosclerosis(6). Elevated blood levels of low-density lipoproteins (LDLs) and hypertension are the most prevalent factors that promote the development of atherosclerosis(7). Numerous studies currently show a link between VD and the development of atherosclerotic plaque, most likely due to immune response regulation(8). The expression of VDR, CYP27B1, and CYP27A1 hydroxylases in immune cells provides insight into these connections(9). The latter is associated with VD activation and is a paracrine/autocrine modulator of atherosclerotic plaque pathobiology(10). Immune cells including dendritic cells and macrophages are impacted by active VD(11). Particularly, VD causes monocytes to change into macrophages, which leads to cellular commitment to the M1 phenotype(12). The production of immunosuppressive cytokines, including prostaglandin E2, and the inhibition of Toll-like receptor (TLR) expression, including TLR2, TLR4, and TLR9, are attributed to the M1 phenotype(13). The manufacturing of pro-inflammatory cytokines is decreased as a result of the downregulation of class II major histocompatibility complex antigens at the cell surface(14).

VD regulates adaptive immune cells, particularly B lymphocytes, preventing them from proliferating, developing into plasma cells, and producing immunoglobulins(15). When it comes to T cells, VD promotes the immunomodulatory functions of Th2, Treg, and Tr1 while suppressing the pro-inflammatory responses that are reliant on Th1 and Th17(16). Furthermore, a study found that in diabetics, the interplay between VD and VDR signaling can reduce the expression of scavenger receptors on the surface of macrophages(1). By preventing LDL cholesterol from building up in foam cells, this process can reduce the risk of vascular atherosclerosis(2). By suppressing the expression of the nuclear factor kappa-light-chain-enhancer of the activated B cells (NF-κB) gene, VDR activation also initiates an anti-atherosclerotic mechanism(3). Interleukin-6 and other pro-inflammatory and prothrombogenic cytokines are downregulated as a result, while thrombomodulin and interleukin-10 are upregulated(4). This alteration of endothelial function prevents the development of atherosclerotic plaques and suppresses vascular calcifications by preventing the creation of foam cells(5). By blocking kariopherin-A4 from inducing NF-κB expression, adequate intracellular concentrations of VD can suppress NF-κB expression, according to another study done on pigs(6). These paracrine/autocrine pathways' primary traits rely on their independence from systemic PTH, calcium, and 1,25-dihydroxylcalciferol levels(7). The inconsistent results from clinical trials evaluating the cardiovascular effects of VD supplementation may therefore be explained by the lack of reliance on traditional regulatory mechanisms(8). When combined, these elements support the finding that the load of atherosclerotic plaques in vivo is correlated with VDR expression(9). Significant atherosclerotic lesions were found in transgenic rats that overexpress 24-hydroxylase, which deactivates 1,25-OH VD(10). Additionally, evaluations of human atherosclerotic plaques obtained from patients undergoing endarterectomy due to carotid stenosis have been conducted(11). These experimental results demonstrated a correlation between intraplaque VDR levels and the expression of M1 phenotype macrophages(12). Low levels of VDR in the downstream regions of carotid plaques predict the likelihood of major adverse cardiovascular events (MACE), in contrast to plasma VD levels(13). Cardiometabolic dysfunction may also be influenced by VD's involvement in the control of visceral and ectopic fat deposition(14). According to the results of certain clinical trials, taking calcium and vitamin D supplements at the same time may lower the risk of

metabolic and cardiovascular disorders as well as fat deposition(15).

V. STROKE

Poststroke patients referred to rehabilitation facilities frequently suffer from malnutrition, which can affect their vitamin levels and nutritional indices(16). Strokes are therefore regarded as the leading cause of disability in the population(1). Since VDD also impacts the poststroke recovery process, its effects seem to extend beyond the risk and severity of stroke(2). Poole et al. found that 77% of the 44 individuals they looked at 30 days following their first stroke had a lower level of 25(OH)D (below 20 ng/mL)(3). Given that 25(OH)D has a biological half-life of nearly three weeks and that a significant drop in 25(OH)D would not be possible during the interval between 25(OH)D sampling and the stroke event, they hypothesized that VDD might have existed prior to stroke(4). According to Liu et al., administering VD is a novel stroke prevention method(5). A vitamin D supplement is intended to help individuals who have had a stroke or are at a higher risk of having one maintain a 25(OH)D blood level of greater than 30 mg/mL(6). It has been suggested that this supplement is a promising and protective treatment(7). The possible mechanisms connecting VDD to an increased risk of stroke were noted by Pilz et al. Low vitamin levels are linked to arterial hypertension, a major risk factor for stroke(8). The mechanism behind this condition seems to be related to the renin-angiotensin-aldosterone system, the prevention of renoprotective, anti-inflammatory, and hyperparathyroidism effects, as well as vasculoprotective qualities(9). Moreover, VDD is linked to an increased risk of type 2 diabetes(10). Other risk factors for ischemic cerebrovascular events include inflammation, prothrombotic conditions, secondary hyperparathyroidism, and atherosclerosis(11). In addition to providing a thorough overview of research on different animal models, Muscogiuri et al. examined the function of VDD in stroke, myocardial infarction, and atherosclerosis and described the mechanism(12). 10,170 respondents were evaluated in a meta-analysis by Brøndum et al. and a large-scale study carried out in Copenhagen(13). 1,256 participants experienced an ischemic stroke throughout the course of the 21-year follow-up period(14). The multivariate-adjusted hazard ratio of ischemic stroke was 1.36 (1.09-1.70) when comparing responders with appropriate VD levels (30.0 ng/mL) to those with acute VDD (10 ng/mL)(15). There was no correlation between the concentrations of VD and the risk of hemorrhagic stroke(16). A meta-analysis comparing the lowest and highest quartiles of 25(OH)D validated the findings of this investigation; in prospective studies, the multivariate-adjusted odds ratio for ischemic stroke was 1.54 (1.43-1.65), with a corresponding hazard ratio of 1.46 (1.35-1.58)(1). Zhou et al. conducted a comprehensive review and meta-analysis of 191 studies to look at the possible link between VD and stroke risk(2). The scientists came to the conclusion that low VD levels are associated with a higher risk of ischemia but not of stroke or bleeding(3). Regardless of race, one study in this meta-analysis showed a link between VDD and stroke risk(4). Low levels of 25(OH)D and 1,25(OH)2D were found to be predictive of fatal stroke in Ludwigshafen's Risk and Cardiovascular Health research, which looked at over 3,000 patients over the course of eight years(5). Low VD consumption and low 1,25(OH)2D concentration were found to be significant risk factors for stroke in another study on vitamins as stroke predictors in older adults(6). Although a number of observational studies have indicated that vitamin D may help prevent stroke, a different study with 25,871 adults found that vitamin D3 supplements (200 IU daily) did not reduce cardiovascular events, including stroke(7).

