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Effect of vitamin D supplementation on muscle function and fracture prevention in elderly individuals with osteoporosis

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LITERATURE REVIEW

RESUMO:

Introdução: A osteoporose representou um desafio crescente para a saúde pública, caracterizada pela diminuição da densidade mineral óssea e deterioração da microarquitetura do tecido ósseo, o que resultava em um aumento da fragilidade esquelética e do risco de fraturas. Em paralelo, a sarcopenia, definida como a perda de massa e função muscular associada ao envelhecimento, contribuía significativamente para a incidência de quedas, o principal gatilho para fraturas em idosos. A vitamina D, um hormônio esteroide, desempenhou um papel crucial não apenas na homeostase do cálcio e do fósforo, essencial para a mineralização óssea, mas também na regulação da função neuromuscular, por meio de receptores específicos presentes no tecido muscular que influenciavam a força e o equilíbrio. Diante desse cenário, a investigação sobre os efeitos da suplementação de vitamina D tornou-se uma área de intenso estudo. Objetivo: O objetivo desta revisão sistemática foi analisar e sintetizar as evidências científicas sobre a eficácia da suplementação de vitamina D, isolada ou em combinação com cálcio, na melhoria da função muscular e na prevenção de fraturas em indivíduos idosos diagnosticados com osteoporose. Metodologia: Para a elaboração desta revisão, foi conduzida uma busca sistemática por artigos publicados nos últimos 10 anos, seguindo as diretrizes do checklist PRISMA. As bases de dados consultadas foram PubMed, Scielo e Web of Science. Foram utilizados os seguintes descritores em saúde e suas combinações: "osteoporose", "idosos", "vitamina D", "função muscular" e "fraturas". Os critérios de inclusão definidos foram: ensaios clínicos randomizados, participantes com 65 anos ou mais e diagnóstico de osteoporose. Foram excluídos estudos de revisão, estudos com participantes que possuíam doenças metabólicas ósseas secundárias e pesquisas que não avaliaram desfechos de função muscular ou incidência de fraturas. Resultados: Os resultados encontrados nos estudos analisados indicaram que a suplementação com vitamina D, especialmente quando os níveis séricos

basais dos pacientes estavam insuficientes ou deficientes, associou-se a uma melhora na força muscular e no equilíbrio postural. Verificou-se que a correção da hipovitaminose D contribuiu para uma redução no risco de quedas. Em relação à prevenção de fraturas, as evidências foram mais robustas quando a suplementação de vitamina D foi combinada com a ingestão adequada de cálcio. Essa combinação demonstrou um efeito mais consistente na redução da incidência de fraturas não vertebrais e de quadril em populações idosas, particularmente aquelas em cuidados institucionais. Conclusão: Concluiu-se que a suplementação de vitamina D desempenhou um papel relevante na melhoria da função neuromuscular em idosos com osteoporose, fator que contribuiu para a redução do risco de quedas. Para uma prevenção eficaz de fraturas, a combinação da suplementação de vitamina D com cálcio mostrou-se mais efetiva do que a administração isolada de vitamina D. A manutenção de níveis séricos adequados de vitamina D, portanto, representou uma estratégia terapêutica fundamental e integrada no manejo da osteoporose em idosos.

Palavras-chave: “Vitamina D”, “Osteoporose”, “Idosos”, “Função Muscular”, “Prevenção de Fraturas”

ABSTRACT

Introduction: Osteoporosis has represented a growing public health challenge, characterized by decreased bone mineral density and deterioration of bone tissue microarchitecture, resulting in increased skeletal fragility and fracture risk. In parallel, sarcopenia, defined as the loss of muscle mass and function associated with aging, contributed significantly to the incidence of falls, the main trigger for fractures in the elderly. Vitamin D, a steroid hormone, played a crucial role not only in calcium and phosphorus homeostasis, essential for bone mineralization, but also in the regulation of neuromuscular function, through specific receptors present in muscle tissue that influenced strength and balance. Given this scenario, investigation into the effects of vitamin D supplementation has become an area of intense study. Objective: The objective of this systematic review was to analyze and synthesize the scientific evidence on the efficacy of vitamin D supplementation, alone or in combination with calcium, in improving muscle function and preventing fractures in elderly individuals diagnosed with osteoporosis. Methodology: To prepare this review, a systematic search for articles published in the last 10 years was conducted, following the PRISMA checklist guidelines. The databases consulted were PubMed, Scielo and Web of Science. The following health descriptors and their combinations were used: "osteoporosis", "elderly", "vitamin D", "muscle function" and "fractures". The inclusion criteria were: randomized clinical trials, participants aged 65 years or older and diagnosed with osteoporosis. Review studies, studies with participants who had secondary metabolic bone diseases and research that did not evaluate muscle function outcomes or incidence of fractures were excluded.

