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Review article

Mixed oxide nanotubes in nanomedicine: A dead-end or a bridge to the future?

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ABSTRACT

Nanomedicine has seen a significant rise in the development of new research tools and clinically functional devices. In this regard, significant advances and new commercial applications are expected in the pharmaceutical and orthopedic industries. For advanced orthopedic implant technologies, appropriate nanoscale surface modifications are highly effective strategies and are widely studied in the literature for improving implant performance. It is well-established that implants with nanotubular surfaces show a drastic improvement in new bone creation and gene expression compared to implants without nanotopography. Nevertheless, the scientific and clinical understanding of mixed oxide nanotubes (MONs) and their potential applications, especially in biomedical applications are still in the early stages of development. This review aims to establish a credible platform for the current and future roles of MONs in nanomedicine, particularly in advanced orthopedic implants. We first introduce the concept of MONs and then discuss the preparation strategies. This is followed by a review of the recent advancement of MONs in biomedical applications, including mineralization abilities, biocompatibility, antibacterial activity, cell culture, and animal testing, as well as clinical possibilities. To conclude, we propose that the combination of nanotubular surface modification with incorporating sensor allows clinicians to precisely record patient data as a critical contributor to evidence-based medicine.

Abbreviations: MONs, Mixed Oxide Nanotubes; TiO2 NTs, Titanium Dioxide Nanotubes; HA, Hydroxyapatite; PVD, Physical Vapor Deposition; Fe3O4, Magnetite; Fe2+, Ferrous Ion; Fe3+, Ferric Ion; XPS, X-ray Photoelectron Spectroscopy; EG, Ethylene Glycol; DMSO, Dimethyl Sulfoxide; FA, Formamide; DMF, Dimethylformamide; NMF, N-methylformamide; ZrO2 NTs, Zirconium Dioxide Nanotubes; HfO2 NTs, Hafnium Oxide Nanotubes; IMCs, Intermetallic Compounds; V2O5, Vanadium Pentoxide; RF, Radio-Frequency; SBF, Simulated Body Fluid; GEP, Gene Expression Programming; MOPSO, Multi-Objective Particle Swarm Optimization; AgNPs, Silver Nanoparticles; GO, Graphene Oxide; HObS, Human Osteoblasts; ECs, Endothelial Cells; VSMCs, Vascular Smooth Muscle Cells; MSCs, Mesenchymal Stem Cells; OPC1, Osteo-Precursor Cell Line; ALP, Alkaline Phosphatase; S. aureus, Staphylococcus Aureus; S. epidermidis, Staphylococcus Epidermidis; E. Coli, Escherichia Coli; Ag2O NPs, Silver Oxide Nanoparticles; ROS, Radical Oxygen Species; hASCs, Human Adipose-Derived Stem Cells; BIG, Bone-Implant Contact; APH, Anodization-Cyclic Precalcification-Heat Treatment; DRI, Drug-Releasing Implants; CAGR, Compound Annual Growth Rate; PSIs, Patient-Specific Implants; CT, Computed Tomography; LEDs, Light emitting diodes; MEMS, Microelectromechanical Systems.

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1. Introduction

In the recent decade, there has been a great increase in patients requiring artificial implants as replacements for damaged tissues such as hip joints and teeth due to the increase of the elderly population [1]. Thus, many efforts have been directed toward identifying appropriate biomaterials for the production of durable medical implants. Among the different kinds of biomaterials, metallic-based materials are the most common replacement compounds for bone treating [1]. Pure titanium (Ti) and its biocompatible-grade alloys have been extensively used as medical implants owing to their high biocompatibility, fatigue life, corrosion resistance, and lower Young’s modulus, compared to other medical implants, e.g., cobalt alloy and stainless steel [2–4]. Despite the inherent benefits of Ti alloys, supplementary exploration is necessitated to attain developed clinical achievements. As this category of alloys is employed in the manufacturing of medical implants, due to insufficient physiological adaptation, increases the risk of implant failure [5–7]. This also causes the detrimental accumulation of wear debris and ions discharge into the biological media [8]. To overwhelmed to insufficient physiological adaptation, increases the risk of implant failure

2. Concept of mixed oxide nanotubes

Fig. 1 shows a schematic side view of various configurations of MONs. In chemistry, a mixed oxide is an oxide with cations of a single element in different oxidation states (Type I) or cations of more than one element (Type II) [54]. These oxide structures are usually produced by the template method. The magnetite (Fe3O4) that includes the Fe2+ (ferrous ion) and Fe3+ (ferric ion) cations in a 1:2 ratio, as well as perovskite compounds i.e. ABX3 (A and B are two cations of very different sizes, and X is an anion that bonded to both), are well-known as typically mixed oxides [55]. During the last decades, the preparation of mixed oxides has been developed as they have several significant properties such as superconductivity, magnetism, ferroelectricity, catalytic activity, and ionic conductivity [55–57]. It must be noted the nanotechnology has led to more efficient mass production, and as expected has become an important industry [58]. Accordingly, numerous attempts have been made to employ nanotechnology in various sectors, for instance in electronics, environmental protection, and biomedical applications [59]. The main reason why nanotechnology has received great attention is that the physicochemical behavior of nanostructured materials is different from those of the bulk materials [60]. Thus, by utilizing these nanostructures, solutions to the problems and limitations associated with the traditional ways can be obtained. From this viewpoint, the preparation and applications of MONs are challenging yet exciting research fields.

On the other hand, an additional definition of MONs can be given by a mixture of different oxides, rather than a mixed M1–M2 oxide (Type III). This type of MONs is commonly produced by electrochemical anodization, where nanotubes with electrochemically tunable morphologies can be produced. For instance, high-resolution X-ray photoelectron spectroscopy (XPS) revealed that the nanotubes developed on the β-Ti-45Nb alloy are composed of TiO2 and Nb2O5, rather than a mixed Ti-Nb oxide [61]. For this purpose, anodization or electrochemical oxidation is a well-known method to prepare the protective layers and self-organized mono- and mixed oxide nanotubes. In view of the fact that the self-organized mono- and mixed oxide nanotubes can be formed on Ti and other valve metals, these unique nanotubular surface modifications have attracted increasing interest for the fabrication of more effective implantable apparatus for biomedical applications [62–64]. In this review, the main focus is not only to provide a comprehensive comparison of the current preparation and characterization of Type III MONs and generate a list of potentially suitable platforms but also to discuss the disadvantages and possible improvements in the fabrication process.

3. 3. comparison between mono and mixed oxide nanotubes

In the past decades, electrochemical anodization for the growth of thick and homogeneous oxide coatings, as well as the development of self-organized nanotubes on different valve metals have received much attention in the literature [65–71]. The electrochemical oxidation is initiated at the interface of metal-oxide followed by the outwards migration of metallic ions under the application of an external electric field. Simultaneously, oxygen ions migrate to the metal-oxide junction and react with cations and materialize into a dense metal-oxide layer. The oxide layer propagates on the condition that the electric field is sufficient to allow ion transmission throughout the oxide, but the procedure eventually ceases, leading to a finite thickness of the oxide layer. In addition to the development of self-assembled nanoporous and nanotube coatings, porous oxide films could also occur under controlled experimental conditions [72]. So far numerous findings have reported the formation of mono- and MONs coatings, with some of their outstanding achievements, are summarized in the following section.
Fig. 1. A schematic side view of various configurations of MONs; type I (like Fe$_3$O$_4$), type II (like FeTiO$_3$), and type III (like TiO$_2$–Nb$_2$O$_5$).

Fig. 2. (a) A schematic view of electrochemical anodization and different generations of TiO$_2$ NTs synthesis via the anodization technique, and (b) key factors for the generation of mono- and mixed oxide nanotubes on different valve metals and their alloys.
3.1. Mono-oxide nanotubes

The first report on the preparation of a self-organized nanoporous oxide film by anodization was performed on Al in an C2H2O4 electrolyte under specific circumstances [73]. The results of this work initiated a new pathway for the anodization of different types of valve metals and triggered thousands of papers for the preparation and application of nanoporous structures. The anodized nanoporous Al2O3 was utilized as photonic crystals and template for the fabrication of various nanostructures, thus several models have been proposed to describe the growth mechanisms of the self-ordered nanoporous alumina [72]. The proposed mechanisms of the self-ordering nanoporous Al2O3 could also be applied in the development of self-organizing nanostructured coatings on various valve metals, e.g. Ti, Zr, Hf, V, Nb, Fe, and Ta [72, 74–80]. Nevertheless, contrary to Al, anodization in an acidic solution causes the formation of a compact oxide coating. Therefore these conditions are inadequate to produce self-organizing nanoporous oxide layers on these metals [72]. To overcome this issue, the presence of fluoride anions is required for the development of self-organizing nanostructured coatings. The main advantage of fluoride is its potential to produce water-soluble metal-fluoride compounds, which prevents the development of metal-oxide layer at the tubular bottom, by a mild but steady chemical dissolution of the metal-oxide layer. The size of the anions is also a vital issue, where the smaller F− ions have a higher migration rate through the oxide lattice compared to the O2− ions. This causes the development of a fluoride-rich film at the metal-oxide interface which is the basis of the nanostructured coating development. Some outstanding books and reviews have described the growth mechanism of mono-oxide nanotube arrays by the anodizing method. In the following section, a summary of the development of some mono-oxide nanotubes under different experimental circumstances has been described [72,81–85].

One specific tactic to decrease the depreciation in body fluids and to improve the wear and corrosion resistance is to generate a homogeneous TiO2 layer on the surface of the Ti implants. In particular, the development of anodic TiO2 NTs has recently received much interest in the modification of metal implants owing to their outstanding biocompatibility and resistance to bio-corrosion. Fig. 2a displays a schematic view of electrochemical anodization, as well as the different generations of TiO2 NTs synthesized via the anodization technique. The rapid oxide dissolution was the chief restriction of the primary generation of nanotube synthesis, leading to nanotubes with less than 1 μm length. Hence, in the second generation, HF was exchanged with KF or NaF to achieve a higher pH and expand the nanotube length up to ~5 μm. Nanotubes with a length of 6 μm could be formed in 0.1 M KF, 1.0 M H2SO4, and 0.2 M C6H8O7 aqueous electrolyte (25 V and 20 h) as the pH was kept to 5 [86,87]. The third generation of synthesis gave more amendments in the NTs length through non-aqueous electrolytes or organic polar solvents, for instance, ethylene glycol (EG), dimethyl sulfoxide (DMSO), formamide (FA), dimethylformamide (DMF), and N-methylformamide (NMF) mixed with HF, NH4F or KF [88–92]. Finally, the fourth generation of nanotube synthesis involves the use of non-fluoride electrolytes [93].

All self-ordering nanotubes produced by electrochemical anodization in various electrolytes on various valve metals and their alloys appear to pursue the same growth principles and the key factors for the generation of nanotubes as shown in Fig. 2b. It is well-known that the diameter and length of nanotube is controlled through the anodization voltage; while the length of nanotubes is governed by the oxide resistance against electrolyte solutions, which also attributes to the voltage of anodization, anodization time, and the oxygen amount delivered by water for the growth of nanotube arrays. As mentioned above, dependent on the anodizing circumstances, self-organized nanostructured coatings can also be formed on various valve metals and their alloys, where the examination and optimization of processing parameters are favorable for obtaining nanotubes with high-aspect-ratio. Thick and smooth zirconium dioxide nanotubes (ZrO2 NTs) could be achieved using organic and mixed electrolytes at a potential of 40 and 20 V, respectively [94–98]. Irregular ZrO2 NTs were produced using a one-pot anodization process without any pretreatment, even in the presence of contaminations as well as surface heterogeneity. To attain highly ordered nanotube arrays, pretreatments on Zr were also proposed to boost the self-organizing process. Electropolishing, dip-etching, and two-step anodizing were carried out on Zr substrates to attain highly self-organized nanotubular arrays. In the same way, hafnium oxide nanotubes (HfO2 NTs) with a high aspect ratio can be fabricated under a broad range of anodization circumstances [99].

With regards to tantalum, certain conditions must be met to achieve the nanoporous and nanotube arrays which are extremely corrosion resistant in the acidic media [100–108]. Based on the literature, Ta2O5 nanotube arrays were grown under an anodization voltage range of 10–20 V after 5–120 s in a mixed H2SO4 and HF electrolyte with 1 wt% H2O. However, prolonged anodization causes the destruction of the nanotubes and the presence of dimples which is most likely due to the development of a thin fluoride-containing layer at the interface of metal-oxide. Similarly, well-aligned anodic nanotubes have been obtained on other valve metals such as niobium (Nb) and tungsten (W) [109,110].