VI. DIABETES

The autoimmune destruction of the pancreatic beta cells is the cause of type-1 diabetes mellitus (T1DM), which results in a total lack of insulin production(8). The primary factors behind the development of type-2 diabetes mellitus are peripheral insulin resistance, systemic inflammation, and beta cell dysfunction(9). The evidence suggests that VDD is connected to each of these functions(10). VD can affect beta cell activity by interacting with VDR receptors and localizing the enzyme 1α-hydroxylase(11). Furthermore, VD may improve insulin sensitivity by increasing VDR expression in peripheral tissues and activating proliferator-activated receptor-gamma receptors in peroxisomes, which play an important role in regulating fatty acid metabolism in adipose tissue and

skeletal muscle(12). In contrast, VD may contribute indirectly to insulin emission and sensitivity by controlling calcium concentrations and modifying peripheral tissue and beta cell membranes(13). Several studies have revealed that the frequency of T1DM is higher in nations with higher latitudes, and the condition is more commonly diagnosed during the winter(14). Many studies have connected VDD in pregnant women to the occurrence of T1DM in children after birth(15). Other studies have investigated VD supplementation's preventive role during early infancy against the development of T1DM, revealing an insignificant incidence of diabetes among children receiving vitamin supplementation(16). The results for type 2 diabetes and insulin resistance have been conflicting. Several studies have connected low levels of 25-hydroxyvitamin D to insulin resistance and pancreatic beta cell dysfunction in Western populations(1). Ock et al. found an inverse connection between insulin resistance and VD in a sample of 1807 healthy Koreans(2). Nardin et al. examined the relationship between diabetes mellitus, coronary artery disease (CAD), and VDD in 1,859 patients undergoing elective angiography for CAD evaluation and found that diabetes is an independent predictor of VDD; however, diabetic patients with VDD had higher CAD prevalence and severity(3). Schafer et al. studied over 5,000 elderly women for 8.6 ± 4.4 years to determine if there was a correlation between VD concentrations and the frequency of type-2 diabetic mellitus (T2DM)(4). They discovered no correlation(5).

VII. HYPERTENSION

The inequality between vasodilation and vasoconstriction generated by various genetic and epigenetic variables (VDD) results in vasoconstriction, which causes severe hypertension (HTN)(6). Chen et al. found a significant clinical drop in blood pressure (BP) among VDD patients with hypertension as a result of VD's antihypertensive effect(7). Similarly, nondipper hypertension is associated with significantly lower levels of VD than dipper hypertension(8). Individuals with hypertension who have a nocturnal fall of 10% in mean daytime systolic and diastolic blood pressure are classified as nondippers, while those with a decrease of 10 to 20% are considered dippers(9). Furthermore, an impaired renin-angiotensin system is a significant risk factor for hypertension, and low VD concentrations are associated with an impaired renin-angiotensin system (RAS)(10). The negative modulation of RAS with VD supplementation demonstrates VD's beneficial involvement in hypertension management(11). Aortic stiffness reduces vascular complications, but hypertension causes atherosclerosis(12). The link between low circulation VD and aortic hardness is independent of classical risk variables and provocative markers among prediabetic participants, indicating that VDD is an important risk factor for hypertension and CVD(13). However, Kang et al. found that gender influences the relationship between VD levels and several health indicators, including blood pressure, glycemic index, lipid profiles, wall thickness of the carotid artery's intima media, and brachial ankle pulse wave velocity, whereas VD serum levels may not be a leading risk factor for arterial stiffness and subclinical atherosclerosis(14). VD regulates endothelial and vascular smooth muscle cell proliferation, and the VDR is located within these cells(15). Endothelial dysfunction is a significant contributor to vascular disorders such as hypertension(16). VDD damaging endothelial cells may trigger HTN(1). Damage to acetylcholine-induced aortic relaxation, increased sensitivity to angiotensin II hypertensive effects, and increased expression of angiotensin II infusion-induced hypertrophy-sensitive myocardial genes in endothelial-specific VDR knockout mice compared to control mice suggest that the endothelial VDR may play a role in endothelial cell function and blood pressure control(2). VDR agonists can also help manage CVD caused by endothelial cell dysfunction(3)

VIII. CORONARY ARTERY DISEASE

Coronary artery disease incidence has been linked to VDD; however, the pathophysiological processes underlying such a relationship have yet to be identified(4) . The main indication for a possible relationship is the presence of VDR in the myocardium, vascular endothelial cells, and fibroblasts, as well as a demonstration through epidemiological studies that the prevalence of both VDD and CAD is enhanced by activating RAAS and increasing anti-inflammatory and decreasing proinflammatory mediators(5). VDD is more common

in acute myocardial infarction (AMI) cases, and preliminary investigations suggest a link between VD and AMI diagnosis in both the short and long term(6). Furthermore, VDD appears to increase as a result of recurrent adverse cardiac events caused by its association with a number of damaged blood vessels, cardiac remodeling, and AMI issues(7). A study was conducted with 18,225 male patients who were followed for ten years(8). Acute myocardial infarction (AMI) instances are the most common cause of VDD, although early research indicates a likely correlation between VD and the diagnosis of AMI over the long term(9). Additionally, VDD seems to rise as a result of recurrent adverse cardiac events brought on by its association with multiple impacted blood arteries, cardiac remodeling, and AMI issues(10). 18,225 male patients who were monitored for ten years participated in the study(11). Even after controlling for other risk factors, the data indicated a relationship between low levels of VD and an increased risk of AMI(12). Furthermore, some prospective studies discovered that hospitalized patients with AMI had a higher frequency of VDD(13). 96% of patients with acute coronary syndrome (ACS) who were admitted to the hospital had low VD, according to another study that had 239 patients(14). Acute VDD and intrahospital death among ACS patients may be independently related, according to several studies(15). A research by Correia et al. looked at 206 ACS patients(16). They found that the incidence of intrahospital cardiovascular death was significantly higher among patients with low levels (<10 ng/mL) of VD (24%), compared to the remaining percentage of patients (4.9%)(1).Notwithstanding these observations, there are now no compelling findings that suggest the benefit of vitamin D supplementation as a crucial cardiovascular safety measure in CAD (2). On the one hand, the information on VD supplementation during primary prevention is extremely sparse and inconsistent(3) . However, the potential benefits of administering VD during the early stages of AMI have not yet been investigated(4). There aren't enough clinical studies explicitly examining the benefits of VD supplementation for AMI patients in terms of long-term results, and only a small number of studies are still looking into how it affects surrogate primary outcomes like inflammation and left ventricular (LV) remodeling(5).