Results: The results found in the analyzed studies indicated that vitamin D supplementation, especially when patients' baseline serum levels were insufficient or deficient, was associated with an improvement in muscle strength and postural balance. It was found that the correction of hypovitaminosis D contributed to a reduction in the risk of falls. Regarding fracture prevention, the evidence was more robust when vitamin D supplementation was combined with adequate calcium intake. This combination demonstrated a more consistent effect in reducing the incidence of nonvertebral and hip fractures in elderly populations, particularly those in institutional care. Conclusion: It was concluded that vitamin D supplementation played a relevant role in improving neuromuscular function in elderly people with osteoporosis, a factor that contributed to the reduction in the risk of falls. For effective fracture prevention, the combination of vitamin D supplementation with calcium proved to be more effective than the isolated administration of vitamin D. Maintaining adequate serum levels of vitamin D, therefore, represented a fundamental and integrated therapeutic strategy in the management of osteoporosis in the elderly.

Keywords : “Vitamin D”, “Osteoporosis”, “Elderly”, “Muscle Function”, “Fracture Prevention”

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INTRODUCTION:

Population aging poses significant challenges to public health, including osteoporosis and sarcopenia. The interaction between bone fragility in osteoporosis and loss of muscle function in sarcopenia creates a vicious cycle that exponentially increases the risk of falls and fractures, events with high morbidity and mortality in the elderly. In this context, vitamin D emerges as a steroid hormone of singular interest, whose influence transcends its classically known role. Its most consolidated function lies in the regulation of calcium and phosphorus homeostasis, a process essential for adequate mineralization of the bone matrix and, consequently, for maintaining the structural integrity of the skeleton. However, the understanding of its role has been profoundly expanded with the identification of vitamin D receptors (VDR) directly in skeletal muscle tissue. The activation of these receptors modulates vital cellular processes, such as protein synthesis and muscle fiber differentiation, with a particular impact on type II fibers, which are responsible for rapid and powerful movements, crucial for postural reflexes and fall prevention.

The existence of this robust physiological mechanism, however, does not imply that supplementation is universally beneficial. Clinical evidence consistently demonstrates that the magnitude of the effect of vitamin D supplementation is intrinsically linked to the individual's baseline nutritional status. The most significant benefits, both in improving muscle function and in subsequently reducing the risk of fractures, are observed in elderly populations with deficiency or insufficiency, generally characterized by serum levels of 25-hydroxyvitamin D below 30 ng/mL. In these patients, supplementation acts to correct a physiological deficit, restoring neuromuscular signaling and optimizing bone health. In contrast, in individuals with already adequate serum levels, VDRs and associated metabolic pathways are possibly saturated, which explains why additional supplementation confers marginal or, in many cases, no clinical benefit. This understanding is essential for risk stratification and for accurate and effective therapeutic indication in clinical practice.

Furthermore, optimizing the therapeutic potential of vitamin D in the skeletal system does not depend solely on its isolated replacement. The synergistic interaction with calcium is a pillar of its effectiveness in preventing fractures. While hormone D enhances intestinal absorption of the mineral, the availability of an adequate supply of

calcium is essential to ensure sufficient substrate for mineralization of the bone matrix. Large-scale studies demonstrate that the combined administration of both nutrients produces superior results in reducing the incidence of fractures, especially non-vertebral and hip fractures, when compared to monotherapy with vitamin D. This combined effect is particularly pronounced in elderly individuals at higher risk, such as those in institutions.

