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Review

An Integrated Overview of Ultraviolet Technology for Reversing Titanium Dental Implant Degradation: Mechanism of Reaction and Effectivity

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Featured Application: UV light exposure, which results in anti-aging ability and renewability of the bioactive surface of the implant, can improve clinical performance and offer a promising alternative to reverse the titanium aging process.

Abstract: Titanium is widely used as an implanted material in various clinical applications, especially in orthopedics and dental implantology. Following manufacturing and storage, titanium dental implants have the ability to undergo aging, which renders a reduction in osteoblast cellular activity during the healing process, so advancement of a surface treatment to recreate bioactive implant surfaces are required. Ultra-violet (UV) surface treatment has been introduced as a potential solution to reverse the aging process via removal of hydrocarbon contamination on the surface. This narrative review aimed to discuss the current understanding of the mechanism of titanium aging and provide insights into the mechanism that improves the biocompatibility of titanium implants following UV treatment. Additionally, the findings from preclinical and clinical studies is integratively presented. A reference search was performed through the PubMed, Embase, and Scopus databases based on the keywords titanium degradation, titanium aging, photofunctionalization, and UV treatment. Emerging data demonstrated the positive effect of UV light on osteoblast cells with enhanced alkaline phosphatase activity in vitro and increased bone-implant contact in animal studies. Despite limited human studies, the data reported here appear to support the benefit of UV light photofunctionalization on titanium surfaces as an alternative to reverse the titanium aging process. The direction of future research should focus on prospective randomized blinded clinical trials.

Keywords: hydrophilicity; dental implant; photofunctionalization; time-dependent degradation; titanium aging; ultraviolet technology; bone–implant contact; implant survival rate

1. Introduction

In medicine, ultra-violet (UV) radiation is widely utilized in conjunction with various devices such as UV germicidal lamps and water purification as well as air and surface sterilization equipment. However, its use in dentistry is not as widely documented. In this field, UV light illumination is used mostly in the forensic identification of restorative materials, photo-polymerization of dental materials, and calculus detection in periodontal disease management. The recent plateau in the field of dental

implantology has challenged many researchers to improve the implant success rate, which in turn has led to the identification of the ability of UV radiation to reverse titanium implant aging. Titanium implant aging, as a unique phenomenon, has been identified to reduce the osteoblastic activity essential for implant–bone integration [1,2]. The actual mechanism of aging in titanium is unknown. The surface of titanium is contaminated by various factors that can lead to aging. Thus, insights into how tissue integration between dental implants could be enhanced by understanding titanium aging and how this phenomenon can be reversed by photofunctionalization would be useful.

The criteria for successful implant therapy lie on a direct functional and structural connection between the living bone and the surface of a load-carrying implant without intervening soft tissue layers [3]. The most common material used for implantology is titanium. One of the current problems in titanium implant therapy is incomplete integration, in which bone–implant contact (BIC) was reported to be only up to 65% in clinical practice. This value is far below the ideal 100% shown in animal studies [4–6]. As the greying population has become a global phenomenon, partial or full edentulism needing implant therapy has also increased. This poses challenges in oral rehabilitation as reduced bone density may decrease the survival rate and more so, the success of implant treatment. The incomplete bone formation around a dental implant is thought to be the result of low cellular attraction to the implant surface. The reduced bone volume, or bone density as seen in aged patients [7,8] may also compromised the BIC as the cellular interaction reduced as a result of cell senescence [9,10].

Bone formation around an endo-osseous titanium dental implant depends on the chemical, physical, and topographical characteristics of its surface [11–13]. Many researchers have shown that physicochemical properties such as hydrophilicity enhance cell adhesion and proliferation [14–16] because of the improvement in cell function by high surface wettability [17–19]. Therefore, current trends in clinical dental implant therapy include modifications of surface treatment to improve the surface properties and surface energy, which in turn increase the wettability of the implant. Considering the ability of titanium dental implants to undergo aging following manufacturing [1,20] renders a reduction in osteoblast cellular [21,22] activity during the healing process, especially in reduced bone density of the elderly [7,8], UV treatment of titanium has been introduced as a potential solution to reverse the aging process via removal of hydrocarbon contamination on the surface and promote cell–titanium implant interaction [23–25]. Given the optical properties of bulk titanium [26], UV irradiation of its surface could enhance its hydrophilicity [27], thereby increasing protein adsorption [28]. Previous review papers have comprehensively addressed issues on the longevity of the titanium surface to remain biologically active following manufacturing [1,2], overview of chairside surface modifications to improve the biofunctionality of dental implants [29], and effect of UV exposure in in vitro and in vivo studies [20,30] up to the time point the reviews were published. To the authors' knowledge, there has been no prior attempt to establish a focused question of whether UV light treatment of the implant surface improved the clinical performance of the implants. Thus, the purpose of this review was to gain an understanding of the mechanism of how bioactive surfaces renewed via UV light exposure on a titanium dental implant surface and to collectively integrate all preclinical and clinical evidence of the photofunctionalization of dental implants.

1.1. Titanium Passivation

Titanium is an extremely reactive metal that undergoes oxidation when exposed to water or air. It forms a tenacious oxide layer (titanium dioxide) that contributes to titanium electrochemical passivity. Titanium dioxide (TiO_2), the formation of which is referred to as passivation, either in rutile or anatase form, is a dense, highly resistant passive oxide film that protects underlying metal from further oxidation and corrosion. Therefore, titanium exhibits high corrosion resistance because of the presence of this oxide film [31].

Theoretically, the proposed oxide layer formation starts with adsorbing oxygen on the surface of pure titanium to produce an oxide monolayer. Subsequently, an electron from the titanium will channel through the oxide layer to further adsorb oxygen, thereby producing oxygen ions [32]. An oxygen

with a valence of only two electrons is relatively electronegative and will readily bind with lightly held valence electrons of titanium to further thicken the oxide layers until the activation energy for ion transport increases and eventually limits further oxide formation [33]. The TiO_2 layers on the titanium surfaces remained susceptible to corrosive attack despite its high corrosion resistance [31], and is chemically stable only in the dark [34]. At any stage, if either anodization or cathodic potential is applied to titanium, the valance state of the titanium ions within the oxide film is disrupted, thereby leading to thickening and solubility/thinning of the oxide layer through reductive dissolution. The passivation of the implant alters surface composition. These changes can be associated with the changes in surface energy [35,36]. Likewise, the thickness and stability of the oxide film are relevant to implant performance because corrosion and ion release into the adjacent tissue are undesirable [37].

In dental implantology, a satisfactory biological response across the entire spectrum of interactions (water–proteins–cells), depending on the chemical and topographic properties of the surface, determines the amount of bone that will come into contact with the biomaterials [13,38]. Moreover, the hydrophilic status of the material surfaces is a representative marker for surface energy and seems to affect the capacity to adsorb proteins and attract cells for interaction [39]. Osteoblast migration and proliferation occur during the initial stage of healing and critically affect the outcomes of bone–titanium integration. Up to the present time, various modifications for improving the physicochemical and topographic characteristics of dental implant surfaces have been investigated. However, a detailed discussion of each surface modification method is beyond the scope of this review.