3.2. Mixed oxide nanotubes

Nanotubular coatings can be fabricated by controlling the anodization conditions, where they can generate not only mono-oxide nanostructures but also MONs. However, the preparation of MONs by electrochemical anodization is not entirely understood because the formation mechanisms are complex, where a wide range of MONs can be produced depending on the type of metal and anodization conditions [55]. The formation of MONs have been observed on binary, ternary, quaternary systems as well on more complex alloy systems such as Ti-Al [111,112], Ti-Mo [113,114], Ti-Nb [61,115–117], Ti-Ta [116,118,119], Ti-Zr [75,116,120–122], Ti-Mn [123], Ti-Al–7Nb [124–126], Ti–6Al–4V [130–132], Ti–35Nb–5Zr [143], Ti–28Zr–8Nb [132,144], and Ti–29Nb–13Ta–4.6Zr [145–147]. The presence of various elements in Ti alloys significantly influences the electrochemical behavior and morphology, as well as the composition of the resultant oxide nanotube arrays. In the presence of different elements, the composition of the as-anodized layer is closely related to the metallic ratio of the alloy. For example, the nanotubes formed on the Ti–Al alloy system consist mainly of titania and alumina, and it is closely related to the ratio of Ti and Al in the base alloy. In some cases, it is not possible to identify the MONs due to the low phase fraction of other oxides relative to the dominant phase (TiO2) [131]. In such cases, it is necessary to perform XPS to distinguish a mixed oxide structure from a mono structure and to measure the elemental composition, and chemical state of the elements in the MONs [61].

3.3. Mixed oxide nanotubes on Ti alloys

Resembling the development of titania nanotubes on pure Ti, the formation of MONs on Ti-based alloys relies on the processing factors, such as pH, anodization time, anodic potential, and fluoride ion concentration. Nonetheless, the morphological features of nanotubular coatings on the Ti alloys are somewhat dissimilar compared to the formation on pure Ti owing to the selective dissolution of the oxide layer in fluoride electrolytes and the solubility of metal fluorides during the anodization process. For ternary systems, both the α and β phases are present with the addition of the other element, where organized nanotube coatings are formed in the α phase, while a combination of nanotubes and nanopores is observed in the two-phase (α + β) component. In the following section, the development of MONs on different Ti alloys is presented [61,85].
3.4. Binary alloys

3.4.1. Ti–Al alloys

Because of the dissimilar oxide morphologies that could be formed on Al and Ti, it is very interesting to assess the electrochemical feature of different compositions of the Ti–Al alloys prepared in an F–comprising electrolyte and to appraise the critical circumstances which control the evolution of one type of morphology to the other. Besides that, the length scale of the self-organization procedure is important, where the well-organized oxide configurations on Al and Ti surface by anodization could be voltage regulated [148,149], but the total self-organizing length is dissimilar for the two substrates. In this regard, the self-organizing properties of anodic oxides on refractory metals are studied in detail [150,151], which has two dissimilar morphologies, the highly organized parallel aligned porous oxide configurations, and the organized arrays of nanotubes. The top-view SEM micrographs of oxide-layers grown on Al, TiAl3, TiAl, Ti3Al, and Ti in 1 M H2SO4 comprising 0.15 wt% HF at potentials of 10, 20, and 40 V are shown in Fig. 3, where the evolution from porous to tubular configuration is detected [150].

As shown in the figure, the self-ordered oxides could be generated over an extensive potential range. The very regular porous configuration is formed on Al, comprising of some hexagonal nanopores with the mean interpore distance ranging from 30 nm at 10 V to 55 nm at 40 V. In contrast, the pores are partly enclosed by bundles of oxide needles owing to the non-uniform etching of the pore walls throughout prolonged anodization in F–comprising electrolytes at lower potentials [152]. It is reported that the morphological features in the self-ordered configurations depend on the anodization voltage and the alloy’s composition, where the tubular division is attributed to the augmented stress due to the rising volume expansion, as changing the composition from Al to Ti [150,151].

3.4.2. Ti–Mo alloys

Previous results on emerging Ti–Mo alloys showed that these alloys are promising as medical implants due to the low elastic modulus, electrochemical constancy in biological media, and high corrosion resistance [153–155]. However, the formation of MONs on Ti–Mo alloy is not free from challenges. For instance, it was suggested that a multi-purpose optimization of the electrolyte solution, especially the F− concentration and water quantity, at 150 V for 20 h, could lead to the development of self-organized MONs on Ti–7Mo alloy. However, the results showed that only porous oxide layers with higher Mo concentration were formed using the proposed approach [156,157]. Given the possible nanotubes generation on binary Ti–Mo alloys and to overcome the challenges, Oliveira et al. [114] studied the formation of self-organized nanotubes on biomedical Ti–Mo alloys (Ti–6Mo and Ti–15Mo) using the electrolyte solution proposed by Ji et al. [158] for pure Ti, to ensure that the matrix configuration is attained at the nanotubes, where the α phase is only formed on the Ti–6Mo, while the β phase is only formed on the Ti–15Mo [159].

From the SEM images as shown in Fig. 4a–e, the nanotubes were formed after 2 h, which are transformed into nanotubes following 4 h, and eventually well-defined, homogeneously distributed MONs with a mean diameter of 90 nm are developed on the Ti–Mo alloy after 6 h. The electrochemical assessments revealed that the MONs formation on the Ti–Mo alloys gave better protective features than the oxide films instinctively developed on the respective alloys [114] (Fig. 4f).

3.4.3. Ti–Nb alloys

Based on previous studies, the titania layer developed on the Ti–14.6Nb alloy showed excellent photocatalytic activity [113]. Besides that, Nb is an alloying element for Ti alloys that are widely utilized for biomedical applications, for instance, the Ti–29Nb–13Ta–4.6Zr alloy [160]. Accordingly, the findings on MONs formed on Ti–Nb alloys provide some essential information for employing MONs coatings on the Ti-based implants for different orthopedic applications [117,161,162]. Also, it is reported that a TiO2–Nb2O5 mixture possesses a higher photocatalytic activity compared to the pure TiO2 [163] and also found that this MONs structure possesses metallic behavior [164], making them potential conducting transparent materials.

In electrochemical anodization, it is vital to reach an equilibrium between the oxide growth and local oxide dissolution, where the equilibrium is sensitive to the F− concentration, as the chemical dissolution of oxide is accompanied by the release of the soluble [TiF6]2− complexes [61]. The different valve-metal oxides undergo dissimilar dissolution kinetics in F−-comprising solutions [165]. From the electrochemical data, the dissolution rate of Nb2O5 is only 1 nm min−1 compared to the dissolution of TiO2 which is 20 nm min−1 [166]. This shows that the formation of Nb2O5 at the anode is more resistant to F− ions compared to TiO2 in 1 M NaH2PO4 with 0.5 wt% HF (pH 4.5) [61]. Thus, the TiO2 dissolution rate in an F−-comprising electrolyte is of crucial importance to the length of the developed nanotubes [167], likely, the growth of the anodic oxides on Ti–Nb alloys differs drastically from the pure Ti. In this context, Ghicov et al. [61] explored the formation of MONs in a binary Ti–45Nb alloy. They reported that the shape and dimensions of TiO2 NTs reinforced with Nb2O5 could be controlled within a wide parameter range. The Nb2O5 undergoes a much lower chemical dissolution rate compared to the TiO2 in the F− solution, thus the nanotube corrosion is hindered upon the formation, which results in the development of longer MONs (Fig. 5a–g). This feature enables the tuning of the TiO2 NTs for particular applications, such as photon absorption and insertion of microbiological species. Furthermore, the MONs possess higher thermal resistance compared to the pure TiO2 NTs, which enables thermal treatment at much higher temperatures.

In this regard, ultrafast MONs development on the Ti–Nb alloy by

![Fig. 3. An overview of the morphologies formed on the different Ti-Al alloys at different anodization voltages grown in 1 M H2SO4 containing 0.15 wt% HF (Reproduced with permission from Ref. [150]).](image-url)
quick breakdown anodization in NaCl–NaClO₄ mixed electrolyte, NaCl, and NaClO₄ solutions at pH 4 was also examined by Jha et al. [116], as shown in Fig. 5h–j. They found that the intense evolution of hydrogen at the Pt cathode took place instantaneously upon anodization. The surface of Ti–Nb alloy is covered with white spots that are distributed very quickly over the surface upon 30 s of anodization. These white spots are the oxide nanotube bundles that form densely around a pit. The results show the formation of two types of morphologies, which are the net-like and free-tubular configurations, were formed using quick breakdown anodization. For the net-like configurations, the MONs show a relatively homogeneous size (30–40 nm in diameter and several tens of micrometers in length), while in the case of free-tubular configuration, the diameter of the nanotubes varies significantly from 20 nm to more than 100 nm (Fig. 5h). In addition to the mixed electrolyte, Fig. 5i and j displays SEM micrographs of nanotubes anodized in NaCl and NaClO₄ solutions, respectively. In NaCl solution, the anodized surface was covered with loosely packed nanotube bundles with net-like morphology (Fig. 5i). On the contrary, the NaClO₄ solution led to the
more uniform coating but the nanotubes are segmented into packets of around 2 μm length (Fig. 5j). Contrary to the NaCl electrolyte, the nanotubes generated in NaClO₄ solution had smooth walls without ripples, thus it can be deduced that the net-like nanotubes are attributed to the presence of Cl⁻, while the stacks of smooth-walled nanotubes are ascribed to the presence of ClO₄⁻. This suggests that the mixed electrolyte possesses the advantage of attaining a large surface coating with a high adhesion strength, which is very important in modern implantology [168,169].

3.4.4. Ti-Ta alloys

Apart from the optimization in structural features of nanotubes (geometry and functionality), another noteworthy aspect of the β-type Ti-based alloys is the bimodal self-assembly. In this arrangement, the nanotubes consist of ordered tubes with different diameter sizes i.e. larger tubes that are surrounded by smaller tubes. In this regard, Tsuchiya et al. [118] explored the development of MONs on the Ti-Ta alloys such as Ti–13Ta, Ti–25Ta, Ti–50Ta, and Ti–80Ta, and examined possible formation mechanism of the bimodal self-organization on these alloys.

They found that the nanotube layers until 50% Ta are composed of tubular configurations underneath the top porous layers, as illustrated in Fig. 6a–i. This type of formation is due to a composition-dependent evolution from nanopores to nanotubes as proposed by Berger et al. [150] for the Ti-Al alloys. The anodization of binary Ti alloys leads to a highly non-uniform surface owing to the selective dissolution of the unstable phases and/or diverse reaction rates on various phases in the alloys. In the case of binary Ti-Ta alloy, there are somewhat large two-phase zones in the phase diagram. Accordingly, the anodized Ti–13Ta, Ti–25Ta and Ti–50Ta alloys exhibit some inhomogeneous surfaces, which can be ascribed to the alloys’ microstructures, where the oxide coatings on Ti–13Ta and Ti–25Ta show a Widmanstätten-type microstructure and the tube diameters on Ti–13Ta and Ti–25Ta consist of random distributions (Fig. 6a–f). In the case of Ti–50Ta alloy, the oxide layer is composed of two zones, (i) black zones, consist of typical nanotubular structures, and (ii) white zones consist of nanoporous structures. From the bottom-view, the anodized Ti–50Ta alloy is composed of two distinct diameter tubes, where the larger tubes are surrounded by smaller tubes (Fig. 6g and h). This shows that an appropriate level of alloying elements is requisite for the nanotube development on two-size scales. Besides that, the Ta concentration significantly affects the nanotube diameter in such assemblies, as shown in Fig. 6i [118].

Fig. 6j–m shows the growth steps of MONs on the Ti–50Ta alloy. As demonstrated in Fig. 6j, a nanoporous layer is initially generated on the alloy surface, followed by the generation of a nanotubular layer developed underneath the nanoporous layer (Fig. 6k). In this step, the nanotube growth occurs at different rates, i.e. the faster tube growth occurs further in lateral directions and consequently, the growth of slower tubes will be stopped. The growth on two alloy phases (α or β) is different, thus the attainable bimodal tube diameters vary in the two phases. Moreover, the chemical compositions of the outermost nanoporous layers depend on the substrate phase that causes a disparity in the nanoporous dissolution rate in diverse zones, leading to an alteration evident in the top-view morphology. The underneath nanotube layers become apparent (Fig. 6i) owing to the dissolution of the nanoporous, which is followed by the drastic etching of the tubes which leads to the nanotube wall thinning and the nanotube surface roughening caused by the preferential etching of the tubes (Fig. 6m) [118]. It is therefore

Fig. 6. Top- and bottom-view SEM micrographs of oxide layers developed on (a–c) Ti–13Ta; (d–f) Ti–25Ta; (g–i) Ti–50Ta by anodization at 20 V for 12,000 s in a mixed electrolyte (1 M H₂SO₄ + 0.15 wt% HF) as well as (j) schematic demonstration of the growth steps of self-organized MONs on Ti–50Ta alloy (Reproduced with permission from Refs. [118]).
suggested that homogenous MONs formation on a single-phase substrate can be attained if the specimen is timely detached from the electrolyte upon the nanoporous layer dissolution [118,170]. Following this study, Jha et al. [116] investigated ultrafast MONs formation on Ti–35Ta alloy by quick breakdown anodization in an electrolyte of 0.05 M NaClO₄ + 0.05 M NaCl in 50:50 vol% of H₂O: C₂H₅OH buffered at pH 4, at 40 V for 120 s, where pronounced localized flower-like nanotube structures are formed. They reported that the oxide nanotubes showed the least homogeneous configuration under the present anodization conditions.

