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REVIEW PAPER

Effect of Oxidative Stress on Bone Remodeling in Periprosthetic Osteolysis

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Abstract

The success of implant performance and arthroplasty is based on several factors, including oxidative stress-induced osteolysis. Oxidative stress is a key factor of the inflammatory response. Implant biomaterials can release wear particles which may elicit adverse reactions in patients, such as local inflammatory response leading to tissue damage, which eventually results in loosening of the implant. Wear debris undergo phagocytosis by macrophages, inducing a low-grade chronic inflammation and reactive oxygen species (ROS) production. In addition, ROS can also be directly produced by prosthetic biomaterial oxidation. Overall, ROS amplify the inflammatory response and stimulate both RANKL-induced osteoclastogenesis and osteoblast apoptosis, resulting in bone resorption, leading to periprosthetic osteolysis. Therefore, a growing understanding of the mechanism of oxidative stress-induced periprosthetic osteolysis and anti-oxidant strategies of implant design as well as the addition of anti-oxidant agents will help to improve implants' performances and therapeutic approaches.

Keywords Oxidative stress · Periprosthetic osteolysis · Implant integration · Inflammatory response

Introduction: Periprosthetic Osteolysis and Implant Failure

Total joint arthroplasty (TJA) is the only fully effective therapeutic choice for patients suffering from end-stage degenerative arthritis. The most frequent types of surgery are total hip (THA) and knee arthroplasty (TKA). Survivorship of total hip arthroplasty (THA) has improved, such that 90% of current implants still function optimally at 15 years or more post-operatively [1]. Despite improvements in modern prosthetic design, 5 to 10% of THA prostheses undergo revision within 10 years [2, 3]. Although osteolysis after THA has been reduced by the use of highly cross-linked polyethylene implant [4], osteolysis and its consequent aseptic loosening remain a major indication for revision surgery, accounting for 55% of THA revision procedures worldwide [5]. Revision surgery leads to an increase in-hospital mortality, higher morbidity, and poorer functional outcome versus primary THA [6–8]. Aseptic loosening is the clinical endpoint of periprosthetic osteolysis, which describes a progressive resorption of bone caused by a host inflammatory response to particulate wear debris [9–11]. Implant materials can release wear particles which may induce adverse reactions in patients, such as local inflammatory response leading to tissue damage, eventually results in loosening of the implant. Implant in ultra-high molecular weight polyethylene (UHMWPE) can undergo oxidation process, further boosting the inflammation, which has been recognized as a potential limiting factor for the longevity of this implants in total joint replacements [12].

Oxidative Stress and Bone

Oxidative stress is defined as an imbalance between the production of reactive oxygen species (ROS) and their elimination by protective mechanisms. Imbalance in this protective mechanism can lead to the damage of cellular component such as DNA, proteins, and lipids [13]. ROS are generated