IX. ACUTE MYOCARDIAL INFARCTION

Since VDD is linked to postinfarction complications and cardiac makeover in AMI patients, it seems to rise as a result of recurrent adverse cardiac events(6). There are several systems that may be responsible for the association between VD and AMI risk(7). VD lowers renin plasma levels, which consequently causes renin levels to drop(8). Inhibitors of the angiotensin-aldosterone system. In 1978, a Danish preliminary investigation examined VD levels in 75 patients with stable angina (43 controls and 53 AMI cases)(9). According to the study's findings, patients with angina or AMI had significantly lower VD levels than the controls(10). In 1990, a different case-control study showed that patients had lower VD than controls(11). But the contrast between winter and spring was far more noticeable(12). Because rising VD quartiles show an inverse association between AMI risk and VD levels, there is a decreased relative risk of AMI(13). Furthermore, these figures have been confirmed among more recent populations(14). Significant cardiovascular events were found to be 80% and 50% more common in those with VDD and insufficiency, respectively, according to a Framingham research that investigated 1,739 patients (15). In particular, compared to individuals with VD levels above 15 ng/mL, patients without a history of CAD and those with VD levels below 10 ng/mL saw a hazard ratio of 1.8 for the development of primary cardiovascular events over a five-year follow-up period(16). Despite adjusting for a number of other cardiovascular risk factors, a study conducted on male patients found that low levels of VD were associated with an increased risk of AMI(1). At a 10-year follow-up, respondents with normal concentrations (above 30 ng/mL) of VD had nearly half the risk of AMI(2). A large-scale investigation comparing the lowest and topmost baseline categories of circulating VD concentration confirmed these findings, with an adjusted pooled relative risk of 1.52 for all cardiovascular occurrences(3). Consequently, there is mounting evidence that VDD is a novel risk factor for AMI(4). Prospective investigations have revealed a higher frequency of VDD among hospitalized patients with AMI, which is consistent with these epidemiological figures(5). According to a study done on 239 ACS patients, 96% of them had VD levels less than 30 ng/mL when they first arrived at the hospital(6).

According to Ng et al., 36% of patients with AMI had acute VDD, while 74% of patients with AMI showed mild levels of VD(7). In their analysis of 206 patients with AMI (7% of whom had STEMI), Correia et al. noted the mean blood level of VD (18.5 ng/mL) and discovered an acute deficiency in 10% of the patients (8). Furthermore, two investigations by De Metrio et al. and Aleksova et al. reported the same findings, claiming that the incidence of hypovitaminosis D among AMI patients was 89% and 68%, respectively(9). Low VD levels are associated with worse outcomes in addition to appearing to be a prevalent independent risk factor for AMI(10). Initial evidence of a likely independent association between VDD and in-hospital death among ACS patients was provided by Correia et al. Following hospitalization, the cardiovascular death rate for patients with VD concentrations <10 ng/mL was 24%, higher than the rate for the remaining patients (4.9%, with a relative risk of 4.3)(11). In their study of 139 STEMI patients, Khalili et al. also discovered a plausible link between hypovitaminosis D and in-hospital increased mortality(12). The study's findings, however, did not show a statistically significant difference in the in-hospital mortality rate between patients with low and normal VD levels(13) . More compelling evidence about the long-term clinical consequences of decreased VD concentrations in AMI has been provided(14). However, VD's lowest quartile (below 7.3 ng/mL) was linked to persisting significant adverse cardiovascular events, according to a study conducted by Ng et al. among 1,259 ACS patients(15). The relationship specifically focused on readmission to the hospital for severe decompensated heart failure or subsequent ACS(16) . In line with these findings, the lowest quartile of VD was a significant predictor of death within a year(1). Due to the increased risk of numerous in-hospital adverse cardiac events, VDD was once again a marginally independent predictor of in-hospital mortality(2). This could be because the research population had a relatively low in-hospital death rate(3). Despite comparable baseline hemoglobin levels, an increased incidence of bleeding needing blood transfusion was linked to VD's lowest quartile(4). This is a significant problem in the context of AMI since bleeding and blood transfusions have a negative impact on results, and effective antithrombotic therapy is the cornerstone of therapy(5). Additionally, a correlation was seen between the occurrence of severe respiratory insufficiency and the lowest VD quartile(6). It is still unknown how VD level and AMI outcomes are causally related(7). Hypovitaminosis D has been found to have a significant correlation with reduced left ventricular performance in over 3,000 individuals undergoing coronary angiography (8). There have been reports linking VDD to heart failure and sudden cardiac death mortality(9). Through a complicated interaction between VDR and 1-hydroxylase, the heart, fibroblasts, and vascular endothelium offer a platform for the activation of VD to the active form(10). This lowers angiotensin I levels, which in turn lowers angiotensin II levels in renal and cardiac tissue(11). VD raises ACE2 levels, which are in charge of converting excess angiotensin II into angiotensin I-7(12). Elevated angiotensin 1-7 levels intensify the positive effects on inflammation and fibrosis, which lower blood pressure(13). Through the formation of heterodimers with RXR and the modulation of VDR gene expression for better cardiovascular health, VDR serves as a platform for overall favorable metabolic effects(14). Lastly, sustaining sufficient VD levels may offer protection against the onset of CVD and its consequences(15). Furthermore, among patients who were very sick, a low level of VD was substantially correlated with the severity of their illness and their mortality(16)