3.4.5. Ti–Zr alloys

The development of nanotubes on the Ti–Zr alloys is widely studied due to the higher structural flexibility of zirconium titanate nanotubes compared to the pure TiO₂ NTs [120,171]. In particular, an extended range of diameter and length of configurations can be formed by altering the anodization potential without loosening the highly ordered character of the substance. In this regard, comprehensive studies on the formation of multilayered oxide nanotubes on Ti–Zr alloys for modifying the configuration of a nanotubular valve metal system by electrochemical anodization are implemented by Yasuda et al. [75,120,122]. For this purpose, the first anodization was executed at 20 V for 15 min followed by a potential sweep from the OCP to 20 V at 20 V s⁻¹, followed by a second anodization step at 20 V for 15 min after an opened circuit for 1 min.

Fig. 7a–f displays the SEM micrographs of the MONs on Ti–Zr alloy. As illustrated in Fig. 7a, a two-layer MONs structure is formed after a two-step anodization process, where the upper and lower layers were formed in the first and second anodization processes, respectively. There is a non-uniformity in the nanotube diameter in the zones, where the potential was switched off and on again. Besides that, the length of the nanotube for each layer is in harmony with the theoretical amount measured from the electric charge in each procedure [122]. The magnified SEM image in Fig. 7b shows that the generation of new nanotubular arrays in the bottom layer begins in the gaps between the present tubes in the top layer. By scraping the multilayer structure, fractures occur between the top (A) and bottom (B) layers, as shown in Fig. 7c. From Fig. 7d, the upper layer shows a tubular structure with a mean diameter and wall thickness of 90 and 10 nm, respectively, with a similar same morphology with the common single anodization. On the contrary, the top of the nanotubes in the bottom layer is composed of pores with a mean diameter of ~20 nm (Fig. 7e), where the remains of the tube bottoms from the nanotubular arrays of the top layer, as well as the development of many pores around them, are the dominant phenomena (Fig. 7f). It was proposed that these pores are the initial points of new tube growth at the bottom layer. Also, as schematically illustrated in Fig. 7g, the new tube growth begins in the gaps between the present tubes [75]. Given the development stages of the nanotubes at the underside, the possible choice for the rate-determining step of the tube expansion is either (i) diffusion of a metal cation or oxygen anion in the solid phase, (ii) charges for oxidation, (iii) chemical dissolution of oxide into the electrolyte, or (iv) diffusion of ions in the electrolyte [122]. Yasuda et al. [122] reported that the anodic current is progressively.

![Fig. 7.](image-url)
decreased with the generation of the nanotubes even at the end of the commencement phase. They assumed that the current decrease is due to the nanotube growth from the (iv) diffusion of ionic species, i.e. either $F^-$, TiF$_6^{2-}$, or ZrF$_6^{2-}$, and accordingly they proposed a diffusion-based model, as provided in Fig. 7h. In this model, the ions are consumed ($F^-$) or formed (TiF$_6^{2-}$, ZrF$_6^{2-}$) merely at the base of the nanotube, and the upper dissolution is insignificant, where it was hypothesized that the ions had a linear dispersion in the electrolyte along a concentration gradient between the tube bottom and the bulk electrolyte. It should be mentioned that the concentration of $F^-$ and ionic species in the bulk electrolyte and at the bottom, respectively, is $c_0$, while the concentration of $F^-$ and the ionic species at the bottom and the bulk electrolyte is zero [122].

The XPS peak positions were compared to the reference peaks [172, 173] to assess whether the oxide tubes consist of a complex [A$_x$B$_y$O$_z$] oxides or consist of a mixture of two oxides [A$_x$O$_z$ + B$_x$O$_z$]. According to the XPS data (Fig. 7i), the nanotubes are amorphous zirconium titanate with an excess of ZrO$_2$ and TiO$_2$, and these oxides are transformed into zirconium titanate upon thermal treatment. Other studies have shown that the anodic nanotubes grown on pure Ti had an amorphous structure [174–176], while the nanotubes formed on pure Zr had a crystalline structure [177,178]. Habsaki et al. examined the anodic coating formed onto Ti-Zr alloys [179], and realized that a homogeneous amorphous oxide layer was developed on the Ti-Zr alloy with the 50:50 wt% composition. It suggests that the crystallinity degree of the MONs could be altered using a base alloy with other compositions. Jha et al. [116] also studied ultrafast MONs development on Ti-Zr alloy, where nanotubes with uniform diameter are randomly oriented.

### 3.4.6. Ti–Mn alloys

It was predicted that the chemical diversity and dimensions of the MONs of the Ti-based alloys possess interesting electronic and physical characteristics, which can be modulated for a wide range of purposes [71,180]. From this viewpoint, organized arrays of MONs on Ti–Mn alloy with α + β microstructure can be a prospective material as both TiO$_2$ and Mn$_2$O$_3$ are extensively employed in energy applications [181, 182]. In addition to this type of approach, the microstructural properties, mechanical behavior, and biocompatibility of low-cost β-type Ti-(6–18)/Mn alloys were examined after the solution treatment, where Ti–9Mn showed the best combination of tensile strength and elongation among the fabricated alloys, and comparable or superior to those of Ti–6Al–4V ELI, for every parameter evaluated. Moreover, the cell viability and metallic ion release ratios are similar to those of the pure Ti, making this alloy encouraging for orthopedic implants [183,184]. Mohapatra et al. [123] presented a comprehensive paper on the development of MONs on Ti-Mn alloy by anodization under ultrasonication in diluted EG comprising F$^-$ ions, where the MONs with a diameter of 20–100 nm and length of 0.5–2.0 μm were formed depending on the processing parameters. The as-anodized nanotubes had a stoichiometry of (Ti, Mn)O$_2$, while annealing at 500 °C in the oxygen atmosphere forms a mixture of anatase + rutile phases of TiO$_2$ and Mn$_2$O$_3$. The Mn-doped TiO$_2$ micro/nanostructure porous film was also fabricated by anodizing a Ti–Mn alloy, where the film heat-treated at 300 °C showed the utmost areal capacitance of 1451.3 mF cm-$^2$ at a current density of 3 mA cm-$^2$, employed as a high-performance supercapacitor electrode [185,186]. Fig. 8a–e shows the surface and cross-sectional SEM micrographs of nanotube arrays in the absence and presence of Mn, where the diameter and length is ~110 nm and ~3.5 μm, respectively.

![Fig. 8. Surface and cross-sectional SEM micrographs of nanotube arrays in the absence and presence of Mn; (a) TiO$_2$, (b,e) TiO$_2$–Mn (3%), (c) TiO$_2$–Mn (7%), (d) TiO$_2$–Mn (10%) (Reproduced with permission from Ref. [186]).](image-url)
Vertically oriented, self-ordered MONs (TiO$_2$–MnO$_2$ NTs) were also prepared by single-step anodization process of Ti–Mn alloys in EG electrolyte [187]. From the microstructural assessments, the anodized specimens were composed of auto-aligned nanotubes over the surface of the Ti–Mn alloys, where the diameter, length and wall thickness of the MONs are in the range of 76–118 nm, 1.0–3.4 μm and 8–11 nm, respectively. The results showed that an increase in the applied potential caused an increased growth in the dimensions, whereas the increase in the Mn content in the alloy resulted in the growth of shorter nanotubes.

3.4.7. Ti–Hf alloys

Long-term experiences reveal that some of the Ti-based alloys suffer inadequate load transfer to the adjoining remodeling bone that may cause bone resorption and ultimate detachment of the prosthetic devices [188]. To solve these difficulties and to attain better performance in terms of mechanical behavior and biocompatibility, new Ti-based alloys comprising non-toxic and non-allergic secondary elements, e.g., Nb, Ta, Zr, Hf, Mo, and Sn have been developed [189]. With regards to Hf, this element is a member of the same group with Ti in the periodic table. This suggests that an alloy of Ti with Hf would be expected to show good physicochemical properties. Besides that, the Ti–Hf alloy system does form any intermetallic compounds (IMCs) that are significant for excellent corrosion resistance [190,191]. On the other hand, electrochemical anodization is an effective approach for the surface amendment of bio-implants which can also be employed in this system. In this regard, Jeong et al. [192,193] presented comprehensive research works on the MONs development and morphological evolution, as well as apatite formability and corrosion behavior of the Ti–Hf binary alloys for metallic biomaterials utilization.

The homogeneous Ti–Hf alloys possess a needle-like microstructure of the α-phase, and nanotubes grown on the Ti–xHf alloys are in the anatase phase after crystallization, as shown in Fig. 9a–h. They reported that homogeneous MONs with Hf contents up to 20 wt% could be grown. It was observed that the increase in the amount of Hf in the alloy resulted in the formation of MONs with a more narrow size, where the MONs had an anatase phase after crystallization, as shown in Fig. 9 a–h. They reported that homogeneous Ti–Hf alloys possess a needle-like microstructure of the α-phase, and nanotubes grown on the Ti–Hf alloys are in the anatase phase after crystallization, as shown in Fig. 9a–h. They reported that homogeneous MONs with Hf contents up to 20 wt% could be grown. It was observed that the increase in the amount of Hf in the alloy resulted in the formation of MONs with a more narrow size, where the MONs had a length of ~1.7 μm and pore diameter of 80–120 nm. These results suggest that the MONs on the Ti–Hf alloys can be modified via changing the Hf content [192,193].

3.4.8. Ti–Co alloy

Based on the literature, a composite of Co3O4 and TiO2 NTs shows excellent performance in lithium-ion batteries [194], supercapacitor [195], wastewater treatment [196], and photoelectrochemical conversion [197]. Furthermore, highly porous Ti–Co alloys are recently being developed for biomedical applications [198]. Two methods are proposed for the combination of cobalt (II, III) oxides with TiO2 NTs; (i) the anodization of Ti foils to create TiO2 NTs followed by the deposition of cobalt (II, III) oxides via different approaches, and (ii) melting the Co and Ti into alloys and the formation of the MONs by electrochemical anodization [199, 200]. In the first method, the cobalt (II, III) oxides were deposited onto the surface of TiO2, leading to agglomeration, shedding, and dissolution of the cobalt (II, III) oxides. On the contrary, the second approach allows the distribution of the cobalt (II, III) oxides in the interior of the TiO2 that would prevail over the above issue and enhance the composite material performance. More recently, Wang et al. [201] and Kobylanski et al. [202] examined the fabrication and characterization of Co3O4-doped TiO2 NT electrodes and TiO2-CoOx composite NTs via a single-step electrochemical anodization process for visible-light-induced photocatalytic reaction, respectively. The diameter, and length of the MONs are almost unchanged with the increase of Co content, thus the diameter and length of the TiO2, TiO2–3%Co, TiO2–6%Co, and TiO2–9%Co NTs are around 61.9 μm and 1.7 μm, 57.5 nm and 1.6 μm, 57.9 nm and 1.6 μm, and 55.0 nm and 1.6 μm, respectively [201]. Another recent work indicated that the increase of the water content in the electrolyte from 2 to 10% caused the development of TiO2-CoOx composite NTs with larger diameters (88–125 nm for 2–10% H2O, respectively). Besides, the thickness of MONs layer has somewhat reduced from 2.3 to 2.0. This shows that higher H2O content leads to the development of MONs with a lower surface area and less photocatalytic activity [202] (Fig. 10a–c). Since highly porous nanostructured Ti–Co alloy is promising for biomedical applications, the formation of nanotubular arrays on the Ti–Co alloys open a new pathway for the development of MONs for various orthopedic applications.

3.4.9. Ti–V alloys

Vanadium (V) is a transition metal, ubiquitously scattered in the water, air, soil, crude oil and is present in biological organisms and is a natural constituent in most living beings. Moreover, there are groups of organisms that utilize V in their biological pathways. This element is a biological constituent, thus it is not surprising that V-based therapeutic drugs have been tested for the treatment of some diseases, especially for the treatment of diseases caused by parasites, diabetes, and cancer [203]. However, in biomedical implants, the presence of V may not give the same effect.

Allergy is an adverse effect on patients with an implanted orthopedic prosthesis. Although Ti is thought to be inert, the allergy towards Ti-based implants is still unknown. Recently, Engelhart and Segal [204] highlighted the case of a patient who experienced systemic dermatitis and implant failure after the surgical placement of a Ti-based alloy plate in the left foot. The prosthesis was detached and the eruption was cleared in the following weeks. Microstructural and electrochemical analyses reveal that the plate and screws suffered galvanic corrosion due to their dissimilar microstructures. This contributes to the in vivo release of vanadium. The patient was patch checked with some metals containing elements of the implant which gave a positive patch test reaction towards vanadium (III) chloride. This confirms the allergy towards V, thus clinicians should be aware of including vanadium as patch testing for patients with a suspected allergic reaction towards implants containing vanadium [204].

As mentioned earlier, self-organized nanotubes could be developed

![Fig. 9. SEM micrographs of MONs developed on Ti–Hf alloy following anodization for 2 h at 10 V in 1 M H3PO4 + 0.5 wt% NaF; top view, cross-sectional, and bottom of (a,b,c,f) Ti–20Hf, and (c,d,g,h) Ti–40Hf alloys (Reproduced with permission from Ref. [192]).](image-url)
successfully on a wide range of valve metals via optimized anodization processes. In some cases such as V, this approach is unsuccessful due to the increased solubility of oxides developed in common electrolytes. Thus, efforts to fabricate nanotubular arrays on Ti–V alloys are undertaken because V$_2$O$_5$ is one of the most favorable oxides for supercapacitor applications [205]. Yang et al. [206,207] found that highly ordered MONs of V$_2$O$_5$–TiO$_2$ NTs can be developed on Ti–V alloys with a vanadium content of up to 18 at% via electrochemical anodization. In this case, V was electrochemically switchable, with a specific capacitance of 220 F g$^{-1}$ and an energy density of 19.56 Wh kg$^{-1}$, with perfect reversibility and long-term stability. This suggests that the MONs structure is an excellent material for supercapacitor applications.

