



Empleo de la ingeniería tisular en la osteoartritis de la articulación temporomandibular (ATM). Revisión de la literatura

Use of tissue engineering in osteoarthritis of the temporomandibular joint (TMJ). A literature review

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Palabras claves:

Células madre, beneficios, articulación temporomandibular, osteoartritis e ingeniería tisular.

Keywords: Stem cells, benefits, temporomandibular joint, osteoarthritis, and tissue engineering

Resumen

Introducción. La articulación temporomandibular (ATM) es una articulación gínglimoartrodial que participa activamente en los movimientos mandibulares, al estar expuesta a presión, alguna estructura puede verse comprometida en su morfología provocando una alteración en las propiedades biomecánicas del cartílago y el hueso, especialmente el cartílago condilar mandibular, pudiendo desarrollar diferentes patologías como es la osteoartritis, que por lo general afecta al cartílago condilar y a los tejidos subyacentes. **Objetivo.** Describir el empleo de la ingeniería tisular como tratamientos de la Osteoartritis en la ATM. **Metodología.** La presente investigación tuvo un enfoque exploratorio y descriptivo con una búsqueda exhaustiva en varias bibliotecas digitales como como *PubMed*, *SciELO*, *Dialnet*, *Google Academic* y *ScienceDirect* aplicando criterios de inclusión y exclusión. **Resultados.** Entre los trastornos temporomandibulares, la osteoartritis es prevalente y se manifiesta con dolor, crepitación y limitación de movimiento. El diagnóstico incluye evaluaciones clínicas y radiográficas avanzadas y los tratamientos varían desde opciones no invasivas hasta intervenciones quirúrgicas, con la ingeniería tisular y las células madre como enfoques prometedores para la regeneración articular. **Conclusión.** Se puede concluir que la ingeniería tisular mediante células madre, se ha destacado como un método prometedor para la reparación de tejidos afectados en esta patología. **Área de estudio general:** Odontología **Área de estudio específica:** Patología bucal. **Tipo de estudio:** Revisión Bibliográfica.

Abstract

Introduction. The temporomandibular joint (TMJ) is a ginglymo-arthrodial joint that actively participates in jaw movements. When exposed to pressure, some structure may be compromised in its morphology causing an alteration in the biomechanical properties of the cartilage and bone, especially the mandibular condylar cartilage, and different pathologies may develop, such as osteoarthritis, which usually affects the condylar cartilage and underlying tissues. **Objective.** Describes the use of tissue engineering as treatments for Osteoarthritis of

the TMJ. **Methodology.** The present research had an exploratory and descriptive approach with an exhaustive search in several digital libraries such as PubMed, Scielo, Dialnet, Google Scholar and ScienceDirect applying inclusion and exclusion criteria. **Results.** Among temporomandibular disorders, osteoarthritis is prevalent and manifests with pain, crepitus, and limitation of movement. Diagnosis includes advanced clinical and radiographic evaluations, and treatments range from noninvasive options to surgical interventions, with tissue engineering and stem cells as promising approaches for joint regeneration. **Conclusion.** It can be concluded that tissue engineering using stem cells has been highlighted as a promising method for the repair of affected tissues in this pathology.

Introduction

The temporomandibular joint (TMJ) is a ginglymoarthrodial joint because it performs translational movements, with sliding and rotational movements to allow several basic functions for our correct development such as speaking, swallowing and chewing, however the ATM is composed of bone structures such as: mandibular condyle, glenoid cavity, articular tubercle of the temporal bone and soft structures such as: articular disc, joint capsule, ligaments and muscles; which are harmonically related when they perform movements such as depression, elevation, laterality, protrusion, retraction and combined mandibular movements, which correspond to a physiological action, however when any structure that forms it is affected, the biomechanical properties of the cartilage and bone are altered, especially the mandibular condylar cartilage. (1, 2, 3, 4).

In addition, there are multiple pathologies that affect the ATM such as arthralgia, myalgia, disc displacement with or without reduction, degenerative joint diseases, subluxation and headaches due to injuries, when these progress progressively the state of the disc and the structures can be evidenced by magnetic resonance (5).