X. HEART FAILURE

New-onset heart failure, MI, and post-MI are all associated with VDD. In VDR null mice, Bae et al. suggested that VDD after MI results in decreased cardiac function and survival rate, while VD signaling promotes cardio protection through anti-inflammatory, anti-apoptotic, and antifibrotic mechanisms(1). Furthermore, inflammatory cytokines such TNF-α, IL-6, and IL-1β, which interfere with heart failure and cardiac disorders, are linked to increased inflammation in VDD(2). These cytokines are reduced when chronic heart failure is treated with VD supplements(3). IL-33 belongs to the family of cytokines called IL-1(4). After myocardial infarction, IL-33 improves cardiac function and survival by preventing cardiomyocyte death through the ST2 receptor Fibrosis, heart failure, and cardiac remodeling are all associated with increased levels of soluble decoy receptors of ST2 (sST2) in the blood(5). Furthermore, cardiomyopathy

remodeling and the worsening of heart failure are linked to hypoparathyroidism and low VD levels(6). Furthermore, an active form of VD called calcitriol regulates heart function and may modulate ST2(7). Consequently, the evolution of heart failure may be regulated by the interactions between the sST2 and VD/PTH axis, which regulate fibrosis and inflammation in the heart(8). Numerous investigations have indicated a substantial correlation between the VD/PTH (1–84) axis and low levels of heart failure, sST2, and VD(9). A low plasma 1,25(OH)2D3/PTH (1-84) ratio and sST2 levels were proposed as important markers of heart failure progression, hospitalization, reduced survival, and cardiac disease-related death(10). However, there is no correlation between the risk of developing heart failure and the levels of PTH, calcitriol, or calcidiol in plasma(11). Since VDD and heart failure are related, taking supplements of VDD may be beneficial(12). However, a number of studies showed that supplementing with VD did not improve or have any beneficial effect on heart failure; these findings may be inconsistent due to genetic variations in the VDR gene (e.g., Fok1)(13). The VINDICATE study's findings that VD improves left ventricular shape and function during HF and that short-term VD supplementation reduces renin action in individuals with persistent HF indicate that VD may be helpful(14)

XI. HEART FAILURE WITH PRESERVED EJECTION FRACTION

The heart pumps normally with this kind of heart failure, but the cardiac muscles are stiff, making it difficult for the heart to pump enough blood(15). A higher risk of hospitalization, disability, and death is associated with HFpEF, which is on the rise, particularly in older persons(16). While the exact origins of HFpEF are unknown, there is growing evidence that VDD may be a significant factor in the disease's development(1). VD is fat-soluble, which is crucial for calcium metabolism and bone health(2). But it also performs a variety of nonskeletal tasks, such as controlling inflammation, cardiovascular health, and immunological function(3). VD is mostly obtained by diet (e.g., fatty fish, egg yolks, and fortified foods) and exposure to sunshine(4). Nonetheless, many people have low VD, particularly those with certain medical conditions, elderly persons, and those with little exposure to sunlight(5). The relationship between VD and HFpEF has been the subject of numerous investigations(6). After controlling for age, NT-proBNP, certain baseline characteristics, and comorbidities, Nolte et al. found that lower concentrations of 25(OH)D were significantly predictive of an increased frequency of hospitalizations due to CVDs and were associated with decreased functional capability among patients with HFpEF(7). According to Ozdemir et al., there was a positive correlation between VD and LVEF in HF patients, which occurred with both the preventive effects of VD and hypovitaminosis(8). People with CVD can reduce their risk of death by taking VD. Patients with heart failure who have low VD have limited physical function(9). VD levels and left ventricular diastolic functioning, including the left atrial volume index, were found to be insignificantly related by Pandit et al. During a 10-year follow-up period, a community-based, longitudinal research of older persons revealed a correlation between low levels of VD and an increased risk of HFpEF(10). Lower VD concentrations were linked to an increased risk of HFpEF in a different study conducted in China that included elderly individuals(11). According to the study's findings, VDD can be a significant risk factor for HFpEF(12). It is not quite clear how exactly VDD might contribute to the development of HFpEF(13). However, in addition to inflammation, which is known to contribute to the development of HFpEF, VD may also be important in controlling cardiovascular function and reducing oxidative stress(14). VD may also enhance endothelial function, which is critical for preserving appropriate blood flow and averting blood vessel damage(15). Few studies have been conducted on the effectiveness of VD supplementation in preventing or treating HFpEF, despite mounting evidence linking HFpEF and VDD(16). According to one study, patients with HFpEF who took large doses of VD supplements showed improvements in heart function markers(1). More research is necessary to determine the ideal amount, duration, and timing of VD supplementation among people with HFpEF, as this study was conducted on a small scale and only included patients with moderate to severe VDD(2). Six months of VD supplementation significantly increases the ejection fraction in elderly individuals with heart failure and VDD, according to Dalbeni et al. Furthermore, it's critical to weigh the possible

advantages and disadvantages of VD supplements against a person's medical background and general health(3). Excessive VD dosages can be harmful and cause symptoms like nausea, vomiting, and renal damage(4). Furthermore, VD supplements may interact with other medications, including steroids and blood pressure meds(5). Therefore, it is essential to speak with a doctor before beginning VD supplementation(6). There is mounting evidence that low VD levels may increase the risk of HFpEF and that people with HFpEF may benefit from taking supplements of VD(7). To fully comprehend the part VD plays in the development and treatment of HFpEF, as well as to establish the ideal dosage, more research is necessary(8). Furthermore, patients should consult their healthcare practitioners to create a thorough treatment plan, since VD supplementation should not be considered a replacement for other tried-and-true treatments for HFpEF(9)