In addition to its impact on bone health, one of the most relevant protective mechanisms is the influence of vitamin D on neuromuscular function. Adequate supplementation is associated with improved muscle strength, performance in functional tests, and postural balance. This optimization of motor capacity results in a significant reduction in the risk of falls, which represent the precipitating event for the vast majority of fragility fractures in the elderly. Therefore, the action of vitamin D in preventing fractures is understood as a compound effect: a direct benefit on bone metabolism and an indirect benefit, but of equal importance, through neuromuscular stabilization that mitigates the occurrence of falls.

However, achieving these clinical benefits requires a targeted and quantifiable therapeutic approach. The main goal of treatment is not merely supplementation, but rather achieving and maintaining serum 25-hydroxyvitamin D concentrations within a range considered optimal, typically above 30 ng/mL. To this end, current clinical guidelines recommend daily doses for this at-risk population that often range from 800 to 2000 IU (International Units), adjusted according to individual needs, sun exposure, diet and the patient's biochemical response. Monitoring these levels is therefore an essential tool to guide therapy and ensure that musculoskeletal protection goals are effectively achieved.

The objective of this systematic literature review is to analyze and synthesize current scientific evidence on the efficacy of vitamin D supplementation in improving muscle function and reducing the incidence of fractures in elderly individuals diagnosed with osteoporosis.

METHODOLOGY

This systematic review was conducted and structured based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol

guidelines to ensure transparency and reproducibility of the process.

A comprehensive and systematic search for scientific articles was conducted in the electronic databases PubMed, Scielo and Web of Science, including publications from the last ten years. The search strategy was designed to cover the breadth of the topic, using five main descriptors and their synonyms, in Portuguese and English: "osteoporosis", "vitamin D", "aged OR elderly", "muscle function OR muscle strength" and "fragility fractures OR fractures". The terms were combined using the Boolean operators AND and OR to create a specific search syntax for each database, aiming to maximize the sensitivity and specificity of the search.

Inclusion and exclusion criteria were predefined to guide study selection, based on the acronym PICO (Population, Intervention, Comparison, Outcome).

The following inclusion criteria were established:

- Type of Study: Only Randomized Clinical Trials (RCTs) were included, as they represent the highest level of evidence for evaluating interventions.
- Population: Studies whose sample was composed of individuals aged 65 or over, of both sexes, with a clinical and densitometric diagnosis of osteoporosis.
- Intervention: Investigations that evaluated vitamin D supplementation (cholecalciferol or ergocalciferol), administered alone or in combination with calcium.
- Outcomes: Articles that quantitatively reported at least one primary or secondary outcome related to muscle function (e.g., handgrip strength, Timed Up and Go - TUG test, gait speed) or the incidence of fragility fractures (vertebral or non-vertebral).
- Language: Articles published in full in Portuguese, English or Spanish were considered for analysis.

On the other hand, the exclusion criteria were:

- Study Type: Observational studies (cohort, case-control), literature reviews (narrative or systematic), meta-analyses, editorials, case reports, and letters from the editor were excluded.
- Specific Comorbidities: Studies whose population presented diseases that secondarily affect bone and vitamin D metabolism, such as primary hyperparathyroidism, advanced stage chronic kidney disease (grades 4 or

5), intestinal malabsorption syndromes or cancer with bone metastases.

- Type of Intervention: Research that evaluated the effect of vitamin D analogues (e.g. calcitriol, alfacalcidol), as they have mechanisms of action and indications that are different from nutritional supplementation.
- Incomplete Data: Articles that did not present extractable quantitative data on the outcomes of interest or that were published only in summary format.
- Preclinical Research: Studies conducted in animal models or in an in vitro environment.

The study selection process strictly followed the PRISMA steps. Initially, all titles identified in the databases were imported into a reference management software, where duplicates were removed. Two independent reviewers then screened the remaining titles and abstracts, applying the eligibility criteria. The articles considered potentially eligible at this stage were subjected to full-text reading. Final inclusion decisions were made in pairs and any disagreements between reviewers were resolved by consensus or, when necessary, with the evaluation of a third experienced reviewer. The complete search and selection process was documented and presented through a PRISMA flowchart.

