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Carriers in mesenchymal stem cell osteoblast mineralization—State-of-the-art

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ABSTRACT

Purpose: Tissue engineering is a new way to regenerate bone tissue, where osteogenic capable cells combine with an appropriate scaffolding material. Our aim was in a Medline Search to evaluate osteoblast mineralization in vitro and in vivo including gene expressing combining mesenchymal stem cells (MSCs) and five different carriers, titanium, collagen, calcium carbonate, calcium phosphate and polylactic acid-polyglycolic acid copolymer for purpose of a meta—or a descriptive analysis.
Materials and methods: The search included the following MeSH words in different combinations—mesenchymal stem cells, alkaline phosphatase, bone regeneration, tissue engineering, drug carriers, tissue scaffolds, titanium, collagen, calcium carbonate, calcium phosphates and polylactic acid-polyglycolic acid copolymer.
Results: Two out of 80 articles included numerical values and as control, carriers and cells, on mineralization and gene expression. β-tricalcium phosphate (β-TCP) revealed elevated alkaline phosphatase activity, and calcium-deficient hydroxyapatite a greater gene expression of osteocalcin when seeded with induced MSCs.
Conclusion: No data are published on titanium used as a carrier in MSC osteoblast mineralization. A meta- as well as a descriptive analysis includes numerical values of test materials and of control reactions from carrier and cells, respectively. Only two articles fulfilled these requirements.

1. Introduction

Autologous bone grafting is the preferred treatment for bone reconstruction due to transfer of osteoprogenitor cells or osteoblasts, osteoconductivity and its osteoinductive capacity of bone (Goldberg and Stevenson, 1987; Behnia et al., 2012). Harvesting of autologous bone grafts is associated with morbidity (pain, blood loss, surgical scars, necrosis), besides the risk of insufficient available volume of grafting material (Younger and Chapman, 1989; Martins et al., 2009; Stockmann et al., 2012). However, researchers seek alternative methods through synthetic or natural biomaterials. These materials, unfortunately, have an inferior osteogenic potential compared to autografts. Therefore biomaterials are combined with osteogenic cells for purpose of improved osteogenesis (Chen et al., 2005; Seitz et al., 2007; Sutter et al., 2009; Behnia et al., 2012; Metzler et al., 2012; Stockmann et al., 2012).

Demineralized bone (DB) and dentin (DD) induces heterotopic osteogenesis in rodents (Bang and Urist, 1967; Glowacki and Mulliken, 1985; Urist, 2002). For clinical practice however, DB and DD act as bone fillers with minimal osteoinductivity (Pinholt et al., 1992, 1994). Therefore tissue engineering is an advance within bone regeneration.

Tissue engineering involves the in vitro seeding of cells onto scaffolds supporting cell adhesion, migration, proliferation and differentiation, and defines the three dimensional (3D) shape of the tissue to be engineered. The carrier should be a scaffold with surface characteristics so mesenchymal stem cells (MSCs) are able to attach, proliferate and differentiate. The optimal scaffold should be biocompatible, biodegradable and osteoconductive to generate new bone formation (Leong et al., 2006; Ben-David et al., 2010).

It is preferable that scaffolds are 3D as a pre-requisite for cells to be able to proliferate while maintaining their ability to differentiate. The success of tissue engineering is dependent on oxygen and nutrient transport to the implanted cells (Laschke et al., 2006; Schumann et al., 2009; Brady et al., 2011). A great limitation of the 3D scaffolds is that

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the cells at the interior of the scaffold have decreased nutrient and oxygen transport and decreased removal of waste products (Stiehler et al., 2009). To secure a high density of colonizing cells and to promote neovascularization when implanted in vivo, the scaffolds should have high porosity, large surface area, mechanical properties and pore size appropriate for the application, and a highly interconnected porous structure (Langer and Vacanti, 1993; Leong et al., 2003; Rezwan et al., 2006; Heo et al., 2009; Martins et al., 2009; Schumann et al., 2009). Scaffold porosity may be inversely related to the mechanical properties of the material. It is important to find a balance of securing mechanical needs of the tissue to be replaced and scaffold porosity which allows tissue growth (Salgado et al., 2004; Hutmacher et al., 2007; Martins et al., 2009).

