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Communication

Role of Vitamin D in Cardiovascular Diseases

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Abstract: Vitamin D represents a group of secosteroids involved in the calcium and phosphate metabolism. The active form of vitamin D, 1,25-dihydroxylcalciferol, exerts its biological mechanisms via the VDR (vitamin D receptor) which acts as a regulator of several target genes. Hypovitaminosis D is associated with many diseases, which are not only limited to the metabolism of the skeleton, but growing evidence links the deficit of vitamin D to cardiovascular, metabolic, immune, and neoplastic diseases. In regard to the cardiovascular system, current evidence shows the presence of VDR in endothelial cells. Moreover, both in vitro and animal experimental models demonstrated that the deficit of vitamin D can promote endothelial dysfunction and atherosclerosis development. Vitamin D can interfere with vascular functions also by affecting the production of vasodilator mediators. VDR is also expressed in left ventricle cardiomyocytes, and hypovitaminosis D can relate to cardiac hypertrophy and heart failure. Randomized clinical trials (RCT) designed to prove the therapeutic role of vitamin D supplementation have been inconclusive to date. The aim of this review is to highlight the main interactions between vitamin D metabolism and cardiovascular diseases; thus, focusing on pathogenic mechanisms and related clinical manifestations.

Keywords: vitamin D; cardiovascular disease; endothelial dysfunction; atherosclerosis; arterial hypertension; heart failure

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1. Introduction

Vitamin D is a group of secosteroids that physiologically improve the intestinal absorption of calcium and phosphate. The most important compounds of the vitamin D group are vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol) [1]. The first association between vitamin D and cardiovascular diseases was reported by Scragg et al. [2], who recognized a seasonality in people suffering from heart disease. In particular, winter was the season when heart diseases were more frequent, possibly due to low levels of vitamin D. Cholecalciferol and ergocalciferol can be taken with food. After food intake, vitamin D2 undergoes two distinct metabolic processes. Firstly, vitamin D2 is metabolized in the liver to 25-hydroxyvitamin D, which in the kidney is, subsequently, converted by the enzyme 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) to its active form, named 25-dihydroxyvitamin D (calcitriol) [3]. The endocrine production of calcitriol is regulated by feedback mechanisms involving bone, calcium, and the phosphorus metabolism. Calcitriol production is stimulated by the parathyroid hormone (PTH), released upon the reduction in calcium plasma levels. Calcitriol in turn directly suppresses the PTH gene transcription and the consequent hormone production, thereby increasing serum calcium levels. Furthermore,

calcitriol also upregulates gene transcription and protein expression of the calcium-sensing receptor. Moreover, vitamin D regulates its own production by inhibiting CYP27B1 [4]. Additionally, under exposure to sunlight, the skin can synthesize vitamin D, namely, cholecalciferol [5]. The amount of sunlight needed to satisfy our vitamin D requirements is dependent on several factors such as skin pigmentation, age, latitude, season of the year, or time of the day [6]. Several diseases can be associated with low vitamin D levels. Rickets has long been recognized as a consequence of vitamin D deficiency. Furthermore, low vitamin D levels can be associated with other chronic disorders, such as atherosclerosis, coronary heart disease, arterial hypertension, heart failure [7], type 2 diabetes mellitus [8], cancer [9], and immunological disease [10]. Even if a pathogenic link between vitamin D deficiency and these diseases was established, the results of randomized clinical trials (RCT) designed to prove the therapeutic role of vitamin D supplementation have been inconclusive to date. However, it should be pointed out that the involvement of the vitamin D system in the pathogenesis of cardiovascular diseases is quite intricate. Indeed, within this context, a relevant role is also played by the autocrine/paracrine pathways locally activated by vitamin D inside atherosclerotic plaques [11,12]. In particular, it has been shown that vitamin D receptor (VDR) expression in human carotid plaques correlates with a reduction in major adverse cardiovascular events (MACE) [12].

