Review article

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Mesoporous Silica Nanoparticles, Methods of Preparation and Use of Bone Tissue Engineering

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ABSTRACT
Biomaterials are a large group of vitally important materials with many different inorganic and organic types. Biocomposites are produced by using materials such as polymer, metal, and ceramics. Bone tissue engineering deals with materials that can mimic the real bone structure found in the body. These materials used in the human body must be capable of many aspects such as their mechanical strength related to the area where they are used, as well as their properties such as biocompatible, biodegradable, and non-toxic. If the material is intended to treat the bone structure, it should be biodegradable, but it should be resistant to degradation if intended to be used for a long time. With the advance in technology, nanoparticles have become appealing in bone tissue engineering due to their many unique properties. In recent years, mesoporous silica nanoparticles (MSNs) have been prominent biomaterials in the medical field due to their properties such as alterable size structure, large pore volume, and surface area. This study aims to give information about the biomedical properties, synthesis methods, and importance of MSNs with unique properties in bone tissue engineering applications. This study is compiled by examining many studies in the literature.

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Introduction

Nanotechnology science includes different fields such as physics, chemistry, biology, environment, engineering and medicine. Developments in nanotechnology and the use of nanoparticles that emerged in the diagnosis, imaging, and therapy of diseases have provided benefits in the medical field [1, 2, 3]. Materials with at least one dimension and particle sizes between 1 and 100 nm are called nanomaterials [4, 5]. They exhibit properties such as good mechanical strength, superior bioactivity and resorbability. In addition, the decrease in particle size causes a significant increase in particle boundaries and changes the general physicochemical properties [5]. Nanoscale materials are a suitable structure for the transport and distribution of related drugs in the treatment of diseases such as cancer, Alzheimer's, and Parkinson's. Nanomaterials can reduce interaction with healthy tissues by targeting sick cells to alleviate the harmful effects of

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chemotherapy [4, 6]. There are many nanoparticles (NPs) used in biomedical applications. Table 1 shows these and their application areas.

Amorphous silica is one of the basic materials that can be produced by sponges, diatoms, limpets and plants, which are abundant in nature, and are widely used in modern industry. It is used in a variety of applications such as cosmetics, heterogeneous catalysis, coatings, bio-imaging and drug delivery, especially due to its morphological controllability [7, 8, 9]. Silica is essentially the largest component of sand and can be produced synthetically. Due to its porous structure, it is suitable for the adsorption of various water-soluble elements. Thanks to its adsorption and photocatalytic properties, silica nanoparticles can be used in the field of concrete and ceramics [10]. In recent years, bioactive glass particles and silica nanoparticles have been used in biomaterials for the development of some biomedical propertiesIt has been reported that with the addition of bioactive silica phase, mechanical strength develops, biocompatibility of osteoblasts and bone formation of polymers are greatly increased [11].

Silica nanoparticles used in the biomedical field can be found in mesoporous (2-50 nm pore size) [12] and non-porous (solid) or a mixture of both, which is amorphous. Porous ones carry their active charges by physical adsorption or chemical bonding, while non-porous ones carry their charges through encapsulation or drug-silane conjugation [13, 14]. The pores and nano size of silica nanoparticles enable the drug release rate to control in order to make the continuous drug delivery effect efficient [15]. It has been pointed out that silica is non-toxic and does not show any side effects in rats even at concentrations as high as 50.000 mgL^{-1} [16]. Silica has been rated as generally considered safe by the Food and Drug Administration (FDA) [17, 18, 19].

Table 1 Biomedical application examples of some nanoparticles

Nanoparticles	**Application**	**Reference**
Gold	Bone filler and its treatment Drug release	[20, 21]
TiO_2	Bone tissue engineering	[22]
Silver	Colon cancer therapy, Bioimaging	[23, 24]
ZnO	Breast cancer therapy	[25, 26]
CuO	Bone tissue engineering, Drug delivery	[27, 28, 29]
CeO_2	Cancer therapy	[30, 31, 32]
Calcium phosphate	Bone regeneration, Cancer therapy	[33, 34, 35]
Magnetic nanoparticles	Drug targeting, Tissue scaffold	[36, 37]
Mesoporous silica nanoparticles (MSNs)	Drug delivery, Bone tissue engineering, Cell monitoring	[38, 39, 40]

While studies on the use of mesoporous silica nanoparticles (MSNs) in drug release have increased rapidly in recent years, studies on its use in bone tissue engineering are increasing at an interesting level. However, studies on the use of MSN in bone tissue engineering are limited. In this study, silica and mesoporous silica nanoparticles with unique biomedical properties and their synthesis methods are discussed. Differently, bone loss, treatment and features of bone structure are briefly examined. In recent years, the usability, healing effect and importance of MSNs in bone tissue engineering applications have been investigated in the light of the literature.