1.2. Titanium Degradation

Aged titanium impaired the migration, attachment, spread, and proliferation of osteoblasts, and such effect is unrelated to the surface topography or texture of implant-based biomaterials [22,40,41]. Biological aging or time-dependent degradation of titanium occurs due to surface contamination over time under ambient conditions upon storage and transfer before reaching the end-users. The mechanism of the degradation process is unknown because of the stability of the oxide layer of titanium, however, progressive accumulation of hydrogen and carbon compounds occurs over time on the surface exposed to ambient temperature [2,28]. When exposed to atmosphere, the TiO_2 surface can bind to hydrocarbons in the air through interactions with carboxyl and amine groups, regardless of the type of surface treatment [42]. This progressive accumulation of organic molecules on the titanium surfaces cannot be avoided [25]. The deposition of hydrocarbons onto the titanium surface is inversely proportional with osteoblast activity [25,28]. In comparisons of UV-treated and untreated titanium surfaces, osteoblast attachment in the former was found to be more profound and was higher in number [43], demonstrating lamellipodia-like actin projections in multiple directions [21] and possessing mature cytoskeletal development on UV-treated surfaces. Osteoblasts on the untreated surface were found to be rounded, lacking cytoskeleton formation, and presented delayed cellular proliferation [41,44]. Time-dependent degradation also caused the implant surface to become more electronegative [45] and hydrophobic [25,40]. The two proposed mechanisms of time-dependent titanium degradation are discussed in this section. The first mechanism involves hydrocarbon compound contamination on the external layers of TiO_2. The second mechanism involves changes in surface energy that resulted from alterations in the electrostatic status of the titanium surface.

1.2.1. Titanium Surface Contamination

The presence of impurities on the surface of an implant affects wettability as these impurities prevent the adhesion and adherence of water molecules. The hydrocarbon contamination of titanium dental implants could occur during machining or surface modifications, sterilization, packaging, and storage prior to clinical use. Even at small quantities, trace compounds such as polycarbonyls or hydrocarbons may alter the implant surface properties. The presence of trace organic impurities or adventitious contaminants on the surface of an implant is unavoidable and is thought to affect the response to protein absorption and cells adjacent to the implant. Hayashi et al. [25] evaluated the

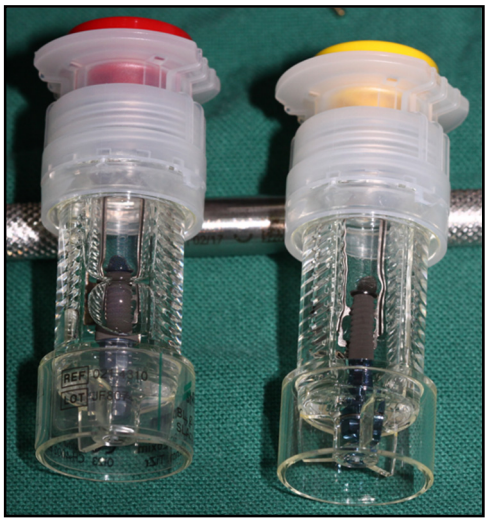
effect of carbon contamination on cell behaviors by regulating the amount of carbon deposited onto the titanium surface using machined oils prior to cell culture. As expected, the specimens treated with acetone and machine oil exhibited a high carbon content and reduced peaks for TiO_2 on the surface [25].

Generally, machined surfaces contained significantly more carbon than the roughened surfaces [17] because the process of machining involves cutting and polishing, in which the implants directly make contact with the machining tools such as organic lubricating fluids [18]. In comparison, the plasma-spraying technique resulted in cleaner surfaces because of the nature of the finishing technique, where the implant surface does not come into contact with machining tools or lubricating fluids and organic contaminants are literally removed during the process due to the high temperature of the plasma spray. Conversely, acid etching either by hydrofluoric or hydrochloric/sulfuric acid dissolves the outermost TiO_2 layers of the implant surface; hence, the hydrocarbon compounds are virtually eliminated alongside the outer layers [35,46]. Notably, traces of foreign materials such as metals, lubricants, detergents, or other specific chemical compounds attach to the implant surface during processing and act as contaminants [39]. Hydrocarbon contamination on the surface was found to alter the surface zeta potential of the titanium surface to become electronegative. This reaction led to the entrapment of air bubbles and the blocking of the protein receptor, thereby interfering with the interaction between the proteins and cells [1,47,48].

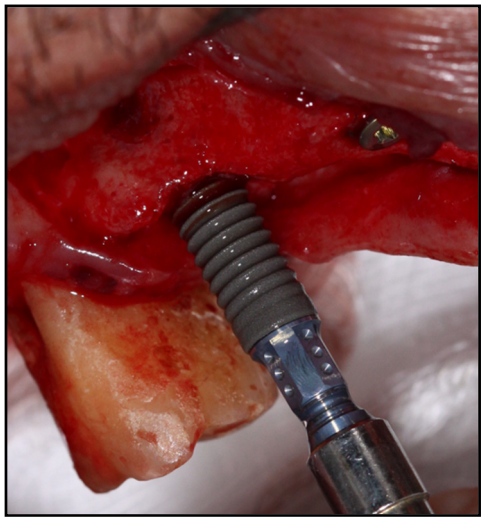
Following manufacture, sterilization is one of the final surface preparations performed before packaging to ensure that the implants prepared are free from bacterial contamination. Interestingly, one further issue highlighted by studying cell–surface interactions is the fact that cleaning and sterilization methods may affect the surface energy of implants [49–51]. Notwithstanding, our effort to reduce bacterial contamination inevitably contributes to non-biological surface contamination of the titanium implants. Thus, autoclaving or ethanol or butanol sterilization creates organic contamination [49,52]. Hence, sterilization via the hydrothermal method [53,54], gamma ray [55], or intense UV light exposure [50,51,56] is recommended to achieve titanium with high surface energy that can induce cell adhesion [41,44] as well as improve cellular activity [22,47] and osseointegration [57,58].

In addition to processing and cleaning, the surface properties of titanium implants are also affected by the storage medium used. To our knowledge, most commercially used titanium implants are provided in sterile, gas-permeable packaging so that they can be stored up to expiry dates of approximately four years following fabrication. Given the nature of the packaging, plastic casing, and absence of light, the chemisorbed hydroxyl groups on the titanium surface are replaced with oxygen and carbon from air. However, the level of hydrocarbon, not hydrophilicity level, was found to be inversely correlated with protein adsorption and cell attachment [25]. The hydrocarbon formation on the titanium surface can start as early as four weeks after the production. Therefore, the amount of hydrocarbon adsorbed on TiO_2 from the time of manufacture to the time of implantation is crucial in determining the initial affinity level for osteoblasts. Choi et al. [59] observed larger spindle-shaped MC3T3-E1 with extended actin filaments on the UV-treated surface of titanium stored in distilled water prior to their experiment. To date, the dental implant system with a SLActive® surface (Institute Straumann AG, Basel, Switzerland) is the only implant system that is rinsed with nitrogen to prevent exposure to air and stored in a glass ampoule containing saline solution (0.9% sodium chloride) following manufacture. The implant is shown Figure 1a. This mode of storage not only improves the initial wetting conditions by lowering the hydrocarbon contaminations, but also maintains a chemically active surface by increasing its surface free energy [60]. This solution is known to protect the TiO_2 surface layer and has an increasing effect after prolonged exposure while maintaining surface wettability. The wettability of the surface increased as the surface is soaked by blood in the clinical view of surgical implant placement as shown Figure 1b. The presence of both Na^+ and Cl^- electrolytes in aqueous solution rapidly repassivates the damaged TiO_2 layers [60,61]. In a study comparing preferable storage media, Wennerberg et al. [62] suggested that, unlike that of pure water, wet storage in aqueous solution reorganized the TiO_2 nanostructures. Kamo et al. [63] suggested

that the use of gas-barrier (vacuum) packaging during shelf storage resulted in better wettability, and hence, greater protein adsorption compared with the use of a gas-permeable container.



