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This is an accepted version of a paper published in *Journal of materials science. Materials in medicine*. This paper has been peer-reviewed but does not include the final publisher proof-corrections or journal pagination.

Citation for the published paper:

Persson, C., Berg, S. (2013)

"Strategies towards injectable, load-bearing materials for the intervertebral disc: a review and outlook"

Journal of materials science. Materials in medicine, 24(1): 1-10

URL: <http://dx.doi.org/10.1007/s10856-012-4776-2>

Access to the published version may require subscription.

The final publication is available at www.springerlink.com

Permanent link to this version:

<http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-184804>

<http://uu.diva-portal.org>

Strategies towards injectable, load-bearing materials for the intervertebral disc – a review and outlook

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Abstract

Currently available treatments for the degenerated intervertebral disc present disadvantages, such as surgical invasiveness and inadequate load distribution results. Load-bearing, injectable materials may be interesting for future therapies, but have not been studied in depth.

In this study, the existing literature was screened for studies on injectable materials for the intervertebral disc and a rationale for load-bearing, injectable materials was formulated.

Requirements for such a material were discussed, partly based on the experience of materials used for similar applications.

Important properties were discussed and found to include biocompatibility, bioactivity, porosity, handling, injectability, working time, setting time, radiopacity, containment and mechanical properties, where several of these properties are linked to one another.

In conclusion, there is a need for consensus on the properties of new materials developed for use in minimally invasive procedures in the spine. A substantial amount of attention may need to be given to non-toxic setting reactions.

Introduction

Clinical driver

Approximately 41% of all Swedish adults suffer from low back pain some time in life, where degeneration of the intervertebral disc (IVD) is one of the major causes [1, 2]. The intervertebral disc constitutes the soft tissue that separates the bony vertebral bodies and provides the spine with a large degree of flexibility. A structurally damaged tissue in this area can be painful both due to the degree of load and movement of this part of the body as well as the large amount of nerves present.

Degeneration of the disc may be due to different factors such as ageing, genetics or possibly overloading of the spine [3]. However, the exact origin of the pain may in many cases remain unknown. When pain killers, anti-inflammatory drugs or exercises are no longer sufficient, surgery is considered as a last option [4]. The aim of the surgery is to provide pain relief and a mechanically stable and working spine. Different surgical options are available, but mainly consist of fusion or total disc replacement (TDR). Many other non injectable options have been investigated experimentally [5-8], and have been reviewed elsewhere [5]. Fusion often involves the use of metallic screws, plates and often PEEK-cages filled with graft material to achieve a bony fusion between adjacent vertebrae. This treatment has for a long time been the standard of care, but leads to a reduced mobility of the treated spinal segment, which in turn alters the load on non treated, adjacent, segments. Approximately 25-30% of patients treated with fusion develop symptomatic adjacent segment disease (ASD) [9-11]. TDR, where metallic endplates and a polymeric or metallic core constitute a ball and cup bearing, has been developed in order to allow for a restored/maintained mobility of the segment (except for in the vertical direction) in order to reduce the risk of ASD, and has been in clinical use for over

20 years. ASD has been found to be reduced in clearly mobile disc prostheses, compared with cases with less mobility [12], and reduced compared to fusions [13].

However, as fusion leads to substantial alterations in the load distribution within the spine, also TDR, with its lack of elasticity for vertical loads might lead to further or residual low back pain [14, 15]. It should be noted, however, that newer designs of TDR have given improved results, and TDR has been reported to give fewer complications and reoperations in comparison to fusion [16]. Both types of interventions are performed using open surgery, which may increase the risks of complications such as blood loss and infections. TDR is, with today's prosthesis design, performed using an anterior extraperitoneal approach, where the content of the abdomen needs to be displaced to get the needed exploration for the implant to be inserted. Although TDR has been found advantageous in comparison to fusions both in terms of hospital costs and clinical outcome, novel problems linked to this method arise. All artificial joints with sliding surfaces are bound to develop wear and if the core is polymeric, it may experience substantial wear and even crack [17, 18]. If the articulating surfaces are both metallic, the wear-rate is too low to jeopardize the integrity of the prosthesis, but the released ions and/or particles can in some individuals start a foreign-body reaction, leading to the growth of so called "pseudo tumours". This is a frequent complication in hip arthroplasty with metal-on-metal articulation, and a few cases have also been reported after TDR [19-21]. This concern, together with the inability of present implants to allow for elastic vertical mobility, as seen in a healthy disc, strongly motivate further development of an artificial disc.