Nevárez-Martínez et al. [208] also studied the growth mechanism and photocatalytic behavior of hierarchical MONs of V$_2$O$_5$–TiO$_2$ NTs on Ti–V alloys. Similar to previous studies, it was observed that the V content in the alloy possessed the strongest effect on the morphology, where the specimen with 5 wt% showed the best self-organization (length = 1 μm, diameter = 86 nm, and wall thickness = 11 nm). Besides that, the V$_2$O$_5$ species are responsible for the photoactivation of e$^-$ and h$^+$ under visible light, and a probable excitation mechanism was proposed. Recently, Han et al. [209] investigated the tribo-mechanical and corrosion properties of anodized Ti–V alloy in the NH$_4$F/H$_3$PO$_4$ electrolyte annealed at different temperatures under different atmospheres. Highly crystalline MONs structures were developed followed by annealing from 200 to 600 °C. An improvement in the wear resistance of the Ti–V alloy was observed due to the high hardness and low coefficient of friction of the MONs structures. Furthermore, the corrosion analysis confirmed that the corrosion resistance of the sample annealed at 200 °C in air atmosphere was drastically higher than that of the bare substrate.

3.4.10. 4.1.10 other binary alloys

In addition to the above-mentioned systems, other binary alloys have also been studied to fabricate MONs structures for various applications. For instance, Liu et al. [210] studied the anodic formation of Ti–Ni–O nanotubes on shape memory alloys via pulse anodization in glycerol-based electrolytes. They examined the effects of anodization parameters and the annealing process on the microstructures and surface morphology of MONs and found that the type electrolyte significantly affected the development of nanotubes (Fig. 11a-c). This result could initiate focused research on the development of shape memory alloys for medical and non-medical applications.

Recently substantial efforts have been concentrated on the investigation of photoactive nanostructured substances, which can be employed as anodes in water photoelectrolytic cells. In this context, Zhang et al. [211] developed a novel hierarchical 3D Ti–Fe–O
nanorings/nanotube configuration by three-step electrochemical anodization of Ti–6Fe (6 wt% Fe) alloy in an EG solution containing 0.3 wt% NH4F and 2 vol% H2O, as shown in Fig. 11d–i. The results showed an improved visible-light photoelectrochemical performance. Also, the heterojunction of the MONs (TiO2–Fe203) gave efficient charge separation. Allam et al. [212] also reported the growth of vertically oriented Ti–Pd mixed oxynitride nanotubes for enhanced photoelectrochemical water splitting. As illustrated in Fig. 11j–l, the morphological features rely on the anodization time and operating voltage. The MONs were utilized in solar-spectrum water photoelectrolysis, which showed a photocurrent density of 1.9 mA cm-2 and a ~5-fold rise in the photoconversion efficacy under AM 1.5 illumination (100 mW cm-2, 1.0 M KOH) compared to the pure TiO2 NTs prepared under the identical circumstances.

Besides that, Basahel et al. [213] studied the fabrication of self-ordered MONs anodized from Ti–Pt alloy with a low Pt content of 0.2 at% for photocatalytic hydrogen production. The MONs structure possessed a mean thickness of 13 μm which were composed of individual tube units with ~120 nm outer diameter. They have shown that prolonged anodization not only leads to the elongation of the nanotubes but also the increased particle density on the walls up to 250 μm-2 (Fig. 11m–q). This unique configuration resulted in a highly active photocatalyst for the production of H2 under UV or visible light radiation.

3.5. Ternary alloys

3.5.1. Ti–Al–V alloys

Ti possesses low density, great biocompatibility, and corrosion resistance owing to the inherent oxide film on the surface, which is a good choice for medical applications [214]. Nevertheless, the inertness of Ti, along with its suboptimal mechanical behavior restricts the life cycle of Ti implants [215]. To overcome these limitations, Ti-based alloys are designed as alternative implant materials that could be microstructurally classified as α, near-α, α+β, metastable β, and stable β [216]. Due to their non-heat-treatable character to maintain the α phase microstructure, the α and near-α Ti-based alloys have little influence on the mechanical behavior. In contrast, the β-based alloys attributable to the BCC crystal structure can be shaped even at low temperatures, which make it a proper option for multifaceted geometries. Merging the advantages of both phases, the α+β Ti-based alloys provide superior fracture toughness, tensile strength, wear-resistance, and heat treatable features enables the preparation of complex geometries for orthopedic purposes [217]. However, several studies have confirmed that the elastic behavior and load transfer from the implant device to the neighboring bone of the α+β type alloys are unsuitable for orthopedic applications [218] and could degrade after implantation [219]. In addition to modifying the chemical composition of the alloys, surface modification techniques such as physical deposition methods, thermochemical surface treatments, and electrochemical anodization have been investigated to modify the surface features of the Ti-based alloys [12,13,220]. In this section, the formation of MONs on ternary Ti–6Al–4V alloy is reviewed.

One of the pioneering efforts to utilize electrochemical anodization as an innovative approach for the surface modification of Ti-based alloys was performed by Dunn et al. [221,222], where porous surface coatings are formed by anodization and incorporating antibiotics onto the oxide surface. Zwilling et al. [223] also reported that anodization on Ti and Ti–6Al–4V alloys in the F- ion solution is an effective approach to attain tunable tubular oxide layers under different anodization conditions [16, 17,65,133,224–262]. Since the Ti–6Al–4V alloy is a dual-phase alloy, the development kinetics of nanotubes are dissimilar for the α and β phases [65]. Macak et al. [132] fabricated self-ordered porous oxide–nanotube layers on Ti–6Al–4V using an effortless electrochemical process in 1 M (NH4)2SO4 electrolytes comprising 0.5 wt% of NH4F. The results revealed that under certain circumstances, self-ordered porous oxide configurations were formed on the alloy surface, which is composed of nanotubes with a diameter and spacing of 100 and 150 nm, respectively. Besides that, the XPS spectra showed that the tubes are MONs with an almost stoichiometric oxide composition, with thicknesses of several hundreds of nanometers [132]. This research was a simple surface modification of Ti-based alloys that has a high potential for biomedical applications. In the same year, Yao et al. [18] tried to generate inimitable nanometer surface characteristics on Ti–6Al–4V
implants using a rapid and somewhat inexpensive electrochemical approach in 1.5 wt% HF and the direct-current voltage was set to 20 V for 10 s to 5 min. They reported that the surface characteristics were dependent on the time duration of the applied voltage. Following these findings, another research was conducted on the anodization of Ti–6Al–4V alloy by Narayanan et al. [6], where various coatings were formed by changing the period of deposition. Park et al. [263] also explored the development of oxide nanotubes on Ti–6Al–4V alloy in glycerol-comprising electrolytes. The treated surfaces exhibited a broad spreading of nanotubular diameters, in which nanotubular arrays with smaller sizes are distributed between the nanotubes with larger diameters. This study also highlighted that the diameters of the nanotubes can only be modified from 88.5 to 122.9 nm using various concentrations of electrolyte from 1 wt% NH4F + 20 wt% H2O to 1 wt% NH4F + 30 wt% H2O at 20 V, respectively [263]. Extensive research has been conducted in the field of nanotubes production on Ti-based alloys, especially the Ti–6Al–4V alloy in the last decade; whereby useful information is available on the impact of anodization on the features of MONs in this system [16,17,65,133,224–262]. One of the most comprehensive studies in this field was performed by Li et al. [254], where they explored the thermal constancy and in vitro bioactivity of nanostructured Ti–Al–V–O formed on Ti–6Al–4V. Following the anodization of the two-phase Ti–6Al–4V alloy, there were two different types of MONs on the surface of the alloy, which are the nanotubes formed in the α-phase area and the irregular nanopores expanded in the β-phase zone. They found that the Ti–Al–V–O nanotubes are stable at a high temperature of 675 °C in the air without collapse, whereas the irregular Ti–Al–V–O nanopores have lower thermal stability, which is in good agreement with our findings [133]. Recently, Atmani et al. [251] synthesized the MONs layer (~80–100 nm) on Ti–6Al–4V alloy using electrochemical anodization in fluoride containing alkaline solution and under different applied voltages (10, 20, and 30 V). Mansoorianfar et al. [247] also studied the fabrication and characterization of nanotube arrays on the Ti–6Al–4V surface for the enhancement of cell treatment in biomedical applications. More recently, a report on effects of the anodization on the morphology of NTs over Ti6Al4V in connection with hard tissue engineering application was presented by Poddar et al. [264], in which the anodization was carried at room temperature at different applied potential, i.e., 20, 25, and 30 V, as well as at a constant potential of 20 V at bath temperatures 30, 45, and 55 °C. As shown in Fig. 12a-f, the nanotube diameter and length increase with increasing the anodization voltage from 20 to 30 V. This suggests that longer NTs can be developed at higher voltages. Besides, dense NTs were formed as anodization was conducted at bath temperatures 45 and 55 °C (Fig. 12g-j). However, they believe that to recognize an exact growth mechanism at higher electrolyte temperature further studies is necessary.

3.5.2. 4.2.2 Ti–Al–Nb alloys

As mentioned above, among the Ti-based alloys, Ti–6Al–4V orthopedic implants are widely been used to substitute hard tissues and in bone fixation strategies due to the great strength, ductility as well as low density. Nevertheless, the main concern of using Ti–6Al–4V alloy in medical implants is the V content which could probably enhance the expressions of pro-inflammatory factors, provoke osteolysis, and have toxic effects in the body [204]. Research on the biological behavior of alloying elements shows that the chemical composition of alloys utilized in medical implants should be improved to reduce the adverse effects. Accordingly, alternative Ti-based alloys containing diverse alloying elements and concentrations are employed to improve the biocompatibility of the orthopedic implants. One such alloy is the Ti–6Al–7Nb [69] which possesses both the α and β phases, in which Al become constant the α phase while Nb as a substitute for V in the Ti–6Al–4V alloy becomes the stable β phase. This alloy is more ductile than Ti–6Al–4V, provides higher formability for making complex parts with excellent corrosion resistance compared to the Ti–6Al–4V alloy [265]. For this reason, this alloy has received significant attention as femoral components of hip prostheses. Even though the integration of alloying elements could improve the physicochemical properties of Ti-based alloys, the bioinert character and the incapability of Ti implants to bond with the bone is still a challenging task and is among the major failure of orthopedic implants. To improve osseointegration, surface modification of the orthopedic implants is vital because the surface-modified implants deliver an improved medium for bone cell purposes, leading to improved incorporation of the implant with the juxtaposed bone tissue [62,82]. To achieve this objective, various surface amendments are proposed to modify the physicochemical features of Ti-based alloys, such as sandblasting, hydrothermal process, sol-gel, physical as well as chemical vapor deposition [266]. Among them, the electrochemical anodization technique has attracted significant consideration owing to the effortlessness, lower cost, and capability of adjusting the surface properties in the nano regime [267].

Macak et al. [132,145] investigated the development of self-ordered nanotubes on Ti–6Al–7Nb via anodization in NH4F solutions, where under particular anodization circumstances the MONs configuration can be developed on the alloy surface. Based on the XPS analysis, the tubes are mixed oxides with an almost stoichiometric oxide composition, which can be grown with thicknesses of several hundreds of nanometers.

Fig. 12. FE-SEM micrographs of NTs diameter and length on Ti–6Al–4V at (a,b) 20 V, (c,d) 25 V, (e,f) 30 V at 30 °C, (g,h) 20 V at 45 °C, and (i,j) 20 V at 55 °C (Reproduced with permission from Refs. [264]).
Mazare et al. [268] also studied the development of nanotubes on the β phase contrasted with the α phase on Ti–6Al7–Nb alloy in an aqueous electrolyte (CH3COOH and 0.5 wt% HF) under 10 V potential. Rafieerad et al. [131] studied the development of MONs on Ti–6Al–7Nb alloy using different electrolytes, i.e. glycerol and EG. They reported that due to the inherent amorphous characteristic of the oxide layer, the diffraction peaks corresponding to MONs are not observed, while the MONs of anatase and rutile are detected following annealing in normal atmosphere at 600 °C for 2 h. The results of microstructural evolution showed that the mean length and diameter of the nanotubes ranged from 2.23 to 4.22 μm and 160–170 nm, respectively (Fig. 13a-d). They also found that the type of electrolyte and subsequent thermal treatment markedly influenced the surface wettability of the treated samples. In the same year, the electrochemical performance and the influence of thermal treatment on the microstructural features of MONs prepared on Ti–6Al–7Nb were comprehensively researched for medical purposes [269]. Recently, Ulfah et al. [140] also reported the formation of silver doped MONs with a mean diameter of 120 nm on Ti–6Al–7Nb alloy. These studies contribute significantly to the development of MONs for different biomedical applications such as medical implants, thanks to the microstructural features, photocatalytic mechanism, and antibacterial activity.