(**a**)



(**b**)

Figure 1. Straumann SLActive® Implant system (Institute Straumann AG, Basel, Switzerland); (**a**) isotonic saline solution as novel storage to maintain surface bioactivity; (**b**) wettability of implant shown as blood drawn onto the implant surface.

1.2.2. Titanium Surface Energy Changes

As mentioned in the previous paragraph, the osseointegration of bone to implant is influenced by the implant's surface characteristics such as surface chemistry, topography, and wettability, along with the presence of impurities. The passivation and thickening of TiO_2 layers occur when an electron from titanium adsorbs oxygen from the air and produces oxygen ions. The ions on the surface are relatively electronegative and continuously maintain electronegative charges in the presence of air when stored in a gas-permeable container over time. Compared with the newly produced highly electropositive implant with high surface free energy [64], the positively charged new titanium surface directly interacts with the negatively charged biological cells. This interaction between the new titanium surface and osteoblasts occurs through electrostatic forces without cell–protein interaction.

Att et al. [47] reported that the application of divalent cations such as calcium ions on a four-week-old titanium surface increased albumin adsorption, whereas application on a new TiO_2 surface exhibited otherwise. Corresponding with the above-mentioned reaction, researchers [47] suggested that the divalent calcium cations deposited onto the old titanium surface act as bridges between the negative TiO_2 surface and the protein molecules. This finding indicates that the electrostatic property of the titanium surface plays a role in protein adsorption and biological interaction and is a critical factor in determining titanium bioactivity.

1.3. Ultra-violet Photofunctionalization on Titanium Surface

UV photofunctionalization is defined as the phenomenon of titanium surface modification with intense UV treatment of specific wavelength and strength including the change in the physicochemical properties [43,45] and the improvement in biological features [21,22]. Two types of UV light were used for this phenomenon. The UVA light acts via the photocatalytic effects of crystalline TiO_2, whereas UVC works via direct photolysis without acting as a photocatalyst. This part of the review aims to discuss how photo-induction of TiO_2 superhydrophilicity occurs and how this can lead to an enhancement of the biological activity of the bone cells. The proposed mechanism of reactions thoroughly discussed below are classified based on how TiO_2 reacted upon exposure to UV light.

1.3.1. Photocatalytic Degradation and Water Decomposition

TiO_2 in any form, either in anatase, rutile, or brookite, exhibit excellent optical properties [26]. They possess powerful photocatalysts for various significant reactions due to their chemical stability and high reactivity. The original water decomposition reaction photocatalyzed by light was proposed by Fujishima and Honda [65]. They suggested that the water molecules decomposed into oxygen and hydrogen with TiO_2 as a cathodic catalyst and in the presence of UV light, following the overall equations below:

$$\text{(oxidation reaction) } TiO_2 + h\nu \rightarrow e^- + h^+ \quad (1)$$

$$\text{(reduction reaction) } 2H_2O + 4h^+ \rightarrow O_2 + 4H^+ \quad (2)$$

$$2H^+ + 2e^- \rightarrow H_2 \quad (3)$$

$$\text{The overall reaction is } 2H_2O + 4h\nu \rightarrow O_2 + 2H_2 \quad (4)$$

TiO_2 surface has been reported to gradually increase in the water-contact angle induced by longer storage period, however, UV irradiation repeatedly regenerated surface amphiphilicity [22,27,28] from the water decomposition reaction. This is a photochemical reaction catalyzed by TiO_2 upon exposure to UV light. Some molecules such as oxygen and water molecules were adsorbed on or desorbed from the titanium surfaces under UV light consisting of wavelengths shorter than its band gap, approximately 415 nm [66] or with an energy above the band gap energy [67]. The photo-induced superhydrophilicity of TiO_2 surfaces was initially explained by an increase in the amount of hydroxyl groups formed through UV light irradiation [27]. During UV light exposure, photoexcited electrons are captured by oxygen molecules, creating holes and forming electron-deficient transition species, which later deprotonate water molecules to form two hydroxyl groups, each coordinated to different titanium cations [33]. This phenomenon creates surface oxygen vacancies at the bridging sites, thereby resulting in the conversion of relevant Ti^{4+} sites to Ti^{3+} sites [42]. The latter are favorable for dissociative water adsorption [57]. In the dark, the hydroxyl groups gradually desorb from the surface in the form of H_2O_2 or $H_2O + O_2$.

Photocatalytic decomposition of organic contaminants is a process different to that of photoinduced hydrophilic conversion. When TiO_2 is irradiated with UV light ($\lambda < 380$ nm: energy greater than the band gap of $TiO_2 = 3.2$ eV), an electron-hole pair is generated. In turn, adsorbed molecules such as oxygen and water molecules are reduced rapidly and oxidized to produce reactive oxygen species such as superoxide ions ($^{\bullet}O_2^-$) and hydroxyl radicals ($^{\bullet}OH$) [32]. These oxygen radicals react with

the inorganic or organic surface impurities, thereby leading to their decomposition and removing the hydrocarbon compounds from the titanium surface [67]. The overall reaction is schematically presented in Figure 2. Greater carbon contamination was observed on non-UV-treated surfaces compared with that on UV-treated surfaces, with carbon content reducing upon UV treatment [25,42,68]. The removal of carbon increased the wettability and altered the surface charge from electronegative to electropositive.

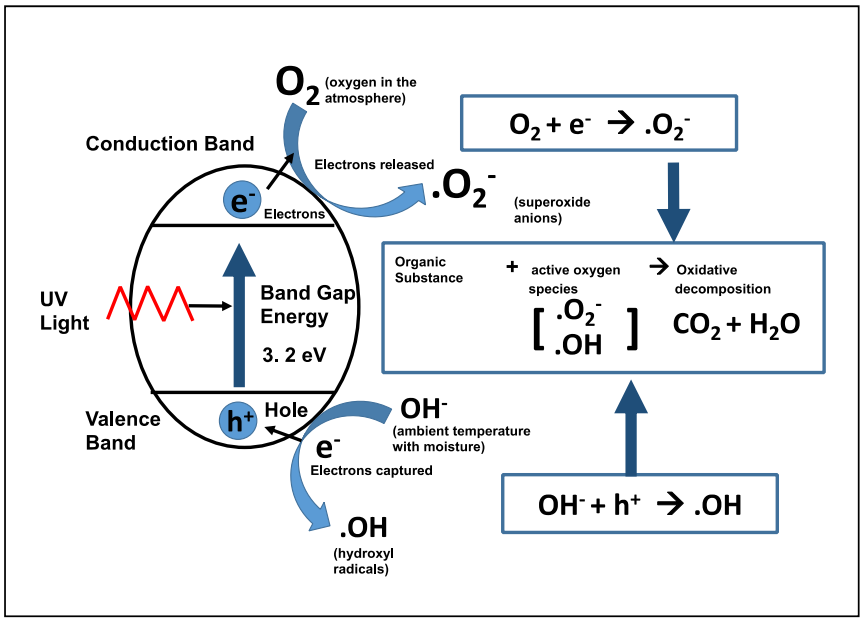


Figure 2. Schematic photoexcitation of an electron on the TiO_2 surface and the creation of holes, which attract water molecules to generate hydroxyl radicals and superoxide ions. (Adapted from [67]).