An injectable material would have a substantial advantage compared to the above-mentioned implants in that it can be implanted using minimally invasive surgery. This would minimize the surgical risks cited above and it could also facilitate and reduce the time and costs of the procedure.

Current, injectable therapies for the disc

The natural disc is limited by bony endplates on each surrounding vertebra, which are covered with a cartilage layer. These enclose a gel-like core, the nucleus pulposus, and fibre bands surrounding the core, the annulus fibrosus. The nucleus has a very high water content, whereas the annulus consists of collagen fibers, with an orientation varying from 47° to 62° with respect to the spinal axis. This fibrous construct resists the expansion of the nucleus laterally [22]. A non-degenerated disc gets its nutrition via diffusion from blood vessels in the bony endplate. Degeneration is in many respects considered a starvation of the disc due to reduced blood supply/nutritional diffusion through the endplates [2], and cellular transplantation into a degenerated disc thus seems questionable. However, several studies have investigated the injection of small amounts of bioactive molecules such as growth factor OP-1 [23], or cell suspensions [24, 25] into the disc in order to promote a regeneration of the disc. Low survival rates and leakage of cells have been found, which may cause heterotopic bone growth [25]. Cells have therefore been embedded in gel-like matrices [26, 24, 27, 28], which have also been investigated on their own without cells and/or bioactive molecules [29, 15]. These hydrogel-based therapies have been a main focus of recent research on nucleus pulposus replacement. Several commercial options are available, e.g. the NuCore®, which has shown promising clinical results for the treatment of herniated discs, but is unproven against low back pain due to disc degeneration [30]. Furthermore, these gels lack mechanical stability unless confined by an intact annulus (where incompressibility can be achieved through water adsorption). Due to the lack of inherent mechanical stability, there is a risk of leakage or displacement, which may occur through the injection site or through the annulus, where fissures and tears may already be present or develop due to the degenerative disease. One attempted solution to this has been to use a polyethylene net, which prevents the gel from expanding excessively due to water absorption, and also partly prevents it from extrusion into the canal. However, this solution is non-injectable, and implant migration has been frequently reported [31]. Several similar methods have been explored experimentally for the substitution of the nucleus pulposus, more or less minimally invasive, e.g. the introduction of an elastic

tube which can be filled with a liquid [5, 32]. Silicone-based injectable materials have also been studied, since as early as the 1960s, and commercialized for nucleus replacement [5, 33, 34], but these also rely on an intact annulus for mechanical stability.

One option for reducing the risk of implant migration may be to include a bioadhesive, which can potentially create a bond between the material and surrounding tissues and also possibly close tears in the annulus [29]. However, there are concerns regarding the toxicity of these compounds, and if new tears form, or for severely degenerated discs, the mechanical properties of the gels are not sufficient.

Rationale for injectable, load-bearing materials for the disc

Since, as presented above, biological therapy seems difficult, replacing the disc with an inherently load-bearing material without the intention of regenerating the disc tissue is an interesting option, in order to provide an efficient augmentation material as well as pain relief. Furthermore, replacing more of or the entire disc, and not just the nucleus, may be beneficial from a biomechanical perspective, as the load is spread over a larger area and issues with subsidence into the endplates may be avoided.

