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Current methods of preventing aseptic loosening and improving osseointegration of titanium implants in cementless total hip arthroplasty: a review

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Abstract

Hip osteoarthritis is the most common joint disorder, and is represented by a degenerative process, resulting in pain and functional impairment. If conservative treatment for hip osteoarthritis fails, the only remaining option is hip arthroplasty. Despite good survival of implants, loosening of components is the most common complication. This leads to revision surgeries, which are technically demanding, expensive, and result in a low satisfaction rate. Uncemented hip replacements require proper osseointegration for increased survival. Physical characteristics of implants include biocompatibility, Young's modulus of elasticity, strength, and corrosion resistance, and each influence fixation of implants. Moreover, implant surface treatments, pore size, pore density, and femoral stem design should be appropriately selected. Patients' optimization of obesity, osteoporosis, cardiovascular disease, psychotic disorders, and smoking cessation are associated with a higher survival of implants. Surgical factors, such as approach, drilling and rasping, acetabular bone coverage, acetabular cup positioning, and implant size, also affect survival of implants. Avoiding drugs, which may impair osseointegration of implants, and having an

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appropriate rehabilitation protocol are important. Future directions include anabolic and anti-catabolic bone-acting drugs to enhance osseointegration of implants. Comprehensive knowledge of the factors mentioned above is important for preventing aseptic loosening, with important socioeconomic consequences.

Keywords
Osseointegration, titanium implant, cementless hip arthroplasty, aseptic loosening, osteoarthritis, surgery

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Introduction

Total hip replacement is a common procedure, which is performed in the acute and chronic settings, with proven success in reducing pain and improving function.[1] In chronic patients, arthroplasty is usually performed after conservative treatment and joint-preserving techniques have failed.[2] Implants that are used are made of metal alloys. Despite the large number of available metals, titanium is preferred in orthopaedic implants because of its mechanical and biocompatibility properties.[3] Titanium implants have two methods of fixation of either using cement (cemented total hip replacements) or by bone ingrowth (cementless total hip replacements).[4] Cementless total hip replacements involve bone apposition on titanium implants, a process called osseointegration.[5] The key to survival of implants is dynamic bone tissue, involving an implant interface, which is a microscopically amorphous structure of approximately 20 to 50 nm.[6] Growth and differentiation factors from activated blood cells are released at the interface and initiate a series of biological events, which lead to bone formation around the implant.[7] A fibrin matrix is first created, acting as a scaffold for bone-forming cells, called osteoblasts.[7] When proper osseointegration of the implant occurs, the interface is almost entirely filled with bone.[7] Failure in osseointegration results in fibrous tissue at the bone–implant interface, resulting in low strength and loosening of the implant.[7] This can be caused by low biocompatibility of implants, surface and design of implants, bone quality, surgical technique, loading conditions, and insufficient bone turnover.[8] Although survival rates of cementless titanium implants at 10 years are satisfactory (85%), this rate decreases to 70% at 15 years.[9] The most common cause for failure of implants is impaired implant fixation (76%), called aseptic loosening.[10] This complication produces pain and instability, aggravated by activity and weight bearing. The diagnosis of implant loosening is based on clinical symptoms and radiological examinations. In X-rays, a progressive radiolucency line or a width greater than 2 mm at the bone–implant interface is a sign of aseptic loosening (Figure 1).[11] Another sign of cementless femoral stem loosening is pedestal sign, represented by endosteal bone formation at the distal end of the femoral stem.[12]

Total hip replacement failure is treated with revision surgeries, which are technically demanding, have a high complication rate,[3] are expensive,[13] and usually result in a low satisfaction rate for patients.[14] Methods of improving implant fixation include choice of implant, preoperative