1.3.2. Direct Electrostatic Interactions

Schneider et al. [66] mentioned that changes of interfacial energies between solid surfaces and liquid play an important role in the photoinduction phenomenon. The irradiation of TiO_2 to UV light results in the excitation of an electron from the valence band to the conduction band of TiO_2, thereby producing negative-electron (e^-) and positive-hole (h^+) pairs. The positive hole on the superficial layer of TiO_2 increases the surface free energy to become more electropositive. The divalent cations following UV-treated titanium surfaces act as direct attractants for cells, and the positively charged TiO_2 surface can attach directly to negatively charged proteins and cells without requiring ionic bridges such as calcium ions (Ca^{2+}) to attract proteins and cells. The electropositive titanium surfaces exhibit a regulatory role by determining their bioactivity and attracting negatively charged proteins, blood, and cells on the titanium surfaces.

Notably, naturally occurring sunlight consists of both UVA and UVC. Although UVC does not penetrate the ozone layer, it can be produced by a germicidal UV lamp. A UV light energy greater than 3.2 eV is required to induce TiO_2 photocatalytic activity [67]. Aita et al. [21] demonstrated that UVA and UVC treatments both produced titanium surfaces with high wettability (contact angle <5°) under different underlying mechanisms. UVA serves as an energy source for the photocatalytic reaction of TiO_2, where the electron-hole pair is generated. Thus, hydrocarbons on the TiO_2 surface are removed via reaction with reactive oxygen species (as presented in Figure 2). UVC induces the photolysis of hydrocarbon compounds from the TiO_2 surface [43,69], thereby causing the latter to decompose directly, which can lead to superhydrophilicity. In the study by Att et al. [41], initial cell osteoblast attachment and proliferation were enhanced on the UVC-treated surface, but not UVA-treated surface, despite comparable increased wettability. Similar cell reactions were also reported by Aita et al. [21] and Gao et al. [70]. In a dog animal model, Hirakawa et al. [71] showed a significant increase in BIC after two weeks of healing with the implant treated with UVA.

2. Search Strategy

The scope of the manuscript covers the mechanism of reaction of both titanium degradation and reversal processes by photofunctionalization, and the clinical efficacy of UV pre-treatment of titanium implants. The inclusion criteria involve original research or review articles published in any language and no restriction with regard to the publication year was applied including 'Online-early', 'Ahead of print', and 'In-press' articles. Given that the knowledge gap and the literature may be diffuse due to the robustness of available evidence, we considered adopting a scoping review approach. The following questions: "how does titanium aged?" and "what are the mechanisms of reversing the aging of titanium?" and "how effective the UV light treatment of implant surface improved the clinical performance of the implants?" were considered in the search strategy. The search was made on the MEDLINE (via PubMed), Embase (via Ovid), and Scopus databases for relevant articles. The strategy used a combination of MeSh terms and free text words of the following keywords: 'photofunctionalization', 'titanium degradation', 'titanium surface', 'ultraviolet' and 'UVA', 'UVC' and 'ultraviolet light' (different key words were connected with OR and AND). Example of the search was: 'photofunctionalization' (All Fields) AND 'dental implants (MeSH terms), ("ultraviolet rays"[MeSH Terms] OR ("ultraviolet"[All Fields] AND ("dental implants"[MeSH Terms] OR ("titanium"[All Fields] AND "implants"[All Fields]) OR "dental implants"[All Fields]) OR ("titanium"[All Fields] AND "photofunctionalization"[All Fields]) AND "animals"[All Fields]). Other relevant references were obtained from the citation in the selected articles. Since this is a narrative review, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement was not strictly followed.

3. Results

A single examiner (MR) performed the data extraction. The aforementioned data were collected and organized into tables. As this review focused on the clinical performance of the UV pretreatment, the in vitro studies utilizing monolayer cell culture approaches were not all included. The selected papers were those that focused on the mono-layer cell culture studies involving osteoblast cells of varying origin (tabulated in Table 2). In most monolayer studies, the specimen used were disc-shaped titanium or titanium alloys [44,72]. Common cells used were bone marrow-derived osteoblasts of Sprague-Dawley rats [44,72]. The osteoblasts showed profound actin projection and lamellipodia-like processes on UV treated titanium or titanium alloy surfaces.

Using the term 'animal studies' or 'animal models' in combination with the above keywords, the search yielded twenty-five (25) articles relating to photofunctionalization of the titanium surface. There was no expert discussion and consensus in selecting articles reporting the effect of photofunctionalization or UV light treatment in animal models. The articles selected were categorized based on the size of the animals used (Table 1 for rats, Table 3 for rabbits, and Table 4), in which either BIC, bone volume, or bone mineral density data are available. In rats, implants were specifically placed in the femur (Table 1), whereas in rabbits, the implants were either placed in the femur or in the tibia (Table 3). In canines and minipigs, the implants were placed either in the maxilla or mandible (Table 3). All implants placed in tibias and femurs were unloaded. In detail, most authors reported significantly increased BIC [57,71,73–79], push-in values [40,44,80–83], bone volume [72,84], or bone mineral [85,86] were noted in all animal models studied for photofunctionalized groups disregarding implant surface modifications/topography. The differences were insignificant for both UV-treated and non-UV-treated reported in four animal studies [87–90].

The literature search did not yield any randomized controlled clinical trials or prospective studies relevant to photofunctionalization other than seven (7) retrospective studies including a case series and case report. There was one (1) clinical trial on the photofunctionalization of titanium in orthopedic patients [91]. No direct data analysis was attempted, as clinical case reports do not provide an adequate source of evidence. The reported data of clinical retrospective studies and case reports are seen and summarized in Table 5.

Table 1. Effect of UV photofunctionalization on rat models.