The ideal engineered cellular bone graft needs to exhibit the following features – the presence of osteogenic cells to generate new bone directly, an appropriate extracellular matrix to provide an osteoconductive scaffold, osteoinductive growth factors to provide signals to the resident cells and an adequate blood supply to support cell growth and function (Goldberg, 2000; Lund et al., 2008).

We chose five main carriers to evaluate; titanium, collagen, calcium carbonate, calcium phosphate and polylactic acid-polyglycolic acid copolymer (PLGA). Titanium is a metal alloy and is bio inert, but it is not biodegradable (Bjerre et al., 2008). The advantage of using titanium is its good mechanical strength, corrosion resistance and biocompatibility (Kang et al., 2010). Recent years have lead to modifying the surface of titanium chemically for improving its surface properties (Kang et al., 2010). A hydrophilic surface is assumed to be advantageous during the early phase of wound healing and during the cascade of events that occurs during osseointegration (Sawase et al., 2008). In titanium dioxide, the oxide surface is hydrophilic and binding structural water and forming OH and O_2 groups. Possibly the creation of a hydroxylated oxide surface enhances the surface reactivity with the surrounding ions, amino acids and proteins in the tissue fluids (Sawase et al., 2008).

Type I collagen is the main organic component of the extracellular bone matrix. Type I collagen may affect the development of an osteoblastic stem cell differentiation and growth positively (Burr, 2002; Reichert et al., 2009; Schofer et al., 2009). A scaffold matrix composed of type I collagen and hydroxyapatite (HA), providing support for MSC growth without compromising their osteogenic differentiation ability, may thus be indicated for bone tissue engineering (Gigante et al., 2008).

Ceramics such as calcium phosphates and calcium carbonates have been used as matrices for bone regeneration, because of the inorganic component of bone is composed of the ceramic calcium hydroxyapatite (Ducheyne and Qiu, 1999; Livingston et al., 2002; Ben-David et al., 2010).

Especially calcium phosphate ceramics have been used for bone tissue repair in orthopedic and dental applications, due to their biocompatibility and osteoconductivity through its ability to induce HA formation in the physiological environment (Mehlisch et al., 1990; Warren et al., 2004; Xin et al., 2005; Zhou et al., 2007; Huang et al., 2009). HA is a bioactive, biocompatible and osteoconductive ceramic material (Mehlisch et al., 1990; Bagambisa et al., 1993; Warren et al., 2004; Zhou et al., 2007; Huang et al., 2008). HA is used as coating material for surface modification of some bioinert scaffolds such as titanium to induce bioactivity and osteoconductivity and as bone tissue-engineering scaffold in which osteogenic cells could be seeded. Nanophase HA may be better than conventional HA due to superior biomimetics and osteoconductivity (Zhou et al., 2007). However HA has limited clinical applications because of its brittleness, difficulty of shaping and an extremely slow degradation rate (Wang, 2003; Huang et al., 2008).

Tricalcium phosphate (TCP) and HA have excellent biocompatibility and osteoconductiveness, due to the resemblance to the mineral phase of bone (Porter et al., 2004; Bjerre et al., 2008). During physiologic conditions, the resorption of HA is almost nonexistent, providing TCP with a biological advantage compared to HA (Mastrogiacomo et al., 2005; Bjerre et al., 2008). TCP has shown improved stability when it is doped by silicon substitution (Si-TCP), which ensures an in vivo degradation time of more than 1 year. Silicate-substituted HA (Si-HA) shows highly organized apatite crystal structure and superior bone remodeling properties as compared to pure HA (Porter et al., 2004; Bjerre et al., 2008). Calcium phosphate-coated chitosan-based scaffolds with incorporated lysozymes may possibly enhance bone bonding, osteoconductive and/or osteoinductive capacity (Martins et al., 2009).