Mesoporous Silica Nanoparticles (MSNs)

Amorphous silica was first recognized as a drug carrier in 1983 [18]. In 1992, Kresge [41] synthesized sequential mesoporous molecular sieves. This breakthrough paved the way for silica-based nanocarriers. In 2001, a mesoporous silica nanoparticle called MCM-41 (mobile crystalline material) [42] was developed for the first time as a drug delivery system for the encapsulation of ibuprofen drug [18]. According to the molar composition of the reaction environment, the pores were reported to be hexagonal (MCM-41, 2D or SBA-15), cylindrical (M41S) [43] or cubic (MCM-48, 3D) structure [42, 44, 45, 46]. TEM image of MSNs in microsphere structure is given in the Fig.1.

Although the pores are in a crystalline structure, the pore walls are amorphous [47]. Amorphous silica shows better biocompatibility, unlike crystalline silica [48]. By 2003, MSNs were functionalized with cadmium sulfide and used for controlled drug release. This study revealed that MSNs have high biocompatibility and high drug delivery efficiency [18].

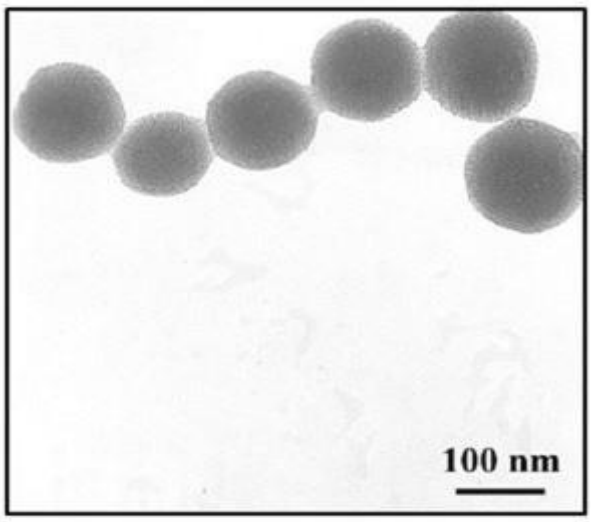

Fig 1 TEM image of MSNs [49]

Thanks to their many unique properties such as high surface area (1000 m^2g^{-1}) [45, 49] adjustable particle shape, easy functionalization of the inner and outer surface, pore volume (1 cm^3g^{-1}) [45], which allows high drug loading, high thermal and chemical stability [50], high adsorption capacity [51] strength [52] and biocompatibility [19], MSNs have become an interesting material in medicine [1, 6, 53, 54, 55, 56]. In recent years, applications in the field of adsorption, catalysis, chemical separation, imaging, targeted anti-cancer agent, drug release, cell monitoring [40] biosensor, and solar cell [57] have been increasing rapidly (Fig. 2) [50, 54, 58].