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by aerobic metabolism in mitochondria [14–16] and include superoxide anions (O2–) hydrogen peroxide e (H2O2) and free radicals such as hydroxyl radical (OH–). ROS can either have beneficial or detrimental effects according to their concentrations. At low concentration, ROS act as signaling molecules to activate physiologic pathways involved in maintaining of cell homeostasis and the regulation functions such as signal transduction, gene expression, and activation of receptors [17]. Oxidative stress is also a key factor of the inflammatory response [18]. During the inflammatory response, the recruitment of different leukocyte types to the site of inflammation involves the production of reactive oxygen species (ROS). Moreover, inflammatory mediators such as cytokines and chemokines can enhance the production of ROS [13]. This detrimental effect of oxidative stress is therefore defined as oxidative damage of cells and tissue. In the latest years, a significant role of oxidative stress has been suggested for surgical trauma, post-surgical healing, and prosthetic implant outcome [19]. For this reason, a growing attention is directed to the role of oxidative stress in bone remodeling in physiological a pathological conditions, in particular in osteolysis due to bone turnover disorders, osteoporosis, arthritis, and implant loosening. Bone is a living tissue undergoing continuous remodeling, and oxidative stress can influence this process by affecting the differentiation and the proliferation of the different bone cell types [20–22]. The remodeling process is the result of the coordinated action of three types of bone cells: osteoclasts, responsible for bone resorption, osteoblasts, responsible of new bone matrix deposition, and osteocytes, which are major players of bone remodelling and interact with osteoclasts and osteoblasts to maintain normal levels of mineralization in response to mechanical load and repair micro fractures and micro-damages [23–25]. Bone remodeling process can be influenced by several factors, including hormones, age, inflammation, and oxidative stress. In particular, oxidative stress exerts opposite effects on the different bone cell types involved in bone remodeling. Recent evidences have shown that oxidative stress can affect osteoclast differentiation and proliferation [26, 27], leading to an unbalance between osteoclast and osteoblast functions, thereby resulting in metabolic bone disease and skeletal disorders, such as osteoporosis and osteolysis [28, 29]. In addition, osteoclasts share common progenitors and features with immune cells [30]; therefore, they can directly produce ROS, which amplify oxidative stress leading to bone erosion. The redox balance is maintained by endogenous anti-oxidant pathways, including the ketch-like enol coenzyme A (CoA) hydratase (ECH)-associated protein (Keap1)/nuclear factor E2-related factor 2 (Nrf2). In response to oxidative stress, Nrf2 is activated and stimulates the anti-oxidant response in order to reduce intracellular ROS. In presence of alteration or inhibition of Nrf2-mediated pathway, ROS levels increase, thereby stimulating osteoclast differentiation and proliferation [27, 31]. Conversely, increased levels of ROS and the consequent oxidative stress inhibit osteoblasts differentiation and induce the apoptosis of osteocytes and osteoblasts [23, 32], thus reducing the bone matrix deposition and shifting the balance towards bone loss. The interplay among osteoclast and osteoblast activity in the bone remodeling process is regulated by several factors, and the most important is the RANKL/RANK/OPG system [30]. The receptor activator of NF-kB ligand (RANKL) is expressed by osteoblasts and osteocytes. It binds to its receptor, RANK, on the surface of osteoclasts and their precursors, regulating the differentiation of precursors into multinucleated osteoclasts and osteoclast activation and survival. Osteoblasts and osteogenic stromal stem secrete osteoprotegerin (OPG), which protects the skeleton from excessive bone resorption by binding to RANKL and preventing it from interacting with the receptor RANK, expressed on osteoclasts precursors [33]. The expression of these regulatory molecules is deeply influenced by oxidative stress. In particular, oxidative stress induces RANKL upregulation and OPG downregulation through the activation of protein kinases, such as ERK1/2 and JNK. OPG is produced by the activation of the osteogenic Want/β catenin pathway and acts as a soluble decoy receptor that is able to compete with RANKL for the binding to the receptor RANK, thereby preventing RANKL-induced bone loss. Oxidative stress blocks the activation of OPG, shifting the balance towards the bone-resorptive action of RANKL and resulting in an increase of RANKL/OPG Ratio, which is considered an important determinant of bone mass in normal and disease states and an index of bone resorption [26]. In addition, oxidative stress has been shown to induce apoptosis of osteocytes [34]. Apoptotic osteocytes induce lining cells to retract from the bone surface, thereby leaving a suitable environment for osteoclasts recruitment and activation, through the production of RANKL. Under oxidative stress, apoptotic osteocyte further stimulates bone resorption by producing sclerotic and DKK-1, two inhibitors on the osteogenic Want/β-catenin pathway [35]. A further confirmation of the impact of oxidative stress on the bone system came from recent studies on space special environment, characterized by microgravity, radiation, vacuum, and extreme temperature[36]. These factors, in particular microgravity and radiation, generate oxidative stress which directly reduces bone formation, by reducing anti-oxidant defense mechanisms [36, 37] and suppressing osteoblastic function during mechanical unloading [38].

