RE-2022-195409-plag-report

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INTRODUCTION

Osseointegration stands as a pivotal concept within the realm of dental implants, signifying the intricate process through which a dental implant integrates with the adjoining bone tissue. This integration results in the formation of a robust and enduring foundation for the replacement tooth or teeth [1]. This term is derived from the Latin words "Osseo" which means bone, and "integration," which means to make whole [1]. Osseointegration primarily depends on the implant placement, healing period, biocompatibility, stability, longevity and maintenance of the dental implant [2,3].

The process of osseointegration begins when a dental implant, typically made of biocompatible materials like titanium, is surgically placed into the jawbone at the site of a missing tooth. This implant post serves as a replacement for the natural tooth's root. Bio-activation as well as surface modification of titanium implants reduces an immune response and allows for successful osseointegration [4]. Cobalt chromium alloys, Iron-chromium-nickel based alloys and ceramics were also used as dental implant materials. Titanium alloys and titanium alloys stays superior to the previous dental implants due to its excellent osseointegrative properties [5]. While pure titanium implants and their alloys exhibit outstanding biocompatibility, mechanical strength, and chemical stability, they are associated with certain disadvantages, including delayed osseointegration and an extended period of post-operative healing. These factors can contribute to the potential failure of dental implants [6]. To address these limitations, implant surface alterations using techniques based on the immobilisation of biologically active organic compounds has been discovered [7].

Surface coating of titanium dental implants is an essential aspect of implant dentistry, as it plays a crucial role in enhancing osseointegration, stability, and long-term success of the implant. There are several surface coatings and treatments that can be applied to titanium dental implants to improve their performance. Some of the commonly used surface coatings and treatments include: Anodic Oxidation (Anodization), Sandblasting and Acid Etching, Plasma Spraying, Blasted Surfaces, Titanium Nitride Coating, Zirconia Coating, Chemical Modifications [8].

Surface modifications using nanomaterials are widely used recently. These nanomaterials make good coating options for dental implants made of titanium (Ti-based) as it enhances implant fixation and encourages soft tissue integration and osteogenesis. In addition, osteoconductive nanoparticles creates a chemical bond with bone to ensure that implants are biologically fixed [9]. In order to achieve better osseointegrative properties, naturally bioactive and antimicrobial polymers like chitosan and graphene oxide have been employed. By exposing bioactive modifications to simulated bodily fluids, specific cellular and tissue reactions can be induced, leading to biomimetic precipitation of calcium phosphate (CaP) [10-12].

Graphene coatings stimulate osteogenic differentiation, cell adhesion, and antibacterial activity. Coating dental implants with graphene oxide can offer several potential benefits. Graphene oxide has demonstrated the ability to enhance osseointegration, the bonding process between the implant and the adjacent bone. The distinctive surface characteristics of graphene oxide promote enhanced bone adhesion, resulting in increased stability and prolonged success of the implant. Graphene oxide possesses antibacterial properties, which can help prevent infections around the implant site [13]. Graphene oxide is generally considered biocompatible. This means it is well-tolerated by the human body and does not provoke a significant immune response. The high surface area and unique properties of graphene oxide can be harnessed for controlled drug delivery. This may allow for the local release of antibiotics or other therapeutic agents to further prevent infection and promote healing. Graphene oxide coatings can improve the visibility of dental implants in imaging techniques like X-rays or CT scans, aiding in diagnosis and follow-up care. The amalgamation of graphene oxide with other biomaterials can augment the surface properties of a material, impart antibacterial attributes, and influence cellular behavior [14,15].

Various studies have been conducted to compare the osteogenic potential, physical properties and biologic properties of titanium dental implants with or without graphene oxide surface modification [16-18]. As these comparative studies conducted are on different forms of surface coatings on titanium implants, the current systematic review aimed to examine and analyse osseointegrative properties of graphene oxide coated Titanium dental implants compared to conventional titanium dental implants without any surface modifications.

METHODOLOGY

The current review was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [19]. This review has been officially registered with PROSPERO and has been assigned the registration number CRD42023413883.

Search strategy

We performed an extensive search across multiple electronic databases, including PubMed, Scopus, Web of Science, and Embase, to identify relevant articles evaluating the osteointegration and biological properties of titanium dental implants coated with graphene oxide. The search utilized key terms such as "graphene oxide," "titanium implants," "osseointegration," "surface roughness," and "surface characteristics," combined using Boolean operators "AND" or "OR" to optimize article retrieval. The inclusion criteria for this review encompassed studies published from January 1, 2012, to December 31, 2022, covering a span of 10 years. The rationale behind this timeframe was to focus on the recently emerged method of surface modification involving graphene oxide coating on titanium dental implants. Consequently, studies published before 2012 were excluded [18]. The details of search strategy are mentioned in table 1.

Study selection:

The studies included were in line with the PICO (Population, Intervention, Comparison and Outcomes) criteria [20]:

- Population: Titanium dental implants
- Intervention(s): surface modification of titanium dental implants with graphene oxide coating
- Comparator(s)/control: Conventional implant or surface modification done with other materials such as chitosan
- Outcome(s): Osseointegration and biological properties of Graphene oxide nano coated titanium dental implants.