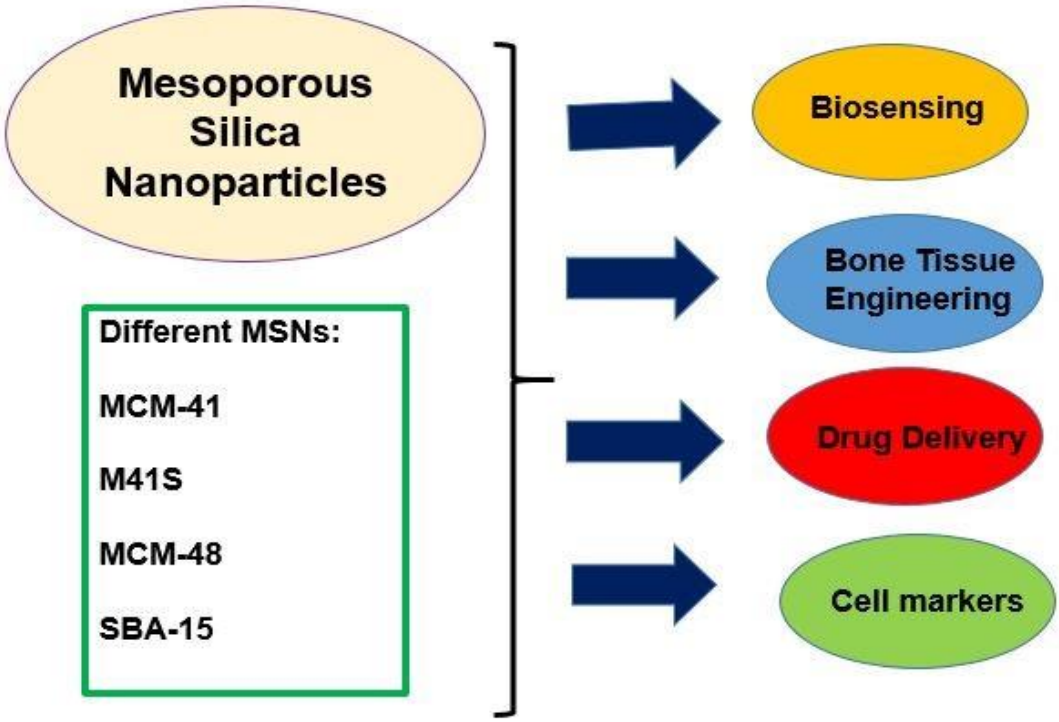

Fig 2 Some common medical applications for MSNs

Hollow mesoporous silica nanoparticles (H-MSNs) attract the attention of researchers due to their large pore volume. Hollow mesoporous silica nanoparticles (H-MSNs) with uniquely sized internal cavities and mesoporous shells are used in fields such as drug release, cancer treatment, bioimaging, and catalysis due to their rare properties such as low density, large surface area, adjustable size, good biocompatibility, and presence of Si-OH bond on the surface [59, 60, 61]. The drug loading capacity and mass transfer properties of the H-MSNs structure are more improved compared to MSNs [55, 61, 62].

Hollow mesoporous silica nanoparticles (H-MSNs) can be produced by a variety of methods, including hard templating and soft templating [63, 64].

Synthesis methods of silica nanoparticles

The formation of silica nanoparticles has two parts, nucleation and particle growth [65]. Silica occurs in nature by condensation of silicic acid. However, in synthetic production, obtained by hydrolysis of alkoxysilanes and subsequent condensation of the hydrolysis products. Cationic or modified cationic surfactant template methods can be used [66, 8]. Stöber method (sol-gel method) [19], reverse microemulsion method, hydrolysis, polycondensation, thermal annealing, spray drying, template method are some of the methods used in the preparation of silica nanoparticles [13]. Since silica nanoparticles are generally produced by flame pyrolysis in dental applications, they have a non-porous structure [48]. Some of the commonly synthesized types of silica nanoparticles and the synthesis methods are given in Table 2.

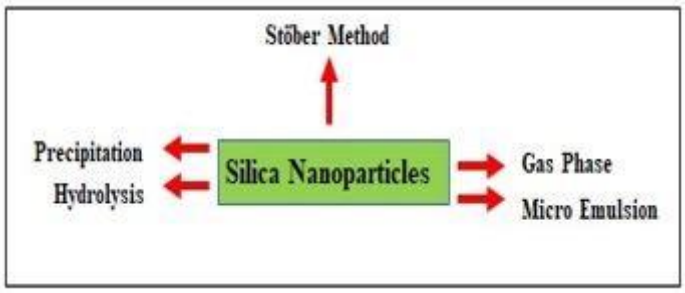

Fig 3 The common methods used in silica nanoparticle production

With the Stöber method, a sequential pore system can be occured with structure-regulating agents [48]. Some studies have been reported in which spherical mesoporous silica nanoparticles were synthesized synthetically by using sodium silicate instead of tetraethyl orthosilicate (TEOS) as a source of silica by Stöber method [9]. Generally, TEOS is chosen as the silica source, distilled water or ethanol for the solvent requirement, and ammonia as the catalyst [65, 9]. Nucleation occurs when soluble TEOS monomers in homogeneous liquid form solid particles. TEOS hydrolyzes to silicic acid, silicic acid condenses to produce silica particles with siloxane bridges (Si-O-Si) [65]. This method offers advantages such as controlling size (Fig. 4), shape, and surface area [19]. Reaction temperature, pH, surfactant, and silica source are factors for controlling these parameters [67]. Another method used to produce silica nanoparticles is the hydrothermal method.