Two main types of potential materials can be distinguished. The first one is the non-degradable type - which should be load-bearing throughout the lifetime of the patient. Since the disc is such a complex structure, where the nucleus provides a high compressive resistance *provided it is properly enclosed by the annulus*, and the annulus gives additional mobility and resistance to torsion and bending through its fibrous structure, it would be very difficult – and perhaps not necessary – to replicate its exact, anisotropic mechanical properties. A second type is the degradable material, which is initially load-bearing, but loses its properties over time during degradation. Here, a second subdivision could be made, into materials that reabsorb/degrade without provoking any type of biological reaction and thus consist of a temporary relief, and materials that reabsorb while inducing a regrowth of the body's own tissue. In the case of the disc, as previously mentioned, tissue regrowth may be

difficult due to the lack of nutrients and blood available at the site. However, this regrown tissue may not need to be fibrous tissue as in the natural, healthy annulus, but may be bone, and the result is thus a non-artificial fusion, with the benefits of being created from existing, surrounding material and without open surgery. This latter concept would hence limit the gain to the then unnecessary surgical fusion procedure, but without achieving the advantages of physiological motion. For the patient-group where TDR is not suitable (spondylolysis, severe facet-joint arthritis etc) this concept could prove to be beneficial.

Previous studies on injectable, load-bearing materials for the disc

Very few studies have looked into load-bearing, injectable materials for the intervertebral disc. Materials that have been used have mainly been inspired by injectable materials for the stabilization of vertebral fractures, used in procedures such as vertebroplasty and kyphoplasty. Here bone cement based on poly(methyl methacrylate) (PMMA) is injected into the vertebral body and hardens in situ through a radical polymerization reaction. Similar to this material, Larraz et al [35, 36] used an amphiphilic macromonomer in combination with traditional (hydrophobic) PMMA and (hydrophilic) HEMA, and in some cases (hydrophilic) acrylic acid, in order to produce an injectable material for the intervertebral disc. The hydrophilic components were added in order to obtain a swelling behavior similar to the natural disc, which would confer viscoelastic properties to the material as well as the possibility to “transport nutrients and metabolism products” [36]. Chondroitin sulphate was added to some formulations with the aim of obtaining regenerative properties as it is a component present in cartilage tissues [36]. High compressive strengths of 30MPa could be obtained with the use of less macromonomer and more HEMA (40 and 60% of the cement’s liquid phase, respectively), together with a swelling rate of 10-100% (higher percentage with the addition of chondroitin sulphate and acrylic acid). Cell viability tests on cured specimen extracts indicated an initial toxic effect, although in vivo tests in rats showed a normal tissue response [35]. However, no data was reported for the injectability and radiopacity of this material.

Another experimental, injectable material intended for the disc was developed by López et al. [37]. This material consisted of a degradable co-polymer of P(DLLA-co-CL), containing ceramic particles of β -TCP or CaCO_3 . The polymers used have a higher biocompatibility than PMMA, which produces high temperatures during polymerization and may contain residual, toxic monomer. A degradable matrix also permits a possible investigation into stimulating the growth of the body's own tissues. The ceramic particles were added to strengthen the material, provide a hydrophilic phase for swelling and also as a means to neutralize potentially acid degradation products. However, low strengths of 0.3-0.8MPa were obtained.

Another approach for disc replacement is an injectable balloon, which is filled with an injectable material in situ [38]. This type of product has been made commercially available under the name of DASCOR, where both the balloon and the injected material consist of polyurethane and is intended as a nucleus replacement [38]. However, although CE mark was approved in 2005, the product has not received FDA approval.

One of the main issues with the use of polymers in injectable biomaterials is that the polymerization reactions often involve toxic components. For the first two studies cited above, monomers and radical initiators are involved, which may be detrimental to the surrounding cells [39, 40]. In the case of the polyurethane [38], the setting reaction (albeit taking place within a balloon) involves the presence of isocyanates, which are toxic. This suggests that different setting reactions are needed, and in the light of this, ceramic based materials and ionic reactions may be more promising alternatives. However, ceramics are fragile and the currently available injectable ceramic cements are not adequate for applications where bending and shear loads may be experienced [41]. A composite material, combining the advantages of polymers and ceramics, may be an option, although finding a biocompatible setting reaction remains a challenge.

Aim of study

In conclusion, not many studies on inherently load-bearing, injectable materials for the intervertebral disc have been performed and no such material appears to be commercially available worldwide. A reason for this may be the difficulties in obtaining an entirely non-toxic reaction when using polymers together with the proximity to the spinal cord, which puts high demands on the biocompatibility of the material.