2. Vitamin D Signaling

The biological effects of vitamin D are mediated by VDR, a cytosolic receptor protein which upon ligand binding migrates to the nucleus, and activates the transcription of target genes. VDR is a member of the nuclear receptor family of transcription factors, and its gene is located on chromosome 12q [13]. VDR activation is triggered by its binding to the active form of vitamin D and to a retinoid X receptor (RXR). As a consequence, the activated heterodimeric receptor complex translocates into the nucleus and interacts with specific nucleotide sequences named vitamin D response elements (VDRE). The latter regulate the transcription of vitamin D-sensitive target genes within hours or days. In addition to this classical signaling pathway, VDR localization has also been detected at the level of cell membrane, so that vitamin D can also elicit quick changes in gene expression. These rapid effects are likely activated by histone modification and other epigenetic mechanisms [14]. Many studies have been conducted, but the tissue distribution of VDR has not been fully elucidated. However, this receptor is certainly expressed in skeletal, bowel, cardiac, and endothelial cells [15]. As VDR is almost ubiquitous, several findings also showed a local presence of CYP27B1; thus, opening new scenarios on how local autocrine and paracrine pathways of vitamin D act, especially with regard to its effects on cardiomyocytes and endothelial cells. Therefore, eventual local tissue deficiencies of vitamin D could be involved in the development of atherosclerotic plaques [11].

3. Vitamin D and Renin–Angiotensin–Aldosterone System

The important role of renin in regulating blood pressure has been well established, and several anti-hypertensive drugs work on the renin–angiotensin–aldosterone system (RAAS). This system is involved in the feedback pathways that regulate fluid volume homeostasis, electrolyte plasma levels, and vascular resistance. Renin is a protease produced in nephrons by the cells of the juxtaglomerular (JG) apparatus, and its synthesis is induced under various conditions such as renal hypoperfusion and the sympathetic nervous system activation. Renin converts angiotensinogen produced in the liver to angiotensin I, that in turn acts as a substrate of the angiotensin-converting enzyme (ACE) expressed in the lungs, with the resulting synthesis of angiotensin II [16]. The latter binds to its receptor; thus, exerting several biologic actions that affect multiple districts, including the brain, heart, kidney, adrenal glands, and peripheral vessels. In order to demonstrate the relationship between vitamin D and RAAS, several studies were based on the in vivo and in vitro disruption of vitamin D pathways, with the aim of recording eventual changes in RAAS activity. Current evidence suggests that vitamin D is a negative regulator of RAAS. In genetic

models of VDR null mice, both renin and angiotensin II levels were higher with respect to wild-type mice [17]. Moreover, systolic and diastolic blood pressure increased in VDR null mice with respect to wild-type. Furthermore, null mice had an increased heart weight, resulting from cardiac hypertrophy. When treated with captopril, both null mice and wild-type animals manifested similar decreases in blood pressure, suggesting that arterial hypertension was due to the overexpression of renin and angiotensin II [17]. Angiotensin II also mediates the thirst and salt craving, as well as the intestinal absorption of water and salt. VDR null mice drunk twice as much as the wild-type mice, with a urinary load that doubled when maintaining normal electrolyte plasma levels. No difference was found in the food intake. When compared to normal mice, VDR null animals excreted with the urine a 39% higher amount of sodium, and a 19% greater quantity of potassium; thus, suggesting that null mice are characterized by an overexpression of angiotensin II, leading to an increased absorption of salt and water [17]. Additional data were obtained using experimental dietary models of vitamin D suppression, based on the dietary intake of strontium, a substance capable of blocking the metabolic pathway driving vitamin D production. In particular, mice subjected to strontium ingestion, exhibited increased levels of renin when compared to animals fed with a normal diet. Further data came out from in vitro models of As4.1 cells, a JG cell-like cell line originated from kidney tumors of Simian Virus 40 Large T (SV40T) antigen transgenic mice [17]. Treatment with vitamin D led to a reduced expression of renin messenger RNA (mRNA) levels, thereby indicating that this vitamin is a negative regulator of renin levels [16,17]. Well-known consequences of excessive RAAS activation include cardiac hypertrophy and hypertension, and both these abnormalities occur in experimental models of vitamin D deficiency. Similar findings have been obtained in nongenetic experimental models of vitamin D deficiency. In a study where hypovitaminosis D was induced by dietary deprivation, blood pressure, heart contractility, and vascular contractility were tested in vitamin D-free diet mice and vitamin D-included diet mice. This study suggests that, in the subgroup of the vitamin D-free diet, systolic blood pressure and myocardial/vascular contractility were increased with respect to the subgroup fed with vitamin D. To exclude that these findings were related to hypocalcemia elicited by hypovitaminosis D, a group of rats was tested during a vitamin D3-deficient diet, allowing normal plasma ranges of calcium and phosphates. Under these experimental conditions, similar results were found with regard to blood pressure and heart/vasculature contractility [18]. A study carried out on a large population of newly diagnosed hypertensive patients detected an inverse and strong relationship between hypovitaminosis D and 1 h post-load glucose in normo-glycemic subjects. The population with hypovitaminosis D and glucose values >155 mg/dl at 1 h post-load glucose had worse metabolic and cardiovascular outcomes; thus, showing multiple subclinical organ damage [19]. RCTs examining possible effects of either vitamin D supplementation or ultraviolet radiation on blood pressure have not been exhaustive. The results of two RCTs suggest that vitamin D supplementation can lower blood pressure in hypertensive patients with low vitamin D levels [20,21]. A meta-analysis suggests that, differently from normal subjects with physiologic vitamin D levels, vitamin D supplementation may decrease blood pressure in hypertensive patients characterized by vitamin D deficiency [22]. However, additional studies are needed for further clarification. The role of vitamin D deficiency in arterial hypertension could be explained not only by RAAS hyperactivation, but also by endothelial dysfunction and atherosclerosis.