XII. ATRIAL FIBRILLATION

The most common arrhythmia, AF affects around 2% of the general population and is thought to be the leading cause of stroke, death, and medical expenses(10). Although a number of relevant risk factors for AF have been identified, including age, heart failure, coronary artery disease, arterial hypertension, surgery, hyperthyroidism, and valvular heart disease, one substantial risk factor is still unknown(11). Low levels of VD have been linked to AF and may be involved in its pathophysiology, according to some study, suggesting that VD may be a target for treatment in clinical settings(12). VD may increase the risk of atrial fibrillation (AF) through direct effects on the atrium or indirect manipulation of cardiovascular risk variables(13). Swelling, which is linked to low VD, is crucial to the pathophysiology of AF(14). It has been discovered that patients with higher C-reactive protein levels are twice as likely to develop AF(15). Moreover, low VD may increase the risk of AF brought on by the activation of the renin-angiotensin-aldosterone pathway, which promotes structural and electrical atrial remodeling and regulates inflammation(16). Consequently, there is a correlation between high levels of left atrial fibrosis and low levels of VD(1). Low VD levels may eventually contribute to AF by increasing the risk factors for its development, such as heart failure, diabetes mellitus, coronary artery disease, and hypertension(2). Despite these findings, there is disagreement among scientists on the relationship between AF and VD(3). According to observational studies, those with VDD are around twice as likely to experience AF as people with normal VD levels(4). The prospective study is still unable to find such a relationship(5). The association between AF and VD in CVD patients or the general population has been evaluated in a number of studies(6). Nonetheless, low levels of VD were consistently linked to an elevated risk of AF incidence in studies that examined the prevalence of postoperative AF, especially after coronary artery bypass grafting(7). This is supported by a meta-analysis that examined dose-response relationships and found that VDD is strongly associated with postoperative AF in patients who underwent CABG surgery and marginally associated with an increased risk of AF in the general population(8). In particular, the results of one study showed that the incidence of AF was increased by 12%, and that the VD levels of CABG patients and the general population were reduced by 10 units, respectively, indicating a linear association(9). Lastly, VD supplementation reduced postoperative AF in patients with CABG surgery and very low VD levels (less than 20 ng/mL), according to Cerit et al. Furthermore, VDD appears to be linked to an increased incidence of AF in younger individuals but not in the elderly, as well as in patients with persistent HF(10). To determine if VD supplements could potentially be used as a preventive measure for AF, it is vital to look into the population and clinical situations where the association between lower levels of VD and an increased risk of AF is more pronounced(11)

XIII. LIPIDS

Inadequate VD concentrations are associated with negative blood lipid levels, while appropriate VD concentrations are associated with favorable lipid profiles, according to observational and interventional research(12). Numerous research have verified these conclusions(13). VD levels were found to be negatively correlated with total cholesterol (TC), triglycerides (TGs), and LDL cholesterol (LDL-C) in a 2016 study involving a group of Polish individuals(14). Another study that examined lipid

parts over 20,000 and 25(OH)D concentrations showed a strong correlation between patients' atherogenic lipid profiles and VDD(15). Furthermore, a number of meta-analyses that evaluated the connection between lipid profiles, VD levels, and VD supplementation have been conducted (16). Eight randomized controlled trials (RCTs) were included in a meta-analysis conducted in 2015 to examine the impact of VD supplementation on lipid profiles(1). The results showed that HDL-C and LDL-C increased while TG levels decreased (2). Because there are fewer trials and more variation in the interventions and results (e.g., dosage of VD supplementation), care must be taken when interpreting these findings(3). There is a negative and substantial correlation between VD supplementation and LDL-C, TC, and TG, according to a large-scale meta-analysis that assessed the effect of VD supplementation on these parameters in 39 RCTs(4). On the other hand, HDL-C levels rose when VD supplementation was used(5). Similarly, co-supplementing VD and calcium (less than eight weeks of supplementation) in obese and overweight patients resulted in a significant decrease in LDL-C, TG, and TC and an increase in HDL-C, according to a meta-analysis that included seven RCTs(6). Polycystic ovarian syndrome has been linked to low levels of VD, especially in obese people with a waist-to-hip ratio higher than 0.85(7). Additionally, VDD may make a person more susceptible to endocrine-metabolic disorders(8). Patients treated with VD supplementation showed a decrease in TC and insulin resistance compared to patients treated with a placebo, according to a meta-analysis of 11 RCTs that included 483 individuals with Polycystic Ovary Syndrome in order to assess the effects of VD supplementation against placebo(9). Nevertheless, PCOS patients' TG and HDL-C levels were not raised by VD supplementation(10). VD supplementation helps control the disease activity and is associated with a negligible chance of developing type 1 diabetes in children by maintaining serum 25(OH)D within an ideal range(11)

XIV. VD SUPPLIMENTS AND CARDIOVASCULAR HEALTH

A recent study examined the cardiovascular outcomes of patients taking omega-3 or vitamin D3 supplements in the general population(12). A total of 25,871 U.S. patients were recruited for the study(13). Men over fifty and women over fifty-five were among the patients(14). A daily dose of 2,000 IU of VD or a placebo was administered to the subjects(15). The main outcomes were decreased rates of stroke, MI, and cardiovascular death, which were tracked by an average of 5.3 years(16). The study's conclusions indicated negligible improvements in cardiovascular outcomes(1). Comparing individuals who received VD to those who received a placebo, no discernible drop in cardiovascular occurrences was seen(2). These results were found to be in line with the Calcium & VD Trial conducted by the Women's Health Initiative(3). The study concluded that using VD pills on a daily basis had no cardiovascular benefits(4). The DIMENSION trial assessed the potential impact of 16-week cholecalciferol supplementation on diabetes patients' endothelial function(5). In particular, the reactive hyperemia score and vascular biological markers were used to assess final improvements(6). In the therapy arm, VD levels were significantly higher. But according to one multivariate regression analysis, endothelial function was unaffected. Cholecalciferol administered prior to a percutaneous coronary procedure did not exhibit any MACE alteration when compared to the control group, according to another study that assessed the likely VD preventive action on the indicator of heart lesions(7). To evaluate the effects of a daily cholecalciferol supplement for a year on disease risk and biochemical markers, a study was conducted among healthy participants at a primary healthcare facility. The study's results weren't encouraging. Serum 25(OH) levels were raised by VD administration; however, no appreciable improvements were seen in cardiovascular risk variables, arterial stiffness, blood lipids, or blood pressure(8). 21,000 participants participated in a D-Health Trial to evaluate the efficacy of VD supplementation in preventing cancer and death(9). The purpose of this study was to evaluate the effects of either monthly oral doses of cholecalciferol or placebos over a period of five years(10). This was followed by an additional five years of passive surveillance utilizing mortality databases and medical records(11). The study's findings, however, were unable to clarify whether VD supplements used any protective measures against the dangers of cancer and death(12). The study came to the conclusion that the information gathered from the observational studies