Species	Studies (Author)	No. of Animals (Sites)	No. of Specimens Type of Specimens	Surface Treatment	Source of UV Light (Light Treatment)	Bone Osseointegration
Sprague–Dawley rats	Aita et al. 2009 [57]	Not stated (femur)	4 cylindrical titanium rod of 1mm diameter and 2mm length.	One exhibited machined surface, turned by a lathe, and the other was acid etched with 67% H_2SO_4 at 120 °C for 75 s.	UV exposure up to 48 h under ambient conditions using a 15 W bactericidal lamp (Toshiba, Tokyo, Japan); intensity; ca. 0.1 mW/cm^2 ($\lambda = 360 \pm 20$ nm) and 2 mW/cm^2 (($\lambda = 250 \pm 20$ nm).	BIC percentage was higher by more than twofold in UV-treated surfaces (98.2%) compared with that of non-treated surface (50%).
Sprague–Dawley rats	Suzuki et al. 2009 [40]	30 rats (femur)	5 titanium cylindrical rod (1mm in diameter and 2 mm in length) each group.	acid etching with 67% (w/w) sulfuric acid (H_2SO_4) at 1208 C for 75 s; sandblasting with 50 mm Al_2O_3 particles for 1 min at a pressure of 3 kg/m; further divided into fresh, 4-week-old, and UV-treated 4-week-old surfaces.	Treatment with UV for 48h under ambient conditions using a 15-W bactericidal lamp (Toshiba, Tokyo, Japan), with intensities of approximately 0.1 mW/cm^2 ($\lambda = 360 \pm 20$ nm) and 2mW/cm^2 (($\lambda = 250 \pm 20$ nm).	Titanium implants with freshly prepared acid-etched surfaces exhibited a two times greater push-in value than those with the 4-week-old surfaces ($p < 0.01$). The push-in value of UV treated specimen increased to the level equivalent to that of the fresh surface.
Sprague-Dawley rats	Ueno et al. 2010 [80]	45 rats (femur)	Cylindric titanium rods in two different lengths (15 longer-2 mm in length; 30 shorter-1.2 mm in length), fabricated from commercially pure titanium.	acid-etched with 67% sulfuric acid at 120 °C for 75 s.	Treated with UV light for 48 h under ambient conditions using a 15-W bactericidal lamp (Toshiba) with intensity of about 0.1 mW/cm^2 ($\lambda = 360 \pm 20$ nm) and 2 mW/cm^2 ($\lambda = 250 \pm 20$ nm).	Push-in value of the longer implants (2.0 mm) was significantly higher than that of the shorter implants (1.2 mm) UV-treated shorter implants showed a higher push-in value compared to untreated groups (long and short implants)
.Sprague-Dawley rats	Ueno et al. 2010 [72]	4 animals for micro-CT test and 5 animals for push-in test	Cylindrical rods (1 mm in diameter and 2 mm in length) made from commercially pure titanium (Grade 2).	The surfaces of the titanium samples were prepared by acid-etching with 67% (*w/w*) sulfuric acid (H_2SO_4) at 120 °C for 75 s.	UV exposure for 48 h under ambient conditions using a 15 W bactericidal lamp (Toshiba, Tokyo, Japan); intensity; ca.0.05 mW/cm^2 ($\lambda = 360 \pm 20$ nm) and 2 mW/cm^2 (($\lambda = 250 \pm 20$ nm).	bone volume was 3.3-fold higher with UV treatment than without UV treatment, whereas at the transitional and bone marrow levels, it was 2.1-fold greater.
Sprague–Dawley rats	Minamikawa et al. 2014 [44]	6 rats (femur)	6 cylinders (diameter, 1 mm; length, 2 mm) made from Ti–6Al–4V alloy.	Implant surface: machine and roughened (blasting with 50 mm Al_2O_3 followed by etching with 19% hydrofluoric acid (w/w) at room temperature for 30 s).	Exposure to UV light for 15 min using a photo device (TheraBeam® Affiny, Ushio Inc, Tokyo, Japan).	Statistically significant higher push-in test for both groups of treated with photofunctionalization.
Sprague-Dawley rats	Hirota et al. 2016 [84]	3 rats for 2 weeks and 4 rats for 4 weeks in each group	Screws (1.5 mm in diameter; 7 mm in length) made of a Ti and Ti alloy (Ti6Al4V) n = 12 for 2 weeks and n = 16 for 4 weeks.	Not stated.	15 min UV exposure using photo device (TheraBeam® SuperOsseo; Ushio Inc, Tokyo, Japan).	bone volume and mineralized tissue formed of the photofunctionalized screws were significantly greater than that of the untreated screws.

Table 1. *Cont.*

Species	Studies (Author)	No. of Animals (Sites)	No. of Specimens Type of Specimens	Surface Treatment	Source of UV Light (Light Treatment)	Bone Osseointegration
Sprague Dawley rats	Ishijima et al. 2016 [81]	Not stated (femur)	24 implants (1 mm in diameter, 2 mm in length) made of grade 2 commercially pure titanium.	All implants were etched in 67% sulfuric acid at 120 °C for 75 s.	Exposure to UV light for 12 min using a photo device (TheraBeam® SuperOsseo; Ushio Inc., Tokyo, Japan).	The average push-in value of photofunctionalized implants was approximately 40% higher than that of untreated implants.
Sprague Dawley rats	Soltanzadeh et al. 2017 [82]	7 rats (femur	14 cylindrical titanium rods (1 mm diameter, 3 mm length) were fabricated from commercially pure titanium (grade II)	Implants were acid etched with 67% sulfuric acid (H2SO4) at 120 °C for 75 s. Photofunctionalization was performed for 12 min, using a UV light device.	Photofunctionalization was performed for 12 min, using a UV light device (TheraBeam® SuperOsseo; Ushio Biomedical).	This study evaluated the biomechanical quality of photofunctionalized titanium under early loading. The average push-in value for photofunctionalized implants was 2.4 times greater than that for untreated implants. 71.4% (2 of 7 implants) of untreated implants met the criteria for osseointegration failures.
Sprague–Dawley rats	Yamauchi et al. 2017 [73]	5 rats (femur)	1 implant each side; implant made from pure Ti and Ti6Al4V (B. Braun Aesculap Japan Co. Ltd. Tokyo, Japan).	Specimens: pure Ti and Ti6Al4V with average surface roughness values of 0.66 and 0.34 μm, respectively.	Exposure to UV irradiation for 15 min using a photo device (TheraBeam® Affiny; Ushio Inc., Tokyo, Japan) at an intensity of 3 mW/cm^2.	Higher BIC of treated titanium surface and titanium alloy (Ti6Al4V) both at two and four weeks compared with non-specimens. The differences were not significant statistically.
Long-Evans Tokushima Otsuka rats	Sugita et al. 2014 [83]	10 healthy and 10 Type 11 diabetic rats (femur)	Cylindric Ti implants (1 mm in diameter, 2 mm in length), fabricated from commercially pure Ti.	Etched with 67% sulfuric acid at 120 °C for 75 s.	Exposure to UV light for 15 min using a photo device (TheraBeam® Affiny, Ushio).	The photofunctionalized implants in diabetic rats had a significantly higher mean push-in value than the other two groups during healing phase ($p < 0.05$).

BIC-bone-implant contact; UV–ultraviolet;

Table 2. Studies comparing the effect of UV photofunctionalization of titanium surfaces on osteoblast cells of varying origins