3.5.3. 4.2.3 Ti–Nb–Zr alloys

Ti and Ti-based alloys are the main metallic materials in biomedical appliances [218], and significant efforts are focused on the substitution of alloying elements (Al and V), presently with non-toxic elements such as Nb and Zr [270,271]. These substituting elements improve the mechanical behavior of the alloys because Nb is a β-stabilizer while Zr promotes the solid-solution hardening of the Ti–Nb–Zr alloys, which improves the mechanical performance of the alloys [272]. Given the biocompatibility of Ti–Nb–Zr alloys, Wang et al. [270] reported a higher cytotoxicity (L-929 fibroblasts) and hemocompatibility of the Ti–22Nb–42Zr alloy, where the substitution of Ti by Nb and Zr did not increase the cytotoxicity as compared to the commercially pure Ti. Moreover, Cremasco et al. [273] studied the cytotoxicity and fibroblast cell adhesion on pure Ti, Ti–6Al–4V, and Ti–25Nb–15Zr alloys, where both alloys exhibited lower toxicity effects after 24 h of cell cultivation. Regarding the surface modification of Ti–Nb–Zr alloys, numerous attempts were done to improve the physicochemical, mechanical, and biological performances. Alam et al. [274] studied the self-organized MONs on Ti–35Nb–5Zr alloy via anodization in aqueous and FA solutions containing NH4F at room temperature. The surface features were affected by the nature of the electrolyte and the applied voltage. The MONs structure exhibited a ~17.5% rise in the photoelectrochemical water oxidation efficiency compared to the pure TiO2 NTs (Fig. 14a-c). In the same year, Qin et al. [275] comprehensively examined the electrochemical anodization and crystallization behavior of Ti–35Nb-xZr (x = 0, 5, 10, 15) alloys in 1 M (NH4)2SO4 containing 0.5 wt% NH4F electrolyte. They found that the Zr addition lowers the anodization voltage, decreases the nanotube diameter, increases the nanotube length, and improves the thermal stability of the alloys. It was also reported that Nb-doped TiO2 NTs possesses a room-temperature hydrogen sensing character, but the hydrogen sensitivity deteriorates with the subsequent introduction of Zr and caused instabilities in a highly concentrated hydrogen atmosphere. Jeong et al. [276] also examined the electrochemical behavior of HA/Ti films on the nanotubular Ti–35Nb–xZr alloy, where the MONs layers were formed by anodization in 1 M H3PO4 electrolyte comprising 0.8 wt% NaF at room temperature. The results showed that the anodized Ti–35Nb–xZr alloy surfaces possessed NT diameters ranging from around 60 to 220 nm and the lengths of NT ranging from around 2.9 μm in the case of Ti–35Nb–3Zr to around 3.6 μm for Ti–35Nb–10Zr. They also found that the Zr contents in the alloy had a great impact on the NT configuration, and two scales of the NT structure were developed as the Zr content increased (Fig. 14d-o). Similar research focused on the formation of MONs structures on different Ti–Nb–Zr alloys was also performed [143,277–280]. Accordingly, the Ti–Nb–Zr alloys appear as potential substitutes for the Ti–6Al–4V alloy in different biomedical devices and medical implants [281].

3.5.4. 4.2.4 Other ternary alloys

In addition to the above-mentioned systems, there are several reports on the electrochemical anodization and the development of MONs on other ternary alloys. For instance, Kim et al. [282] investigated the morphology of hydroxyapatite nanotubes coated on the surface of Ti–35Nb–xHf alloys as implant materials. For this purpose, different Ti–Nb–Hf alloys were produced by arc melting and heat-treated for 12 h at 1000 °C in an argon atmosphere followed by water quenching. Then, MONs development on these alloys was attained via anodization in H3PO4 electrolytes with 0.8 wt% NaF at room temperature. The hydroxyapatite was deposited onto the MONs by radio-frequency (RF) magnetron sputtering method. The morphology of the alloys was transformed from a needle-like to an equiaxed configuration with decreased Hf content and α′′ phase, while the β phase was enhanced when the Hf content was increased. At lower Hf content, the tip of the nanotube with the β phase was coated with the HA film, while the α′′ phase was free from the HA coating. Similar research by Park et al. also

Fig. 13. Top and cross-sectional FESEM images of MONs developed on Ti–6Al–7Nb alloy using different anodization electrolytes, (a,b,e,f,i,k) EG and (c,d,g,h,j,l) glycerol, before and after heat treatment at 450 and 600 °C for 2 h (Reproduced with permission from Ref. [131]).
reported the formation of tubular structures on this alloy [283,284]. Other research groups examined the formation of MONs on Ti–30Nb–xTa alloys via anodization in 1 M H3PO4 electrolyte with 0.8 wt% NaF [285]. The XRD analysis revealed that the phases in these alloys transformed from a duplex (α’ + β) to solely β phase with the increase of Ta concentration. The as-anodized alloys possessed an amorphous structure and the SEM images showed that the mean diameters of the smaller and larger nanotubes in the absence of Ta are around 100 and 400 nm, respectively, while the smaller and larger MONs in the presence of Ta possessed diameters of around 85 nm and 300 nm, respectively. Besides that, as the Ta concentration increases from 0 to 15 wt%, the mean length of the MONs increases from 2 to 3.5 μm. The EDS results confirmed that the nanotubes consist of the Ti, Nb, Ta, O, and F elements. Fornell et al. [286] explored the development of self-ordered Ti(Nb, Sn) oxide nanotubes with a tunable aspect ratio and size distribution on the surface of Ti–21Nb–11Sn alloy via anodization in 0.3 M NaF + EG/water (50:50) electrolyte solution at voltages ranging from 5 to 50 V. These nanoarchitectures offer improved functionalities in extensive applications, such as biomedical, optoelectronic, photocatalysis, sensors, and electrochromic devices. In another study, Jeong et al. [287] investigated the effects of different applied potential in a two-step anodization process in a 1 M H3PO4 electrolyte and the solution of this electrolyte with 0.8 wt% NaF, to organize the morphological features of MONs on Ti–30Ta–xZr alloys. The corrosion resistance was improved by increasing the Zr content in the Ti–Nb(Ta)–Zr alloy. The development of MONs on Ti–Al–Zr alloy was also assessed in organic electrolytes by anodization [288], where MONs with a length of around 6.13 μm, a pore diameter of 116 nm, and a wall thickness of 55 nm were formed at 50 V for 24 h in FA and glycerol mixtures (volume ratio 1:1) with 1.0 wt% NH4F. It was reported that the as-anodized nanotubes were amorphous and the crystallization occurred after thermal treatment in air at 400 and 600 °C for 3 h. Nanotubular films on Ti–2Al–1.5Mn alloy could also be formed via anodization in aqueous ammonium fluoride solutions at 20 V for 3 h [289]. These results show an improvement in the photo-absorption in the visible region and the photoelectrochemical response, thus could be used in solar applications.

3.6. 4.3 quaternary alloys

Quaternary β Ti-based alloys are receiving significant consideration as medical implant materials due to their very low Young’s modulus analogous to human bone and outstanding biocompatibility [290]. The main objective of emerging such alloys is to reduce Young’s modulus disparity between the bone (10–30 GPa) and the medical implant, which enhances the load sharing between them [291]. In this regard, different quaternary alloys such as Ti–Nb–Ta–Zr alloys (including Ti–4Nb–4Ta–15Zr [292], Ti–29Nb–13Ta–4.6Zr [293], and Ti–35Nb–5Ta–7Zr [294]) were investigated. Among them, the Ti–35Nb–5Ta–7Zr possesses a lower elastic modulus (55 GPa) and thus is considered as one of the best options for medical implants [290]. However, works on the physicochemical, mechanical, and biological features of the MONs on such quaternary alloys are restricted [295]. Anodic oxidation of the Ti–Nb–Ta–Zr alloys gives dissimilar formation rates owing to the dissimilar electrochemical oxidation rates of these elements in the alloy [146]. As a result, the dissolution was more selective, and homogenous self-ordered anodic nanotubes grow to different sizes, where tubes with a larger diameter are adjacent with eight tubes with a smaller diameter.

The nanotube growth initiates from two films – an outer nanoporous layer and a nanotube layer – from the potential sweep using a potentiostat. The outer nanoporous film dissolves in the electrolyte, thus prolonged anodization time is necessary to expand the nanotubes when the applied potential is low [147]. Recently Chiu et al. [295] presented a delicate anodizing process for the fabrication of quaternary Ti–Nb–Ta–Zr–O MONs which gave high-performance PEC water splitting. The MONs showed a higher photoactivity compared to the pristine TiO2 NTs. The higher photoactivity is because of the incorporation of alloying elements which improve the number of charge carriers, adjust the electronic configuration, and improve the hole injection kinetics for enhanced water splitting. They found that the anodization time could be tuned to attain the required nanotube length for different samples (Fig. 15a-d), which eliminates the effect of nanotube length on the PEC performance. Based on these findings, the MONs structures could be utilized for effective PEC water splitting for solar hydrogen production. The non-toxic and biocompatible features of this nanoarchitecture could achieve a distinct yet practically viable application in biotechnologically important fields, such as PEC biosensing and PEC biofuel reforming [295].

On the other hand, compared to the crystalline alloys, glass-forming amorphous Ti-based alloys possess superior features, e.g. higher strength and wear resistance, as well as and in part a lower elastic modulus and comparable corrosion resistance. In this context, some
glass-forming Ti-based alloys, such as the Ti60–Zr10–Si15–Nb15, are fabricated for implant purposes [296]. These alloys have very low corrosion rates in simulated body fluid (SBF) and sufficient apatite forming capability [297]. Also, an Nb comprising alloy possesses enhanced glass-forming capacity and mechanical behavior compared to the Ti75–Zr10–Si15 [298]. The anodization behavior of the glassy forms of Ti-based alloys is still in the preliminary stages of the investigation. For the first time, two glass-forming Ti-based alloys, the Ti75–Zr10–Si15 and Ti60–Zr10–Si15–Nb15 alloys were anodized in an EG-containing electrolyte to form nanotubes [299].

As these alloys are amorphous, they have no grain arrangement that is particularly interesting for the anodization of crystalline Ti, where the grain organization plays an important role in the consistency of the nanotubes [300]. As illustrated in Fig. 16a–h, the anodization of Ti75–Zr10–Si15 and Ti60–Zr10–Si15–Nb15 alloys in EG-based electrolytes produce highly ordered MONs. Smaller diameter nanotubes (~116 nm for Ti75–Zr10–Si15 and ~90 nm for Ti60–Zr10–Si15–Nb15) and shorter nanotubes (~11.5 μm for Ti75–Zr10–Si15 and ~6.5 μm for Ti60–Zr10–Si15–Nb15) could be formed on both amorphous alloys compared to TiO2 NTs grown on Ti foils under the same conditions. The TEM images in Fig. 16g and h shows a double-wall configuration of the as-anodized amorphous MONs with enriched Ti in the internal walls of the nanotubes, while Si is concentrated in the external walls, where the Zr and Nb are uniformly scattered. In addition to the glass-forming Ti-based alloys, the development of MONs on other quaternary alloys are also investigated for biomedical purposes, such as the Ti–Nb–Mo–Sn alloy. In this context, Mello et al. [301] explored the development of MONs with diverse morphological features on a Ti–30Nb–4Sn substrate with the gradual addition of Mo, wherein the impacts of anodization parameters, substrate roughness, and alloy composition were also examined. Although the martensitic phase was suppressed throughout with the rapid cooling owing to the Mo addition, all compositions exhibited a lower elastic modulus suitable for biomedical applications. The results revealed that the Mo addition increases the nanotube length and decreases the internal and external diameters. Also, the polished substrate favored the formation of uniform MONs layers. More recently, three different quaternary alloys, the Ti–6Al–4V–xZr [302], Ti–24Nb–4Zr–8Sn [303], and Ti–xNb–Ag–Pt [304], were investigated of their ability to form the MONs layer on these alloys. In the first case, Zhang et al. [302] investigated the formation of MONs on the Ti–6Al–4V–xZr alloys (x = 0, 20, 30, 40, 51) via electrochemical anodization in the mixture of 98% EG + 2% deionized water + 0.2 mol.L−1 NH4F at 20 V from 5 to 300 min. They reported that the anodization was comparatively intense and the wear resistance was improved with the addition of Zr. In the second case, Majchrowicz et al. [303] fabricated self-organized MONs on a commercially pure α-phase Ti, single β-phase Ti–24Nb–4Zr–8Sn alloy and α + β-phase Ti–13Zr–13Nb alloy via electrochemical anodization in EG-based electrolyte with F- ions at a constant voltage of 20 V for 2 h. Despite employing the same processing factors in all specimens, the MONs formed on three different substrates showed different morphology: ribbed walls for the Ti and smooth walls for the Ti–24Nb–4Zr–8Sn and Ti–13Zr–13Nb alloys. In addition, the homogeneity and height of the MONs are controlled by the presence of alloying elements and the phase composition of both Ti alloys.