Inclusion criteria

Two reviewers (SR and VK) independently evaluated titles and abstracts to identify potentially suitable studies. Any uncertainties were resolved through discussion with a third reviewer (SK). The inclusion criteria for the chosen studies encompassed English language research articles with complete full-text manuscripts. Additionally, all in vitro studies, clinical trials, randomized clinical trials, comparative studies, and cross-sectional studies relevant to the topic were considered for inclusion, while case reports, case series, narrative reviews, and single-arm longitudinal studies were excluded. Abstracts without accompanying full-text articles were also excluded from the conduct and reporting of the present systematic review.

Data extraction:

The articles obtained following the literature search underwent scrutiny by the study investigators to eliminate duplicated or irrelevant studies. Subsequently, two reviewers (SR and VK) independently conducted further screening of the remaining articles to assess their eligibility for inclusion in the systematic review. For each study, the following factors were meticulously noted: Author name(s), study design, type of coating, method of coating, surface characteristics, mechanical properties, cell adhesion, and antimicrobial properties.

Quality assessment

Risk of Bias assessment: The quality assessment of the studies included in the review was conducted using the QUIN Tool, specifically designed for evaluating the risk of bias in in-vitro studies. This tool assesses bias across 12 domains, encompassing clearly stated aims and objectives, a comprehensive explanation of sample size calculation, detailing of the sampling technique, information about the comparison group, methodology explanation, operator details, randomization process, method of outcome measurement, details of the outcome assessor, blinding, statistical analysis, and presentation of results [26].

RESULTS

The current systematic review focused on determining whether osseointegration and the biological properties of graphene oxide nano coated titanium dental implants are superior to conventional or other nanomaterial-coated titanium dental implants. The study entailed a comparative analysis of contact angle and surface roughness between conventional/chitosan-coated titanium implants and graphene oxide-coated titanium implants.

Study selection

The electronic search was conducted through three distinct stages. In the initial stage, a total of 127 articles were initially retrieved by employing specified keywords in the electronic databases. Two independent reviewers (VK and SR) conducted this search. The titles of the retrieved studies were then screened to ensure they met the eligibility criteria outlined by the PICO framework. Moving on to the second stage, abstracts of all selected titles were meticulously screened, and the complete texts of 39 studies deemed potentially pertinent were identified for the third stage. Notably, 33 studies were excluded at this stage as they assessed parameters beyond contact angle, surface roughness, and biocompatibility.

In the third stage, a detailed review was conducted on the complete texts of the 39 identified studies. Ultimately, 6 studies were selected for inclusion in this review [11,21-25]. One of the reviewed articles exhibited a discrepancy in measurement presentation for outcomes (contact angle and surface roughness), resulting in the exclusion of these studies from the quantitative analysis [11]. (Table 2)

Risk of bias assessment

Every study included in the analysis demonstrated a moderate risk of bias. None of the studies furnished details pertaining to sample size calculation or the employed sampling technique. Details of blinding of the examiners was unclear in the included studies. (Table 3)

DISCUSSION

Graphene oxide has recently demonstrated remarkable achievements in dentistry, spanning the treatment of oral cancer, regenerative dentistry, drug delivery, and antibacterial applications [23]. Liu et al. (2011) conducted a review in the domain of oral disease treatment, emphasizing the potential application of graphene oxide as a restorative material for addressing dental caries. The review underscored the utilization of graphene oxide due to its superior physicochemical and mechanical characteristics. Furthermore, the study highlighted its compatibility with glass ionomer cements, demonstrating the capability to improve the mechanical properties of composites without compromising their aesthetic attributes or their ability to release fluoride [27].

Graphene and graphene oxide have demonstrated characteristics with potential anticaries effects, inhibiting the colonization of S. mutans and P. gingivalis. Moreover, these materials exhibit the capability to stimulate the differentiation and proliferation of human dental pulp stem cells (hDPSC) and stem cells from periodontal ligaments (PDLSC). This property is conducive to the regeneration of dental pulp and periodontal ligament tissues [25,28].

Graphene oxide finds extensive use in dental implants owing to its notable surface energy, mechanical strength, and biointegration properties. The incorporation of graphene in implants is primarily driven by its capacity to physically interact with biomolecules such as enzymes, proteins, or peptides. Graphene exhibits exceptional biocompatibility, efficiently stimulates and matures stem cells, and possesses long-term durability. Furthermore, the substantial surface area of graphene is a crucial aspect with significant potential for future bio-functionalization [27]. Titanium implants are coated with both graphene oxide and reduced graphene oxide (rGO) showcased their inherent ability to induce osteogenic differentiation. This characteristic is of particular significance for the long-term success of dental implants in comparison to conventional surface treatments like grit-blasting, acid etching, and micro-arc oxidation [29,30].