Studies	Source of UV	Wettability (Contact Angle Formed with Water)	Source of Osteoblast Cells	Results	Other Parameters
Han et al. 2008 [92]	1000 W high-pressure mercury lamp (300–600 nm range with a maximum intensity at 365 nm). Specimens treated for 0.5 and 2 h at room temperature.	Contact angle reduced from 17.9 ± 0.8° to 0° for all specimens treated with UV.	SaOS-2 human osteoblast-like cells, derived from a human osteosarcoma.	Significantly higher cell attachment on UV treated specimens at Days 1, 2, and 3 compared to untreated specimens.	Cells were flattened, spread out uniformly over the surface and displayed numerous filopodia extensions noted on UV-treated surface specimens
Aita et al. 2009 [21]	UVA generated from 6 W mercury lamp with intensities of ca. 2 mW cm^{-2} (λ = 360 ± 20 nm) and 0.0 $mWcm^{-2}$ (λ = 250 ± 20 nm) UVC was derived from 15 W bactericidal lamp with intensity; ca. 0.1 mW/cm^{-2} (λ = 360 ± 20 nm) and 2 mW/cm^{-2} (λ = 250 ± 20 nm). Exposure of light up to 48 h.	The untreated control has 90° contact angle. The measured contact angles were 4.5° and 0° for the UVA- and UVC-treated surfaces, respectively.	Human mesenchymal stem cells (MSCs).	UV-treated machined surface exhibited filopodia-like cell processes developed in multiple directions. Cells were larger and the cellular processes stretched to a greater extent on UVC-treated acid-etched surfaces than on untreated acid-etched surfaces.	Higher ALP compared with the control. The area of mineralized nodule is greater on UV-treated titanium surfaces. No differences in terms of cell viability were observed among all the test groups, but the UVC-treated surface showed less necrotic cells.
Hori et al. 2010 [22]	Surface topography: machined, acid-etched and sandblasted surfaces UV treatment using 15 W bactericidal lamp with intensity of approximately 0.1 mW/cm^2 [λ = 360 ± 20 nm] and 2 mW/cm^2 [λ = 250 ± 20 nm] for 48 h.	Contact angle of these surfaces decreased to <5° after UV treatment, thereby indicating the restoration of superhydrophilicity of these aged Ti samples.	Human mesenchymal stem cells (MSCs).	The UV-treated surface showed substantially stronger cell attachment than the fresh surface after 24 h of incubation. Cell appears larger and lamellipodia-like cell developed in multiple direction in UV-treated surface, regardless of the age of the specimen.	Higher protein adsorption (40–60%) noted on titanium discs treated with UV. The ALP activity higher and area of mineralized nodules were greatest on the UV-treated aged specimen
Gao et al. 2013 [70]	15 W UVA mercury lamp (generates maximum intensity light at 360 nm) 15 W UVC bactericidal lamp (generates maximum intensity light at 250 nm) Exposure up to 24 h.	Untreated surface-65.34°. UVA-treated surface = 44.64°. UVC-treated surfaces = 3.41°.	Human osteoblast-like (MG-63).	Significantly higher number of cells adhered ($p < 0.05$) at Day 1 and significantly higher proliferative activity was observed ($p < 0.01$) after 5 days on the UVC-treated surface compared to UVA-treated and untreated surfaces.	-
Altmann et al. 2013 [93]	Specimens were exposed to UV light in a UV irradiation chamber for: UVA light with 17 J/cm^2 UVC light with 345 J/cm^2.	The contact angle of water droplet on the untreated implant surfaces was 32.5° and dropped to 8.5° following exposure.	Primary human alveolar bone osteoblasts.	Demonstrated the dendritic spread of osteoblasts on treated surfaces, but the morphology did not differ significantly between treated and non-treated surfaces.	Regardless of UV treatment, significant differences in DNA concentration were detectable between treated and non-treated specimens.
Minamikawa et al. 2014 [44]	Ti–6Al–4V alloys used UV light treatment using a photo device (TheraBeam Affiny, Ushio Inc., Tokyo, Japan) for 15 min exposure	Non-treated: 85°, indicating superhydrophobic surface Treated surface: 0.0°, indicating superhydrophilic surface	Bone marrow-derived osteoblasts from Sprague–Dawley rats.	Cells are larger, stretched with initiation of lamellipodia-like actin projections in multiple directions and mature cytoskeletal development on treated surface. Majority of cells on the untreated surfaces were rounded and did not project cell processes or show cytoskeletal development.	Higher ALP activity on the treated surface. The expression of vinculin was more intense and extensive in cells cultured on treated surfaces at this very early stage of culture.

ALP-alkaline phosphatase

Table 3. Effect of UV photofunctionalization on rabbit models.

Species	Studies (Author)	No. of Animals (sites)	No. of Specimens Type of Specimens	Surface Treatment	Source of UV Light (Light Treatment)	Bone Osseointegration
Japanese white rabbits	Sawase et al. 2008 [85]	6 rabbits (tibia)	1 implant each side; cpTi screw implant (Nobel Biocare RP Mark III fixtures).	Post-annealed from titanium implant tetra-isoproxide plasma by the plasma source ion implantation.	UV irradiation for 24 h.	Bone mineral content was higher in UV-treated surface implant The difference was statistically significant ($p = 0.027$).
Japanese white rabbits	Jimbo et al. 2011 [74]	12 rabbits	2 implant each side of proximal tibia.	Anodized porous TiO2 implants.	Specimens were irradiated with UV at a peak wavelength of 352 nm for 24 h.	BIC in UV treated group was significantly higher than un-treated group.
New Zealand white rabbits	Park et al. 2013 [75]	14 rabbits (tibia)	each rabbit received either 4 control or test implants.	(i) Anodized at 300 V (ii) Anodized at 300V then UV irradiated for 24 h.	UVC irradiation via 15-W bactericidal lamp for 24 h at intensity of 253.7 nm.	Values for BIC on test group was higher than control.
Swedish lop-eared rabbits	Hayashi et al. 2014 [87]	9 rabbits (tibia)	18 commercially pure titanium discs (cpTi, diameter 6 mm; thickness 1 mm, grade 4).	Titanium-coated discs.	Irradiation with UV (wavelength 352 nm, 6 W) for 24 h.	The BIC for both groups were almost similar; no statistical analysis was carried out due to small number of animals.
Japanese white rabbits	Yamazaki et al. 2015 [94]	5 rabbits (femur)	5 implants in each group.	Acid-etched pure titanium screw implants, irradiated with UV-C prior to experiment.	Exposure to UVC for 48 h under ambient conditions using a 15 W bactericidal lamp (UV Bench Lamp, 15 W, XX-15S, 254 nm, 100 V, Funakoshi Corporation, Tokyo, Japan) at an intensity of ~3 mW/cm^2.	Increased bone volume on pre-irradiated surfaces at any stage of healing phase.
New Zealand white rabbits	Shen et al. 2016 [77]	40 rabbits (femur and tibia)	160 screw-shaped implants	Sand-blasted and acid-etched, divided into new and old group and further divided into UV and non-UV treated, and stored in distilled water.	15 W bactericidal lamp (Toshiba) for 24 h prior to experiment; with intensities of approximately 0.1 mW/cm^2 ($\lambda = 360 \pm 20$ nm) and 2 mW/cm^2 (($\lambda = 250 \pm 20$ nm).	Direct bone implant contact, more trabeculation, denser and higher bone matrix in group of implants treated with UV regardless of surface treatment ant storage
New Zealand white rabbits	Kim et al. 2017 [86]	12 rabbits (tibia)	2 implants on each tibia Commercial titanium implants (Dio Co., Busan, Korea).	Hybrid sand-blasted and acid-etched; UV treatment (UV+), the implants were also treated with alendronate (ALN+).	Treatment with UV at 189.4 nm and 253.7 nm wavelengths for 2 h under ambient conditions using a UVO-Cleaner® (Jelight Company, Irvine, CA, USA).	Significantly higher bone volume ($p = 0.025$) observed in the UV and ALN treatment group (UV+/ALN+) than that in the UV+/ALN and UV/ALN+ groups.

Table 3. Effect of UV photofunctionalization on rabbit models.