Oxidative Stress in Aseptic Periprosthetic Osteolysis

Inflammation is the typical response to implanted biomaterials, and it is an essential process to determine the success of wound healing and implant integration [39–44]. Indeed, after arthroplasty, a wound-healing reaction is activated around the prosthetic device in order to remodel the surrounding tissue

and promote osteointegration [43]. In vitro and in vivo evidences showed that prosthetic bioproducts come in contact with innate immunity receptors on the surface of immune cells, triggering an acute inflammatory response, characterized by the release of inflammatory, cytokine, chemokine, and ROS, aimed to remodel the surrounding tissue in order to adapt to the prosthetic implant [45–49].

Nevertheless, an excess or a chronic evolution of the inflammatory response can lead to tissue damage, resulting in periprosthetic osteolysis, which is characterized by a low-grade chronic inflammation [26, 40]. The result of a long-term activation of the inflammatory response in the tissue surrounding the implant is the activation of osteoclast at the bone-implant interface and the consequent bone resorption, eventually resulting in periprosthetic osteolysis a prosthetic loosening. Aseptic loosening is one of the major complications of arthroplasty, in particular hip and knee arthroplasty, limiting the implant longevity, according to for at least 50% of the cases of prosthetic revision surgery [5, 12, 50–52]. The chronic inflammation is triggered by wear debris originated from the prosthetic biomaterial [53]. In the prosthetic joint, the continuous adhesion and abrasion of the softer material on the bearing surface generate wear debris [54, 55]. These wear particles are known as the main agent causing periprosthetic osteolysis [56–61]. Wear particles can be generated from the surface of the implant, but also from the contact point of modular implants [62]. The range and size of particles wear debris are heterogeneous: smaller particles are generated during repeated rolling movements and by sliding and rotational motion on bearing surface by adhesion and abrasion, while larger particles originate from surface fatigue [63]. The size of wear particles isolated from periprosthetic tissue has a range of 0.1 to 1000 μm, but the majority belongs to the range of 0.1 to 10 μm. In particular, particles in the range 0.1–10 μm undergo phagocytosis by macrophages, which trigger the release of inflammatory mediators, such as IL-1, IL-6, and TNF-a, as well as ROS, that induce the recruitment and the differentiation of bone-resorbing osteoclast at the bone-implant interface. Since the most used biomaterial for prosthetic devices is polyethylene (PE), PE wear debris is considered the major players in inflammatory-driven osteoclastogenesis. Several evidences in vivo and in vitro suggested that a crucial role of this inflammatory response is played by ROS and that oxidative stress is significantly involved in wear debris-induced osteolysis. Recent evidences identified a high level of oxidative stress biomarkers in periprosthetic tissue of patients undergoing aseptic loosening [19], where high levels of gene related to oxidative stress, as well as the activation of gene related to the loss of osteogenic activity, were associated with an increase of ROS and local inflammation [64]. A similar result was described in vitro in bone cell lines exposed to wear particles [63, 65, 66]. Increased leveled ROS not only contribute to amplify the chronic inflammation, but promote RANKL-mediated osteoclast differentiation. The use of specific anti-oxidant or inhibitors of NADPH oxidase, responsible for ROS production, not only reduces ROS production but also bone-resorption activity of osteoclasts, both in vitro and in vivo [67]. In addition, alteration in the synovial levels of anti-oxidant enzymes was found in patients with aseptic loosening, suggesting a direct role of aberrant oxidative stress response in the development of aseptic loosening [68]. A recent study suggests that two oxidative stress markers, namely, plasma malondialdehyde (MDA) and total anti-oxidant capacity (TAC), could be more informative to predict the onset and progression of wear debris-induced chronic inflammation [69]. Similarly, a study on total hip arthroplasty (THA) aseptic loosening induced by osteolysis found an increased expression of oxidative stress response enzyme, cyclooxygenase-2 (COX2), and intercellular nitric oxide synthase isoform (iNOS) and the increase on high mobility box group 1 (HMBG1), an oxidative stress response osteoclast differentiation factor, in patients with periprosthetic osteolysis[53]. This study also suggests that the monitoring of the serum levels of these molecules, in correlation with bone remodeling plasmatic markers, could be a sensitive tool for the early detection of periprosthetic osteolysis [53]. Most of the studies about periprosthetic osteolysis are focused on the osteoclastic function, but a variety of cells are involved in this process. Indeed the bone-implant interface is composed of a series of bone multicellular units (BMU), composed of different cell types (osteoclasts, osteoblasts, and other cell of the mesenchymal stem cell lineage). Recent studies described the effect of prosthetic wear particles on these different cell types. Wear particles stimulate osteoblasts to promote osteoclastogenesis and osteolysis [70] and to involve macrophages in the production on inflammatory cytokine and in bone matrix degradation [71]. Osteolysis induced by wear particles is also promoted by osteocytes [72] by upregulating resorptive and inflammatory pathways. Besides macrophages and osteoclasts, osteoblasts can also phagocytosis wear debris and produce inflammatory mediators such as IL-6, TNFα, and IL-β in response to the debris and soluble factors that regulate osteoclastogenesis [73–76]. Human primary osteoblasts are reported to produce high levels of IL-6 in response to wear particles [77] and are affected by oxidative stress produced by prosthetic wear debris [78]. In this context, a recent study investigates the production of different cytokines and osteoimmunological biomarkers that might be involved in the alteration of bone formation-resorption homeostasis, promoting aseptic loosening of the implant [74]. In particular, the presence of an anti-oxidant agent in the prosthetic biomaterial induces a change in the osteoblast osteoimmunological response that has a positive effect on the osteolysis induced by wear debris, reducing aseptic loosening of the implants [74]. This study underlined