Besides the lack of an adequate material, there are no standards describing the criteria for an injectable material for the disc. Some criteria could be assumed to be the same as those for vertebroplasty. However, despite being in use since the 1980's, there is no standard for materials used in vertebroplasty either. This study aims to map the requirements for injectable, load-bearing materials for intervertebral disc replacement. Possible strategies for achieving such a material are also briefly discussed.

Requirements for injectable, load-bearing materials for the intervertebral disc

A summary of the requirements for injectable, load-bearing materials for the intervertebral disc can be found in Table 1. These are described and discussed in more detail in the following subsections.

Biocompatibility

Firstly, the material should not produce any toxic by-products nor possess a high curing temperature that could be detrimental to surrounding cells [42]. Residual, toxic components are also a concern and the materials should be tested for in vitro cytotoxicity in accordance with the ISO standard [43]. Since the setting reaction may take place inside the body in the case of an injectable material, both direct contact as well as extracts in contact with the material during setting should be tested for cytotoxicity. Furthermore, several types of cells may be of interest here: the material may be in contact with bone as well as cartilage and

ligaments, calling for tests on e.g. osteoblastic cells and chondrocytes, and possible effects on neuronal cells should also be evaluated due to the proximity of nerves and the spinal cord. The origin of the cells in terms of e.g. species and cell line vs. primary cells should also be chosen with care. Further tests should obviously include in vivo biocompatibility.

As previously mentioned, the materials that have been investigated so far all contain, to some extent, unsafe components. However, no complete investigation of their cell response has been performed. Larraz et al. [35] investigated the effect on African green monkey fibroblastic cells of their cured material, and found no cell attachment and proliferation of the cells, and viability assays on extracts showed a decreased viability of cells when materials containing acrylic acid were used, which however returned to normal after seven days. However, in vivo tests in rats showed what the authors concluded to be a normal tissue response [35]. In the case of the DASCOR device no peer-reviewed data appears to be readily available in terms of cell response, although early clinical results for the DASCOR device suggest it is biologically safe [44],

Sterilization of the initial components has also been an issue for both acrylic and ceramic cements, where different types of sterilization procedures (e.g. EtO gas or γ -irradiation) may have detrimental effects on the material properties [45, 46]. The material should therefore ensure adequate properties also after sterilization.

Bioactivity

Both permanent and degradable materials would benefit from a good adhesion to surrounding tissues, in order to prevent extrusion. Bioadhesives may be investigated for this purpose. Glutaraldehyde is one option, and has been evaluated as an addition to nucleus replacements since it can react with amines on proteins of the extracellular matrix, creating covalent crosslinks [29]. However, glutaraldehyde may have toxic effects and thorough biocompatibility studies need to be made if a similar compound is chosen.

In the case of degradable materials, they should degrade at an adequate rate as well as induce the regrowth of the patient's own tissue, i.e. bone when aiming for a fusion. Some bioactivity could be conferred through the addition of ceramic materials which are known to be conducive to bone formation, e.g. calcium phosphates or calcium carbonates [37]. The injectable materials can also be used as carriers for drugs, e.g. ions and molecules that are favorable for tissue regrowth [35], such as strontium ions in the case of bone.

Porosity

If the aim is for the material to result in a fusion, a certain type and degree of (interconnected) porosity may be needed. Micropores ($<10\mu\text{m}$) can be sufficient for circulation of body fluids but macroporosity ($>100\mu\text{m}$) is needed for cell colonization [47].

Handling

The material should be easy to prepare and handle by the surgeon. Commonly used cements in the spine have a variety of working times, which also depend on the room temperature, and this may be a cause for concern in the clinic. Furthermore, manual mixing introduces a factor of uncertainty, as the properties may depend on the homogeneity of the material. Where several preparation steps are needed, there is a higher risk for mistakes, and it may also be time-consuming. A minimal amount of manipulation required by the surgeon is therefore ideal, in order to ensure time-efficient, repeatable results. A pre-mixed material may thus be of interest [48].

