REVIEW ARTICLE

Applications of Hafnium and Other Transition Metals in Medicine -A Review

Vaishnavi Rajaraman*, Padma Ariga, Saravanan Sekaran, Dhanraj Ganapathy, Deepak N Veeraiyan

Department of Prosthodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India

Received: 20th August, 2023; Revised: 01st December, 2023; Accepted: 24th January, 2024; Available Online: 25th March, 2024

ABSTRACT

Transition metals in the periodic table have been used in biological systems naturally. Synthetically, many materials have been used in the field of prosthodontics for the replacement of missing teeth. The research on these materials originally began from titanium which belongs to group 4 of the transition elements in the periodic table. Titanium has also established itself as the gold standard in prosthodontic and orthopedic replacements. After titanium, zirconium and hafnium were explored for the same purpose and till date researchers have been working on its feasibility. Extending this research, various metal options were studied by multiple biomaterial companies and researchers. Hafnium in the periodic table, which belongs to the group 4 elements, was also explored sufficiently. Nanoparticles are proven to have properties like strength, being lighter and cleaner, and contributing to smarter surface systems. This property has led to great contributions in the field of biomedical research and biomaterial development. Due to increased awareness of nanoparticles, metal nanoparticles are extensively studied for various biomedical applications. At the nanoscale, the properties of particles may change in unpredictable ways. This review highlights the use of transition metals in biology, including emphasis on the metal nanoparticles for biomedical applications.

Keywords: Biomaterial, Hafnium, Metal, Metal oxide nanoparticles.

International Journal of Pharmaceutical Quality Assurance (2024); DOI: 10.25258/ijpqa.15.1.77

How to cite this article: Rajaraman V, Ariga P, Sekaran S, Ganapathy D, Veeraiyan DN. Applications of Hafnium and Other Transition Metals in Medicine -A Review. International Journal of Pharmaceutical Quality Assurance. 2024;15(1):512-514.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Transition Metals in Biology

Transition metals like iron, cobalt, copper, and molybdenum are vital to the chemistry of living systems.[1] Iron is one of the most significant transition metals that has a function in living systems.[2] Cobalt is an essential trace element with biochemical action related to vitamin B_{12} and its coenzymes.[3] Copper assists iron in the body to form red blood cells. It also helps keep blood vessels, nerves, immune system, and bones healthy. Molybdenum is a trace element in animal diets. Research to discover the role of transition metals in biological systems has been in motion.[1] Various applications of these metals have been researched, including their potential as biomaterials in the human body.[4] Traditionally, metals are considered for load bearing with fatigue strength to withstand the forces in the bony areas.[5] Titanium is known for being the gold standard material, and titanium alloys' application is rising rapidly owing to their favorable properties.[6] Ceramic biomaterials on the other hand have properties like hardness and wear resistance which can be used as articulating surfaces in joints and teeth. Zirconia is also an upcoming biomaterial that is non-toxic, inert metal oxide and biocompatible in soft tissues. Additionally, it also is radiopaque and corrosion resistant.[7,8]

Owing to high success rates, titanium implants are commonly used in medical and dental practice. This said, there is a challenge when using this in patients with systemic illness like osteoporosis, irradiated bone, diabetes and chronic/heavy use of tobacco. These scenarios may benefit from porous tantalum trabecular implant (PTTM).[9,10] The invention of porous tantalum metal has been proven for increased strength and biocompatibility in dental, craniofacial, and orthopedic implants. They have also shown promising healing in the grafted sites.[11] The geometry of porous tantalum metal offers low modulus of elasticity and high volumetric porosity. These implants allow for enhanced osseointegration in a volumetric manner, which was thought to be a breakthrough compared to conventional titanium.

**Author for Correspondence: vaishnavir.sdc@saveetha.com*

Nanoparticles - The Game Changer

Nanoparticles (NPs) have been researched in the last decade, for applications in technology and medicine.[12] The conjugation of miniscule size and unique amalgamation of physical and chemical properties is their major advantage to be used in biomedical applications.[13] It may be any biomaterial from ceramic, metal carbon or polymer. Owing to their smaller size and likeness to protein molecules physiologically, they can modernize diagnostics, imaging and treatment aspects.[14,15]

Metallic nanoparticles have been one of the major materials explored and put to use frequently. Different processes are involved in the synthesis of metallic nanoparticles. It can be categorized into top-down or bottom-up methods. The former method involves breaking down larger-sized molecules into nano-sized materials by mechanical, chemical and/or physical treatments. Nanoparticles here are produced in naked form, which can aggregate further and therefore loses purpose in biomedical applications.[16,17] In the latter method, individual atoms or molecules combine in solid, liquid, gas phase or microfluidic technology to form nanoparticles. The most common method however appears to be the bottom-up process (chemical reduction) in metallic nanoparticle synthesis. The reason for this being its flexibility, cost-effectiveness and production of homogeneous particles. The biological process of manufacturing has become common due to attributes like inexpensiveness, non-toxicity, eco-friendliness and sustainability. The nanoparticle development for imaging in medicine and gene or drug delivery in a phase of drastic expansion in the current decade.[18,19] There is a demand for stringent testing for biological security of synthesized nanoparticles.