that oxidative stress affects not only osteoclast activity, but also osteoblast function in the process of periprosthetic osteolysis.

Different prosthetic biomaterials can induce oxidative stress on bone cells, leading to implant failure. ROS can be produced on a metal surface as intermediate product of the cathodic half-reaction of corrosion. Electrochemical polarization of Ti6Al4V to stimulate the cathodic half-reaction induced oxidative stress in macrophages, osteoblasts, endothelial cells, and osteoclasts [65]. Tricalcium phosphate (TCP) wear particles have been described to induce oxidative stress in mouse calvaria [79]: in presence of TCP wear particles [79], serum levels of tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β), and interleukin-6 (IL-6) were increased, while total anti-oxidation capacity (T-AOC) and superoxide dismutase (SOD) activity were decreased. Metal-on-metal hip arthroplasty is associated with high levels if cobalt and chromium ions, which can induce oxidative stress and affect, bone cells. In particular, cobalt and chromium ions were reported to reduce OPG/RANKL ratio and osteoblast activity, and to alter glutathione, superoxide dismutase, and catalase levels, leading to oxidative stress [80]. The mechanisms of oxidative stress-induced periprosthetic osteolysis are summarized in Fig. 1.

Recently, different in vivo studies evaluated different strategies to prevent periprosthetic osteolysis. Veronesi