4. Vitamin D and Endothelial Dysfunction

Vitamin D plays relevant roles in VDR+ endothelial and vascular smooth muscle cells. Therefore, it is reasonable that vitamin D significantly affects vascular contractility and the evolution of vascular calcifications. Vitamin D can influence the vascular structure and function in different ways. It is well known that nitric oxide (NO) is a powerful vasodilator and vasoprotective agent, whose synthesis is regulated by several factors, also including vitamin D and its receptor. Some studies suggest that vitamin D and its receptor could play

an important role in regulating NO synthesis [23]. Observational studies have identified a link between insufficient vitamin D levels and increased oxidative stress, or a lowered antioxidant capacity [24]. One study conducted on patients with chronic kidney disease under conservative treatment showed a correlation between circulating levels of serum 25-OH vitamin D levels and artery dilation, assessed through the evaluation of brachial artery flow; thus, indicating an inverse correlation between circulating levels of vitamin D and arterial caliber. Moreover, this study showed that pro-atherosclerosis cytokines plasma levels are higher in patients with hypovitaminosis D. In particular, soluble vascular cell adhesion molecule-1 (sVCAM-1) and soluble E-selectin levels were higher in patients with vitamin D deficiency, when compared to subjects with normal vitamin D levels [25]. A similar study also demonstrated that in the absence of VDR expression, there was a deteriorated vasodilator response to acetylcholine [26]. Further mechanisms involve the endothelial 1-α-hydroxylase26 and activated vitamin D that can modulate the growth of both cell types [27,28]. Functional changes induced by vitamin D include the activation of vasodilatory and antithrombotic gene programs. For instance, coronary vascular smooth muscle cells exposed to 1,25-OH D exhibit a reduced expression of thrombogenic genes and an increased production of fibrinolytic and vasodilatory genes [29]. Genetic models of VDR−/− mice are also associated with hypercoagulability. A study demonstrated that ADP-induced platelet aggregation was augmented in VDR null mice and with normal calcium plasma levels. In this model different substances involved in the hemostasis were altered. In particular, the gene expression of antithrombin and thrombomodulin was downregulated, whereas gene expression of the pro-thrombotic tissue factor was upregulated. The same study used a pro-thrombotic insult to test the difference between wild-type mice and VDR null mice, evaluated under normal and low plasma calcium levels. The pro-thrombotic agent was exogenous lipopolysaccharide, that caused an exacerbation of multiorgan thrombosis, associated with enhanced levels of tissue factor and lower levels of antithrombin and thrombomodulin, regardless of the plasma calcium levels. This evidence supports the hypothesis that vitamin D, acting directly on endothelial cells through its receptor, affects the endothelial system by modifying the production of pro- and anti-thrombotic substances [30].