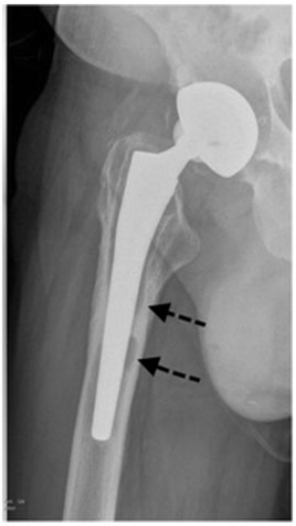

Figure 1. Radiolucency zones greater than 2 mm (black arrows) at the femoral stem showing aseptic loosening[11]

optimization of patients, surgeon's experience, surgical technique, systemic drugs, rehabilitation protocol, and adjuvant techniques. Other techniques, such as bone tissue engineering using stem cells and scaffolds, are still under development.[15,16] This review discusses the current methods and their effect on osseointegration of titanium implants. Our review focusses on cementless total hip replacement. We consider that a thorough knowledge of current methods for improving survival of implants is important for preventing a low satisfaction rate of patients and important socioeconomic consequences produced by failure of hip replacement.

Methodology

The review was conducted by identifying research papers in the electronic PubMed database using the following keywords: titanium osseointegration, titanium implant fixation, titanium loosening, total hip replacement osseointegration, total hip replacement aseptic loosening and cementless hip replacement. Research articles and reviews in the past 15 years were considered.

Titanium in medical applications

Titanium is a better alternative to steel in medical implants because of improved biocompatibility, the strength to density ratio, corrosion resistance and a lower modulus of elasticity.[17] Titanium alloys further enhance the properties of pure titanium and are classified according to microstructure as alpha (α), near-(α), alpha-beta (α-β), metastable β, and stable β.[17] β alloys are best for use in the medical field because of a higher strength, superior corrosion resistance, and low elastic modulus.[17] The most common β alloy is Ti-6AL-4V, which additionally contains aluminium (an α phase stabilizer) and vanadium (a β phase stabilizer).[18]

Biocompatibility

The most important property of titanium regarding osseointegration is due to a low electrical conductivity, which leads to formation of an oxide layer.[19] This facilitates adhesion of osteoblasts to the surface of titanium and produces better implant fixation compared with other metals. Nevertheless, titanium implants are still considered foreign bodies by the immune system and fibrosis around the implant occurs.[3] Chemical ion release further amplifies the inflammation process and more fibrous tissue is produced.[3] This alters osseointegration by restricting osteoblast cells to create bone ingrowth at the surface of the implant, thus leading to aseptic loosening and failure of the implant. An important factor of a high survival rate of implants is limitation of fibrous tissue production due to inflammation and good osteoblast activity. This can be achieved by

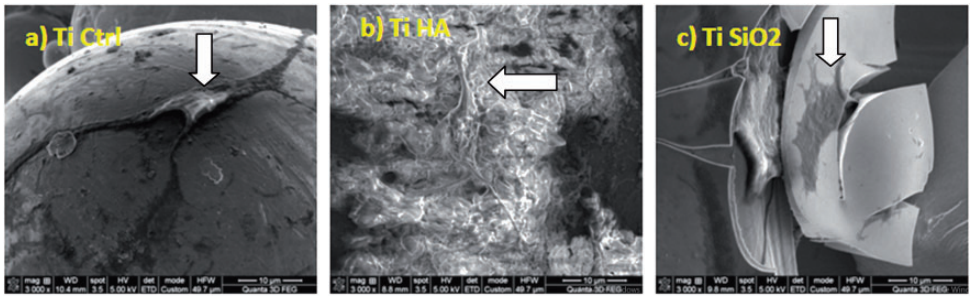

Figure 2. Scanning electron microscopy images of titanium implants seeded with osteoblasts cells (a) Ti6Al7Nb implants as a control (TiCtrl) seeded with osteoblast cells (arrow shows cells surrounded by bone matrix). (b) Titanium implants coated with hydroxyapatite (TiHA) and seeded with osteoblast cells (arrow shows a strong matrix deposition with cells surrounded by bone matrix). (c) Titanium implants with bioactive silicatitanate coating ($TiSiO_2$) seeded with osteoblast cells (arrow shows a large flattened cell with numerous extensions) (magnification, $\times$3000).[20]

bioactive coating of the implant surface with hydroxyapatite, silicotitanate, or by functionalization of implant surfaces with cells, stem cells, or osteoblast cells. Bioactive coatings can lead to benefits in terms of cell adhesion, differentiation, and bone matrix formation, especially in the case of hydroxyapatite[20] (Figure 2).