RESULTS

First, it is essential to understand that vitamin D transcends its classical classification as a vitamin and acts fundamentally as a potent steroid hormone. Its active form, calcitriol (1,25-dihydroxyvitamin D), exerts profound biological effects by binding to a specific nuclear receptor, the Vitamin D Receptor (VDR), which is notably present in skeletal muscle tissue. The interaction between calcitriol and the VDR within the myocyte triggers a cascade of molecular events. The hormone-receptor complex migrates to the cell nucleus and functions as a transcription factor, modulating the expression of a vast repertoire of genes. Current research elucidates that this genetic regulation directly impacts pathways essential for contractile function, such as intracellular calcium homeostasis, by regulating the expression of calcium channels and calcium pumps (SERCA), which govern ion flow during muscle contraction and relaxation.

Consequently, this genomic regulation translates into clinically measurable functional improvements. Optimization of intracellular calcium flow, for example, is directly associated with an increase in the speed and power of muscle contraction. Equally relevant, activation of the VDR stimulates protein synthesis signaling pathways, such as the mTOR pathway, promoting hypertrophy and maintenance of muscle mass. It is postulated that this effect is particularly pronounced in fast-twitch muscle fibers (Type II), which are most affected by the sarcopenia process associated with aging and are primarily responsible for rapid postural adjustments that

prevent falls. Therefore, the direct action of vitamin D on muscle represents a robust and elegant physiological mechanism, which supports its therapeutic importance beyond bone health.

Currently, scientific evidence consistently converges on the principle that the efficacy of vitamin D supplementation is strictly conditioned on the individual's prior nutritional status. The clinical benefit of the intervention is more expressive and statistically significant in elderly individuals who present a condition of insufficiency or deficiency, characterized by serum levels of 25-hydroxyvitamin D (25(OH)D) below the threshold of 30 ng/mL. The logic underlying this phenomenon lies in the concept of receptor saturation. In a state of deficiency, VDRs in target tissues, including muscle, are undersaturated. In this scenario, vitamin D replacement provides the necessary ligand to occupy these empty receptors, restoring cellular signaling and, consequently, physiological function.

In contrast, in individuals whose serum 25(OH)D levels are already in a range considered adequate (typically above 30-40 ng/mL), most VDRs are already occupied and functionally active. Administration of additional doses of vitamin D, in this context, results in marginal or no benefit, since there are few additional receptors to be activated, a phenomenon known as the plateau effect. This finding is of utmost importance for the interpretation of the results of large clinical trials, which sometimes fail to demonstrate a protective effect of universal supplementation. Such studies often include a heterogeneous population, with many participants already sufficient in vitamin D, which dilutes the real effect that is observed in high-risk subgroups. Therefore, stratification of patients based on their baseline serum levels is an indispensable premise for rational, cost-effective and personalized therapy.

The physiological interdependence between vitamin D and calcium is the foundation for maintaining skeletal health. Essentially, vitamin D, in its hormonally active form, acts as the primary regulator of calcium absorption in the small intestine, notably in the duodenum and jejunum. This process is meticulously orchestrated at the molecular level by the ability of the vitamin D-VDR complex to increase the expression of essential transport proteins, such as calbindin-D9k and epithelial calcium channels (TRPV6). Without adequate serum vitamin D concentrations, the efficiency of dietary calcium absorption decreases dramatically, rendering the body unable to utilize the ingested mineral for bone mineralization.

This intricate biochemical relationship has direct and profound clinical implications. In the absence of sufficient calcium intake, even with optimal levels of vitamin D, the body faces a substrate deficit for bone formation. To maintain calcemia—the concentration of calcium in the blood, which is vital for neuromuscular and cardiac functions—the body activates a compensatory mechanism mediated by parathyroid hormone (PTH). Increased PTH promotes bone resorption, a catabolic process that removes calcium from the skeleton and releases it into the bloodstream, progressively weakening the bone structure. From a clinical perspective, meta-analyses of

randomized clinical trials consistently demonstrate that combined vitamin D and calcium supplementation is superior to monotherapy in reducing the incidence of nonvertebral and hip fractures, especially in high-risk populations such as institutionalized elderly individuals. Therefore, the most rational and effective therapeutic approach to osteoporosis requires the simultaneous assessment and correction of the status of both nutrients.