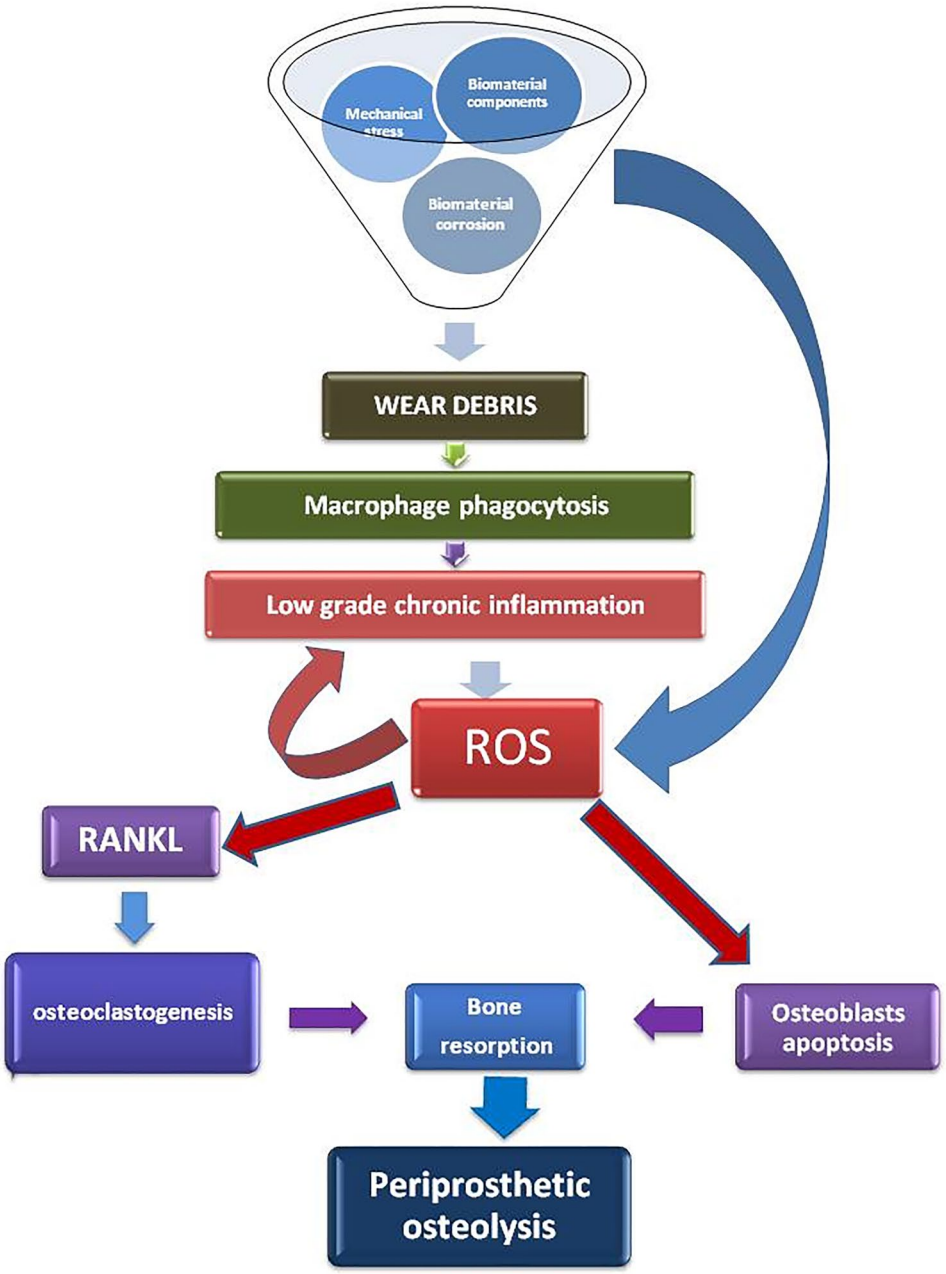

Fig. 1 Oxidative stress and aseptic periprosthetic osteolysis

et al. evaluated the use of pulsed electromagnetic fields and platelet-rich plasma alone and combined for the treatment of wear-mediated periprosthetic osteolysis, suggesting that this approach can be considered a safe, mini-invasive, and conservative therapy for counteracting osteolysis and prompting bone formation around implants [81]. Similarly, Bin Hu et al. showed that microbubble injection in bone canals enhances the inhibitory effect of low-intensity pulsed ultrasound (LIPUS) on debris-induced osteolysis and further strengthens the mechanical fixation of implants in an early-stage osteolysis model in vivo [82]. Other studies evaluated potential drug therapies to prevent periprosthetic osteolysis: metformin was shown to be able to attenuate osteolysis induced in mouse calvaria by the particles, inducing a reduction in osteoclast number and polarization of macrophages to an anti-inflammatory functional phenotype [83]. Melatonin can also be considered a promising therapeutic agent for the prevention and treatment of peri-prosthetic osteolysis. Indeed, melatonin was described as able to promote bone regeneration and reduce bone resorption at osteolytic sites caused by titanium-particle stimulation, by activating Wnt/β-catenin signaling pathway and enhancing osteoprotegerin mediated osteogenic differentiation, thereby suppressing osteoclastogenesis [84].