The effect of cultivation of cells on implants with bioactive coatings can induce a double interaction as follows: (1) coatings allow cellular adhesion and differentiation; and (2) cells act on the substrate that is partially degraded (Figure 3).

Young's modulus of elasticity

Young's modulus measures the rigidity of an object. This measurement is important in hip implants because a low Young's modulus, indicating less rigidity, is required for preventing stress shielding of bone.[21] Stress shielding is an inappropriate mechanical force transfer from metal to bone and occurs because of a difference in stiffness of bone and metal.[18] Stress shielding results in an increased bone resorption, decreased bone remodelling process, and an increased rate of aseptic loosening.[21] An ideal implant has a Young modulus resembling that of bone (10–30 GPa). The titanium alloy Ti-6AL-4V has a Young modulus of 110 GPa,[21] whereas stainless steel is approximately 180 GPa.[18] Besides alloy composition, implant structure can also affect Young's modulus. Particularly, a porous structure can be adjusted to resemble that of bone.[22] The elasticity modulus can also affect survival of implants.[23] A low Young modulus results in more micromotion, which produces fibrous tissue instead of bone at the bone–implant interface.[23] A compromise therefore needs to be made to prevent stress shielding (when a low Young modulus is required) and to prevent aseptic loosening caused by micromotion (when a high Young modulus is required).

Strength

Titanium offers the best strength-to-weight ratio of all metals, and this ratio is over 50% higher than that of steel.[24,25] Addition of elements make titanium alloys more resistant to ultimate tensile strength (ability to withstand a pulling force), yield strength (force required to induce permanent deformation), and elongation.[26]