TEOS or sodium silicate can be used as a source of silica. However, the hydrothermal method has defects such as cost and high energy consumption that prevent large-scale production [57].

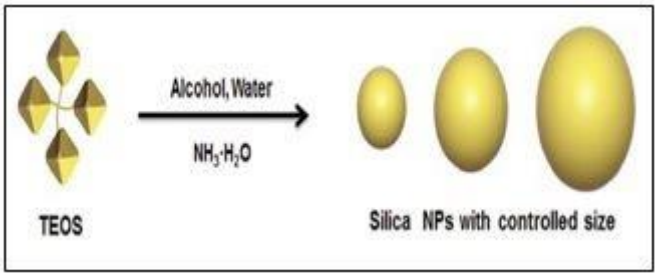

Fig 4 The schematic reaction of MSNs synthesis by using TEOS as silica raw material with Stöber method [14]

Table 2 Common production methods of silica nanoparticles and silica sources used

Silica Nanoparticles	Method	Silica source	Referans
SiO_2 NPs	Sol-gel process	TEOS	[68]
MSNs	modified interfacial synthesis procedure	TEOS	[38]
MSNs	Sol-gel process	Sodium silicate	[9]
MCM-41	Sol-gel process	TEOS	[43]
Silica NPs	Stöber method	TEOS	[69]
H-MSNs	modified hard template and etching routes	TEOS	[62]
Silica NPs	Stöber	TEOS	[70]
MCM-41	Non-hydrothermal gelation	TEOS	[57]
H-MSNs	One pot synthesis	TEOS	[59]
MCM-41 and MCM-48	Direct hydrothermal	TEOS, Sodium silicate	[47]
SiO_2 NPs	Stöber method	TEOS	[19]
MSNs	Sol-gel	TEOS	[71]
MCM-48	Sol-gel	TEOS	[45]
MSNs	Modified Stöber	TEOS	[52]

Bone Structure and Mesoporous Silica Nanoparticles

A bone, an essential tissue in the human body, protects other tissues and organs in the body by structurally supporting it and provides the mechanical support that the body needs by storing hematopoiesis and minerals (Ca^{+2} and PO^{4-}) [72, 73, 74]. Bone tissue has a complex and compatible structure consisting of many organic and inorganic components in the macro and nanoscale range [75]. The bone organ consists of calcium phosphate and is a hard mineralized structure containing hydroxyapatite

($Ca_{10}(PO_4)_6(OH)_2$), bone marrow, collagen, cartilage, endosteum, periosteum, blood vessels, nerves, osteoblasts, osteoclasts, osteocytes, osteogenic cells and water. The composition of bone tissue, which performs many mechanical functions, may vary depending on factors such as age, gender, and anatomical location of an individual [54, 76, 77, 78, 79]. Differences in the chemical composition of hydroxyapatite change the physical properties and solubility of the structure. The amount of mineral phase is 60-70% by weight, and the amount of water is between 5 and 10% by weight. The remaining is an organic composition of collagen and other proteins [79]. In the skeletal system, there are more than 206 bones in the limbs (cylindrical shape and providing movement), short bones in the wrists (supporting), flat bones in the skull (flat and with a large surface area), and irregular bones in the pelvis and vertebrae. Bones are either in a compact or spongy form [72, 80].

Tissue engineering is a discipline that includes many sciences that study bone structure and bone mechanics [81], involving the clinical sciences, engineering, and biology sciences, which includes osteoconductive scaffolds for organs or bones that have lost their function and the formation of osteogenic agents [77, 82]. Tissue transplantation is performed for many organs worldwide, and bone ranks second in this order [71]. Although bone has the ability to repair itself, bone deficiency or defect may occur due to severe traumatic injury, surgical removal of tumors, cancer, inflammation, age-related bone diseases [83], or congenital diseases and can be repaired with bone graft [73, 84]. Bone deficiency and defects are an important, serious, and social problem all over the world and there is a need for further research and development of biomaterials used for bone tissue therapy [73]. The treatment of bone defects can be difficult due to limited bone grafts. Therefore, metals, polymers, bioceramics, polymer-ceramic composites [75] are used in the treatment of bone defects [71, 84]. These materials, especially polymers and ceramics, have the ability to form a suitable environment for mechanical strength, cell proliferation, and attachment, and to mimic extracellular matrix [84]. Although metallic scaffolds seem to be suitable materials for treatment, they cause some limitations due to toxic ion release and lack of bioactivity [71]. An ideal material used in artificial bone applications should be biocompatible, biodegradable, osteoconductive [11] non-toxic, easy to manufacture and purchase [85]. It should show a direct degradation and preserve its structural integrity, taking into account the healing rate of the tissue in the