Osteoarthritis is the pathology that usually affects the condylar cartilage and also the adjacent tissues, producing symptoms that alert the patient, which is why Treatment is aimed at reducing joint pain, improving the ability to move, function properly and thus prevent progressive joint destruction, so that current treatments are based on non-surgical and surgical procedures that They often represent challenges, as conventional treatments

tend to focus on improving symptoms and quality of life, but in many cases the complete reversal of this disease through such treatments is not feasible, although they are effective but their long-term sustainability may be limited. This is because they address the patient's well-being temporarily, as they do not always manage to address the underlying cause of the problem.(1, 3, 4).

Tissue engineering has therefore rethought the use of stem cell-based therapies which help regenerate affected tissues, becoming a promising treatment that replaces injured cells. To this end, two types of stem cells have been proposed according to their origin: embryonic and non-embryonic or adult, which, regardless of their etiology, will allow the objective of bone remodeling and remodeling of affected tissues to be met. Although there are not many studies describing the benefits, the present research focuses on describing the use of tissue engineering in TMJ osteoarthritis.(1–3, 6).

Methodology

The present research had an exploratory and descriptive approach with an exhaustive search, focused on collecting information on the application of stem cells in the treatment of TMJ Osteoarthritis, whichIt was carried out through extensive research in various digital libraries such asPubMed, SciELO, Google Academic, Dialnet and ScienceDirect, from 2018 to February 13, 2023 in English and Spanish,Search planning used specific terms from two classification systems: Medical Subject Headings (MeSH) and Health Sciences Descriptors (DeCs),In addition, keywords from indexed journals were used. The selected keywords were: Stem cells, benefits, temporomandibular joint, osteoarthritis and tissue engineering,which were used for the searchunifying them with logical connectors OR and AND.

Search strategy

Table 1.Search strategy

Search method	Search tree	Total
Pubmed	((mother cells) AND (temporomandibular joint)) AND (benefits) (Osteoarthritis) (tissue engineering))Filters: Free full text, Case reports, Literature reviews and Clinical trials.	15
Scielo	((mesenchymal stem cells) AND (temporomandibular joint)) Filters: in the last 5 years	6

Table 1. Search strategy (continued)