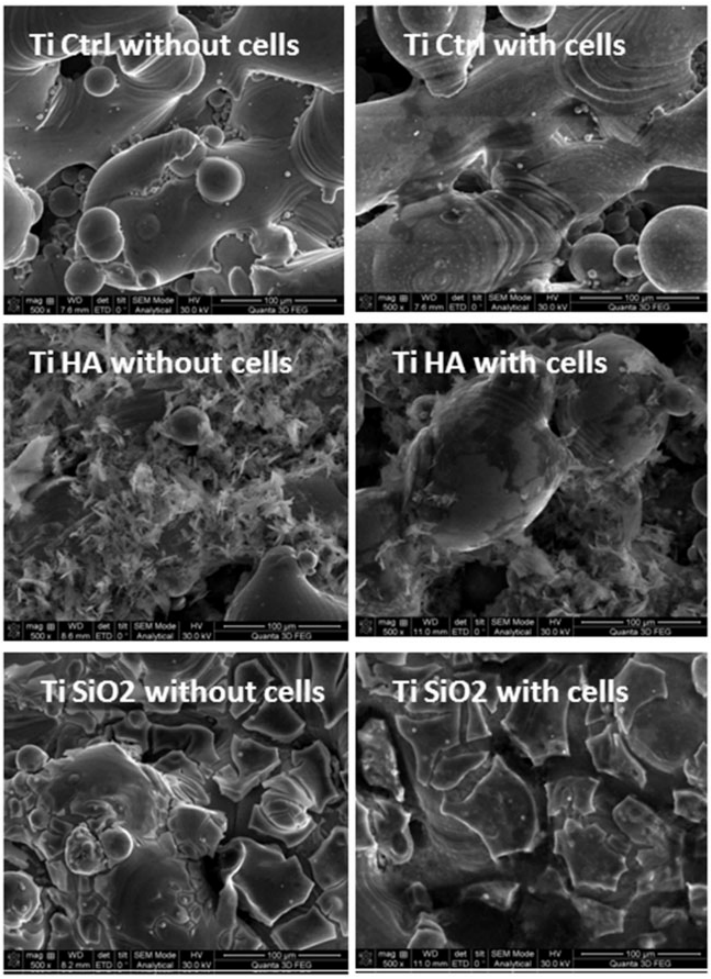

Figure 3. Scanning electron microscopy images of titanium implants seeded with dental follicle stem cells Left panel: untreated titanium implant (TiCtrl), hydroxyapatite-coated titanium implant (TiHA), and silica-titanate-coated titanium implant ($TiSiO_2$) without cells. Right panel: TiCtrl, TiHA, and $TiSiO_2$ implants with dental follicle stem cells after 21 days of cell culture (magnification, $\times$500).

Corrosion resistance

Metal ions released from implants (see Figure 4) promote local inflammation, which leads to excessive fibrous tissue formation.[27] As a result, the production of strong bone bridges by osteoblasts, which are intended to anchor the implant, are restricted. Moreover, cytotoxic metal ions can damage osteoblast cells that can no longer form bone ingrowth. These local implications impair osseointegration of implants and play a major role in aseptic loosening. Ion release can also cause systemic damage. Aluminium might cause neurological pathologies (e.g., amyotrophic lateral sclerosis or Parkinson's disease), while vanadium can produce cellular mutations.[27]

The ideal metal that is used in hip replacement implants should have the

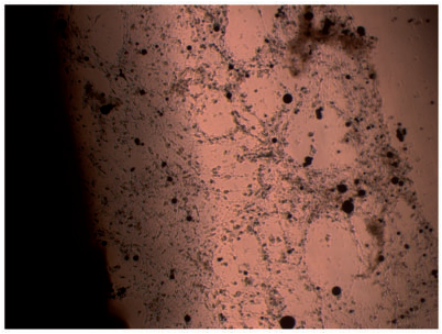

Figure 4. *In vitro* release of metal ions from a titanium implant

following features: high biocompatibility, high strength, lightweight, corrosion resistant, non-toxic, cost efficient, and a Young elasticity modulus similar to that of bone. Although some of the titanium alloys that are currently on the market fulfil some of these requirements, better materials are expected to be found in future implants.

Chemical compositions of titanium alloys change when searching for better biocompatibility. Implants containing Ti-24Nb-4Zr-7.9Sn (TNZS) and Ti6Al7Nb alloys have better fixation and bone-to-implant contact.[28,29] Ti-35Nb-4Sn and TNZS have a Young modulus of approximately 40 GPa, which closely matches the bone's elasticity properties, and thus prevents stress shielding.[21] Toxic-free element alloys, such as Ti-13Nb-13Zr, Ti-12Mo-6Zr, and Ti-12Mo-6Zr-2Fe, could be preferred in future medical use.[17,26] The alloys mentioned above are still under development for orthopaedic use.

Preoperative methods of improving hip implant osseointegration

Selection of implants

Titanium surface treatments have been intensively studied. Techniques include plasma spraying, hydroxyapatite coating, acid etching, sand blasting, alkali heat treatment, plasma treatment, ion implementation, and more recently, nanotechnology.[30,31] The most common technique is surface coating and acid etching, with proven enhancement in osseointegration.[30] Hydroxyapatite and porous coatings are currently the most commonly used treatments.[32] A meta-analysis comparing these two types of coatings showed a lower incidence of aseptic loosening in the hydroxyapatite coating group than in the porous coating group.[32] Kim et al.[33] preformed a study on 110 hips with a mean follow-up of 15.6 years. They showed that hydroxyapatite coating on titanium stems did not affect survival of the implant. Newer surface coatings containing silicatitanate[34] or growth factors, such as bone morphogenetic protein (BMP), are still under development. Ion implementation increases implant fixation, but it is still an expensive and less commonly used technique.[30]