did not support the use of VD as a defensive agent by healthy people(13). Furthermore, the risk of CVD was not reduced by the cholecalciferol supplement(14). In order to determine whether taking a cholecalciferol supplement every day for 12 weeks could help healthy individuals lower their blood pressure, heart rate, and other CVD risk factors, another study was carried out(15). Although this treatment raised serum levels of 25(OH)D, it had no effect on CVD risk(16). Low levels of VD were linked to a 44% increase in CVD risk and an increased death rate associated with CVD, whereas another study evaluated the relationship between CVD and serum 25(OH)D concentrations and found no significant effect(1). In order to evaluate the cardiovascular benefits of VD supplementation for a year, regardless of calcium supplementation, another meta-analysis was conducted in which 21 RCTs were included(2). The findings indicated that while the secondary endpoint included the final changes including stroke, cerebrovascular accidents, MI cardiovascular death, and all-cause death, the primary endpoint was an amalgamation of MACEs(3). VD supplementation did not significantly change MACE, individual cardiovascular endpoints (stroke, MI, cardiovascular mortality), or all-cause death, according to the results of this meta-analysis(4). These research' findings support the notion that taking vitamin D supplements has no significant positive effects on cardiovascular health(5). Because VD toxicity may be promoted by high dosages, cases of VD that generate toxic symptoms are extremely rar(6). Hypercalcemia brought on by VD poisoning may result in prolonged cardiac arrhythmias due to a shortened QT interval(7)

XV. VD TOXICITY

Signs & Symptoms-

In addition to the usual symptoms (abdominal pain, fatigue, constipation, anorexia, nocturia, and polyuria) that are directly brought on by these abnormalities, hypercalciuria or hypercalcemia is linked to VD poisoning(8). In many instances, the symptoms of hypercalciuria or hypercalcemia are negligible(9). However, as demonstrated in case reports and case series, more serious problems including renal failure, dehydration, and nephrocalcinosis can arise from the long-term maintenance of minor biochemical abnormalities or the emergence of acute electrolyte disturbances(10).

Toxic Threshold Levels-

There is currently no widely recognized 25OHD level that acts as a cutoff point for the emergence of risk(11). This threshold, however, usually falls between 250 and 750 nmol/L(12). Current pediatric clinical research with large dosages of VD have concentrated on this threshold, even though there is no evidence that children show biochemical abnormalities or symptoms with 25OHD concentrations at or slightly >250 nmol/L(13). Because levels over this threshold are determined to be supraphysiological that is, they cannot be reached with a healthy diet or significant sun exposure using it for dosage studies makes sense(14). Furthermore, there is no proof that 25OHD levels greater than 200 nmol/L have any advantages(15).

Risk Factors for VD related toxicity-

It is a rare occurrence that primarily occurs due to inherited sensitivity or improper ingestion of high dosages of VD, despite clinical and public warnings over its toxicity(16) . Since the 1950s, there has been concern about the safety of consuming more than 4,000 IU of VD each day(1). This period coincided with the widespread use of a daily VD intake of about 4,000 IU/day and was marked by an increase in idiopathic infantile hypercalcemia patients(2) . This little outbreak resulted in hypocalcemic seizures and a decrease in the daily intake of 400 IU to prevent rickets(3). It was argued that rare inherited illnesses (<1:10,000) that increase susceptibility to VD toxicity were responsible for many, if not all, of the instances of idiopathic infantile hypercalcemia(4). It would be wise to avoid excessive VD consumption in this specific subset of patients, as those with Williams syndrome may have heart abnormalities as part of their range of reasons(5). Many low-level studies suggest that high doses of VD, which would result in a shorter-term aggregated intake of 600,000 IU or more, may be excessive and lead to hypercalciuria, hypercalcemia, and ultimately nephrocalcinosis(6). Furthermore, a prospective clinical investigation including pediatric patients supports this circumstantial evidence by demonstrating that healthy children who received large dosages of 600,000 IU on an intermittent basis mostly repeatedlyhad considerable rates of hypercalcemia(7). After a diagnosis is determined and

the cause of the VD is a ddressed, blood pressure levels often gradually drop below toxic limits(8). Usually, this results in both biochemical abnormalities and the resolution of symptoms(9). Nephrocalcinosis was observed to continue in some patients even after stopping VD. According to a study of the literature on nephrocalcinosis, children with VD-resistant rickets, a rare genetic condition, have been found to have the majority of VD-related illnesses(10). In these situations, concurrent phosphate ingestion may be connected to the syndrome(11). Once more, a review of case reports and series shows that nephrocalcinosis only occurs in healthy children when intentional or inadvertent cumulative VD consumption exceeds 600,000 IU(12). Two studies investigated daily high-dose VD at levels close to but not exceeding the Institute of Medicine's upper limit, while four studies used megadoses ranging from 100,000 to 150,000 IU, according to an analysis of interventional studies in pediatric patients that focused on VD supplementation(13). Hypercalciuria, or increased calcium excretion in the urine, was not documented in any of the trials. It would be wise to avoid giving toral VD dosages at or close to 600,000 IU in light of these findings(14)