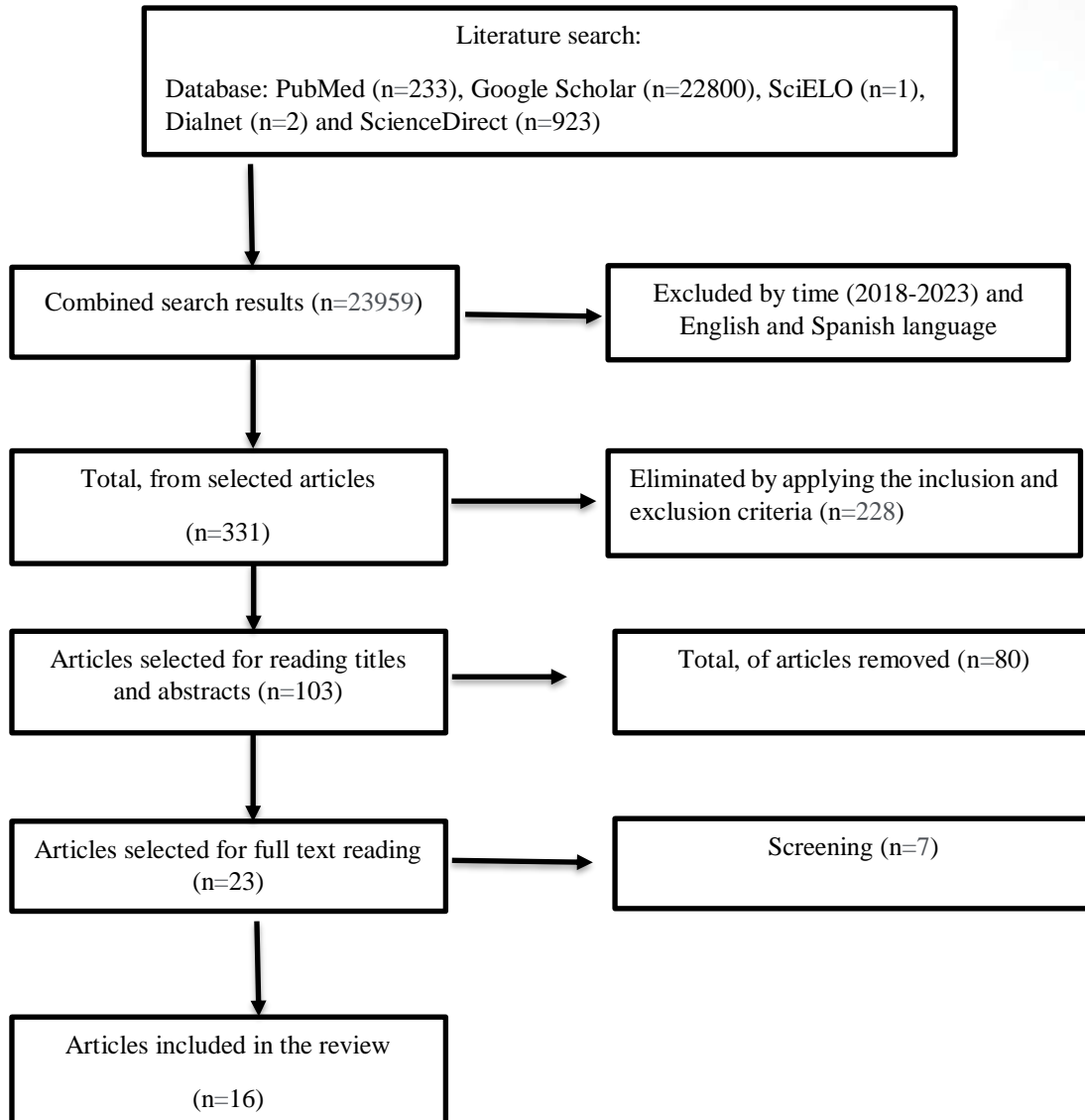
Search method	Search tree	Total
Google Scholar	((mother cells) AND (temporomandibular joint)) OR (Benefit) Filters: Open access, Case reports, Literature reviews, Systematic reviews and clinical trials in the last 4 years.	71
Dialnet	((mother cells) AND (temporomandibular joint)) OR (Benefit) Filters: Open access, Case reports, Literature reviews, Systematic reviews and clinical trials in the last 4 years.	1
Sciencedirect	((mother cells) AND (temporomandibular joint))(tissue engineering)Filters: Review articles, Research articles, in the last 5 years	10
Total		103

Note: After the initial search, language and temporality filters were applied, as well as selection criteria, to finally obtain a total of 103 articles to be evaluated.

Ethical aspects

From an ethical perspective, the literature review study does not entail any risk because it is based solely on document analysis, without performing medical treatments or experiments on human beings. Therefore, it was not considered necessary to obtain informed consent.

Figure 1. Literature search flowchart



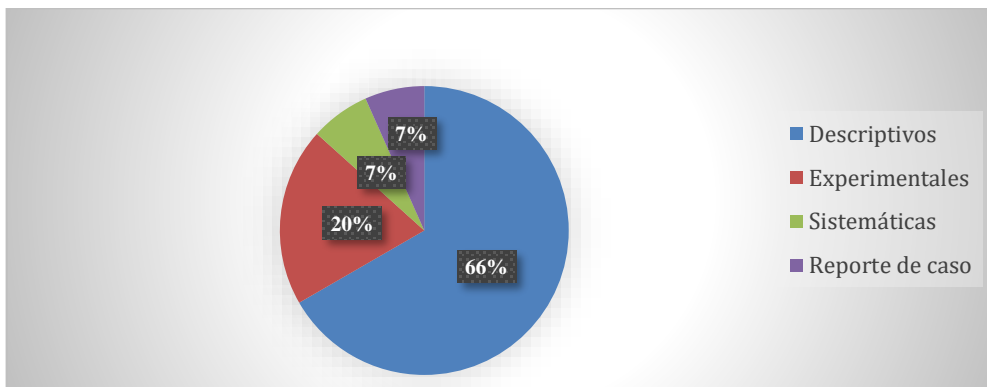
The flowchart shows the results obtained from the search in digital databases, which were selected and organized using filters based on criteria to include or exclude information.