Cementless hip titanium implants have a porous surface for proper bone ingrowth. The shape, dimension of pores, and pore throat size affect osseointegration of implants. A concave shape, wide pore throats, and dimensions between 150 to 600 μm facilitate bone ingrowth.[35,36] More specifically, a 600-μm pore size has a better fixation compared with 300- and 900-μm pores.[36] In terms of density, a porosity of $> 40\%$ is optimal for bone ingrowth.[37]

A special category is represented by porous metals, such as porous tantalum monoblock.[38] The structure of porous metals resembles that of bone, with a high volumetric porosity (70–80%). This structure is intended to provide better bone ingrowth.[38,31] A study that compared porous tantalum monoblock cups with porous-coated titanium monoblock cups in primary total hip replacement showed a lower incidence of radiolucency and aseptic loosening in porous tantalum

monoblock cups.[39] Because of the high cost, porous tantalum is currently most frequently used in revision hip replacements.

Surface energy is defined as the intermolecular forces between two surfaces and plays an important role in osseointegration of titanium implants.[40,41] A positively charged surface makes the implant hydrophilic, thus promoting protein adherence within the bone–implant interface and producing a stimulatory effect on osteoblasts.[42] These processes are important mainly in the early stages of osseointegration.[42] Factors that affect surface energy are roughness, surface treatment, implant composition, sterilization, and handling during implantation.[41,43] A method of quantifying the hydrophilic/hydrophobic property (wettability) of an implant involves placing a drop of the desired liquid on the surface of the material and then measuring the angle formed between the metal baseline and the tangent to the drop at the solid–liquid–gas boundary.[41,43] This is called the contact angle. The optimum range of wettability for proper osseointegration of implants has not been determined yet.

These mechanical and chemical properties can also increase the rate of bacterial adhesion and biofilm formation. Studies have reported an increase in *Staphylococcus epidermidis* with increased implant wettability and in *Streptococcus sanguinis* when a more porous surface is used.[44] As soon as bacteria colonize the titanium implant, they form a complex of microbial cells contained in an extracellular matrix, called biofilm.[45] Biofilm is more likely to form on rough and hydrophobic surfaces, but some bacteria can be more adherent to hydrophobic surfaces.[45,46] The matrix protects bacteria from antibiotics, thus making resolving the infection impossible without surgical treatment.[45]

Femoral stem design is another important factor of osseointegration of hip implants. Stems have been classified by Khanuja et al.[47] into seven types. The type 1 stem, which is engaged in metaphysis in the coronal plane because of a thin conformation, has three points of fixation in the femoral canal: proximally and distally on the posterior aspect of the femoral canal and anteriorly in the middle portion.[47] This is the only type that does not require femoral reaming, known to induce thermic necrosis. A previous study showed a 17-year survival of type 1 femoral stems of 98.8%.[47] The type 2 stem has a wider proximal part, thus ensuring metaphyseal engagement in the coronal plane and in the sagittal plane.[47] Aseptic loosening was found in only 0.5% of these stems at 15 years of follow-up.[47] The type 3 stem design facilitates fixation mostly in the metaphyseal–diaphyseal junction area. Twenty-year survival rates for type 3 stems were reported as 95.5%.[47] The type 4 stem has a porous coating on almost all of its length and has a survival rate at 22 years of 98%.[47] The type 5 stem is used in complex joint replacements because of its modularity. The rate of aseptic loosening of this type of stem was reported as 0.25% at a mean of 11 years.[47] The type 6 stem is more anatomical, taking into account the proximal femur curvature. A previous report showed that no revision was required in 471 patients who had the type 6 stem with a mean follow-up of 8.8 years.[47] Short femoral stems are still under debate because of inconsistent results. Some femoral stems have a survival rate of 92.3% at a mean of 6.1 years,[48] which is less compared with standard stems. In contrast, a review by Stulberg et al.[49] showed that short femoral stems have a similar survival rate to long femoral stems. Types 1, 2, and 4 stems have good survival at a minimum of 15 years, but more studies are required to compare the survival of femoral stems according to their design.