The material should have a long shelf-life. This has been an issue in particular with ceramic cements, which have experienced altered properties over time, depending on the type of measure taken to stabilize the cement [49, 45].

Injectability/Injection system

In vertebroplasty, needle sizes of 10-13G are commonly employed [50], and use of the same type of needles may be supposed for an injectable system for the disc. However, whereas the trabecular bone is porous and contains marrow, which is relatively easy to displace, the

degenerated disc may consist of very dense, fibrous material and heterotopic bone may also be present. There may therefore be a need for creating a substantial amount of space before injection of the material. Complete removal of the tissue that the injectable material is intended to replace may be important in order to ensure an adequate filling and thereby the intended load distribution. This could be done through the use of e.g. shavers, rongeurs and expansion devices, perhaps in combination with enzymes [51, 52]. However, removal of substantial amounts of disc material may raise additional concerns of leakage, which need to be solved.

Injectability is commonly measured as the mass percentage of cement extruded from a syringe with a certain force (commonly 100-300N, representing manual injection) [53, 54]. However, for curing materials, this injectability varies over time and it is important to report a range of time points for which the material is likely to be applied as well as the injection velocity. Better yet, relating in a reliable manner the viscosity found with rheometers to the injection force found in a syringe, would permit the use of viscosity-time curves to predict, in an easy way, the injectability of the cement at different time points. Based on the Hagen-Poiseuille law [55], a 3ml syringe, a 11G needle and a flow rate of 0.1ml/s, a viscosity of up to 1000Pa.s would still be injectable with a manual force of 300N. Preliminary tests in our lab [56] suggest that the viscosity calculated from these types of injections and estimated with the Hagen-Poiseuille law, can be related to the viscosity found with a parallel plate rheometer, in the case of a PMMA-based bone cement. It would thus be sufficient to perform a series of rheometer tests in order to estimate the injectability over time.

Working and setting times

For injectable biomaterials, a long working time but short setting time are desired, in order to allow enough time for the surgeon to inject the material before it sets, but once the material is inside the body it should set rapidly, in order to avoid leakage into surrounding tissues.

Working time can be defined as the time up to which the material is still injectable, whereas the setting time can be defined as the time at which the material has achieved mechanical

stability. However, the working time may be better defined as the range of time for which the material has a viscosity high enough to minimize leakage, but low enough to allow injection. There is currently no standard available for measuring the working time of injectable biomaterials, but viscosity measurements as the ones cited in the previous section may be useful in estimating this. Another option is to measure the time at which the material is still injectable through a certain needle gauge size.

The setting time can be determined using temperature measurements in the case of exothermic reactions, as in the ASTM F451 standard [57] for acrylic bone cements. In the case of ceramic cements, the Gillmore needle method [58] is commonly used to determine the setting time by applying standard weights to the setting body. However, although the setting time obtained with the Gillmore needle method may be 10-15min for some ceramic cements, it may take many hours for the cement to reach its maximum strength [59]. A different criterion for the setting time may be of interest here, which better relates to the clinical situation, e.g. the time at which the material can support the loads within the spine. The desired time for mechanical stability and maximal strength would also depend on whether the procedure is performed on a patient under general anesthesia with muscle relaxant, or local anesthesia with high compressive forces due to muscle activity.

Optimizing the working and setting time generally involves settling for a compromise, since the two usually are closely related. Only in the case of premixed ceramic cements, where e.g. glycerol is added to obtain an injectable paste, one can obtain a longer working time, since in this case, the setting starts only once the material is inside the body [48]. PMMA based bone cements used in vertebroplasty should generally have a working time of 6-10 minutes and a setting time of approximately 15 minutes [45]. In order to achieve a longer working time and shorter setting time with these cements, high-viscosity cements (with e.g. a high powder to liquid ratio and far gone in the reaction) are injected using devices such as spindle drives.