For the selection of studies of interest, the following inclusion and exclusion criteria were used. The inclusion standards considered in this study covered various types of research: randomized controlled trials (RCTs), literature reviews, case reports, systematic reviews with and without meta-analysis, as well as articles in English on the use of stem cells in TMJ osteoarthritis. Articles in Spanish that dealt with mesenchymal stem cells for the regeneration of degenerative joint diseases, all published in the last five years, were also

included. In contrast, books, theses, epidemiological studies, letters to the editor, articles without access to the full text or outside the scope of indexed journals were excluded.

In the bibliographic search, 23,959 articles were initially obtained, of which 233 belong to PubMed, 1 to SciELO, 22,800 to Google Academic, 2 to Dialnet and 923 to ScienceDirect.

Figure 2.Types of studies



This pie describes the types of study that belong to the scientific articles that support the bibliography of this study.

Results

The ATM is the connection between the jaw and the temporal bone of the skull, allowing movements such as opening and closing the mouth, and also allowing movement. Due to its laterality and protrusion that are essential for functions such as chewing, swallowing and speaking, this joint plays crucial roles in essential life activities such as chewing, swallowing and speaking (3, 7).

When there are problems in this area, it is known as temporomandibular disorder, which refers to a varied set of conditions that affect the muscles used for chewing, the joint that connects the jaw to the skull, and other structures related to this area of the body. This set of conditions is recognized as the main cause of pain in the orofacial region that is not associated with dental problems (2, 6, 7).

TMJ problems can have various causes and the etiology of these temporomandibular disorders can be multifactorial. Some of the factors that have been associated with TMJ problems include: dental malocclusion, bruxism, injuries or trauma, stress, arthritis, structural problems, genetic factors and it is even related to deforming oral habits such as biting nails or persistently chewing gum (5, 7, 8).

Temporomandibular disorders can be categorized into a variety of conditions, ranging from masticatory muscle complications, TMJ dysfunctions, persistent restriction of

mandibular movements, and problems associated with mandibular growth. Specific TMJ disorders include inflammatory conditions that are named after the injured region, such as: inflammation of the joint capsule, inflammation of the synovial membrane, inflammation behind the joint disc, and joint degeneration, respectively (9, 10).

Among the challenges that can arise in the TMJ, such as those related to the condyle-disc complex, mobility restrictions, degenerative joint diseases, and congenital or development-related problems, osteoarthritis stands out as the most prevalent condition. It is estimated to affect approximately 8% to 16% of the general population and can manifest in one or both joints (9, 10).

Osteoarthritis is a chronic and progressive degenerative condition that may involve the wearing away of the cartilage in the joint and affect the surrounding tissues, it can cause pain in the jaw, crepitation, limitation in mandibular movements and in more advanced cases, deformities in the joint. People with TMJ osteoarthritis may also experience inflammation and discomfort in the affected joint, it should be mentioned that it can be the result of various factors, including aging, natural wear and tear of the joint, previous injuries, dental malocclusion, genetic and hormonal factors (3, 7, 9, 11).

Recognizing temporomandibular joint degeneration due to osteoarthritis It is based mainly on the evaluation of clinical characteristics, complemented by radiographic analysis, with recent introduction of technologies such as imaging techniques such as magnetic resonance imaging and computed tomography, because has increased the effectiveness of diagnosis. However, accurate diagnosis remains a challenge in terms of health, due to significant limitations and considerable socioeconomic costs (3, 6).

The choice of treatment strategies is tailored to the severity of the disorder, with preference initially given to more cautious approaches. Noninvasive alternatives such as patient counselling, the use of drugs, physical therapies, interocclusal devices, prosthetic rehabilitation, as well as minimally invasive interventions such as arthrocentesis, hyaluronic acid injections, intra-articular corticosteroids, platelet-rich plasma (PRP), ozonized oxygen therapy and arthroscopy are highlighted. In severe cases, when conservative treatments are ineffective, more intrusive surgical interventions focused on the joint become necessary (7).

From this perspective, the use of tissue engineering using stem cells is positioned as a promising strategy in the field of regenerative therapy. Mesenchymal cells originate mainly from two sources, namely, embryonic stem cells and adult-derived stem cells, which include mesenchymal cells, play a central role in this innovative perspective (7, 10).