Optimization of patients

Obesity is one of the most important risk factors for primary hip osteoarthritis. Moreover, patients with a body mass index greater than 35 kg/m^2 have double the incidence of titanium implant aseptic loosening following a total hip replacement.[50] This is one of the main reasons, along with an increased risk of prosthetic joint infection, for doctors to include weight loss in their preoperative optimization plan.

Osteoporosis has a negative effect on osseointegration of titanium implants.[51] Studies have shown that a low body mass index increases migration of implant components and delays osseointegration of the femoral stem.[51] Oestrogen binds to oestrogen receptor alpha in osteoblasts, producing osteogenic activity, and indirectly reduces osteoclast activity by the RANKL/OPG signalling pathway.[52] Therefore, oestrogen deficiency found in osteoporosis increases osteoclast activity, decreases the osteoblast life span, and reduces the ability of mesenchymal stromal cells to differentiate into osteoblasts.[52] To the best of our knowledge, no studies have examined the effect of osteoporosis treatment on titanium implant fixation started before hip replacement surgery. Because of the high incidence of osteoporosis in this group of patients, we consider that further research is required.

Cardiovascular disease, cancer, and psychotic disorders have a higher risk of titanium implant failure, according to a study performed on 96,754 patients with primary hip and knee osteoarthritis.[53] However, we have found no evidence to support whether treatment of these comorbidities affects titanium implant survival. Other comorbidities, including neurodegenerative diseases, diabetes mellitus, and pulmonary diseases, have no effect on hip titanium implant survival.[53,54]

Smoking increases the risk of aseptic loosening by three times as shown by a meta-analysis by Teng et al.[55] With regard to smoking cessation, former smokers (non-smokers within 30 days before surgery) have no difference in complications compared with current smokers, at a mean follow-up of four years.[56] Therefore, smoking cessation before surgery is not related to short- and medium-term titanium implant loosening. However, more studies are required to determine when should patients start ceasing smoking before and after surgery for better results. Alcohol intake is not associated with an increase in the rate of titanium implant aseptic loosening.[50] The lack of data does not allow a clear conclusion, but experts consider that elective patients should enrol in a smoking cessation programme 6 to 8 weeks before surgery.[57]

Accordingly, we suggest preoperative optimization of patients undergoing elective hip replacement, including weight reduction, smoking cessation, controlled cardiovascular disease, and psychotic disorders.

Surgeon's experience

Fender et al.[58] analysed 1198 primary hip replacements. They found that the risk of failure was four times greater when performed by a surgeon who undertook less than 30 hip replacements per year compared with a surgeon who performed more than 60 hip replacements per year. Their study was performed on hip replacements that were performed in 1990. We consider that newer titanium implant properties and design could reduce the difference between experienced and unexperienced surgeons in terms of implant survival.

Intraoperative methods of improving hip implant osseointegration

The first surgical step to affect aseptic loosening is the approach used. In the Swedish Hip Arthroplasty Register, the

anterolateral approach was shown to be associated with the highest risk of revision owing to aseptic loosening because of a higher rate of titanium cup malpositioning.[59] Another recent study also showed a negative effect of the anterior approach on the risk of stem aseptic loosening compared with non-anterior approaches.[60] The anterior approach can affect the acetabular cup and femoral stem implant positioning. Therefore, we recommend good exposure if an anterior approach is used for good implant positioning to be achieved.

Excessive drilling and rasping to ensure a proper fit of the components produce mechanical and thermal damage to the bone and impair bone ingrowth.[61] A good fit of implants within the bone is a priority. Gaps of more than 50–150 μm lead to excessive fibrous tissue and affect osseointegration of titanium implants.[61] Stability is another important aspect. Micromotion of up to 30 μm is beneficial for bone growth and motion over 150 μm may impair osseointegration of the implant.[31]