area where it is used [86]. Studies have shown that the viscoelasticity and time-dependent behavior of bone should be taken into account and play an important role in implant design optimization [74]. In addition, the biomaterial should be porous enough to allow the tissue to develop, vascularize and neuronize within the material [86]. Bones can be of different structures. For example, bone marrow is present in the trabecular bone canals and the level of porosity ranges from 50% to 90% [87]. Inorganic and organic composite materials aim to mimic the structure of a real bone. Therefore, creating bioactive materials by combining the hardness of a polymer phase with the compressive strength of an inorganic phase improves the strength and resistance properties [80].

Frequently used ceramic biomaterials are inorganic materials with high biocompatibility, non-toxic or non-carcinogenic properties, stable and light structure, thus used as implants and filling materials. However, their mechanical strength is low [88]. Researchs have focused on mesoporous structures that can also be used as drug delivery agents and have high biocompatibility [89]. Although there are many studies explaining the high biocompatibility of MSNs, studies on toxicity are limited. The reason for this may be that the structure and composition of the MSN used have different properties, surface areas, surface loads, and differences in the cell type and tissues studied [1]. It is a suitable material for targeted drug release and controlled drug release due to its shape, size and easy functionality [71]. However, MSN needs surface modification to deliver drugs in a targeted and controlled manner [49].

The biodegradability of MSN is affected by particle size and shape, porosity, physiological environment components and duration [90]. Yamada et al. reported small size amorphous silica particles dissolve more easily than colloidal silica. However, small size silica has been reported to increase cell toxicity. Particles that are not very small and have a large surface area increase their degradability as their contact surface with water increases. In addition, it has been concluded that the outer surface width is more important in degradability [91]. Many studies have attempted to improve the biodegradation of MSN. It is thought that MSN doped with metals degrades faster. This is because the Si-O-Si bond is stronger than the Si-O-M (M: metal elements) bond. Si-O-Si network structure makes the biodegradability of MSN difficult. Therefore metal modified MSN can break down more easily. Further studies are needed to improve MSN's degradability [53]. Hao et al. reported that changing PEG to MSN affected the rate of degradation. As

MSN started to degrade from the particle surface, MSN-PEG facilitated degradation through the particle. It was also seen that the spherical MSN deteriorated faster than the rod-shaped MSN [90].

A bone structure is a living mineral filled with cells [78]. Silicium is an important material for bone formation [92]. Silicium has been used in the treatment of teeth and bones for half a century due to its properties such as strength and biocompatibility [19]. Amorphous silicate network-based materials can link to bone matrix [93]. Silicates stimulate type I collagen formation and osteoblastic differentiation. Silicates are needed for the formation and calcification of bone tissue in metabolic processes [69]. In bone, it links to glycosaminoglycans and it is needed to form crosslinks between collagen and proteoglycans. Although present in all tissues in the body, it is mostly found in bone structure later in skin, hair, arteries, and nails [92]. Studies have shown that silica nanoparticles improve bone mass to modulate the differentiation of osteoblasts in mice and culture and also inhibit the differentiation of osteoclasts [19]. It has been reported that Si ions released from the MSNs structure support mineralized nodule formation, colagen synthesis, and osteoblast expression of osteogenic related genes [12]. Also, thanks to the adjustable size of MSNs, they can easily match the size range of natural bone fragments (such as hydroxyapatite crystals). This makes them promising candidates for bone tissue repair [54].