The analysis focused on studies that evaluated Osseointegration properties, utilizing available data from the selected studies, including contact angle and surface roughness. Additionally, the application of reduced graphene oxide as a surface coating in titanium implants was also explored. Both reduced graphene oxide and graphene oxide coating renders similar surface characteristics to the titanium implant. Other characteristics such as Raman Shift, surface energy and biologic properties (cell proliferation, Alkaline Phosphatase [ALP] activity and biofilm thickness were not assessed as the study results of these parameters were presented in different measurements (either in percentages or in abr units) and at different time duration. Hence the quantitative analysis of same was not performed due to the differences in data presentation. However, study by Shin et al.,2022 showed that reduced graphene oxide nanocoated titanium dental implants have high cell proliferation rate and ALP activity within 21 days [21]. Cell attachment was also observed to be higher in reduced graphene oxide coated titanium implants. Kang et.al., 2021 also reported a higher mineralization with reduced graphene oxide coated titanium dental implants [23].

Quantitative assessment of the selected studies was conducted to evaluate surface characteristics, specifically surface roughness and contact angle (refer to Fig. 2, 3). In the comparison between Graphene Oxide-coated titanium implants and Chitosan/control implants, the latter exhibited a lower contact angle and higher surface roughness. These findings suggest enhanced adhesion to the periosteum. Notably, research has demonstrated that reduced graphene oxide coating, when combined with concentrated growth factors, facilitates the differentiation of implants into osteoblasts. This acknowledgment highlights its potential as a revolutionary material for altering dental implants and acting as a foundational structure for the regeneration of bone tissue.

Shin et al. and Kwak et al. suggested that increased rGO concentration on the surfaces of titanium implants leads to rougher surfaces capable of absorbing exogenous proteins, thereby promoting cell proliferation and osteogenic differentiation [21,31].

The recognized antibacterial mechanisms of GO currently include the physical breakdown of the cell membrane and the induction of damage through oxidative stress. Generally, materials based on graphene are known to generate oxidative stress, primarily through reactive oxygen species, resulting in antibacterial effects and significant harm to bacterial cells [17]. Another antibacterial mechanism of GO involves the dispersibility and trapping capacity of its oxygen-containing functional groups [32]. In accordance with the insights from the review, the reduction of graphene oxide has been observed to enhance antibacterial capabilities by diminishing bacterial colonization on graphene oxide-coated titanium implants. Notably, a substantial enhancement in osseointegrative characteristics has been evident, as evidenced by elevated alkaline phosphatase activity and increased cell proliferation around the graphene oxide-coated titanium implants. These findings underscore the multifaceted benefits of optimizing graphene oxide configurations for improved antimicrobial and osseointegrative performance in the context of dental implants. The hydrophobic nature of graphene oxide plays a role in preventing bacterial cells from adhering to each other, and this hydrophobic contact can lead to the breakdown of the bacterial membrane, exerting an antibiotic effect [12,33,34].

The expression of ALP, and extracellular matrix proteins such as RUNX2 and COL1A1 that promotes osteoblast differentiation appears to be improved by rGO as well [35]. Several studies have shown that through the activation of the focal adhesion kinase (FAK)/P38 pathway, improved bone mesenchymal stem cells (BMSC) adhesion capacity, and proliferation, GO can trigger early osteogenic differentiation of BMSCs [36]. Additionally, hMSC (human mesenchymal stem cells) adhesion, migration, and proliferation can be controlled by graphene oxide [37-39]. Hence graphene oxide coated dental implants serves higher chances in success of dental implants due to its improved biological and mechanical properties compared to conventional/ chitosan coated dental implants [40]. Moreover, it is imperative to conduct clinical trials and studies to thoroughly evaluate the biocompatibility, mechanical properties, and long-term performance of graphene oxide-coated titanium dental implants, ensuring a comprehensive understanding of their advanced properties.

Considering the scarcity in in-vitro studies conducted in comparing the biological properties and antimicrobial properties of graphene oxide surface coated titanium dental implants, more studies could be conducted in future. Studies comparing graphene oxide coated titanium dental implants with other bioactive surface modification materials such as ceramic and composites would also determine the superiority of biological, mechanical and antimicrobial properties of graphene oxide surface coating.

CONCLUSION

Utilizing graphene oxide as a coating for titanium implants creates a highly biocompatible surface, promoting enhanced integration with surrounding tissues and reducing the risk of rejection or complications. The exceptional mechanical strength and flexibility inherent in graphene oxide further contribute to the durability and longevity of the implants, ensuring not only effective integration but also sustained long-term performance. The success or failure of dental implants hinges on various factors, including implant location, the load-bearing capacity of the underlying bone, and the overall health of the patient.

In conclusion, the potential transformation of implantology is embodied in graphene oxide-coated titanium dental implants, driven by advancements in biocompatibility, osseointegration, antibacterial properties, and controlled drug delivery. Continued research and thorough scientific inquiry have the potential to position these implants as significant contributors to considerably improved patient outcomes, a reduction in complications, and an overall enhancement in the quality of life for individuals in need of dental implants.

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