One important aim during surgery is appropriate placement of the acetabular component. Too horizontal a position, meaning host bone coverage of the acetabular component less than 60%, is correlated to aseptic loosening.[62,63] Furthermore, too horizontal positioning of the cup is also associated with impaired titanium implant fixation.[63] Therefore we recommend e placement of the cup to be approximately 45 degrees horizontal inclination. Another factor that we consider affects implant fixation is acetabular cup anteversion, but no studies have correlated this factor with the rate of aseptic loosening. Apart from inclination, good containment of the cup in the acetabular cavity is essential to ensure good bone ingrowth.[63]

Stem size can predict implant survival, as suggested by Bergin et al.[64]. More specifically, the authors noted that patients with larger stem sizes and lower bone to stem ratios had more stable implants up to 20 years.[64] Femoral head size can also affect the prognosis of aseptic loosening. Although revision rates for dislocations are lower for femoral head sizes > 32 mm, revision for aseptic loosening is higher when > 32-mm femoral head sizes are used.[65]

From the surgical point of view, good stability and host bone coverage are the most important factors affecting osseointegration.

Postoperative methods of improving hip implant osseointegration

Systemic drugs that enhance bone metabolism

Many systemic drugs have been tested to improve bone metabolism, thus increasing bone apposition on the surface of titanium implants. Most systemic drugs that were tested in implant osseointegration were first described in treating osteoporosis. Systemic drugs are classified by their effect on bone into the following: anabolic (parathyroid hormone peptides, prostaglandin EP4 receptor antagonists, vitamin D, DKK1 antibody, and anti-sclerostin antibody), anti-catabolic (calcitonin, bisphosphonates, the RANK/RANKL/OPG system, and selective oestrogen receptor modulators), and both anabolic and anti-catabolic mechanisms (simvastatin and strontium ranelate).[6]

A recent review showed that all of the drugs mentioned above mostly had a beneficial effect on titanium implant osseointegration[6] in animal models. The major disadvantage of most drugs is the lack of clinical trials. We could only find five relevant clinical trials. One trial was performed by Sköldenberg et al.[66] regarding risedronate, which is a bisphosphonate. They found a decrease in bone resorption

around implants in the risedronate-treated group. In a clinical trial, Hansson et al.[67] showed that the alendronate-treated group had no enhancement of fixation in uncemented knee arthroplasties compared with the control group. Zoledronic acid was also proven to be beneficial in preventing aseptic loosening in hip replacements by a clinical trial performed by Friedl et al.[68] However, pamidronate does not affect cup migration.[69] With regard to newer treatments, human anti-RANKL antibodies represented by denosumab are undergoing a clinical trial for treating periprosthetic osteolysis.[70]

Rehabilitation protocol

Wolf et al.[71] showed no difference in bone mineral density around implants when they compared immediate full weight bearing and partial weight bearing in cementless titanium total hip replacements at 5 years. The same result was obtained by other studies.[65,72,73] Therefore, limitation of weight bearing after surgery should be revised. Avoiding high impact activities is associated with a decrease in aseptic loosening.[74]

Postoperative drugs

Painkillers are frequently used by patients with hip osteoarthritis. In our experience, most of these drugs are represented by nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are the least safe of painkillers in terms of osseointegration.[6] NSAIDs impair the osseointegration process of titanium implants by inhibiting cyclooxygenase-2. This results in decreased levels of prostaglandins, which are important in promoting inflammation and supply of bone-formation cells.[6] Therefore, we suggest choosing acetaminophen (paracetamol) for mild to moderate pain and opioids for severe pain[6] in patients following total hip replacement.

Pulmonary embolism is one of the most dangerous complications after total hip replacement. Therefore, thomboprophylaxis is an important part of the postoperative protocol. A review by Mavrogenis et al.[31] showed that enoxaparin, warfarin, dalteparin, and unfractionated heparin are factors that may inhibit titanium osseointegration, by supressing osteoblast activity in cell cultures.[6] However, fondaparinux does not show a negative effect on implant fixation.[31] Moreover, previous studies have shown that aspirin is a good option for preventing deep vein thrombosis and pulmonary embolism after hip replacement.[75] However, no studies have shown an interaction of aspirin with osseointegration, and therefore, it should be taken into account.