Currently, the scientific literature presents few studies that address the use of mesenchymal cells for the regeneration of TMJ disorders. Despite this limitation, numerous exhaustive studies have been carried out on the use of these cells in degenerative diseases of the knee. The knee has been compared to the temporomandibular joint in both its function and its anatomy and related diseases.(9, 10, 12).

In current clinical practice, bone marrow stands out as the main source for cartilage repair, being extensively investigated, either in its sole application or in combination with scaffolds, despite associated limitations, such as morbidity at the donor site. Mesenchymal stem cells obtained from the inside of the bone that have demonstrated, through continuous injections, the ability to rescue cartilage degradation and abnormal remodeling of subchondral bone. This process leads to notable improvements in bone volume, thickness and cartilage health, while reducing the loss of glycosaminoglycans. In addition, a promotion of cartilage matrix production, protective activation of chondrocytes, is observed, which leads to a reduction in programmed cell death of chondrocytes in the surrounding matrix (7, 9, 13).

It is worth mentioning that the combination of injections along with tissue engineering emerges as an advanced solution to effectively address severe osteonecrosis disorders in the TMJ, as it offers an encouraging perspective for the repair and regeneration of joint components in the context of TMJ (14, 15).

Table 2. *Compilation of clinical trials involving stem cells*

Article	Species	Intervention	Procedure	Result
Temporomandibular joint osteoarthritis: Regenerative treatment with a stem cell containing advanced therapy medication (ATMP). Köhnke et al. 2021 (4)	Rabbits	-AB Serum -Hyaluronic Acid -mesenchymal stromal cells -Mesenchymal stromal cells in hyaluronic acid	Therapy began with a single joint injection, administered randomly to 28 rabbits in 4 groups. After 4 additional weeks, the animals were sacrificed and the removed joints were examined histologically.	In the groups that were treated with stromal cells, more cartilage tissue was noted to be integrated in the areas around the cartilage defect after the injection of stem cells into the joint. This indicates that there is considerably more potential for regeneration in TMJ osteoarthritis and that it is an effective treatment option.
Conditional deletion of Adrb2 in mesenchymal stem cells attenuates	Mice	Subchondral bone	Mice were crossed with Adrb2 (adrenergic receptor)	Stem cells could attenuate abnormal changes induced by

osteoarthritis-like defects in the temporomandibular joint. Suna et al. 2020 (11)	mesenchymal stem cells	flox mice to generate mice lacking expression of a class of cellular receptors that respond to catecholamines, which are related to the processes involved in osteoarthritis, and were then injected with subchondral bone mesenchymal stem cells (MSC) which express high levels of ADRB2.	erosion of TMJ articular cartilage in mice, indicating that ADRB2 may serve as a potential target for treatment.
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Table 2. *Compilation of clinical trials involving stem cells (continued)*

Article	Species	Intervention	Procedure	Result
Identification of human joint fibrocartilage stem cells with a distinct fibrocartilage capacity. Bi et al. 2020 (15)	-Chuman cells in vitro studies -MRat condylar cartilage defect model	-Chuman fibrocartilage stem cells -Mesenchymal stem cellshuman orofacial	The experiment began with the association of human fibrocartilage progenitor cells (hFCSCs). Their potential was then compared with human orofacial mesenchymal stem cells (hOFMSCs) in laboratory settings and in animal models of condylar cartilage defects in rats.	Stem cells offibrocartilagehuman exhibited typical characteristics of mesenchymal stem cells, with a significantly stronger cholandrogenic capacity compared to mesenchymal stem cellshuman orofacial in both study groups.

The species that have been used so far with all bioethical permits in conjunction with the Declaration of Helsinki are detailed. In addition, the type of intervention in the sample or species is detailed, with their respective results, which denote positivism in the efficacy of using these types of stem cells for the treatment of TMJ osteoarthritis.

Discussion

In recent research, it has been highlighted that the use of stem cells emerges as a useful method to treat this disorder. These cells can be obtained from various sources, such as bone marrow, umbilical cord, muscle, adipose tissue, dermis, peripheral blood, liver, dental pulp and synovial fluid of the temporomandibular joint. Their ability to repair tissues, promote regeneration and modulate the immune system is adapted according to the degree of damage present in the joint (7).