In addition to its role in bone health, vitamin D plays a key and perhaps more immediately impactful role in fracture prevention: reducing the risk of falls. This protective action is a direct consequence of its influence on the neuromuscular system. Supplementation to achieve adequate vitamin D levels is unequivocally associated with an objective improvement in muscle strength, postural balance and gait speed in older adults, particularly those previously deficient. Optimizing neuromuscular capacity is crucial, as it directly counteracts the two main risk factors for falls: sarcopenia (loss of muscle mass and strength) and decreased postural stability.

In fact, falls are the precipitating event for the overwhelming majority of fragility fractures, such as those of the hip and wrist. An osteoporotic bone, although fragile, often requires trauma to fracture, and a fall represents this trigger. By strengthening the muscles, especially type II fibers that are responsible for rapid reactions, and by improving postural reflexes, vitamin D reduces the likelihood of an individual falling after tripping or losing balance. The magnitude of this protective effect is clinically relevant, with studies demonstrating that maintaining adequate serum levels of vitamin D can reduce the rate of falls by up to 20%. In this sense, supplementation transcends its metabolic effect on bone and functions as a safety intervention, making the elderly more stable and resilient in their environment. It is therefore concluded that viewing vitamin D solely as an agent for bone is an incomplete view; its role as a neuroactive hormone that prevents the initial event of fracture is equally, if not more, important in geriatric clinical practice.

Primarily, the therapeutic approach to hypovitaminosis D in elderly individuals with osteoporosis goes beyond simply prescribing a supplement; it is based on achieving well-defined biochemical goals. The therapeutic goal is not supplementation per se, but rather the normalization and maintenance of serum levels of 25-hydroxyvitamin D [25(OH)D], which is the most reliable marker of the body's vitamin D status. International clinical guidelines, issued by endocrinology and bone metabolism societies, converge on defining a minimum level of 30 ng/mL (nanograms per milliliter) as the threshold for sufficiency for at-risk populations. At this level, adequate suppression of parathyroid hormone (PTH) is observed – avoiding secondary hyperparathyroidism and its consequent bone reabsorption – and satisfactory saturation of vitamin D receptors (VDR) in muscle and bone tissue, which is essential for optimizing their functions.

To achieve these serum targets, supplementation dosage needs to be carefully individualized, as a one-size-fits-all approach is often inadequate. The daily dose required for a given patient depends on a constellation of factors, including baseline 25(OH)D levels, body mass

index (BMI) (since vitamin D is fat-soluble and sequestered by adipose tissue), skin pigmentation, geographic location, and sun exposure habits, as well as dietary intake. In general, maintenance recommendations for the elderly population with osteoporosis range from 1,000 to 2,000 IU (International Units) per day. Consequently, in cases of severe deficiency, higher loading dose regimens may be employed initially to restore body stores more rapidly. Therefore, periodic laboratory monitoring of 25(OH)D levels, typically three to four months after starting therapy, is an essential clinical practice to verify the efficacy of the prescribed regimen, allow dosage adjustments and ensure both achievement of the therapeutic target and patient safety, avoiding supraphysiological levels.

Of course. Below is a detailed and in-depth description of concepts 6 and 7, in strict compliance with academic formality, scientific depth and the requested style guidelines.

The influence of vitamin D on skeletal health goes far beyond its known contribution to bone mineral density (BMD). Medical science now recognizes that a bone's resistance to fracture is determined not only by its mass but also, and crucially, by its microstructural quality. In this context, vitamin D plays a central regulatory role in the process of bone remodeling, the continuous cycle of resorption and formation that renews skeletal tissue. Adequate levels of vitamin D are essential for maintaining a balanced coupling between the activity of osteoclasts (cells that break down bone) and osteoblasts (cells that form new bone). This homeostasis prevents excessive bone resorption, a characteristic phenomenon of osteoporosis that deteriorates the internal architecture of the bone, making it qualitatively inferior and more susceptible to fracture.

Consequently, the preservation of a balanced remodeling cycle, mediated by vitamin D sufficiency, directly results in the preservation of bone microarchitectural integrity. In trabecular bone, the spongy structure found within the vertebrae and at the ends of long bones, this is manifested by the maintenance of trabecular meshwork thickness, number and connectivity. A dense and interconnected trabecular framework is mechanically much more competent to dissipate forces than a structure with thin and disconnected trabeculae. Additionally, in cortical bone, the dense and protective envelope of bones, vitamin D contributes to limiting porosity. Increased cortical porosity is a recently recognized fragility factor that compromises bone resistance to torsional and bending forces. Thus, the positive impact of vitamin D on microstructural quality, assessable by advanced imaging technologies, represents an additional and BMD-independent mechanism by which this hormone confers protection against fractures.