Metal oxide nanoparticles (MONPs) are studied in detail for their application in nanomedicine, dentistry, immunotherapeutics and sensors in biological environments.[20] Studies on antifungal, antiviral and antimicrobial properties are also quite popular.[21] With a variety of MONPs, the cytotoxicity should also be evaluated, especially pertaining to MONPs size, concentration, type and method of synthesis.[22] *In-vivo* clinical trials on long-term adverse effects on health should also be studied in further research. Hence the advantages and disadvantages are challenges in biomaterial science. Besides disadvantages, a new avenue has been discovered with nanoparticles.[23]

The growing advances in the development of bioengineered MONPs help in multidisciplinary therapy and pathology diagnosis. MONPs and their nanotechnologies have proven beneficial in smart drug delivery and non-invasive imaging.[18,24] Researchers in oncological treatments are constantly studying the use of nanoparticles. This will open new ventures in safer and effective treatment options.

TiO_2 is an often used biomaterial due to its property to induce cell adhesion, cell migration, osseointegration and wound healing.[25] One of the most promising inorganic materials for biomedical purposes is nanocrystalline hafnium oxide (HfO_2).[26] Hafnium has a large X-ray cross-section capture and relatively low toxicity, which makes it a promising theranostic agent for X-ray therapy. Given the high penetrating ability of nanoparticles and their significant accumulation in the tumor local zone, this approach will ensure the maximum tumor-damaging effect under ionizing radiation. The targeting of nanoparticles to the tumor zone can be increased due to their functionalization with compounds having high affinity with tumor cell receptors, such as riboflavin. Thus, HfO_2 nanocrystalline is a promising compound for designing an effective targeted radiosensitizer for radiotherapy. However, little is known about their cytotoxicity as in general with all nanoparticles.

Hafnium - A Newer Transition Metal

Hafnium is a passive metal, non-corrosive and inert in biological environments. It has advantages like inertness, strength, ductility, resistance to corrosion and mechanical damage. Hafnium has been suggested as a biomaterial potential for prosthetic applications. It has attracted focus as a biomaterial with low modulus of elasticity and/or shape-memory and cytotoxicity comparable to titanium.[27] It is prudent that for bone bonding, apatite formation is a prerequisite. Hf-based materials have been researched for their osteogenic potential and have shown promising bone and soft tissue integration.[28] In previous studies, *in-vitro* murine osteoblastic cell lines were used to evaluate niobium, tantalum, hafnium and zirconium metals and also establish their biocompatibility.[29]

CONCLUSION

The field of biomedicine is surging due to increasing demand. Biomaterials are utilized for parts of the human body as stents in blood vessels, artificial valves in heart, stents, prosthetic implants in skeletal and dental structures. The target of current studies worldwide is manufacturing or indigenously developing implants that can function much longer without failure or reintervention. Thus, exploration of ideal material with or without superficial coatings is of utmost importance. Therefore, a detailed assessment of the factors that influence the biocompatibility and toxicity of NPs is essential for the safe and sustainable development of the emerging nanoparticles.

FINANCIAL SUPPORT AND SPONSORSHIP

This work was supported by Saveetha Institute of Medical and Technical Sciences, Saveetha Dental College and Hospitals, Saveetha University, and M/s Trend Fashions India Pvt Ltd.

AUTHORS CONTRIBUTION

Authors 1 and 2: Data curation, investigation, original draft preparation, software. Author 3. Visualization, writing, validation. Author 4: Conceptualization, reviewing, supervision.

REFERENCES

1. Lo KK-W: Inorganic and Organometallic Transition Metal Complexes with Biological Molecules and Living Cells. Academic Press; 2016.
2. Dunford BH, Dolphin D, Raymond KN, Sieker L: The Biological

Chemistry of Iron: A Look at the Metabolism of Iron and Its Subsequent Uses in Living Organisms Proceedings of the NATO Advanced Study Institute held at Edmonton, Alberta, Canada, August 13 – September 4, 1981. Springer; 1982.