β-tricalcium phosphate (β-TCP) is a synthetic calcium phosphate ceramic used alternatively to an autologous bone graft (LeGeros, 2002; Matsuno et al., 2006, 2008). β-TCP is similar in its molecular composition to human bone (Huang et al., 2009). However it has low compressive strength (Miranda et al., 2008).

Calcium-deficient hydroxyapatite (CDHA, $Ca_9(PO_4)_5(HPO_4)OH$) is a ceramic with a high specific surface area (SSA), 20–80 m^2/g, which is very similar to that of natural bone, about 80 m^2/g. β-TCP has a lower SSA, less than 0.5 m^2/g. Cells adhere more easily to high SSA ceramics than to low SSA scaffolds (Kasten et al., 2003, 2006).

A combination of the bioactive ceramic HA and the biodegradable polymer poly(ε-caprolactone) (PCL), a commercial polymer, may take advantage of the properties of both materials. PCL degrades slowly in vivo, has a good biocompatibility and formability, while HA is similar to bone mineral and has greater surface energy and surface activity (Heo et al., 2009).

PLGA is a commonly used synthetic polymer within tissue engineering and drug delivery (Quaglia, 2008; Shi et al., 2009). Polymers derived from D, L-lactic and glycolic acids as PLGA are biocompatible and biodegradable (Visscher et al., 1985; Fournier et al., 2003), and its nontoxic hydrolytic degradation products, lactic and glycolic acid, are metabolized in vivo (Gopferich, 1996; Stiehler et al., 2009). PLGA has good mechanical strength, excellent processability which can secure flexible structures, as well as a tailored degradation rate (Giteau et al., 2008; Shi et al., 2009).

The purpose of the current study was to evaluate state – of the art of the mentioned different carriers combined with MSCs in osteoblast mineralization in vitro and in vivo within mineralization and gene expression for purposes of a meta- or a descriptive analysis.

2. Materials and methods

A Medline search (Pub Med) was carried out May 2012, and studies published in English from January 2000 to May 2012 were included in the review within the inclusion and exclusion criteria, Table 1.

Table 1
Inclusion and exclusion criteria as well as outcomes measures.

Inclusion criteria	Exclusion criteria	Outcomes measures
Valid statistics	Diffuse statistics	Mineralization
After January 2000	Before January 2000	Gene expression
Published in English	Published in other languages	
Control (carrier without cells)	No control (carrier without cells) presented	
Calcium phosphate carrier	Other carriers than included	
Titanium carrier	Size or volume of carrier not presented	
Collagen carrier	Number of cells not presented	
Calcium carbonate carrier	Cartilage formation	
PLGA carrier		

The following MeSH words were used in different combinations – "mesenchymal stem cells", "alkaline phosphatase", "bone regeneration", "tissue engineering", "drug carriers", "tissue scaffolds", "titanium", "calcium carbonate", "calcium phosphates", "collagen" and "polylactic acid-polyglycolic acid copolymer". Example of search (Table 2): Search #12 MeSH words "mesenchymal stem cells", "alkaline phosphatase", "tissue engineering", and "calcium phosphates", results in 28 articles, where 20 articles where presented in previous search and eight articles were excluded. Titles and abstracts were screened, and full-text analysis was performed in relevant publications. All combinations in the MeSH search had "mesenchymal stem cells" and "alkaline phosphatase" as MeSH words, Table 2.