5. Vitamin D, Inflammation, and Atherosclerosis

Several findings currently suggest that there is a link between the vitamin D system and the development of atherosclerotic plaques, possibly mediated by a modulation of immune responses. These interactions can be explained by the expression, within immune system cells, of VDR and CYP27A1 and CYP27B1 hydroxylases. The latter are implicated in the activation of vitamin D; thus, implementing its role as an autocrine/paracrine modulator of the pathobiology of atherosclerotic plaques [31,32] Macrophages and other immune cells, such as dendritic cells (DC), are affected by active vitamin D. In particular, vitamin D promotes monocyte to macrophage transition, thereby driving cellular commitment towards the M1 phenotype. The latter is responsible for the production of immunosuppressant cytokines such as prostaglandin E2, as well as for the inhibition of Toll-like receptors (TLR) TLR2, TLR4 and TLR-9 expression. The consequent downregulation of class two major histocompatibility complex (MHC) antigens at cell surface results in a decreased synthesis of pro-inflammatory cytokines [33,34]. Vitamin D also regulates adaptive immune cells, specifically acting on B lymphocytes by inhibiting their proliferation, their maturation into plasma cells, as well as their production of immunoglobulins [35]. In regard to T lymphocytes, vitamin D suppresses Th1- and Th17-dependent proinflammatory responses, and also promotes Th2, Treg, and Tr1 immunomodulating activities [36]. Furthermore, another study showed that the signaling originated by vitamin D-VDR interaction can downregulate scavenger receptor expression on the macrophage surface in diabetic patients; thus, avoiding the passage of LDL cholesterol in the foam cells and preventing vascular atherosclerosis [37]. An additional anti-atherosclerotic mechanism is mediated by VDR activation, leading to the inhibition of the nuclear factor kappa-light-chain-enhancer

of activated B cells (NF-κB) gene expression, associated with the downregulation of pro-inflammatory and pro-thrombogenic cytokines such as interleukin-6 (IL-6), as well as with the upregulation of thrombomodulin and interleukin-10 (IL-10). This endothelial modulation suppresses vascular calcifications and prevents the development of atherosclerotic plaques by inhibiting foam cell formation [38]. Another study, carried out on pigs, revealed how intracellular adequate levels of vitamin D can downregulate NF-κB expression by inhibiting kariopherin-A4 (KPNA4), a protein that promotes NF-κB expression [39]. The main feature of these autocrine/paracrine pathways relies on their independence from the systemic levels of calcium, PTH, and 1,25-dihydroxylcalciferol. Therefore, the disengagement from such classical regulatory mechanisms may explain the inconclusive results yielded by clinical trials evaluating the cardiovascular outcomes of vitamin D supplementation. All these considerations can justify the association between VDR expression and the in vivo atherosclerotic plaque burden. In transgenic rats overexpressing 24-hydroxylase, an enzyme that inactivates 1,25-OH vitamin D, marked atherosclerotic lesions was detected [40]. Moreover, interesting evaluations have been conducted on human atherosclerotic plaques obtained from patients undergoing endarterectomy for carotid stenosis. These experimental observations demonstrated that intraplaque VDR levels correlate with M1 phenotype macrophage expression. Differently from plasma vitamin D concentrations, low VDR levels inside the downstream portions of carotid plaques predict MACE risk [12]. The involvement of vitamin D in the regulation of visceral and ectopic fat deposition could also contribute to cardiometabolic dysfunction. Indeed, the results of some clinical trials suggest that the concomitant supplementation of vitamin D and calcium may decrease fat deposition and reduce the risk of cardiovascular and metabolic abnormalities [41,42].