Radiopacity

The materials need to possess a very high radiopacity – cements used in the spine contain up to three times as much radiopacifier as cements used for the fixation of hip and knee prostheses. Visibility is critical when operating close to the spinal cord, both during and after the procedure. In the case of the previously mentioned materials investigated for use in the disc [35-38], none mentions the addition of specific radiopacifiers in the material. There appears to be no radiopaque component in the amphiphilic macromonomer based material [35, 36]. There are ceramic particles in the degradable material cited previously, which may infer a certain amount of radiopacity, but this was not evaluated [37]. For the polyurethane product, there is no mention of a radiopacifier within the final material, although a balloon is injected with a radiopaque material before its extraction and insertion of a second balloon, which is then filled with polyurethane [44].

The radiopacity should be evaluated under similar conditions to those used during the clinical procedure (60-130kV, 3.2-10mAs [60]) and compared to a control, such as PMMA formulations designated for use in vertebroplasty. Aluminium scales should be X-rayed simultaneously to the specimens and the radiopacity should be expressed in mmAl, for easier comparison between studies. Cements used in vertebroplasty and cements containing similar amounts of radiopacifier have been found to have a radiopacity of 1-3mmAl [61-63].

Containment

The risk for leakage and implant extrusion into surrounding tissues needs to be minimized. In a worst-case scenario, the implant can protrude into the spinal canal, possibly giving rise to neurological problems. A balloon containing the actual material, as in the case of the DASCOR device [44, 38], is therefore an attractive solution. However, although the natural endplates are concave and may thus be able to contain a material to a certain extent, they may look very different in patients with degenerative disc disease. Therefore, materials that are able to form a bond with the endplates or the bone would give a lower risk for implant

extrusion. As discussed in the previous section on bioactivity, bioadhesives may be an option here, although their toxicity needs to be thoroughly evaluated.

The material should have an appropriate cohesion, i.e. not disintegrate easily within the body, in order to reduce the risk for complications. Another cause for worry is the implant being extruded through the hole it was injected through. However, a degenerated disc may have tears that could pose a bigger problem than the injection hole.

Naturally, the material needs to be able to sustain the loads experienced within the spine in order to further avoid extrusion, and these are specified in the next section. Possible implant extrusion should be assessed in biomechanical cadaver tests.

Mechanical properties

In the case of a permanent material, it should ideally withstand the loads in the spine for the lifetime of the patient. For degradable materials, they should be load-bearing until the body's own tissue has been reconstructed and can carry the load.

The compressive modulus of the nucleus pulposus has been found to be 1MPa (under constrained compression) [64]. The annulus fibrosus, constraining the movement of the nucleus, has been found to exhibit nonlinear behavior in tension, with - in the circumferential direction - a tangent modulus of 2-5MPa in the toe-region (for physiological strains, up to 6%), and 29MPa in the linear region (higher strains) [65]. In the axial and radial direction the modulus is much lower (0.4-1MPa) [22]. However, as previously mentioned, the natural disc has a complex structure, which may not be possible nor necessary to reproduce. Also, the properties found in vitro may not reflect those experienced in vivo. In fact, in daily life the intervertebral disc may be subject to pressures of 0.1-2.3MPa (in the case of a person weighing 70kg) [66], suggesting that the disc, as well as a replacement material, needs to be able to withstand at least this amount of pressure, for several million repetitions. The ASTM F-2423 [67] and ISO 18192 [68] standards for wear testing of total disc replacements cite up to 2kN of compressive load (lumbar disc) plus various degrees of flexion-extension, lateral

bending and rotation for 10 million cycles (Table 2). This number of cycles is considered conservative, and is expected to exceed those experienced in vivo. ASTM has approximated 125,000 significant motions within the spine per year, which means 10 million cycles would represent up to 80 years in vivo. It should also be noted that the loads experienced in the lumbar region may be far higher than those in the cervical region, and there are thus different requirements in terms of mechanical properties for implant materials used in different regions of the spine (Table 2).

The wear testing should not give rise to any osteolytic wear particles, and wear particles should be analysed separately with in vitro cell tests for cytotoxicity before further animal studies.

One issue of the above standards is that bovine serum solutions are recommended as testing medium. Although this may be relevant for joint wear testing, and it has been suggested that a similar fibrous capsule with pseudo-synovial fluid is formed around total disc replacements, there is no data on the exact characteristics of the surrounding fluid of TDR's and it may also be different for the materials discussed in this paper. Testing in phosphate buffered saline (PBS) solution (at 37°C) may be as relevant as serum for the bench testing.