Fig. 15. Top and tilted-view SEM images and typical TEM images of (a) pristine TiO2 NTs, Ti–Nb–Ta–Zr–O mixed-oxides formed in the presence of different H2O contents in the electrolyte (b) 20, (c) 10, and (d) 0.9 vol% (Reproduced with permission from Refs. [295]).
concluded that the anodization of Ti-based alloys results in the formation of nanotubular arrays with a mixture of stoichiometric oxides – the TiO$_2$, Nb$_2$O$_5$, ZrO$_2$, and SnO$_2$. In the third case, Kim et al. [304] studied the morphology changes of Ti-$x$Nb-Ag-Pt nanotube alloys with the Nb content via anodization at 30 V for 2 h in 1 M H$_3$PO$_4$ + 0.8 wt% NaF at 25°C. The microstructural assessments showed that the needle-like configuration on α and α′ steadily vanishes with the increase of Nb, while the β-phase equilibrium structure appears with decreased particle size. In addition, the morphology of nanotubes could be altered depending on the Nb content. Consequently, as the Nb content increases, the highly ordered MONs degrades into irregular nanotubes, wherein the disparity in dissolution region at the bottom of the nanotubes was dependent on the Nb content.

3.7 4.4 combined approaches

In addition to direct anodization of Ti alloys to develop MONs on the alloy surface, there are some different combined approaches, such as the PVD-assisted electrochemical anodization [74,127,129,136,166,253,305–309] and hydrothermal-assisted electrochemical anodization [310]. In an innovative approach, Rafieerad et al. [166] examined the optimization of TiO$_2$–Nb$_2$O$_5$–Al$_2$O$_3$ mixed oxide nanotubes on Ti–6Al–7Nb alloy substrate using the PVD technique. The Ti–6Al–7Nb substrate was sputtered by a niobium layer followed by the electrochemical anodization in EG/NH$_4$F/ionized water (5 wt%) electrolyte, where the parametric optimization for higher mechanical strength was performed by the Taguchi method. For the first time, the same group also proposed a gene expression programming (GEP)-based model as a secure and precise approach to forecasting the mechanical strength of the PVD coated Nb, to form a combination of oxide nanotubes on the alloy surface. The results indicated that the values obtained from the GEP model are very close to the experimental design by the Taguchi method [307]. They recently proposed a multi-objective particle swarm optimization (MOPSO) algorithm as a precise approach to optimize the as-sputtered Nb parameters. The validated MOPSO experiments with maximized outputs corroborated the enhanced implant efficiency [129]. These results are effective for the optimization of nanostructured implants with different surface properties. In a similar work, the same group fabricated highly ordered ZrO$_2$–TiO$_2$–Nb$_2$O$_5$–Al$_2$O$_3$ nanotubes via PVD of a zirconium coating onto Ti–Nb alloy implant, followed by anodization at 60 V between 30 and 300 min [127]. More recently, they reported a novel approach for an optimized PVD deposition process, anodization, and spin coating, to improve the mechanical, tribocorrosion performance, anti-bacterial and osteoblast cyto compatibility behavior of the Ti–6Al–7Nb implant. In this regard, silver nanoparticles/graphene oxide (AgNPs/GO) decorations on combined nanotubular coating are also developed. This hybrid approach could be also utilized in the fabrication of various complex multifaceted nanotubes for a variety of orthopedic ailments [124].

4. In vitro studies for biomedical applications

The anodic mono-oxide nanotubes with outstanding properties have attracted much attention for various potential applications as anticorrosion, self-cleaning thin films, and paints to sensors [311], electrocatalysis, and water photoelectrolysis [312], dye-sensitized and
solid-state bulk heterojunction solar cells [313], photocatalysis [314]. These nanostructures are also used in biomedical applications as biocompatible materials to enhance osseointegration, drug delivery systems, and advanced tissue engineering [43,315–318]. On the other hand, electrochemically developing MONs on various Ti-based alloys has been increasing in popularity as a chemical way to augment the existing and endow new properties to them. However, it is ambiguous whether this tactic can elicit properties strong enough to make MONs competitive for commercial purposes in medicine and elsewhere.

Fig. 17 shows some potential applications of MONs in various industries, for instance in orthopedic applications. In the following sections, we will provide an overview of current efforts toward MONs biomedical applications.

4.1. Mineralization abilities

In implant studies, bioactivity implies the development of bone-like HA on the implant as soaked in SBF. Recent research has reported that the HA creation kinetic as well as development in SBF is improved in the existence of a nanotubular configuration, probably due to the high specific surface area. As the NTs are developed on Ti, nearly all the osteoblast functions are preserved or amended, which could promote quicker bone regeneration around the implants without compromising the density. Also, the ordered nano configurations of the implant surface advance the osseointegration process via in vivo mechanical interlocking with the bone [136].

The HA formation onto anatase TiO$_2$ NTs is greater compared to other phases i.e. amorphous or rutile, possibly because of a closer lattice matching with the HA phase [319]. The anatase phase generates a solid and homogeneous apatite layer on the surface upon soaking in SBF for 30 h. The soaking of crystallized NTs in SBF for 14 days caused the development of a dense apatite layer on NTs, approving high bioactivity chiefly as a result of the formation of the anatase phase. The NTs could also be treated by NaOH to enhance the bioactivity and to stimulate HA formation. The as-formed TiO$_2$ NTs encourage the growth of bioactive sodium titanate with particularly fine nanofiber configuration on the NT edges. As soaking in the SBF, the sodium titanate nanofibers persuade nucleation and development of the nanostructured HA coating on the implant surface [320]. It was also reported that the MONs surface modification showed enhanced in vitro bioactivity, where a dense bone-like apatite film was developed on the mixed oxide nanotubes upon 10 days immersion in SBF from the MOPS algorithm [129]. Similar behavior was also detected for the AgNPs/GO loaded TiO$_2$–Nb$_2$O$_5$–Al$_2$O$_3$ MONs, where remarkable improvements in the bioactivity of AgNPs/GO loaded MONs was observed compared to the bare substrate and MON coatings. This suggests that the surface modification enhances the hydrophilic behavior and bioactivity of metallic implants, and accordingly boosts the cell connection, enlargement, and dispersion. The surface modification could also improve the implant cytoskeletal organization [124]. It should be noted that lengthy nanotubular arrays with broader apertures increase the nucleation sites for the growth of calcium phosphates, leading to a homogeneous and dense apatite layer on the implant. Daihua et al. [321] studied the preparation of HA-MONs coating on Ti–6Al–4V via the hydrothermal-electrochemical method. The HA-MONs was directly formed onto the surface of Ti–6Al–4V as the applied voltage was between 110 and 140 V. They also provided the formation mechanism of the porous oxide film and HA. Characteristic apatite particles were also developed on the anodic MONs in Ti–15Mo, Ti–13Nb–13Zr, and Ti–6Al–7Nb alloys after alkali treatment which can be considered for dental implants [322]. These observations show that there are still many challenges to estimating MONs’ biomineralization ability, especially in the case of binary, ternary, and quaternary Ti-based alloys.

4.2. Biocompatibility

The cell-implant interplay is a significant process for effective clinical implantation while the surface adaptation in the nano regime considerably alters the cellular response [43,68]. The impact of TiO$_2$ NTs on the cellular reaction was studied on different types of cells such as human osteoblasts (HObs), fibroblasts, chondrocytes, endothelial cells (ECs), vascular smooth muscle cells (VSMCs), epidermal keratinocytes and mesenchymal stem cells (MSCs) [323]. The reactions of ECs and VSMCs towards TiO$_2$ NTs indicate that the NT surface considerably enhances the EC proliferation, but decreases the VSMC proliferation. The reformed behavior of both EC and VSMC in the presence of NT arrays is advantageous for stent and other vascular applications [324]. Park et al. [325] examined the effect of highly-defined space variation between the TiO$_2$ NTs with six different diameters on the MSCs response and their differentiation into bone-forming cells. The experimental outcomes showed that apart from the chemistry of the surface, the nanoscale geometry also influences the cell response towards the biomimetic surface. The adhesion, propagation, relocation, and differentiation of the MSCs were maximized on the NTs with 15 nm tube diameter. The NTs with larger diameters resulted in decreased cell differentiation while the NTs with 100 nm diameter caused cell death. Das et al. [41] investigated the influence of anodic TiO$_2$ NTs on HObs via an osteo-precursor cell line (OPC1) from human foetal bone tissues. The TiO$_2$ NTs were formed via electrochemical anodization at 20 V for 2 and 4 h. The anodic NTs have a wall thickness of 39–51 nm, a length of 288–600 nm, and an inner diameter of 51–54 nm. In order to evaluate the bone cell-material interplay, the NTs grown in 4 h were employed owing to their homogeneous configuration and improved surface features. The NTs were treated by thermal annealing at 580 °C. The NTs exhibited improved cell growth and adhesion by forming filamentous arrangements with sufficient anchorage locations for filopodia

Fig. 17. Schematic representation of potential applications of MONs in various industries, for instance in orthopedic applications.
expansion. The nanostructures also showed early differentiation by intensified alkaline phosphatase (ALP) activity and considerable bone cell proliferation, from an MTT assay of a polished Ti control surface. These findings confirmed the developed osteoconductivity of TiO2 NTs contrasted to typical polished Ti surface [320]. The biocompatibility analysis of MONs grafted on the surface of commercially pure Ti, Ti-6Al–4V and Ti-6Al–4V-ELI was conducted to present a novel platform for human pre-osteoblast cell (MC3T3) adhesion and proliferation [58]. The study shows that MC3T3 cells interact in a different way with MONs of dissimilar Ti alloys, where the adverse response to the pre-osteoblast cells was not observed. These findings suggest that osteoblast cell activity can be drastically improved through MONs surface engineering, and thus provide a suitable platform for orthopedic implants.

4.3 Antibacterial activity

Titania nanotubes have suitable biocompatibility seeing that they exhibit some antibacterial behavior, low cytotoxicity, appropriate firmness, and cytocompatibility [325,326]. Nevertheless, Ti-based materials possess inadequate antibacterial properties and many attempts have been conducted to improve their antibacterial activities, e.g. surface improvements of titania nanotubes using incorporation of AgNPs into the tubular structure for medical implants [51,327].

The implant infections ascribed to the adherence of antibiotic-resistant bacteria on the surfaces could not be healed through usual antibiotics and frequently result in implant exclusion to eliminate the infection. Hence, there is an increasing demand for complementary tactics for the healing of medical tool-related infections without the consumption of antibiotics. A surface amendment is particularly important to reduce the bacterial connection onto the surface of the implant. With regards to bacterial inactivation, TiO2 NTs have some distinct advantages compared to other Ti-6Al–4V coatings. The bacterial reactions towards Ti-6Al–4V with dissimilar surface topographies exhibited a considerable reduction in the development of Staphylococcus aureus (S. aureus) and Staphylococcus epidermidis (S. epidermidis) on the TiO2 NTs in contrast to the usual Ti surface. It is well-established that the level of bacterial development on the TiO2 NTs intensely counts on the nanotube diameter so that the 20 nm diameter NTs possessed improved antibacterial behavior compared to the 80 nm diameter NTs. Also, rutile could present higher antibacterial efficiency relative to anatase [320,328].

The NTs could be used for the encapsulation and identified transport of antibacterial agents. Popat et al. [11] employed TiO2 NTs for the identified transport of gentamicin off-implants at the implantation zone. The liberation kinetics of gentamicin from these nano configurations and its impact on the bacterial adhesion were explored. The outputs of these assessments corroborated the superior capacity of the nano configurations for the antibiotic drug encapsulation, whereby the bacterial linkage on the NTs decreased drastically [11].

The antibacterial efficiency of the medical alloys covered with TiO2 NTs could be boosted through the integration of other antibacterial mediators, e.g., AgNPs. In this context, Lai et al. [320] decorated AgNPs onto the TiO2 NTs to enhance the implant confrontation against Escherichia coli (E. Coli) as a Gram-negative bacteria. Mei et al. [51] prepared TiO2 NTs by integrating nanosized silver to enhance the antibacterial efficiency of dental implants against post-surgical bacterial infections. The amount of silver reserved the nanotubular morphology and effectively sterilized the oral pathogens. The results showed that the operation of inferior plasma voltages could give rise to an amassing of a high level of Ag on the surface, which notably compromised the biocompatibility of the sample. On the contrary, a low level of silver decoration was detected at high plasma voltages. The specimens produced at a high voltage are stated to possess continued antibacterial behavior owing to the adequate silver decoration in the right depths of nanotubes [328].