Species	Studies (Author)	No. of Animals (sites)	No. of Specimens Type of Specimens	Surface Treatment	Source of UV Light (Light Treatment)	Bone Osseointegration
New Zealand white rabbits	Miki et al. 2019 [88]	6 rabbits (femur)	Titanium discs made of Ti–6Al–4V.	The treatment was divided into (i) control; (ii) S-100®; (iii) UV light and further categorized into fresh, 1 week, and 4 weeks old.	UV source: 15 W germicidal lamps for 48 h (λ = 253.7 nm, National Osaka, Japan).	No data available for comparison of the UV group. Only S-100 group was compared with control
.New Zealand white rabbits	Lee et al. 2019 [79]	4 rabbits (tibia)	8 screw-shaped implants (3.3 mm in diameter and 7 mm in length).	The treatment was divided into (i) machined surface; (ii) SLA; (iii) machine surface treated with UV light.	UV source: 15 W bactericidal lamps (G15T8, Sankyo Denki, Tokyo, Japan), for 48 h. The intensity was approximately 5 mW/cm^2 (λ = 254 ± 20 nm).	BIC for UV treated group was significantly higher than SLA and machined groups during early healing phase. At 28 days, the BIC of treated group were similar to SLA group.
New Zealand rabbits	Sanchez-Perez et al. 2020 [89]	5 rabbits	20 commercial implants-Ticare Quattro Inhex (Mozo Grau, Vallalid, Spain).	As received and UV treated group.	Irradiation using 6 W UVC source for 15 min (254 nm) (VL-6C model, Analyzer, Murcia, Spain).	No significant difference in BIC of between photofunctionalized and untreated implants.

BIC = bone–implant contact; SLA = sand-blast acid etched; ISQ = Implant Stability Quotient; UV = Ultraviolet

Table 4. Effect of UV photofunctionalization on big animal models.

Species	Studies (Author)	No. of animals (sites)	No. of Specimens Type of Specimens	Surface Treatment	Source of UV Light (Light Treatment)	Bone Osseointegration
Beagle dogs	Hirakawa et al. 2013 [71]	6 dogs (alveolar bone)	4 implants in each animal.	TioBlast™ (Astra Tech, Denstply, Mannheim, Germany) and titanium tetraisoproxide plasma in a plasma source ion implantation (PSII)–post annealed coated, treated with UVA.	Specimens were exposed with UVA (FL15BL-B, NEC, Tokyo, Japan) for 24 h. Intensity of the UV-A light was 2.0 mW/cm^2 at a peak wavelength of 352 nm.	BIC value of the experimental (I-PSII) group was significantly ($p <$ 0.05) higher than that of the control (I-Ti) group after the healing period of 2 weeks. no statistical differences in the BIC and bone area values between the control and the experimental groups after 4 weeks.
Mongrel dogs	Pyo et al. 2013 [76]	4 dogs (alveolar bone)	4 implants on each jaw.	Commercially available dental implants with sandblasted and acid-etched surfaces.	Exposure to UV light for 15 min using a photo device (TheraBeam® Affiny; Ushio, Inc., Tokyo, Japan) immediately before implantation.	BIC in the cortical zone was significantly higher (95%) for photofunctionalized implants than for untreated implants (70%). RT value higher for UV-treated group at four weeks of healing.
Beagle dogs	Ishii et al. 2016 [95]	3 dogs (alveolar bone)	12 implants.	Standard Implant bone level type, SLA RN; (Straumann, Basel, Switzerland).	UV-light irradiation was performed using a photo device (TheraBeam® Affiny; Ushio Inc., Tokyo, Japan) for 15 min.	This study evaluated the progression of peri-implantitis in photofunctionalized implants. The bone resorption lesser in light treated implants.
Beagle dogs	Kim et al. 2016 [78]	4 female dogs (alveolar bone)	32 implants (one-wall defects created with split mouth design study, 4 implants in each side)/	sandblasted and acid etched (Osstem Implant System TS II SA Ficture, Busan, Korea), defects were filled with bone graft.	UV-light irradiation was performed using a photo device (TheraBeam® Affiny; Ushio Inc., Tokyo, Japan) for 15 min.	No significant different found in all groups, with or without UV treatment and bone grafting in term of new bone, Group with UV treated implant and bone graft showed increased in bone volume.
Minipigs	Mehl et al. 2018 [90]	3 Minipigs (alveolar bone)	48 implants (split mouth design, 8 each side of the jaw)	Abrasive-blasted acid-etched surface.	Exposure to UV light for 15 min using a photo device (TheraBeam® SuperOsseo, Ushio, Tokyo, Japan)	Both ISQ values and overall BIC were not significantly different between both groups.

BIC = bone–implant contact; SD = Standard deviation; ISQ = Implant Stability Quotient; UV = Ultraviolet

Table 5. Effect of UV photofunctionalization in humans.

Studies	Types of Study	Subjects	Results	Other Findings
Funato and Ogawa 2013 [96]	Case series	Four partially edentulous patients with seven implants of identical micro-roughened surfaces were photofunctionalized with UV light. Osseointegration speed was calculated by measuring the increase in per month.	ISQs ranging from 48 to 75 at implant placement and increased to 68 to 81 at loading. In particular, implants with low primary stability (initial ISQ < 70) showed large increases in ISQ during loading.	Mean marginal bone level ranged 0.35 ± 0.71 mm at the crown placement and remarkably increased to 0.16 ± 0.53 mm in one year, with coronal gains in the marginal bone level that surpassed the implant platform evaluated by peri-apical radiograph.
Suzuki et al. 2013 [97]	cross-sectional retrospective analysis	Total of 33 implants in 7 patients were follow-up up to 3 months.	Osseointegration assessed by ISQ and OSI For all the implants, the ISQ at 6 weeks was higher than ISQ at placement.	Comparison of ISQ (initial) and ISQ (6 weeks) made based on the literatures. ISQ varies from 65-85, and generally increased after week 6 of healing.
Funato et al. 2013 [58]	Retrospective analysis	Retrospective study analyzed 95 consecutive patients who received 222 untreated implants and 70 patients who received 168 photofunctionalized implants over a follow-up period of two and a half years.	The success rate was 97.6% and 96.3% for photofunctionalized and untreated implants, respectively.	The healing time before functional loading was 3.2 months in photofunctionalized implants and 6.5 months in untreated implants. ISQ increase per month for photofunctionalized implants ranged from 2.0 to 8.7, depending on the ISQ at the placement, and it was considerably higher than that of untreated implants.
Funato et al. 2014 [98]	Case report	2 cases.	Confirmed hydrophilicity of implants and titanium mesh following exposure to UV light; Radiographic evidence confirmed the osseointegration for both cases.	. Both cases showed satisfactory aesthetic and function following restoration of teeth with implants at 1-year follow-up.
Kitajima and Ogawa 2016 [99]	Cross–sectional retrospective analysis	55 patients with ISQ less than 60.0 during initial implant placement were followed-up for 2–3 years.	Average ISQ1 (initial) 50.4 ± 7.7 Average ISQ2 (uncovered) 74.3 ± 5.7.	Overall increased in ISQ value during Stage 2 surgery
Hirota et al. 2016 [100]	Case-control (retrospectives)	Total implants included: 25 photofunctionalized 24 as received and placed in regular or complex cases.	OSI were used to evaluate the implant stability in complex cases: OSI for photofunctionalized implants = 4.2 ± 3.2. OSI for 'as-received' implants = 0.2 ± 0.9. In simultaneous sinus lift procedure OSI for photofunctionalized implants = 5.5 ± 3.5. OSI for 'as-received' implants = 0.2 ± 1.1.	Implant stability was evaluated by measuring ISQ at the placement (ISQ1) and at the stage-two surgery (ISQ2). Photofunctionalized implants showed significantly higher ISQ2 values (greater than 60) than the as-received implants, regardless of primary stability and innate bone support during placement surgery.
Hirota et al. 2018 [101]	Retrospective analysis	Total patients: 219 Total implants: 563 implants (underwent implant therapy from 2005 until 2017).	Risk of early implant failure significantly reduced with OR = 0.30 Low implant failure rate of 1.3% (as opposed to 4.3% of risk of early implant failure without photofunctionalization).	Postoperative wound breakdown as of the risk of early implant failure with OR = 0.21. Implant failure rate was 10.0% with presence of postoperative wound breakdown during healing period and 1.0% failure rate without the breakdown of wound postoperatively.
Tominaga et al. 2019 [91]	Clinical trial	13 patients underwent lumbar surgery, age ranges from 55–82 years old.	Bone density evaluated via computed tomography scanning showed no difference in both groups at any timepoint.	Carbon attachment was less in UV-treated group evaluated using x-ray photoelectron spectroscopy.