In the case of a permanent implant, the above are the mechanical requirements that the material should fulfill in order to maintain mechanical resistance as well as mobility in the spinal segment, and they can be tested preclinically in commercially available simulators, such as the Endolab Spine simulator (Rosenheim, Germany), AMTI simulator (AMTI Boston, MA, USA), Bose Spinal disc fatigue/wear test instrument (Bose corporation, Electroforce systems group, MN, USA), MTS Bionix spine wear simulator (MTS systems corporation, MN, USA) and ProSim 5DOF Spine Wear Simulator (Simulation solutions, Manchester, UK). However, the mobility criteria (flexion/extension, bending and rotation) may no longer be valid for severely degenerated discs where the loss of disc height has lead to facet joint arthritis. In this case, if fusion would be preferred, compressive fatigue strength alone may be

of greater interest, similar to what would be relevant in the vertebral body. However, whereas there is a standard for fatigue testing of acrylic bone cements used for the fixation of joint implants (tension-compression dynamic loading) [69], there is no such standard for vertebroplasty. The compressive failure load for whole vertebrae has been found to lie between 1.2-5.5kN [70]. Taking into consideration the range of pressures found in the disc in vivo [66], an initial, conservative suggestion could be to test the devices in compressive dynamic loading at 0.1-5MPa for 10 million cycles. Alternatively, the compressive loads suggested in the ISO and ASTM standards as part of the TDR loading scenario could be used as a starting point for specimens of similar size. However, guidance on this type of testing should be provided by a standards testing committee.

Although the above type of test would be of interest as a first evaluation, and requirements might differ between patient groups, the injected material may be subject to shear and bending loads. It is difficult to say to what extent, and what properties the material should have, but as a conservative measure, one can start from the healthy annulus properties and the wear testing standards cited above. A standard is also available for quasi-static bending testing of acrylic bone cements [71], and it is suggested that this is followed as far as possible in terms of methods for the quasi-static flexural properties.

Finally, as previously mentioned, in the case of a degradable implant, the implant needs to fulfill the strength requirements only until the surrounding tissue has grown sufficiently strong to support the load itself. However, finding such a compromise may be difficult and require a large amount of testing. This could be investigated in a first instance through in vitro testing in phosphate buffered saline or other relevant solutions, depending on the degradation process of the material. If the degradation occurs through enzymatic reactions, tests can be performed under such conditions, e.g. in lipase solutions [72]. Naturally, in vivo tests evaluating the material degradation rate, bone regrowth and the corresponding mechanical properties will be needed. Due to any underlying pathologies, the material composition may

need to be adjusted through e.g. the addition of bioactive components in order to stimulate bone growth.

In the case of a degradable material, where the aim is to induce an auto-fusion, the requirements both in terms of material properties and how it is introduced are likely to vary. In cases with an adequate disc height but inadequate posterior elements, such as in spondylolysis, an in situ application of the material would be sufficient. On the other hand, in cases with a considerable loss of disc height, this would have to be corrected at the procedure, to restore lordosis and open the neural foramina.

Out of the inherently load-bearing materials investigated for use in the disc, only the polyurethane has been investigated under dynamic loading conditions [38]. This device was found to have an approximate fatigue limit of 3MPa in compression (10 million cycles were considered run-out).

Strategies towards injectable, load-bearing materials for the intervertebral disc

In the light of the above, a few examples of strategies are discussed below.

Reinforcement of currently available ceramic cements may be one way forward. These cements are not strong enough for load-bearing applications, but present the degradability and osteoconductivity needed for a fusion. A strengthening of these materials may be achieved through the fabrication of a hybrid material, where there is a chemical interaction on a molecular scale between the ceramic part and e.g. an organic or another inorganic material. This type of material route may also be useful for investigating non-degradable materials for the disc. Preliminary testing in our lab suggests that high-strength, non-fragile materials may be created this way [73]. However, attention needs to be paid to using material combinations that possess a biocompatible setting reaction, without the involvement of e.g. toxic monomers

or reaction initiators. An ionic setting reaction may be of interest to this end, such as those occurring in glass ionomers.