XVI. VD AND COVID-19

In circumstances when there is a deficit of this nutrient, VD treatment may reduce the incidence of viral respiratory tract infections (15). As an immunomodulatory hormone with anti-inflammatory and antibacterial qualities, vitamin D is an essential part of the immune system(16). This finding could explain the protective and advantageous effects of VD in preventing the spread of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus, reducing viral replication, and accelerating viral clearance(1). Likewise, VDD is associated with CVD and damages the cardiovascular system(2). People with a history of cardiovascular disease are observed to have a higher severity of COVID-19(3). Myocardial injury has been observed in approximately 25% of patients with the condition, with several going on to develop significant cardiac symptoms such arrhythmias, biventricular HF, and, less commonly, cardiogenic shock and death(4). VD has a number of advantageous impacts(5). It has anti-inflammatory qualities, regulates the adaptive immune system, promotes the expression of many molecules involved in the antioxidant defense system, lowers oxidative stress and cellular oxidation, and exhibits vasoprotective effects(6). Furthermore, VD is crucial for encouraging the expression of several molecules involved in the antioxidant defense system(7). Additionally, it alters immune function, aids in the removal of viruses, and reduces inflammatory reactions by reducing the synthesis of inflammatory cytokines like interleukin-6, -8, -12, and -17(8). VD levels are associated with lower levels of interleukin-6, which contributes to the cytokine storm that occurs in critically ill patients and is linked to a worse prognosis for COVID-19(9). Kox et al. conducted a small-scale investigation to compare the cytokine levels of critically ill COVID-19 patients with those of patients with other critical illnesses(10). A decreased acuteness of disease despite acute lung injury was explained by the study's findings, which showed that plasma levels of TNF, interleukin-6, and interleukin-8 were much lower in COVID-19 patients than in septic shock patients with acute respiratory distress syndrome(11). Therefore, the study's conclusions suggest that a cytokine storm may not be the source of COVID-19 severity(12). Similarly, VD increases the lungs' levels of angiotensin-converting enzyme-2, a crucial receptor for severe respiratory disease(13). One study looked into the connection between COVID-19 prevalence and VD concentrations(14). When a COVID-19 test was administered, those with low VD levels had a far higher chance of testing positive than those in the normal range(15). Furthermore, compared to people with normal VD concentrations who were not supplemented, those who received VD supplementation prior to the outbreak did not show an increased risk of catching COVID-19(16). This implies that taking VD supplements could help prevent against COVID-19(1). When taken together, these results suggest that high-dose VD treatment may reduce the risk of COVID-19 severity and death by quickly restoring circulating VD concentrations(2). Persons with chronic illnesses (such as the elderly, smokers, obese persons, people with type-2 diabetes, and African Americans) have lower VD levels, which can result in more severe SARS-CoV-2 infectivity(3). VDD might be a significant risk factor for the severity of COVID-19 infection(4). Therefore, VD supplementation may be beneficial for those who are at risk for VDD(5). This method is regarded as safe,

accessible, and reasonably priced(6). However, there is currently not enough scientific proof to support the clinical routine use of VD in COVID-19 patients(7). The usefulness of high-dose VD supplementation in reducing the risk of COVID-19 infectivity and severity has been the subject of an intense debate(8). Therefore, more clinical research is required to gather more solid proof regarding the effect of VD in reducing hospitalization and fatality rates(9). Determining if VD supplementation lowers the risk of SARS-CoV-2 virus infection is also necessary(10)

XVII. VD IN NONCARDIAC SURGERY

VDD has been discovered in an increasing number of patients with a variety of clinical circumstances; as a result, these individuals are seen by different medical specialties(11) . Anesthesiologists who treat patients in intensive care units and long-term pain clinics, as well as surgeons who treat patients following noncardiac surgery, have also identified VDD in their patients(12). VDD may affect these patients' results(13). Recent years have seen a great deal of discussion on these topics, and it has been noted that low VD greatly increases mortality and is positively connected with longer hospital stays and readmissions to the intensive care unit within 90 days(14). One meta-analysis's findings showed that among elderly patients with sepsis, severe VDD may be independently linked to an increased risk of mortality(15). One study found that low VD levels were associated with increased mortality in sepsis patients admitted to a hospital , while another study found that optimal VD concentration reduced mortality risk in patients undergoing noncardiac surgical treatment(16). The important immunomodulatory role of VD and its link to chronic illnesses may help to explain these findings(1)

XVIII. ANESTHESIA CONSIDERATION

Vitamin D is an essential fat-soluble vitamin that is essential for maintaining calcium homeostasis and bone health(2). VDD has been connected in recent years to a number of adverse health outcomes, including diabetes mellitus, cardiovascular disease, and cancer(3). For the anesthesiologist performing cardiac surgery, VDD may result in a number of negative outcomes, such as compromised immune function, heightened risk of post-operative complications, compromised bone health, and elevated risk of cardiovascular disease(4)

XIX .IMPAIRED IMMUNE FUNCTION

VD has a significant impact on immune system regulation(5). VDD has been linked to a higher risk of infections and slowed wound healing, which can be especially troublesome when heart surgery is being performed(6). Due to the intrusive nature of the surgical procedure and the requirement for extended hospital stays, patients undergoing cardiac surgery are already at an increased risk of infection(7). By affecting immune cell function and reducing the synthesis of antimicrobial peptides, VDD may further raise this risk(8). In order to avoid infections in patients with VDD, anesthesiologists may need to take additional precautions(9). This can entail making sure patients receive the right preventive antibiotics and putting in place stringent infection control procedures, like hand hygiene and environmental cleaning(10). In patients with VDD, anesthesiologists may also need to keep a closer eye on wound healing since poor wound healing can result in surgical site infections and a longer recovery time(11)

XX. INCREASED RISK OF POSTOPERATIVE COMPLICATIONS

A higher incidence of surgical complications, including infections, arrhythmias, and acute kidney damage (AKI), has been linked to VDD(12). When it comes to heart surgery, these problems can be especially troublesome because they can result in longer hospital stays, higher medical expenses, and a lower patient quality of life(13). Approximately 30% of patients may experience an arrhythmia during or after heart surgery, making them a common consequence(14). An increased risk of arrhythmias, including ventricular tachycardia and atrial fibrillation, has been linked to VDD(15). Anesthesiologists may need to keep a closer eye out for any indications of arrhythmias in patients with VDD and modify their treatment regimens accordingly(16). This can entail giving antiarrhythmic drugs like amiodarone or beta-blockers and making sure electrolyte abnormalities like hypokalemia and hypomagnesemia are addressed(1). Up to 10% of

patients may develop an infection following heart surgery, making infections another frequent side effect(2). An increased incidence of infections, including pneumonia and surgical site infections, has been linked to VDD(3). It may be especially important for anesthesiologists to keep an eye out for infection symptoms in patients with VDD and modify treatment regimens as needed(4). This could entail giving the right antibiotics, making sure you drink enough water, and improving your diet(5). Up to 30% of individuals may have some kind of AKI following heart surgery, making it a major side effect of the procedure(6). Due to its involvement in controlling blood pressure and renal function, VDD has been linked to an increased risk of AKI(7). It could be necessary for anesthesiologists to keep a closer eye out for symptoms of AKI in patients with VDD and modify their treatment regimens accordingly(8). This could entail avoiding nephrotoxic drugs, maintaining proper hydration, and improving hemodynamics(9).