3. Results

The MeSH search resulted in 80 different articles. Following screening of titles and abstracts by defining the chosen inclusion—and exclusion criteria, 51 potential publications were found relevant and full-text analysis was performed. Out of the 51 articles, nine articles (Kasten et al., 2005, 2006; Champa Jayasuriya and Bhat, 2010; Korda et al., 2010; Weir and Xu, 2010; Xu et al., 2010; Chen et al., 2011a; Kruger et al., 2011; Barhanpurkar et al., 2012) were included in the present study. 71 studies (Yang et al., 2003; Ignatius et al., 2004; Liu et al., 2004; Pang et al., 2004; Takahashi et al., 2004; Yin et al., 2004; Hosseinkhani et al., 2005a; 2005b; Pang et al., 2005; Turhani et al., 2005; Abramovitch-Gottlib et al., 2006; George et al., 2006; Ku et al., 2006; Moioli et al., 2006; Nuttelman et al., 2006; Shih et al., 2006; Weissenboeck et al., 2006; Hwang et al., 2007; Rust et al., 2007; Sun et al., 2007; Zhou et al., 2007; Bjerre et al., 2008; Gigante et al., 2008; Huang et al., 2008; Matsuno et al., 2008; Schofer et al., 2008; Valarmathi et al., 2008; Vermonden et al., 2008; Diederichs et al., 2009; Heo et al., 2009; Huang et al., 2009; Kim et al., 2009; Liu et al., 2009; Martins et al., 2009; Mei et al., 2009; Nair et al., 2009; Niu et al., 2009; Park et al., 2009; Pereira et al., 2009; Schofer et al., 2009; Schumann et al., 2009; Shi et al., 2009; Stiehler et al., 2009; Wen et al., 2009; Binulal et al., 2010; Breyner et al., 2010; Cordonnier et al., 2010; Duan and Wang, 2010; Hess et al., 2010; Liu et al., 2010; Nandakumar et al., 2010; Sittichokechaiwut et al., 2010; Wang et al., 2010; Zhang et al., 2010; Bjerre et al., 2011; Broese et al., 2011; Chen et al., 2011b; Fan et al., 2011; Gandolfi et al., 2011; Janicki et al., 2011; Lee et al., 2011; Li et al., 2011; Liu et al., 2011; Miranda et al., 2011; Sala et al., 2011; Shafiee et al., 2011; Silva et al., 2011; Zhou et al., 2011; Zou et al., 2011; Tseng et al., 2012; Yang et al., 2012) did not meet the inclusion criteria and were therefore excluded from this analysis. Among studies included no publications were present on calcium carbonate and titanium as carriers.

Numerical values of defined outcomes were not presented in any of the publications. Outcomes in all included articles were exclusively presented as figures and tables. The corresponding authors of the included nine articles were contacted to obtain numerical values of their studies. Subsequently two (Kasten et al., 2005, 2006) out of the nine articles are presented by numerical values.

Tables 2 and 3, show outcome measures from the two (Kasten et al., 2005, 2006) included articles with enclosed numerical values of carriers and cells, separately, tested for mineralization and gene expression for purposes of control.

Kasten et al. (2006) shows elevated alkaline phosphatase (ALP) activity for β-TCP carrier and even more for β-TCP platelet-rich plasma (PRP) carrier seeded with MSCs and a greater gene expression of osteocalcin (OC) within the CDHA PRP carrier. Kasten et al. (2005) shows a higher ALP activity for β-TCP carrier seeded with MSCs, and a greater gene expression of OC within demineralized bone matrix (DBM) carrier seeded with induced mesenchymal stem cells.

4. Discussion

In this systematic review numerical values of the outcomes of mineralization and gene expression of mesenchymal stem cells combined with the carriers titanium, collagen, calcium carbonate, calcium phosphate or PLGA were only obtained in two out of nine included articles (Kasten et al., 2005, 2006). Carriers and cells, separately, were not tested for mineralization and gene expression for purposes of control in the 71 excluded articles (Yang et al., 2003; Ignatius et al., 2004; Liu et al., 2004; Pang et al., 2004; Takahashi et al., 2004; Yin et al., 2004; Hosseinkhani et al., 2005a, 2005b; Pang et al., 2005; Turhani et al., 2005; Abramovitch-Gottlib et al., 2006; George et al., 2006; Ku et al., 2006; Moioli et al., 2006; Nuttelman et al., 2006; Shih et al., 2006; Weissenboeck et al., 2006; Hwang et al., 2007; Rust et al., 2007; Sun et al., 2007; Zhou et al., 2007; Bjerre et al., 2008; Gigante et al., 2008; Huang et al., 2008; Matsuno et al., 2008; Schofer et al., 2008; Valarmathi et al., 2008; Vermonden et al., 2008; Diederichs et al., 2009; Heo et al., 2009; Huang et al., 2009; Kim et al., 2009; Liu et al., 2009; Martins et al., 2009; Mei et al., 2009; Nair et al., 2009; Niu et al., 2009; Park et al., 2009; Pereira et al., 2009; Schofer et al., 2009; Schumann et al., 2009; Shi et al., 2009; Stiehler et al., 2009; Wen et al., 2009; Binulal et al., 2010; Breyner et al., 2010; Cordonnier et al., 2010; Duan and Wang, 2010; Hess et al., 2010; Liu et al., 2010; Nandakumar et al., 2010; Sittichokechaiwut et al., 2010; Wang et al., 2010; Zhang et al., 2010; Bjerre et al., 2011; Broese et al., 2011; Chen et al., 2011b; Fan et al., 2011; Gandolfi et al., 2011; Janicki et al., 2011; Lee et al.,