The injectable balloon that is filled with material, as in the DASCOR device, is an attractive solution also for future studies, as a containment of the material is facilitated. This would reduce the risk for leakage and implant extrusion. However, an adhesion to the endplates is likely to be important here. Also, if a fusion is aimed for, the balloon material may have to be degradable. If an increase of disc height is intended, the balloon needs to be pressurized during the setting time.

Another option may be looking at the injection of an already set material. A material which can be transferred through a vertebral injection needle and then expand within the disc space may be a way of using e.g. polymers that set before insertion, hence avoiding any issues associated to the setting reaction.

Due to the small amount of work done on injectable, load-bearing materials for the disc, computational simulations may be an option to quickly and cost-efficiently evaluate new material combinations.

Conclusions

In this work, the requirements of future injectable, inherently load-bearing materials for the intervertebral disc have been discussed. Some of the most important properties were discussed and it could be concluded that there is a need for consensus on the target values of many of these properties as well as methods for assessing the same. For example, injectability and working times needed of new materials for use in minimally invasive procedures in the spine as well as a standard loading profile for fatigue tests of these types of materials need to be defined. Future material studies may benefit from focusing on hybrid materials, non-toxic

setting reactions and bioadhesives. The possible clinical advantages of these new procedures would be significant both for the patients and for the society.

Acknowledgements

Funding from the Carl Trygger Foundation is gratefully acknowledged.

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Table 1. Requirements for injectable, load-bearing materials for the intervertebral disc.

Property	Permanent materials	Degradable materials
<i>Biocompatibility</i>	Non-toxic	
<i>Bioactivity</i>	<ul style="list-style-type: none"> ➤ Bioadhesion preferable ➤ Therapeutic agents optional 	<ul style="list-style-type: none"> ➤ Bioadhesion preferable ➤ Osteoinductivity required for bone regrowth ➤ Therapeutic agents optional
<i>Porosity</i>	-	Macroporosity
<i>Handling</i>	<ul style="list-style-type: none"> ➤ Easy to prepare and handle by the surgeon ➤ Long shelf-life 	
<i>Injectability</i>	Injectable through 10-13G needles at 100-300N or with handheld device	
<i>Working time</i>	6-10 min, ideally as long as possible	
<i>Setting time</i>	Approximately 15min, ideally as short as possible once inside the body	
<i>Radiopacity</i>	High (>1mmAl)	
<i>Containment</i>	Risk for implant extrusion needs to be minimized	
<i>Mechanical properties</i>	The material needs to resist common loads to the spine for a minimum of 10 million cycles	The material needs to resist common loads to the spine until it is replaced by the body's own tissue

Table 2. Input conditions for wear simulation of cervical and lumbar total disc replacements, according to the ISO 18192 and ASTM F-2423 standards.

	Cervical		Lumbar	
Test Profile	Displacement control	Load control	Displacement control	Load control
Axial load	N/A	50-150N (ISO) 100N (ASTM)	N/A	600-2000N (ISO) 1200N (ASTM)
Flexion / extension	$\pm 7.5^\circ$	N/A (ISO) $\pm 2\text{Nm}$ (ASTM)	$6^\circ/3^\circ$ (ISO) $\pm 7.5^\circ$ (ASTM)	N/A (ISO) $\pm 10\text{Nm}$ (ASTM)
Lateral bending	$\pm 6^\circ$	N/A (ISO) $\pm 2\text{Nm}$ (ASTM)	$\pm 2^\circ$ (ISO) $\pm 3^\circ$ (ASTM)	N/A (ISO) $\pm 10\text{Nm}$ (ASTM)
Axial rotation	$\pm 4^\circ$ (ISO) $\pm 6^\circ$ (ASTM)	N/A (ISO) $\pm 4\text{Nm}$ (ASTM)	$\pm 2^\circ$ (ISO) $\pm 6^\circ$ (ASTM)	N/A (ISO) $\pm 12\text{Nm}$ (ASTM)