6. Vitamin D and Heart Failure

Both VDR and hydroxylases necessary to form active vitamin D are expressed in ventricular cardiomyocytes. Current in vivo evidence suggests that the loss of the activity of the vitamin D signaling pathway can induce the remodeling of cardiomyocytes and the extracellular matrix, and the administration of the active form of vitamin D can reduce or prevent this remodeling, by acting on anatomical, functional, molecular, and genetic aspects of cardiac hypertrophy and dysfunction that lead to heart failure with preserved ejection fraction (HFpEF). HFpEF is characterized by an increased filling pressure, cardiac hypertrophy, and diastolic dysfunction, with a normal value of ejection fraction. A study conducted on a mice model of hypertension and left ventricular hypertrophy (LVH), induced by a high-salt diet, showed that the group treated with paricalcitol (PC) had reduced LVH with respect to the control group (13%). Moreover, echocardiographic parameters of hypertrophy such as interventricular septum, posterior wall, and left ventricle (LV) mass increases were reduced in the interventional group. Similar echocardiography findings were found in a population with end-stage renal disease and, also in this setting, the administration of PC reduced the cardiac hypertrophy signs [43]. To exclude that these findings were due to a different pressure overload between the two groups, continuous wireless telemetries for seven consecutive days were performed, and no differences were found in the mean arterial pressure (MAP) between the two groups. Molecular markers of heart failure as brain natriuretic peptide (BNP) and atrial natriuretic factor (ANF) were also reduced in the PC group. The mechanism used by vitamin D to improve cardiac function is not fully understood, but the evidence that VDR is expressed on cardiomyocytes suggests an activation of intracellular pathways leading to a modified gene expression. Microarray gene analyses demonstrated that in the PC-group mice, the expression of hypertrophy-related genes, such as myosin heavy-chain isoform, α-tropomyosin, and NF-κB, was downregulated [43]. Evidence of changes in genetic expression came from another mouse model of cardiac hypertrophy induced by transverse aortic constriction (TAC), where the expression of collagen III, fibronectin, and TIMP-1 (tissue inhibitor-1 of matrix metalloproteases) was reduced by the use of PC or losartan [44]. Further evidence suggests that vitamin D pathway activation stimulates calcium uptake, increases contractility in

wild-type, but not in VDR knockout mice, and improves diastolic function [45,46]. In VDR knockout animal models, cardiomyocytes develop hypertrophy and cardiomegaly [47,48]. A study conducted on newly diagnosed treatment-naïve hypertensive patients, showed that hypovitaminosis D was a strong predictor of increased left ventricular mass index [49]. By interfering with collagen and metalloproteinase production, vitamin D can also affect the heart extracellular matrix. Vitamin D-deficient mice develop cardiomegaly, associated with increased extracellular space and collagen. Moreover, VDR knockout mice express high levels of matrix metalloproteinases, and are also characterized by increased fibrosis and low concentrations of tissue inhibitors of metalloproteinases [50].

7. Vitamin D Supplementations and Cardiovascular Health

The Vitamin D and Omega-3 Trial (VITAL) is a recent RCT that aims to investigate cardiovascular outcomes in patients taking omega 3 or vitamin D3 supplementations in the general populations. The study sample consists of 25.871 patients, including men aged >50 years and women aged >55 years, recruited all over the United States, receiving placebo or a 2.000 IU daily dose of vitamin D. The primary endpoints were decreases in myocardial infarction, stroke, and death from cardiovascular causes tracked for a median of 5.3 years. The VITAL trial did not find any significant benefits in regard to cardiovascular outcomes. Indeed, only a not significant reduction in cardiovascular events was observed in the group treated with vitamin D when compared to the placebo [51]. These results were consistent with the Women's Health Initiative Calcium and Vitamin D Trial (WHI CaD), which found no cardiovascular benefits from daily vitamin D supplementation [52]. The DIMENSION trial evaluated the potential impact of a 16-week cholecalciferol supplementation on endothelial function in patients with diabetes. In particular, the eventual improvements referring to vascular biomarkers and reactive hyperemia index were assessed. Vitamin D levels significantly increased in the treatment arm. Nevertheless, a multivariate regression analysis did not detect any effect on endothelial function [53]. A further controlled study aimed to evaluate the possible protective action of vitamin D on markers of heart lesions showed that cholecalciferol, administered before a percutaneous coronary procedure, did not elicit any MACE change in comparison to the control arm [54]. In a primary care setting, the authors of the BEST-D trial studied in healthy subjects the effects of a 1-year daily supplementation of cholecalciferol on disease risk and biochemical markers. Similar to the above-mentioned data, the results of this trial were also not encouraging. Indeed, vitamin D supplementation enhanced serum 25(OH) concentrations, but no significant improvements were reported with regard to cardiovascular (CVD) risk factors, blood pressure, arterial stiffness, and blood lipids [55]. The D-Health Trial evaluated in more than 21,000 subjects the eventual efficacy of vitamin D supplementation about the prevention of cancer and mortality. In particular, this RCT assessed the effects of either placebo or monthly oral administrations of cholecalciferol during a 5-year period, followed by further 5 years of passive monitoring, based on the access to health records and death registries. The results of this study did not clarify if vitamin D supplementation exerted any protective action on cancer and mortality risks, and the authors concluded that data obtained from observational investigations are not useful to support the utilization of vitamin D in healthy subjects as a protective agent [56]. Moreover, cholecalciferol supplementation did not reduce the cardiovascular risk [57]. Another double blind, placebo-controlled RCT investigated if a 12-week daily supplement of cholecalciferol could be useful in healthy subjects to decrease blood pressure, heart rate, and other CVD risk markers. However, although this treatment increased the serum levels of 25(OH)D, the CVD risk did not improve [58]. A recent meta-analysis evaluated the eventual correlation between serum 25(OH)D levels and CVD incidence. No significant relationship was found, though low vitamin D levels correlated with a 44% increase in the relative risk of CVD (incidence–mortality combined), as well as with an enhanced mortality related to CVD [59]. Another meta-analysis included 21 RCTs to evaluate the cardiovascular benefits of a vitamin D supplementation over one year, regardless of calcium supplementation. The primary endpoint was a combination of