Table 2
Results of the MeSH search. Each search includes four MeSH words, comprising "mesenchymal stem cells", "alkaline phosphatase", "bone regeneration or tissue engineering", and a scaffold. Results represent number of articles.

Search	MeSH word	MeSH word	Results	Presented in previous search	Included	Excluded
#1	Bone regeneration	Drug carriers	1	0	0	1
#2	Bone regeneration	Tissue scaffolds	15	0	0	15
#3	Bone regeneration	Titanium	0	0	0	0
#4	Bone regeneration	Calcium carbonate	0	0	0	0
#5	Bone regeneration	Calcium phosphates	13	9	2	2
#6	Bone regeneration	Collagen	7	2	0	5
#7	Bone regeneration	PLGA	2	2	0	0
#8	Tissue engineering	Drug carriers	2	1	0	1
#9	Tissue engineering	Tissue scaffolds	30	7	0	23
#10	Tissue engineering	Titanium	0	0	0	0
#11	Tissue engineering	Calcium carbonate	0	0	0	0
#12	Tissue engineering	Calcium phosphates	28	20	0	8
#13	Tissue engineering	Collagen	34	14	0	20
#14	Tissue engineering	PLGA	7	4	0	3

Table 3
Outcome measures from the two included studies. Data represent results at four and eight weeks. Calcium-deficient hydroxyapatite (CDHA), platelet-rich plasma (PRP), β-tricalcium phosphate (β-TCP), demineralized bone matrix (DBM), hydroxyapatite (HA).

Author	Method	Type of cell	Type of carrier	Result ng p-nitrophenol/μg protein
Kasten P et al., 2006	ALP assay	Human bone marrow MSCs 2×10^5 cells/ceramic	CDHA:	
			-Empty	12.54 and 16.70
			-With MSC	74.65 and 68.09
			-With induced MSC	94.65 and 126.98
			CDHA with PRP:	
			-Empty	23.05 and 13.24
			-With MSC	148.90 and 180.41
			-With induced MSC	124.30 and 116.85
			β-TCP:	
			-Empty	19.67 and 18.51
			-With MSC	188.91 and 168.32
			-With induced MSC	132.19 and 92.88
			β-TCP with PRP:	
			-Empty	26.14 and 19.16
			-With MSC	297.09 and 140.68
			-With induced MSC	149.59 and 124.55
Kasten P et al., 2005	ALP assay	Human bone marrow MSCs 2×10^5 cells/ceramic	CDHA:	
			-Empty	12.54 and 16.70
			-With MSC	74.65 and 68.09
			-With induced MSC	94.65 and 126.98
			β-TCP:	
			-Empty	19.67 and 18.51
			-With MSC	188.91 and 168.32
			-With induced MSC	132.19 and 92.88
			DBM:	
			-Empty	20.59 and 15.74
			-With MSC	22.16 and 10.27
			-With induced MSC	8.75 and 12.14
			HA:	
			-Empty	36.65 and 20.65
			-With MSC	52.94 and 88.03
			-With induced MSC	34.30 and 280.40
Kasten P et al., 2006	ELISA kit, OC	Human bone marrow MSCs 2×10^5 cells/ceramic	CDHA:	
			-Empty	0.739 and 0
			-With MSC	1,072 and 0.227
			-With induced MSC	1,258 and 0.703
			CDHA with PRP:	
			-Empty	0.084 and 0
			-With MSC	1,577 and 1,183
			-with induced MSC	0.885 and 2,672
			β-TCP:	
			-Empty	1,089 and 0.409
			-With MSC	1,015 and 0.264
			-With induced MSC	0.792 and 0.081
			β-TCP with PRP:	
			-Empty	0.713 and 0
			-With MSC	0.729 and 0
			-With induced MSC	0.629 and 0.102
Kasten P et al., 2005	ELISA kit, OC	Human bone marrow MSCs 2×10^5 cells/ceramic	CDHA:	
			-Empty	0.739 and 0
			-With MSC	1,072 and 0.227
			-With induced MSC	1,258 and 0.703
			β-TCP:	
			-Empty	1,089 and 0.409
			-With MSC	1,015 and 0.264
			-With induced MSC	0.792 and 0.081
			DBM:	
			-Empty	6,984 and 2,496
			-With MSC	6,819 and 2,098
			-With induced MSC	7,601 and 6,728
			HA:	
			-Empty	1,075 and 0
			-With MSC	0.919 and 0
			-With induced MSC	0.735 and 0