Anti-Oxidant Strategy to Prevent Implant Failure

Reactive oxygen species generated by local tissue cells and from implant surfaces have been suggested to determine implant failures [85]. Reactive oxygen intermediates produced at implant-bone interfaces act as strong chemoattractants for the recruitment of immune cells leading to surrounding tissue damage and fibrosis. In addition, ROS produced by immune cells can directly lead to the corrosion of the implants [40, 86]. An imbalance between excessive ROS generation and an insufficient anti-oxidant defense mechanism reduces bone-implant osseointegration, further inducing aseptic loosening. Thus, there is a need for biomaterials with bioactive surface coating with anti-oxidant properties to improve implant osteointegration, stability, thus improving the effective lifespan [87]. Several anti-oxidant strategies have been explored to reduce ROS formation in different prosthetic biomaterials, ranging from surface functionalization to material doping with anti-oxidant agents, according to the different implant biomaterial, as well as nutritional supplementation. Titanium and its alloys display a high biocompatibility, but they can also cause various side effects in the human body [88]. Indeed, titanium biomaterials may induce an innate/adaptive immune: in particular, this material induces the production of pro-inflammatory cytokines and enhance free radical generation in the periosteum covering titanium implant [89]. In titanium (Ti) substrates, in order to improve the anti-oxidant activity for enhanced bone formation, multilayered structure composing of chitosan-catechol (chi-C), gelatin (gel), and hydroxyapatite (HA) nanofibers was added, resulting in a significative increase of implant osteointegration, and promotes osteogenesis under conditions of oxidative stress [87]. An emerging anti-oxidant agent against titanium particles induced aseptic loosening is resveratrol. It has been widely reported that resveratrol has anti-proliferative, anti-oxidative, anti-inflammatory, and analgesic effects in many experimental models [90–93] Preclinical studies provided accumulating evidence on its efficacy in ameliorating the degenerative articular damage that mostly attributed to its pleiotropic properties [94, 95]. Moreover, many pieces of evidence have displayed resveratrol as one of the nutraceutical candidates for OA therapy in human [96, 97]. A recent study showed that the use of resveratrol as an "add-on" medication with meloxican (Mlx) was superior in terms of safety and efficacy to Mlx alone for the treatment of pain and improvement of physical function in patients with knee osteoarthritis (OA) [98]. As anti-oxidant agent in the context of implant biomaterials, resveratrol has been described by a recent study as having anti-oxidant effects of on titanium—particles exposed macrophages, in terms of downregulation of oxidative enzymes, such as NADPH, iNOS, catalase, SOD, and pro-inflammatory cytokines, such as TNFα and NfKB [67].

The flavonoid, naringenin, (4′,5,7-trihydroxy-flavanone), a polyphenol compound found in the human diet [99], mitigates titanium dioxide (TiO2)-induced chronic arthritis in mice: naringenin has been recently reported to ameliorate TiO_2 particles induced bone resorption by inducing anti-oxidant and anti-inflammatory [99]. One of the main biomaterials utilized in arthroplasty is the ultra-high molecule weight polyethylene (UHMWPE) for its survivorship properties compared to alternative prosthetic materials such as metal-on-metal and ceramic-on-ceramic [100–104], despite the propensity to generate wear debris [105], which represent the major limitation of long-term success for total joint arthroplasty [106, 107]. Therefore, the main focus of UHMWPE development is to minimize host response that leads to aseptic implant loosening. The first-generation UHMWPE devices were sterilized using high-dose gamma irradiation [108, 109] which has the adverse effect to produce free radicals trapped in the final product [110]. These ROS can lead to oxidative degradation of the UHMWPE device, as observed in components stored for a long time in air-permeable packing prior to implantation [56]. In addition, ROS can also trigger host response in terms of inflammation and osteoclast activation, ultimately resulting in periprosthetic osteolysis. In order to solve this problem, temperature-driven manufacturing operation was introduced to reduce ROS production in the UHMWPE manufacturing process [111]. These additional processes have anyway some drawbacks, such as the reduction of mechanical properties and only a partial protection against oxidation, because the