ISQ = Implant Stability Quotient; OSI = Osseointegration Speed Index; OR = Odds Ratio

The literature search found that several methods have been applied as the source of ultraviolet light with various wavelengths. The source of UVA light was mainly from a mercury lamp (6–15 W) with exposure time ranging from 2 h to 24 h [92]. Meanwhile, the UVC light source was from a 15 W bactericidal lamp and exposure time ranging from 2 h to 48 h [72]. Some studies used photo-generated devices (Figure 3), which are available commercially to treat the implant surfaces at chairside, with an exposure time of only around 12–15 min [82,83,90].

Figure 3. Therabeam® SuperOsseo, (Ushio Inc., Tokyo, Japan).

4. Discussion

The concept of surface finish or topography on the biological response to an implant was studied by Albrektsson et al. [102]. The chemical and physical surface properties [103] such as surface topography and roughness, surface chemistry, and surface energy affect the initial cell response at the cell–material interface, enhance cell proliferation and differentiation, and eventually affect the rate and quality of new tissue formation. Surfaces with high wettability can influence the bonding strength, promote protein adsorption, and enhance cell adhesion compared with hydrophobic surfaces. However, surface modification techniques appear to affect the wettability, hydrophobicity, and surface charge of certain implants and alter the extent of protein adsorption [18,19]. For the past years, UV light treatment has been applied to enhance the biological properties of the titanium surface by altering its surface chemistry without altering the surface topography. The use of UV light to condition the implant surface has emerged from the knowledge of the photocatalytic degradation properties of TiO_2 based on the photo-induced hydrophilicity and decomposition reaction described above [32]. The effect of photofunctionalization on different surfaces was evaluated by many researchers, and the production of superhydrophilic surfaces with increased and accelerated bone-implant integration was demonstrated in in vitro [21,22,93] and in vivo [58,73,87,96,98] studies.

The following paragraphs aim to provide a brief and crucial overview of the adhesion behaviors of osteoblast cells on superhydrophilic surfaces following UV photofunctionalization. The effects of UV photofunctionalization on osteoblasts are summarized in Table 2. The wettability values are also highlighted in this table. These studies (although not an exhaustive list) suggest that the UV-light exposure of biomaterials (titanium) enhances the migration, attachment, and proliferation of osteoblasts and its lineage. From this table, it can be seen that different types of osteoblasts may show a similar positive response toward the UV-enhanced surface. In contrast, however, Altmann et al. [93] found that primary human alveolar osteoblast morphology and initial attachment were not affected by bioactivation via UV photofunctionalization, but were influenced by surface topography. Similar results were also reported by Hayashi et al. [104]. As seen in their experiments, no differences were observed in the morphology of osteoblasts or in their induction and activity when primary human

osteoblast cells were subjected to implants with UV light surface activation. As they assumed that the indifferent morphology was due to the lack of stimulatory factors in the growth media used to culture the already differentiated osteoblasts, the negligible effect of UV light could be related to the dissimilarities of TiUnite surface treatment. The TiUnite by Nobel Biocare Implant System has an anodized coating of TiO_2 layers with S_a and S_{dr} values of 1.1 µm and 37%, respectively. Hence, their study supported the findings of Mustafa et al. [38], who demonstrated that the proliferation and differentiation of cells derived from human mandibular bone were enhanced by the surface roughness of the titanium implant. Furthermore, Cochran [13] reported that implants with rough surfaces offered more significant advantages than those with smoother surfaces, especially in compromised bone. In addition, Henningsen et al. [105] showed that the argon-plasma-treated surface was superior to the UV-treated surface of the same topographical specimens. These findings could encourage future research on the utilization of a surface conditioning tool other than UV technology without altering the surface topography.

The success of early- and late-stage osseointegration in association with surface conditioning with UV light was also established via various animal experiments. The evidence from animal research provided us with information on where histological sections could be obtained and where bone volumes could be measured. Animal research has indicated that photofunctionalization of implants prior to insertion into the bone has a positive impact on BIC [57]. In addition, micro-computed tomography (micro-CT) was used to evaluate the bone formation and volume, and the biomechanical strength of the bone–implant integration assessed with the push-in test was higher compared with those of non-treated implants. Direct association between photofunctionalization and osseointegration was found. Tables 1, 3 and 4 summarize some selected studies utilizing different animal models of varying sizes, in which BIC or bone volume (BV) were evaluated. Given the circumstances, systematic reviews of preclinical studies in this subject matter could be initiated. Notably, non-human primates such as monkeys have anatomies that are more similar to the human anatomy and histology than any other animal. Thus, they may offer a high degree of relevance to humans, both in specific physiologic and biochemical similarities. Most studies have utilized small animals [57,73,85], which are clinically substandard, so the influence of UV irradiation on functionally loaded implants is not possible to evaluate. Similar studies on the photofunctionalization of dental implants utilizing non-human primate models are yet to be found in the literature. Thus, this animal model could be a direction of research prior to future clinical studies on humans. To date, studies on the effect of photofunctionalization in humans, especially randomized controlled trials, are yet to be reported. Currently, only retrospective case controls [100] and case series [58,96] have been reported. Table 5 summarizes the findings from the literature that pertain to the effect of UV light treatment on osseointegration in humans. Therefore, to validate the current findings, future research should focus on prospective randomized blinded clinical trials.

5. Conclusions

This review explores the extent of the current knowledge and significant publications in the field of TiO_2 photocatalysis, especially from the perspective of the reversal of time-dependent degradation of titanium dental implants via photofunctionalization. Titanium dental implants age in an inevitable manner during their inventory and distribution as well as during storage before use. Therefore, the clinical performance based on BIC is below the ideal value of 100%. Addressing this nature of titanium, the anti-aging effect and renewability of its bioactive surface upon exposure to UV light provide clinical and scientific significance for the use of titanium as a dental implant material. Although there is increasing evidence of the positive impact of UV light treatment on osteoblast activity, limited human trials and the relevant in vivo studies do not allow us to make robust conclusions.

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