2011; Li et al., 2011; Liu et al., 2011; Miranda et al., 2011; Sala et al., 2011; Shafiee et al., 2011; Silva et al., 2011; Zhou et al., 2011; Zou et al., 2011; Tseng et al., 2012; Yang et al., 2012). Data were subsequently considered too sparse for a meta-analysis. The numerical value of an outcome of a carrier combined with mesenchymal stem cells comprises reactions from both the carrier and from the cells. Therefore measurements of each of these, carrier and cells, were deemed necessary for evaluation as basis for a meta- as well as a descriptive analysis. Since only two experiments including separate measurements of the carriers, for purposes of control, were the two published experiments by Kasten (Kasten et al., 2005, 2006) a descriptive analysis was performed on these two.

Kasten et al. (2006) showed elevated ALP activity for β-TCP PRP seeded with human bone marrow MSCs and for induced human bone marrow MSCs compared to the same carrier without any cells. β-TCP combined with PRP showed also higher numerical values for ALP activity compared to the carriers CDHA, CDHA combined with PRP and β-TCP, separately. In the other study, Kasten et al. (2005) also showed elevated ALP activity for β-TCP seeded with human bone marrow MSCs or with induced human bone marrow MSCs compared to the same carriers without any cells. Additionally, numerical values for outcomes of the carrier β-TCP were increased in comparison with the values for the carriers CDHA, DBM and HA. As OC is produced by osteoblasts, it is often used as a biochemical marker for the bone formation process and subsequently a high serum OC level is relatively well correlated with serum calcium (Parker et al., 2010). In the publication Kasten et al. (2006), the carrier CDHA combined with PRP and seeded with human bone marrow MSCs or with induced human bone marrow MSCs revealed the highest expression of OC compared to the value of the control and to the other carriers (Kasten et al., 2006). However, in Kasten et al. (2005) expression of OC was increased through DBM seeded with induced human bone marrow MSCs. These findings do not reveal any optimal carrier and titanium has not been used as a carrier.

5. Conclusion

There are no publications on titanium used as a carrier in MSC osteoblast mineralization. The numerical values of an outcome of a carrier combined with MSCs comprise reactions from carriers as well as from cells, respectively. Measurements of each of these, carrier and cells, are deemed necessary for evaluation as basis for a meta- as well as a descriptive analysis. In only two publications, data as control on a carrier without cells were included, however results on an optimal carrier were inconclusive. Since in vitro results are supposed to support clinical applications mechanical properties are also important to consider, however, there was no evidence for an outstanding biomaterial.

Conflict of interest statement

All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence our work.

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