implants still need to be sterilized with gamma irradiation at the end of the process, exposing the device to some extent of oxidation. For this reason, a new approach was developed to stabilize UHMWPE in order to provide oxidation resistance without reducing UHMWPE fatigue strength. This approach is based on the incorporation of anti-oxidant agents into the resin or diffusion it into the already consolidated and radiated UHMWPE [112, 113]. One of the main anti-oxidant agents used to stabilize UHMWPE is α-tocopherol, also known as vitamin E [114], which is able to stabilize proxy radicals formed by oxidation and can also react with alkyl macroradicals [114, 115]. Vitamin E incorporation has been shown to have no detrimental effect on UHMWPE cross-link density, which is the major factor affecting UHMWPE wear resistance [114, 116]. Recent studies also showed that vitamin E stabilization of UHMWPE increased osteoblast response to oxidative stress, inducing cellular mechanism aimed to cell survival. Vitamin E anti-oxidant effect influences the secretion of osteoimmunological factors [74], shifting the bone turnover balance toward bone protection. This suggests that vitamin E stabilization of UHMWPE could contribute to reduce oxidation-induced osteolysis and the consequent loosening of the prosthetic devices, therefore improving the longevity of total joint replacements [73]. Anti-oxidant approach to prevent oxidative stress-based arthroplasty complication can be also based on nutrition supplementation. Arthrofibrosis is a debilitating complication after total knee arthroplasty (TKA) [117, 118] and the pathogenetic mechanism based on inflammatory process induced by free radicals and oxidative stress, responsible for the aggressive proliferation of fibroblasts and accumulation of fibrotic tissue. Vitamin C is one of the most effective hydrophilic anti-oxidants in biological fluids [119–121] preventing free radical-mediated oxidative damage to biological macromolecules including DNA, proteins, and lipids [122]. Patients undergoing TKA showed severe peri-operative vitamin C depletion. Vitamin C supplementation has been shown to prevent peri-operative vitamin C depletion and might have a protective value for the development of post-operative arthrofibrosis. Similarly, supplementation with melatonin, which is known to have anti-aging anti-oxidant effects [123], increased bone mass around the prostheses in a mouse model of osteoporosis, ameliorating mitochondrial oxidative stress response and promoting osteogenesis [124, 125]. Oxidative stress-induced osteolysis characterizes also other bone disorders, such as osteoporosis or osteoarthritis, and several anti-oxidant approaches have been directed to prevent bone loss in these diseases. Dihydrometacin, a natural compound with anti-inflammatory and anti-oxidant effect [126, 127], or corosolic acid [66], a plant derived anti-oxidant agent, were shown to reduce lipopolysaccharide (LPS)-induced oxidative stress, inhibiting ROS production and increasing anti-oxidant pathways. Similarly, thymoquinone, the main bioactive component of the black seed oil, showed anti-osteoclastogenic properties by inhibiting both inflammation and ROS production in osteoclast progenitors [128]. The promising results of these studies may suggest extending their use also in the prevention of oxidative stress-induced periprosthetic osteolysis.

Conclusion

The success of implant performance and arthroplasty is based on several factors, including biomaterial characteristic, local microenvironment, tissue response, and host-implant interplay. In this context, oxidative stress plays a crucial role, because an excess of ROS affects both the host response and the implant component, leading to oxidative stress-induced osteolysis, ultimately resulting in aseptic loosening. Therefore, a growing understanding of oxidative stress-induced periprosthetic osteolysis and strategies to control oxidative stress by implant design and anti-oxidant agents will help to improve implant performances and evaluate therapeutically approaches.

Wear debris can originate from prosthetic biomaterial as a consequence of mechanical stress, biomaterial component, or corrosion. These particles undergo phagocytosis by macrophages, inducing a low-grade chronic inflammation and ROS production. ROS can also be directly produced by prosthetic biomaterial oxidation. On the one hand, ROS amplify the inflammatory response; on the other hand, they stimulate both RANKL-induced osteoclastogenesis and osteoblast apoptosis, resulting in bone resorption, leading to periprosthetic osteolysis.

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