For bone treatment, silica nanoparticles can be used like bioceramic particle [70]. However, the bioactivity and osteogenesis ability of MSNs used alone is limited. The polymer matrix can be used to increase the specific surface area and pore volume [48], or the bone-forming bioactivity of MSNs can be increased by adding nutrients important for the human body such as calcium and magnesium [12]. Silica nanoparticles consist of two surface groups, hydrophobic siloxane and hydrophilic silanol group [48]. Silanol-containing surfaces can be functionalized with appropriate organic molecules that provide better control in the release of bioactive substances that bind to the mesoporous channels and organic coatings of MSNs [82]. A large pore volume also increases biological degradation, so it is possible to determine the type of interactions that occur in contact with the cell [67]. Therefore, those with unique surface properties and porosity emerged as bioactive materials for bone regeneration [42]. It is also known that the silicate used as an additive improves the mechanical properties and structure of the final product [69].

Beck and his working group investigated the relationship between 50 nm sized silica nanoparticles with bone metabolism. The results revealed that osteoblast differentiation and mineralization occurs and they reduce osteoclast differentiation. In studies conducted on mice, it has been determined that injected nanoparticles are beneficial in increasing bone mineral density [16]. Another study using polymeric scaffolds for bone regeneration used MSNs for drug release. Qui et al. designed the aminated MSNs they synthesized as the delivery vehicle for dexamethasone (DEX). Polylactic acid/poly (ε-*Caprolactone*) (PLA/PCL) was used as a nanofibrous scaffold and composite with DEX loaded MSNs. This drug-loaded composite scaffold presented significant osteogenic differentiation and mineralization [82].

In a study where MSN was synthesized using TEOS as a source of silica, peptide release was tested in vitro. Adsorption results have shown that MSNs have superior loading capacity and long duration peptide release rate. It has been observed that the functionalization of MSNs with peptide increases bone matrix mineralization [12]. MSNs can also be used to reinforce biomedically used polymers. Mechanical strength of some polymer membranes used in bone therapy needs improvement. For example, by adding MSNs to the electrospun poly (ε-caprolactone) membrane, it can be used as a composite for bone treatment. The addition of MSNs has been shown to improve the tensile properties of the material [70].

Wang et al. used the synthesized H-MSNs for bone tissue regeneration. When the in vitro release properties of H-MSNs loaded with Ibuprofen (IBP) were examined, it was determined that there was rapid release for the first 12 hours, and then the drug release slowed down and continued for 60 hours. Hydroxyapatite formation was observed by examining the bioactivity of the SBF (simulated body fluid) solution. Experiments were continued with in vivo studies. H-MSNs and IBP-H-MSNs were implanted in the bone defects. New bone tissue formation was observed in both of them 4 weeks after the procedure [89].

In a study focusing on bone therapy, functionalized MSNs loaded with Alendronate and Ibuprofen was used. Bone tissue treatment was performed by delivering drugs with MSNs [38]. In another study, poly-lactide-co-glycolide as a biodegradable polymer was used to create the MSNs-polymer scaffold [39]. Both studies had positive results.

Martinez-Carmona et al. have synthesized MSNs using the Stöber method. MSNs have been used for bone cancer treatment. Doxurubicin (DOX) used as anticancer drug loaded on MSNs. In the results, it was determined that it has approximately 100% antitumor activity against osteosarcoma cells [52]. Kanniyappan et al. (2021) have investigated the biocompatibility and bioactivity for bone tissue engineering in vitro (fibroblast cells and osteosarcoma cells) and in vivo (in zebrafish), using a very high concentration of MSNs. As a result of extensive biological studies, MSNs have been reported to be non-toxic and biocompatible, as well as osteogenic and angiogenic. These biomedical properties of MSNs make them an important material for bone tissue engineering [71].

Conclusion

In recent years, nanomaterials are used frequently in bioengineering. Despite its nanoscale dimensions, it has paved the way for its use in medical research due to its large surface area, quantum effects and porous structure. Bone loss or treatment of bone defects is a vital and serious issue in terms of quality of life. There is a need for porous, biocompatible and non-toxic materials in bone tissue engineering. MSNs have become an important material in bone tissue engineering due to their adjustable pore size, particle shape and functionality. It is promising due to its use as an implant material and its therapeutic properties. As a result of this evaluation, the fact that MSNs can both treat the bone organ and mimic bone tissue thanks to its porous structure proves to be an important biomaterial. Research is needed on the improvement of biodegradability and toxicity. However, biodegradability can be improved by modifying MSNs with metals or polymers. It is predicted that MSNs will be a more used material in bone tissue engineering in the future.

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