It is worth mentioning that this therapeutic approach has been highlighted as a potentially promising strategy to address the degeneration and tissue damage associated with osteonecrosis in this specific joint, however, Zhang mentions that there are multiple long-term consequences of manipulating certain structures of the TMJ joint (3, 16).

Studies by Zuleni mention that the versatility of obtaining progenitor cells provides a unique ability to differentiate into various cell types, including chondrocytes and osteoblasts. This implies that these cells can contribute to the regeneration of both cartilage and bone, key components affected in osteonecrosis. There are even studies such as that of Boulos Rita that report that stem cells can play a crucial role in modulating the inflammatory process associated with osteonecrosis, thus contributing to the reduction of inflammation and the improvement of the local microenvironment in the TMJ (1, 2, 7).

In the scientific literature, many authors such as Leon Victor, Gong de Shan, and Gonzales have expressed promising interest in addressing TMJ osteonecrosis. Studies supporting the ability to repair damaged tissue, relieve inflammation, and potentially improve joint function in cases of osteonecrosis have been documented (6, 15).

Suna et al. (11) explained that hyaluronic acid also seems to be a promising means to improve differentiation capacity, which would be useful for obtaining more treatment options. However, other authors mention that there are several methodological and practical limitations for clinical application (6, 11).

Cachari in his literature review mentions that optimizing stem cell collection and application techniques, as well as a more complete understanding of the specific mechanisms that govern their function in tissue repair, are critical areas for future research, however, most authors detail that research is crucial to determine their long-term clinical viability and their ability to increase the well-being of patients suffering from this disorder(8).

Conclusions

- Osteoarthritis is a persistent and progressive condition that damages the cartilage and surrounding tissues of the TMJ, causing pain, crepitation, limitation in jaw

movements and, in advanced cases, joint deformities. Although various treatment approaches have been developed, including non-surgical and surgical procedures, many of them have limitations on the state of well-being on a permanent basis.

- Tissue engineering using stem cells, particularly mesenchymal stem cells, has been highlighted as a promising approach for the recovery of affected tissues in TMJ. These cells have the ability to rescue cartilage degradation and abnormal subchondral bone remodeling, leading to remarkable improvements in cartilage health and promotion of cartilage matrix production.
- The TMJ plays crucial roles in essential life activities such as chewing, swallowing, and speaking. However, when this joint is affected, it can lead to a diverse set of musculoskeletal and neuromuscular conditions known as temporomandibular disorders, with osteoarthritis being the most prevalent condition.
- The use of stem cells in the treatment of temporomandibular joint (TMJ) osteoarthritis offers a promising prospect in the realm of regenerative therapy. Although more research is still needed to fully understand the efficacy and safety of these therapies, existing studies suggest that progenitor cells, especially those found within the bone, in conjunction with tissue engineering techniques, could offer a promising advanced solution for the treatment of TMJ osteoarthritis. This opens new doors to more effective and long-lasting treatments to improve the lifestyle of individuals with this debilitating condition.
- It is worth mentioning that several potential mechanisms of action have been identified, including differentiation into cartilage cells, modulation of inflammation and secretion of growth factors, however, further clinical and preclinical research is required to adequately evaluate the protection, efficacy and long-term viability of progenitor cell therapies in patients with TMJ osteoarthritis.

Conflict of interest

There is no conflict of interest in relation to the presented article, so it is a bibliographic review, and does not require informed consent.

Authors' contribution statement

Author 1: A thorough review of the relevant scientific literature has been carried out, contextualizing and supporting the study appropriately. The most recent advances in the field have been considered, which has allowed a firm theoretical foundation to be established. It not only provides a solid theoretical framework, but also highlights current

trends and gaps in existing research, ensuring that the study is based on robust and up-to-date evidence, adding value and rigor to academic work.

Author 2: She reviewed and corrected drafts of the manuscript, ensuring that the content was clear and accurate. She also supported the interpretation of the results and the writing of the conclusions. It is worth mentioning that she helped with constructive feedback, ensuring that academic and ethical standards were met.

In summary, the contribution of Deicy Paulina Macas Sanmartin and María Isabel Cabrera Padrón in this scientific article has been fundamental for the development and successful completion of the study.

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