Sarraf et al. [74,328] recently prepared highly-ordered MONs decorated with Ag2O nanoparticles for enhanced in vitro performance of Ti–6Al–4V (Fig. 18a and b). Compared to the uncoated sample (Ti–6Al–4V), the MONs have a bacteriostatic impact and restrained the enlargement of E. coli cells in 6 h of immersion, however, the cell regrowth commenced after 24 h of immersion. On the contrary, the Ag2O NPs-decorated MONs decreased the quantity of viable E. coli cells and finally eradicated 100% of the bacteria during 2 h of immersion, without bacteria reexpansion following 24 h immersion. The antibacterial activity of this nanostructure is based on the synergistic impact of the TiO2 NTs, straight interaction with silver oxide nanoparticles (Ag2O NPs), and predominantly the liberation of silver ions. The results showed that the control (Ti-based alloy substance) and pure tantalam had no antimicrobial activity against E. coli propagation during 24 h of immersion, while the thermal-treated MONs and Ag2O NPs-decorated MONs considerably diminished the E. coli activity during 2 h (P < 0.001) immersion without bacteria regrowth after 24 h immersion. The samples were treated and exposed to secondary sterile examinations to compare with the antibacterial performance of the nanotextured coatings. In contrast to the Ag2O NPs-decorated MONs, the thermal-treated MONs nanotubes had decreased antibacterial activity after sterilization, confirming the effective function of Ag2O NPs in attaining an enduring antibacterial behavior. The improved antibacterial activity of Ag2O NPs-decorated MONs is due to the synergistic influence of Ta2O5 NTs, the liberated silver ions, and straight connection with the Ag2O NPs. The Ag2O NPs have a large surface-area-to-volume ratio, thus possess an active connection area with the bacteria. Ag2O NPs possess a significant ability to disintegrate bacterial cells, by diffusion or adhesion of the silver ions on the membranes of the bacterial cell and eliminate the undesirable effects on the adjacent mammalian cells, compared to the pure nanoparticles. It is well established that the cell damage arising from Ag-based antibacterial materials is more prominent in the gram-negative bacteria compared to the gram-positive counterparts. Hence to realize the antibacterial behavior of Ag2O NPs, E. coli cells were cultured as representative gram-negative bacteria. The size and morphology after adhesion with the nanotubular structure and Ag2O NPs were investigated. From the FESEM observations, the bacteria culture on the MONs (Fig. 18c) shows the typical features of intact E. coli cells with a smooth surface without structural imperfections and rod-shaped morphology. On the contrary, the E. coli cells on the Ag2O NPs decorated on the MONs surface (Fig. 18d) showed structural deficiencies, i.e. membrane disintegration (white arrows) and leakage of intracellular components (brown arrows). The antibacterial activity of Ag2O NPs on E. coli cells is in agreement with the reports of Ag NPs and Ag+ ions [328]. From the data, the disintegration of the cell membrane and the subsequent leakage of the intracellular substances is the most important disinfection mechanism of the Ag2O NPs. The Ag+ ions released from the Ag2O NPs spread into the bacteria cells and release radical oxygen species (ROS). Concurrently, the Ag+ ions interact directly with the phosphorus and sulfur compounds, such as DNA, RNA, and enzymes, which suppress the bacteria proliferation [328].

The antibacterial behavior of AgNPs/GO/MONs composite coatings was also explored as shown in Fig. 18e and f. This figure shows the factors of the R0 and Rα amounts versus the E. coli and S. aureus bacteria. As can be seen, there are great disparities between the antibacterial mediation of the Ti–6Al–7Nb implant and the modified samples. The similar-circumstance plate assay was done to investigate the antibacterial activity of the samples. The results showed that such favorable antibacterial efficiency could be attained using the 1:6 AgNPs/GO decorated MONs composite coating. Remarkably, the structural integrity of the metal oxide layer enhances the antibacterial efficiency. Because of this effect, the surface modification of NTs by GO resulted in modest antibacterial behavior [124].
4.4. Cell morphology, adhesion, viability and proliferation

Several assessments have provided evidence that MSCs, osteoclasts as well as osteoblasts exhibit size-selective responses as the dimension influences the cell interplay, in which the optimum diameter size for the cell linkage, propagation, enlargement, and differentiation fluctuates between 15 and 100 nm. It was specifically confirmed that the TiO$_2$ NTs arrays with 70 nm average diameter are the most favorable nanostructure for the osteogenic differentiation of human adipose-derived stem cells (hASCs). Smith et al. [330] found enhanced dermal fibroblasts and reduced epidermal keratinocyte linkage, propagation, and differentiation on nanostructured titania (diameter 70–90 nm, length 1–1.5 μm). It was also reported that the nanotubular configuration profitably encouraged cell propagation and functions in endothelial cells, but was diminished in vascular smooth muscle cells by determining the EdU (a Thymidine analog) which was integrated into the propagating cells [324]. Also, it was mentioned that the hydrophobic/hydrophilicity of the titania nanotubular coatings is an important factor that supports the cell actions, which can be regulated by altering the diameter of the nanotube. Park et al. [331] cultured green fluorescent protein-labeled MSCs on TiO$_2$ NTs with various diameters to provide a deeper understanding of the influence of these nanoarchitectures on bone-forming cells and stem cells response, to induce cell activity which is responsive to the nanostructured coatings. The results gave maximum cell activity for nanotube diameters around 15–30 nm. Such lateral spacing precisely denotes the predicted lateral spacing of integrin receptors in focal contacts on the extracellular matrix, making the clustering of integrins into smaller spaces, resulting in the best possible integrin activation. When the diameter of tubes is larger than 50 nm, severe impairment of cell scattering and cell adhesion takes place, while a nanotube diameter of 100 nm resulted in cell apoptosis. The surface modification loaded with bioactive factors, in addition to the size of the nanotubes must be considered for optimized biomedical applications. The development of HA is very important for the osseointegration of bone implants. The superior adhesion of TiO$_2$ NT arrays on the electrodeposited HA is described by the adhesive tape examination and the live/dead cell staining assays, which is necessary for primary bone integration. These findings also demonstrate that the strongest adhesion of the HA surface with the nanotube arrays is at 560 nm. Moreover, the nanotubular arrays can certainly reinforce the collagen type I expression in vivo testing which takes into account the primary bone matrix protein in bone formation [82].

Several reports have compared the linkage and development of human cells on oxide nanotubes with various sizes and morphologies. Brammer et al. [332] revealed that the cell elongation significantly increases with the nanotube diameter to around 100 nm. Nonetheless, a larger nanotube diameter also influences the cell elongation. Also, increasing the diameters of nanotubes led to decreased cell linkage, due to the increased spacing between the tubes, though a greater gap could increase the dispersion of the cell. The results of the bioassay verified that outstanding cell adhesion was demonstrated by the TiO$_2$ nanotubes with diameter ~ 100 nm. Park et al. [331] fabricated a nanostructured oxide layer (diameter 15–100 nm) and accomplished the in vivo analysis. The results revealed that the nanostructured oxide layer with a diameter of 15 nm leads to increased cell adhesion, propagation, and viability, compared to a smooth surface. The increase of the nanotube diameter to 15–50 nm led to a decrease in cell adhesion, cell proliferation, and cell viability. The cell adhesion, propagation, and viability decreased even further when the nanotube diameter was enlarged to 50–100 nm [333].

The HOb morphology and adhesion on the Ag$_2$O NPs-decorated MONs for 2 h (where the white arrow show membrane disruption and the red arrow shows intracellular leakage); antibacterial activities opposed to E. coli and S. aureus bacteria in the (e) medium (Rp) and (f) on the samples (Ra); Ti-6Al-7Nb workpiece, thermal-treated TiO$_2$-Nb$_2$O$_5$-Al$_2$O$_3$ MONs (AMO), GO loaded TiO$_2$-Nb$_2$O$_5$-Al$_2$O$_3$ MONs (AGO), 1:12 AgNPs/GO loaded TiO$_2$-Nb$_2$O$_5$-Al$_2$O$_3$ MONs (AG1/12) and 1:6 AgNPs/GO loaded TiO$_2$-Nb$_2$O$_5$-Al$_2$O$_3$ MONs (AG1/6). One-way analysis of variance (ANOVA) followed by Tukey–Kramer post hoc test (P < 0.05) (Reproduced with permission from Ref. [74,124,328]).
behavior following seven days of incubation, demonstrating the positive impacts of nanotopography on the stimulation of distinctive phenotypic features and propagation of the HOb cells [74,328]. The confocal laser-scanning microscopy images also showed a homogeneous spreading of the HOb cells on the surface of the Ag2O NPs decorated-MONs with increased cell numbers at the intervals. Fig. 19 shows the reflexes from the fix seeded osteoblasts on the unprocessed and processed Ti–6Al–7Nb alloy. From this figure, the cells are appropriately attached and proliferated through the samples with relevant bioactivity characteristics. As can be seen, the cells are alive and in good health, as verified through a distinctive polygonal osteoblastic cell morphology after the first day of cell culture. The cells are mostly floating in a large part of the nanotubular arrays. The FESEM micrographs show that the cells are partly connected to the unprocessed Ti–6Al–7Nb after the first day of cultivation due to the inherent bioactivity of the substrate. However, the mutual action of metallic substrates with osteoblast in extended culturing times and implantation phase is an important issue that should be considered in developing nanostructured implants [124].

In agreement with the MTT-ALP analysis, the microscopy observations in Fig. 19 demonstrate that the cells are still viable on the nanostructured surfaces following the first, third, and fifth days of cell culture. This figure clearly shows the bone cell populations on top of the nanostructured surfaces. Confocal microscopy of hFOB cells seeded on different samples shows a typical lens-shaped feature of the live osteoblast cells with natural cell development dynamics. From the day-1 images, live cells are identified in nearly all the samples, where the quantity of discerned live cells suggests that MONs wrapped with GO (AG0) and MONs wrapped with 1:12 AgNPs/GO (AG1/12) present higher biocompatibility compared to other samples. From the day-3 images, a few sound cells are observed on the MONs wrapped with 1:6 AgNPs/GO (AG1/6) and annealed MONs. In contrast, a large number of cells are found on top of the AG0 and AG1/12. This suggests that the incorporation of GO into the nanotubular arrays improves the cytocompatibility behavior of the Ti–6Al–7Nb implant by forming a prospective bioactive platform. From the day-5 results, the seeded osteoblastic cells are more flowing and form intense islands with a similar trend. Thus, more osteoblast cells have wrapped the specimen surface after five days of growth compared to the day-3 growth [124].

5. In vivo studies

In general, there is insufficient in vivo data to recognize the reasons for the improved osseointegration and osteoconductivity of the nanostructured implants. However, some investigations of in vivo behavior on titania nanotube arrays with diverse properties are performed [44,316,334-339]. For instance, the electrochemical behavior, surface features and improved in vivo bone reaction of nanostructures titania on microstructured surfaces of blasted, screw-formed Ti-based implants has been studied by Sul et al. [316], where the surrounding implant had a well-settled trabecular architecture with some alterations in the newly created bone constructions in the periosteal and endosteal sections. In the periosteal area, active developments of woven bone were detected, where the alkaline phosphatase activity is known to be more pronounced than in the endosteal region. In the endosteal area, newly created bone is obviously recognized by the demarcation lines between dark and pale stained bone tissue on both basic fuchsin and toluidine blue-stained regions. Close bone/cell contact was monitored on both implant surfaces. Direct bone/cell contact is normally detected in a very thin rim of bone tissue in the marrow cavity area of the titania nanotube surfaces. In the direct bone/cell contact area defined by the LM observations, further high-resolution SEM micrographs often exhibit near interfacial contact distance or truly direct contact with the fluorinated titania nanotubular arrays but reveal no direct bone/cells contact with the blasted implant surfaces. These show some common histological features of the electrochemically modified implant surfaces compared to the non-bioactive surfaces [316]. Von Wilmowsky et al. [340] first investigated the in vivo behavior of the bioactivity of nanotube arrays. The in vivo results on adult pigs demonstrated that the Ti-based implants with a nanotubular configuration influence the bone development by improving the osteoblast function. Also, they found that a stronger implant-bone connection could be achieved if the implants are covered with nanotubes. One of the unexpected benefits of nanotubular coatings on the implant surface is that the nanostructured coating also endures
shear forces induced by the implant insertion. Nonetheless, with regards to the complex in vivo culture, the negative effects of the nanotubes towards cell growth could be established if the cell propagation is undesired.

The influence of different nanotube diameters (30, 70, and 100 nm) on the procedure of bone connection to the implant surface after 1–5 weeks of establishment, was also studied in vivo. The findings showed that the titania nanotubes control the bone creation at the interface of bone-implant to attain an appropriate osseointegration process. Besides, the dynamic bone deposition was detected in the chronological fluorescent labeling images. Contrary to the usual titanium implants, the bone-implant interaction and the level of gene expression are considerably enhanced in the implants with nanotubular coatings (especially the nanotubes with 70 nm diameter) [320]. Lv et al. [341] verified the substantial influence of nanotopography on the differentiation of hASCs in bioassays. They proved that a nanotubular structure with an average diameter of 70 nm at 20 V anodization is sufficient to supply the optimum conditions for osteogenic differentiation of the hASCs.

To approximate the osseointegration rate, Moon et al. [342] detached Ti implant screws from animal models following implantation and established that the interaction of an implant with the adjacent bone increased significantly following the development of the nanotubes. Jang et al. [338] investigated the impact of TiO₂ NTs on the osseointegration of orthodontic miniscrews. The miniscrews were inserted into the New Zealand white rabbit legs for in vivo studies. The TiO₂ NTs were endowed with a rough surface while the miniscrew with TiO₂ NTs exhibited the highest BIC ratio of 52.8% with enhanced osseointegration. The results confirmed that the TiO₂ NTs on the thread valley of the Ti miniscrew are well preserved from the in vivo assessment. To assess the biomechanical behavior of Ti–6Al–4V miniscrews are also exposed to anodization-cyclic precalcification-heat treatment (APH), and their potential clinical applications are outlined [235].