MACEs. Secondary endpoints included the eventual changes involving myocardial infarction, stroke, or cerebrovascular accidents, cardiovascular mortality, and all-cause mortality. According to this meta-analysis, vitamin D supplementation did not elicit any significant changes in MACE, single cardiovascular endpoints (myocardial infarction, stroke, cardiovascular mortality), or all-cause mortality [60]. The above studies are consistent with the evidence that vitamin D supplementation does not seem to induce relevant benefits for cardiovascular health. The occurrence of acute toxic effects of vitamin D supplementation are quite rare, because vitamin D toxicity can be induced only by very high dosages. The toxic effects of vitamin D may include hypercalcemia, that can promote cardiac arrhythmias sustained by a shortened QT interval [61].

8. Potential Impact of Calcium and Phosphate on Cardiovascular Risk

Because vitamin D is a key factor in the regulation of calcium/phosphate absorption and metabolism, it is quite logical that a relevant association can occur between changes in the levels of these metabolites and the overall cardiovascular risk [62]. Indeed, several experimental and clinical studies suggest that calcium, phosphate, and vitamin D can play an important role in the pathogenesis of cardiovascular diseases. Since calcium, phosphate, and vitamin D are closely connected, they constitute a biological axis that should be considered with regard to all these three components and their reciprocal relationships. However, their coordinated roles in the development and progression of cardiovascular disorders have not yet been clearly elucidated. In fact, within the very complex scenario of the global cardiovascular risk, rationally designed clinical trials have so far failed to shed light on the real consequences of calcium/phosphate/vitamin D deficiencies or supplementations [63].

9. Conclusions

Vitamin D represents a group of secosteroids involved in the calcium and phosphate metabolism; an adequate food intake and sunlight exposition are necessary to reach sufficient levels of vitamin D. Different diseases can be associated with low levels of vitamin D, that are not only related to bone and calcium metabolism diseases. Indeed, current evidence suggests a direct involvement of hypovitaminosis D in cardiovascular diseases. Both in vitro and in vivo animal models showed that vitamin D deficiency can cause or worsen endothelial dysfunction, favoring the onset and progression of atherosclerotic plaque. Endothelial dysfunction and RAAS modulation have been shown to be implicated in the development of arterial hypertension due to vitamin D deficiency in animal reversible models, where the reintegration of vitamin D restored or improved the cardiovascular impairment. Vitamin D deficiency in animal models is also related to heart hypertrophic remodeling, characterized by biochemical and echocardiographic changes similar to the findings of the HFpEF. Even if the association between hypovitaminosis D and cardiovascular disease is well established in animal models, several trials and meta-analyses performed to prove eventual cardiovascular benefits of vitamin D supplementation in humans have been inconclusive, thereby never reaching significant results referring to MACE. Further studies are, thus, needed to eventually prove the supposed benefits of vitamin D supplementation.

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