Heterotopic ossification can be prevented by administration of indomethacin, and studies have not shown a negative effect in the long term for implant fixation.[31]

Selective serotonin reuptake inhibitors (SSRIs) are an important group of antidepressants. SSRIs are associated with an increased risk of implant failure,[76] by acting on a serotonin transporter (5-HTT) on bone cells with a negative effect on bone formation.[77] Such a treatment is recommended to be replaced in patients with a hip replacement.

Diuretics are commonly used in treating oedema of different causes. Loop diuretics may be associated with a negative effect on osseointegration of implants.[78] The proposed explanation for this effect is related to hypercalciuria produced by loop diuretics, which alters bone metabolism.[79] Alternatively, thiazides can be used.

Antihypertensive drugs have not been associated with an increase in aseptic loosening, and thus are considered safe to use.[80]

Adjuvant therapies

Low-intensity pulsed ultrasound, initially developed for accelerating fracture healing,

Table 1. Protocol of managing patients undergoing uncemented total hip arthroplasty

Period	Category	Best choice
Preoperative	Implant	Porous implant or coated with hydroxyapatite Pore size of 600 μm >70% pore density. Types 1, 2, and 4 femoral stem design
	Patients' optimization	Treatment of cardiovascular disease and psychotic disorders Body mass index < 35 kg/m^2 Smoking cessation
	Surgical team	More than 60 total hip replacements per year performed by the surgeon
Intraoperative	Surgical technique	Avoid the anterior approach if good exposure is difficult to obtain Avoid excessive drilling and rasping Obtain good stability of the implant Obtain acetabular bone coverage of > 60% Acetabular cup horizontal inclination of approximately 45 degrees Good containment of the acetabular cup Selection of bigger femoral stems to fill the medullary canal
Postoperative	Systemic drugs that enhance bone metabolism	Use of systemic drugs that act on bone metabolism (e.g., risedronate and zoledronic acid)
	Rehabilitation protocol	Immediate weight bearing is accepted Avoid high impact activities
	Postoperative drugs	Avoid nonsteroidal anti-inflammatory drugs, and use acetaminophen for mild to moderate pain and opioids for severe pain instead Replace selective serotonin reuptake inhibitors Replace loop diuretics with thiazides

has a positive effect on titanium osseointegration in an animal model.[81,82] This technique increases bone mechanical pull-out force and new bone formation around the implant.[81,82] Unfortunately, no clinical trials on low-intensity pulsed ultrasound on osseointegration have been conducted. Therefore, further research is required for this technique to be applied in patients.

Pulsed electromagnetic fields are another approach, which increases osseointegration in an animal model by promoting bone anabolic metabolism.[83] There have been no clinical trials regarding this method. Therefore, further research on this issue is required.

Conclusion

Considering that aseptic loosening is the most frequent cause for revision surgery in total hip arthroplasties, many techniques of enhancing osseointegration of implants have been studied, and many are still under research. Proven methods can be divided into preoperative, intraoperative, and postoperative methods. Preoperative methods include selection of porous

implants for tantalum or hydroxyapatite coating for titanium, an implant pore size of approximately 600 μm, a density of more than 70%, and types 1, 2, and 4 femoral stem designs. Preoperative optimization of patients, including weight reduction, smoking cessation, and controlled cardiovascular disease and psychotic disorders, are also recommended. An experienced surgical team also reduces the risk of aseptic loosening. Intraoperatively, by avoiding excessive drilling and rasping, but obtaining good stability of the implant, good bone coverage and containment are important elements for good fixation of the implant in the long term. Postoperative use of systemic drugs with effects on bone metabolism, such as risedronate and zoledronic acid, avoiding high impact activities, and NSAIDs, SSRIs, and loop diuretics lower the risk of aseptic loosening in total hip replacement. With horough knowledge of current proven methods, each stage of hip reconstructive surgery can be adjusted to prevent the need for revision surgery and maintain the overall good satisfaction rate of primary hip replacement (Table 1).

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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