This approach resulted in a MONs coating which covered with a dense apatite film, as shown in Fig. 20a–d. According to Fig. 20e–h, for the untreated samples, both after 3 and 6 weeks, the surface mainly exhibits interface fracture patterns between new bone and miniscrews. On the contrary, the surfaces of the APH sample display cohesive fracture patterns within newly shaped bone at both steps. The APH treated specimens exhibited better bioactivity and biocompatibility compared with untreated and anodized and heat-treated specimens. The in vivo results of APH-treated miniscrews possessed greater removal torque and bone-to-implant contact than did untreated miniscrews following both 3 and 6 weeks (p < 0.05). Besides, early accumulation of compactly mineralized bone surrounding APH-treated miniscrews was detected, indicating proper connecting to the treated surface [235], as illustrated in Fig. 20i–l.

The integrity during fixation and exploitation are two research topics related to the implants with a nanotubular oxide layer, in addition to the damage beginning and expansion stages. In numerous reports, damages of the nanotubes developed on the implant surface were detected by various techniques, e.g., micro scratch as well as nanoindentation. Shemtov-Yona et al. [343] explored the damage on the surface of nanostructured Ti and Ti–6Al–4V dental implants following elimination from the tissues. The results revealed that the anodized implant surfaces are free from damages. It was found that the nanotubes formed on Ti-based screws were devastated and detached at the screw edge, whereas the other segments of the implant screw reserved the tubular configuration with suitable incorporation with the animal tissue. Shemtov-Yona et al. [344] also reported that the nanotubes coating (length up to 1 μm) was free from damages following the implantation step. These findings show the significant progress in terms of improving and controlling bone-forming functionality for advanced orthopedic implant applications [72]. Recently, in a comprehensive study, Bose et al. [43] examined calcium phosphate coated 3D printed porous Ti with a nanoscale surface amendment for medical implant purposes, as schematically shown in Fig. 21. This figure displays the influences of the combination of doped calcium phosphate coating with nanoscale surface modification of porous Ti on early step osseointegration in a rat distal femur model. This nanoscale surface modification can also be employed on the stem zones of a total hip or knee arthroplasty to develop various MONs layers to commence early bone integration at the implant interface, which ultimately can result in enhanced healing [345].

6. Clinical trials

In general, the medical achievement of orthopedic implants is strongly connected to the early osseointegration stage, which depends on the implant surface properties. There are still numerous challenges to
overcome before the full utilization of nanotubular surface modification, especially MONs in various fields of medicine. The main contradiction is that the most favorable microstructural features and geometry of the nanotube arrays differ between different research groups. Thus, it is better to render the in vitro consequences into in vivo applications through animal models and ultimately in clinical trials. Although there are significant shreds of evidence that stem cells can be seeded into the nanotubes for their enlargement and intensification [72], such clinical studies on anodic nanotubes for implant applications are still scarce.

Nowadays, the DOTIZE® technology established by DOT America is a leading anodization process employed in the industry for the production of nanostructured implants. Benefiting from this technology allows the production of an oxide layer with a maximum thickness of 5 μm, giving rise to nanoroughness on top of the implant with improved biocompatibility, as well as corrosion and wear resistance with no substantial alterations in the dimensions [333]. Nobel Biocare® is also a marketable dental implant treated by anodization. The anodization of titanium-based alloys towards the fabrication of medical implants is composed of the following stages. First, the substances are located in a cleaner tank and thoroughly rinsed. Then, the substances are etched in a specific solution, in which the soaking period for complete etching depends on the solution. The tank anodizing stage comprises the usage of a voltage and current. The processing period of this stage can be extended over the substances are eliminated and thoroughly washed [333].

Losic et al. [346] described the recent developments on new approaches for drug release from nanotubes for the design of nanotube-based drug-releasing implants (DRI) with improved performances, such as expanded drug release and zero-order liberation kinetics and remotely activated release. Anodic nanotubes possess great potential to enhance the efficiency of Ti-based implants as a surface coating because of their biocompatibility, high surface area, and capability of promoting bone growth. Nevertheless, there are two concerns required to be clarified before more advancing anodic nanotubes technology as a drug carrier: (i) uncontrolled liberation of drug and (ii) poor mechanical behavior [347]. To overcome these issues, efforts have focused on developing a drug carrier using a composite of biodegradable polymer/anodic nanotubes [347–350]. Instances of primary medical purposes of titania nanotubes towards bone healing and medical implants, cardiovascular stents, dentistry and cancer treatment are accessible [333,351–353]. These attitudes can be further developed by using various MONs surface modifications, which can be promising strategies for improving bone-implant interaction and accelerating the healing time [124,129]. However, anodic nanotube research in orthopedic directions is still in its infancy and there is a long distance to go in clinical use. The biological interactions between cells and anodic nanotubes, especially MONs are required to expand from the cellular stage to the molecular phase and from morphological alterations to molecular changes. It is well-established that the diameter of nanotubes has direct effects on adhesion, scattering, and growth of osteoblast and mesenchymal stem cells, thus the consistency and basis of this development as well as other factors stimulating cells’ performance are obliged to be further discovered [82].

7. Future directions

Despite vast global advances in orthopedic implants [354]; however, there are no standardized schemes for evaluating fracture healing, with physicians relying on X-rays that are merely helpful at later steps of healing [355]. The global orthopedic tools market is expected to drop from $52.7 billion in 2019 to $39.3 billion in 2020 at a compound annual growth rate (CAGR) of −25.6%. This decrement is predominantly due to the COVID-19 outbreak and the measures to contain it [356]. Numerous medical care services in affected countries have been entirely closed or have been merely presenting minimal treatment for emergency cases. Accordingly, orthopedic surgeries have been delayed or even canceled owing to the nation’s lockdown [357–359], whereby the production of orthopedic devices and implants has been sharply decreased thanks to prolonging factory closures. The global orthopedic tools market is then expected to resume and raise at a CAGR of 5% from 2021 and overtake $63.6 billion in 2023 [356].

With the growth of the medical implants market, there is great potential for the smart implant systems, which can incorporate with current orthopedic hardware platforms to give physicians information about each patient’s healing trajectory [355,360]. In this regard, Parkes [361] recently discussed how intelligent implantable materials are varying the way bone diseases and damages are treated. In general, implants can be smart in two approaches, either through additively fabricated to produce patient-specific implants (PSIs) through computed tomography (CT) or via integrating sensors that are utilized to heal fractures. In this approach, sensors can compute the strain applied to the implant, showing the extent of fracture healing. Accordingly, surgeons could recognize the best time for the patient to progress to the next step of treatment and could recognize healing difficulties much earlier. In the initial stages, internal sensors could gather detailed information about
scrutinizing the healing progress via regular measurements at the fracture zone, and further allow early evaluation of risk for nonunion [355, 362]. The main applications of this smart design seem to be in orthopedic implants (such as knee and hip arthroplasty, spinal fusion as well as fracture fixation) and dental implants, where physical stimuli are obtained using special technology used in implants. Osteoarthritis of the knee is one of the most widespread musculoskeletal pathologies worldwide. Smart knee implants take an important part in the properties of knee biomechanics. From the data of intelligent knee implants, the peak force such as walking after total knee arthroplasty is around 1.8–2.6 times of the body weight and occurs in the middle of the tibial tray. Wholly in vivo purposes for fixed intelligent knee implants are still part of applied research and not part of clinical practice. Due to the importance of bio-functionality of permanent intelligent knee implants, future applications of these implants must involve the protection of the knee from external forces which hasten the wear, implant loosening, or premature collapse of the implant [363]. Osteoarthritis is also a frequent problem found in the hip. The enthusiasm towards in vivo intelligent hip implants is presently associated with applied research, and not towards clinical applications for the specific care of the patient. Accordingly, records from intelligent hip implants could be used to describe the load circumstances for testing and authenticating the in vitro function of implants [364, 365]. Besides this, intelligent implants can present some vital information about the function of posture, motion, and muscle activation in spine biomechanics, which is very essential as the spine loading takes a crucial part in the disease process and the therapeutic process for patients with lower back pain. Scrutinizing the loads on an intelligent fracture fixation device during weight-bearing is proof of the strengthening and fracture healing [363]. Despite the above description, the sensor concept may not very practical particularly at the outer surface as the cellular layer will cover that within few hours and beyond a few days, those sensors generally don’t function [366].

On the other hand, smart implants probably have a better future in the field of spinal and dental implants [367–372]. In this context, a self-directed intelligent dental prosthesis has been introduced by Van Ham et al. [367] for rapid rehabilitation, wherein the device can connect wirelessly with an exterior transceiver, which enables a patient-tailored approach. A monolithic human oral motion-powered smart dental implant with suitable mechanical strength has been proposed by Park et al. [368] as an ambulatory photo-biomodulation therapy modality, wherein the system could convert human oral movements into well-regulated light irradiances. This feature is made possible through the energy collecting from dynamic human oral movements using the developed piezoelectric dental crown, a linked circuit, and micro light emitting diodes (LEDs), as illustrated in Fig. 22. The findings of this comprehensive study not only lead to highly advanced multi-functional implants to avoid peri-implant complications and

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**Fig. 22.** Smart dental implant system, (a) ambulatory photobiomodulation therapy enabled by smart dental implant maintains overall oral health, whereas common dental implant without therapeutic function can trigger severe oral diseases, (b) the schematic vision of smart dental implant assembly on the basis of screw-retained dental implant design including (c) two-phase composite dental crown, linked electronics, and micro LEDs, (d,e) SEM micrographs of the dental material, (f) Raman spectrum of barium titanate nanoparticles, (g) prototype smart dental implant on a US penny, and (h) two dissimilar kinds of joined circuits for continuous or pulsed wave, i.e. CW or PW (Reproduced with permission from Ref. [368]).
lessen the risk of implant failure, but also could be employed to other orthopedic implants prone to continuous exposure to bacterial burdens. Regarding the smart spinal implants, many efforts have been made to set up various sensing tactics; nevertheless, they fail to provide mechanical sensing necessities or deficiency in vivo translatability [373–376]. To this aim, polymeric-based sensors and Micro-electromechanical Systems (MEMS) possess desirable characteristics that correspond to the characteristics needed to measure the load in the body. However, these approaches have not yet been widely examined in orthopedics. Whereas inductive powering is favorable, wireless energy transmission and telemetry are ongoing research topics [371]. This outlook recommends a systematic consideration of the pertinent biomechanics to recognize the relevant sensing factors, simultaneous treatment of sensing and powering features, as well as exploitation of energy harvesting aimed at sensing and data transmission.

On the other hand, as described above, the anodic nanotubes have a higher surface area than the flat implant surface and can overcome the current clinical implant restrictions by creating extra spaces for cell interaction remarkably at the cell-extracellular matrix level. Furthermore, the enhanced bioactive layer of inward growth of anodic nanotubular arrays on Ti and its alloys can deliver superior adherence of the nanotubes layer to the substrate, dismissing the difficulties of infiltrating interfacial bonding of the present ceramic coatings. Besides that, the nanotubes may afford similar features with the natural bone topography (pore size/diameter ~ 60–100 nm) that could modify the interference of bone cell response. Therefore, the combination of nanotubular surface modification and biosensor offers smart orthopedic implants that effectively advance the cell-interplay with the implant materials and may improve osseointegration. This also provides some important physical data from inside the body, such as pressure, force, strain, displacement, proximity, and temperature [377]. This could significantly decrease the number of patients admitted to the hospital. Apart from the above explanations, intelligent orthopedic implantation for clinical practice is a challenging task, because the integration of the current sensor technology requires some substantial modifications of the implants [378]. Also, the physicochemical properties of anodic nanotubes, in particular, MONs for various orthopedic applications should be assessed in detail [307]. Thus, nano surface modification and biosensors for next-generation intelligent orthopedic implants should be simple, tiny, robust, and reasonably priced [363], wherein deeper insights into their biomechanical function is vital before choosing a proper sensing mode. Based on innovative medical approaches, it is conceivable that a new generation of smart orthopedic implants will eventually become available to surgeons and enable intensive medical care.

8. Conclusions

One-dimensional anodic nanotubes are promising biomaterials in a broad range of biomedical applications due to their large surface-to-volume ratio, low-cost, chemical stability, outstanding biocompatibility, and resistance to bio-corrosion. In the field of orthopedic implant manufacturing, nanosurface modifications have been widely studied in the literature for improving implant performance, however, the scientific and clinical understanding of MONs are still in the initial phase. One of the most important questions in this regard is whether the development of MONs is an effective strategy to develop the properties of medical implants or an ineffective research approach? Based on the literature, a wide range of MONs can be formed on different binary, ternary, quaternary, and more complex Ti-based alloys by controlling the anodization conditions. However, the formation mechanism of MONs in different systems is complex and the presence of various elements in the system directly impacts the electrochemical performance, morphology, and composition of the resultant MONs. The studies included in this review showed anodizing is a convenient way of adjusting some, but not all features in MONs and should be strengthened ideally in combination with other treatments like thermal treatment. In addition to direct anodization of Ti-based alloys, there are different combined methods, e.g. PVD-assisted anodization, which could be also utilized in the fabrication of various complex multifaceted MONs for a variety of orthopedic purposes. It was proposed that the integration of nanotubular surface modification and biosensor may result in smart orthopedic implants that not only make progress the form, fit, and function of implants, but also provide important physical data from inside the body, such as strain, force, pressure, proximity, temperature and displacement, which can be effective in clinical care. However, this smart orthopedic implantation is a challenging task for clinical practice because the integration of MONs and biosensor needs more scrutiny and some optimization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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