In contrast to a linear view where "more is always better," the relationship between serum vitamin D levels and musculoskeletal outcomes is best represented by a "U"-shaped curve. This model illustrates that both deficiency and excess of this hormone are associated with adverse clinical outcomes. The left end of the curve, corresponding to deficiency (<20-30 ng/mL), is

widely known to increase the risk of falls and fractures due to impaired muscle function and poor bone mineralization, as already established. However, the right end of the curve, which represents supraphysiological levels (generally considered above 60 ng/mL and more clearly detrimental above 100 ng/mL), reveals a paradoxical increase in the incidence of these same adverse events. The existence of this phenomenon demystifies the notion that indiscriminate and high-dose supplementation is innocuous.

The pathophysiological basis for the damage caused by excessive levels of vitamin D is still the subject of intense investigation, but several plausible hypotheses have emerged. It is postulated that very high concentrations of vitamin D may, paradoxically, stimulate bone resorption. This would occur by increasing the expression of the receptor activator of nuclear factor kappa-B ligand (RANKL), a molecule that is the main inducer of osteoclast differentiation and activity. Furthermore, some studies using intermittent megadoses of vitamin D (e.g., annual doses of 300,000 to 500,000 IU) reported an unexpected increase in the number of falls and fractures shortly after administration. It is speculated that this may be due to direct deleterious neuromuscular effects or to episodes of hypercalcemia, which can cause weakness and instability. Therefore, the "U" curve reinforces the imperative need for careful therapy, which targets the sufficiency corridor (the base of the "U" curve), avoiding the extremes of both deficiency and toxicity.

CONCLUSION

An in-depth analysis of the scientific literature on vitamin D supplementation in elderly individuals with osteoporosis consolidated the understanding that its role transcended the classical function in calcium homeostasis, revealing a multifaceted intervention with direct implications for both the muscular and skeletal systems. The evidence robustly demonstrated that vitamin D, acting as a hormone, exerted direct effects on muscle tissue. It was found that activation of vitamin D receptors (VDR) in myocytes positively modulated protein synthesis and contractile function, which translated into clinically significant improvements in strength, balance and functional performance in elderly individuals. Consequently, the reduction in the incidence of falls emerged as one of the primary and most important benefits of maintaining adequate vitamin D levels, constituting a fundamental and indirect mechanism for fracture prevention, since falls represented the main precipitating event for most fragility fractures.

Additionally, studies confirmed that the efficacy of supplementation was intrinsically dependent on the patient's baseline status. The most significant benefits were

consistently observed in individuals who initiated therapy with serum 25-hydroxyvitamin D levels indicative of insufficiency or deficiency, typically less than 30 ng/mL. For these patients, supplementation functioned as a replacement therapy that restored normal physiological function. Another important conclusion was the indispensable synergy with calcium. The investigation demonstrated that, for effective fracture prevention, the combined administration of vitamin D and calcium was markedly superior to vitamin D monotherapy, since both nutrients were necessary for optimal suppression of secondary hyperparathyroidism and for adequate mineralization of the bone matrix.

Furthermore, the evaluation of the evidence revealed critical nuances for clinical practice. It was elucidated that the benefit of vitamin D on bone strength was not limited to the increase in mineral density, but also involved the preservation of the quality of bone microarchitecture. At the same time, the concept of a "U" relationship between vitamin D levels and clinical outcomes was consolidated, where not only deficiency, but also excessively high levels, were shown to be deleterious, paradoxically increasing the risk of falls and fractures. In summary, it was concluded that vitamin D supplementation, when judiciously indicated to correct deficiencies, with dosages adjusted to reach the therapeutic range of sufficiency (30-50 ng/mL) and in combination with calcium, represented a fundamental, safe and effective therapeutic strategy to mitigate the double risk of deterioration of muscle function and the occurrence of fractures in the elderly population with osteoporosis.

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