XXI. IMPAIRED BONE HEALTH

VDD can lead to a variety of bone-related issues, such as osteoporosis and fractures, and is crucial for bone health(10). Patients undergoing heart surgery might be immobile for prolonged periods of time, which could make any underlying bone issues worse(11). Anesthesiologists may need to take precautions against or control these issues, such as making sure patients receive enough pain treatment, promoting early mobility, and administering calcium and vitamin D supplements as necessary(12). Bone resorption and decreased bone density might arise from VDD's increased parathyroid hormone (PTH) levels and impaired calcium absorption(13). Fractures can become more likely as a result, which can be particularly problematic for individuals who are immobile following heart surgery(14). Patients with previous bone disorders or those at risk for complications related to bone health may require anesthesiologists to pay special attention to bone health(15). Anesthesiologists may also think about other methods to support bone health in addition to vitamin D and calcium supplements, include maximizing diet, promoting weight-bearing activities, and tracking bone density with methods like dual-energy X-ray absorptiometry scans(16). Anesthesiologists can reduce the risk of problems and enhance the results of heart surgery by actively maintaining bone health in patients with VDD(1)

XXII. INCREASED RISK OF CVD

An increased risk of CVDs, such as hypertension, heart failure, and myocardial infarction, has been linked to VDD(2). VDD may increase the already elevated risk of cardiovascular problems for patients undergoing heart surgery(3). In order to reduce the risk of cardiovascular problems before and after surgery, anesthesiologists may need to take additional precautions while handling patients with VDD(4). This could entail keeping an eye out for symptoms of myocardial ischemia, managing fluids appropriately, and improving blood pressure control(5). VDD may have wider effects on the general perioperative treatment of patients undergoing heart surgery in addition to these particular effects(6). For instance, VDD has been linked to a higher risk of delirium and cognitive decline, which may affect the course of recovery and results following surgery(7). Anesthesiologists might need to think about how VDD might affect these results and take precautions against any unfavorable impacts(8). All things considered, VDD may have serious repercussions for anesthesiologists doing heart surgery(9). It is important for anesthesiologists to understand the possible hazards and take precautions to avoid or control any consequences(10). Prior to surgery, patients may be screened for VDD; their diet and supplements may be optimized; and they may be closely watched for indications of infection, arrhythmias, AKI, bone-related issues, and CVD(11). Anesthesiologists can enhance the overall perioperative treatment and help patients undergoing heart surgery achieve better results by proactively treating VDD(12).

XXIII. CONCLUSIONS

All things considered, the relationship between VD and cardiovascular risk is intricate and still poorly understood(13). There is conflicting evidence from RCTs regarding the use of VD supplements for CVD prevention or management, despite observational studies suggesting that low concentrations of VD may be associated with an increased risk of CVD(14). VD may affect cardiovascular risk through a number of

possible processes, such as its effects on oxidative stress, inflammation, blood pressure, glucose metabolism, and lipid metabolism(15). Further research is necessary to elucidate the role of vitamin D and determine which populations may benefit most from supplementing, as well as to determine the ideal amount and duration of VD administration for cardiovascular health(16). In the meanwhile, people must continue to lead healthy lives that include regular exercise, a varied and balanced diet, and quitting smoking because these are proven ways to lower cardiovascular risk(1). It's crucial to discuss the possible advantages and disadvantages of VD supplementation with one's healthcare professional and to adhere to their suggested management plan if one has low levels of VD or other risk factors for CVD(2).

REFERENCES

[1] Vitamin D deficiency and risk of cardiovascular diseases: a narrative review. Kheiri B, Abdalla A, Osman M, Ahmed S, Hassan M, Bachuwa G. Clin Hypertens. 2018; 24:9.

[2] Vitamin D and cardiovascular disease: potential role in health disparities. Artaza JN, Contreras S, Garcia LA, et al. J Health Care Poor Underserved. 2011; 22:23–38.

[3] Vitamin D in health and disease: current perspectives. Zhang R, Naughton DP. Nutr J. 2010; 9:65.

[4] Steroid hormone vitamin D: implications for cardiovascular disease. Demer LL, Hsu JJ, Tintut Y. Circ Res. 2018;122:1576–1585.

[5] Overview of general physiologic features and functions of vitamin D. DeLuca HF. Am J Clin Nutr. 2004; 80:1689–1696.

[6] Yeast as a biological platform for vitamin D production: a promising alternative to help reduce vitamin D deficiency in humans. Kessi-Pérez EI, González A, Palacios JL, Martínez C. Yeast. 2022; 39:482–492.

[7] 25(OH)D3-enriched or fortified foods are more efficient at tackling inadequate vitamin D status than vitamin D3. Guo J, Lovegrove JA, Givens DI. Proc Nutr Soc. 2018; 77:282–291.

[8] Vitamin D deficiency and cardiovascular diseases. Jorge AJL, Cordeiro JR, Rosa MLG, Bianchi DBC. Int J Cardiovasc Sci. 2018; 31:422–432.

[9] Vitamin D and cardiovascular disease: an update. Zittermann A, Pilz S. Anticancer Res. 2019;39:4627–4635.

[10] Vitamin D and cardiovascular disease. Wang TJ. Annu Rev Med. 2016; 67:261–272.

[11] Is hypovitaminosis D a risk factor for heart failure? Hagău AC, Pușcaș A, Togănel R, Muntean I. Life (Basel) 2023;13:372.

[12] Vitamin D and cardiovascular health. de la Guía-Galipienso F, Martínez-Ferran M, Vallecillo N, Lavie CJ, Sanchis-Gomar F, Pareja-Galeano H. Clin Nutr. 2021; 40:2946–2957.

[13] Vitamin D for skeletal and non-skeletal health: what we should know. Charoenngam N, Shirvani A, Holick MF. J Clin Orthop Trauma. 2019; 10:1082–1093.

[14] Vitamin D supplementation guidelines. Pludowski P, Holick MF, Grant WB, et al. J Steroid Biochem Mol Biol. 2018;175:125–135.

[15] Resurrection of vitamin D deficiency and rickets. Holick MF. J Clin Invest. 2006; 116:2062–2072.

[16] Vitamin D metabolism, mechanism of action, and clinical applications. Bikle DD. Chem Biol. 2014; 21:319–329.