3. Santos AJM, Khemiri S, Simões S, Prista C, Sousa I, Raymundo A: The importance, prevalence and determination of vitamins B6 and B12 in food matrices: A review. Food Chem. 2023, 426:136606.
4. Trautwein AX: Bioinorganic Chemistry: Transition Metals in Biology and Their Coordination Chemistry. Wiley-VCH; 1997.
5. Elbadawi M: Progress in Bioactive Metal And, Ceramic Implants for Load- Bearing Application. 2016.
6. Luckey HA: Titanium Alloys in Surgical Implants. ASTM International; 1983.
7. Kiechle S, Liebermann A, Mast G, et al.: Evaluation of one-piece zirconia dental implants: An 8-year follow-up study. Clin Oral Investig. Published Online First: 5 June 2023. 10.1007/s00784-023-04935-1
8. Borgonovo AE: Edentulous Rehabilitation with Zirconia Dental Implants- 10 Years Follow-up. 2017.
9. Wang X, Zhou K, Li Y, Xie H, Wang B: Preparation, modification, and clinical application of porous tantalum scaffolds. Front Bioeng Biotechnol. 2023, 11:1127939.
10. Cui J, Zhang S, Huang M, Mu X, Hei J, Yau V, He H: Micro-nano porous structured tantalum-coated dental implants promote osteogenic activity in vitro and enhance osseointegration in vivo. J Biomed Mater Res A. Published Online First: 3 April 2023. 10.1002/jbm.a.37538
11. Liang D, Zhong C, Jiang F, Liao J, Ye H, Ren F: Fabrication of Porous Tantalum with Low Elastic Modulus and Tunable Pore Size for Bone Repair. ACS Biomater Sci Eng. 2023, 9:1720–8.
12. Shukla AK: Nanoparticles in Medicine. Springer Nature; 2019.
13. Rajeshkumar S, Parameswari RP, Jayapriya J, et al.: Apoptotic and Antioxidant Activity of Gold Nanoparticles Synthesized Using Marine Brown Seaweed: An In Vitro Study. Biomed Res Int. 2022, 2022:5746761.
14. Soloviev M: Nanoparticles in Biology and Medicine: Methods and Protocols. Humana Press; 2016.
15. Agarwal V, Maiti S, Vaishnavi Rajaraman RS: The cytotoxic effect of silver nanoparticles derived from amla fruit seed extract. Journal of Coastal Life. Published Online First: 2022.
16. Bharathi D, Thiruvengadam Nandagopal JG, Lee J, Ranjithkumar R: Facile Synthesis and Characterization of Chitosan Functionalized Silver Nanoparticles for Antibacterial and Anti-Lung Cancer Applications. Polymers . 2023, 15.: 10.3390/polym15122700
17. Rajakumar G, Sudha PN, Thiruvengadam M: Synthesis, Bioactivity Evaluation and Application of Plant-Based Nanoparticles. Molecules. 2023, 28.: 10.3390/molecules28124783
18. Nikolova MP, Joshi PB, Chavali MS: Updates on Biogenic Metallic and Metal Oxide Nanoparticles: Therapy, Drug Delivery and Cytotoxicity. Pharmaceutics. 2023, 15.: 10.3390/pharmaceutics15061650
19. Misra SK, Rosenholm JM, Pathak K: Functionalized and Nonfunctionalized Nanosystems for Mitochondrial Drug Delivery with Metallic Nanoparticles. Molecules. 2023, 28.: 10.3390/molecules28124701
20. Lewkowitz-Shpuntoff HM: Coupling Saccharides and Saccharide Analogues to Metal Oxide Nanoparticles for Drug Delivery Systems. 2010.
21. Francis DV, Jayakumar MN, Ahmad H, Gokhale T: Antimicrobial Activity of Biogenic Metal Oxide Nanoparticles and Their Synergistic Effect on Clinical Pathogens. Int J Mol Sci. 2023, 24.: 10.3390/ijms24129998
22. Shah KK, Rajaraman V, Shanmugam R: Green synthesis of coffee bean and xylitol mediated Zinc oxide nanoparticles and the assessment of its antioxidant activity. J Popl Ther Clin Pharmacol. 2023, 30:387–92.
23. Amin N, Almasi A, Ozer T, Henry CS, Hosseinzadeh L, Keshavarzi Z: Recent Advances of Optical Biosensors in Veterinary Medicine: Moving Towards the Point of Care Applications. Curr Top Med Chem. Published Online First: 18 July 2023. 10.2174/1568026623666230718163613
24. Gulia K, James A, Pandey S, Dev K, Kumar D, Sourirajan A: Bio-Inspired Smart Nanoparticles in Enhanced Cancer Theranostics and Targeted Drug Delivery. J Funct Biomater. 2022, 13.: 10.3390/jfb13040207
25. Sun L, Chen X, Chen R, et al.: Balancing the antibacterial and osteogenic effects of double-layer TiO2 nanotubes loaded with silver nanoparticles for the osseointegration of implants. Nanoscale. 2023, 15:2911–23.
26. Jayaraman V, Bhavesh G, Chinnathambi S, Ganesan S, Aruna P: Synthesis and characterization of hafnium oxide nanoparticles for bio-safety. Materials Express. 2014, 4:375–83.
27. Rajaraman V, Rajeshkumar S, Nallaswamy D, Ganapathy D: Cytotoxic effect and antimicrobial activity of chitosan nanoparticles and hafnium metal based composite: Two sides of the same coin- an in vitro study. J Pharm Res Int. 2020, 122–31.
28. Rajaraman V, Nallaswamy D, Ganapathy D, Rajeshkumar S, Ariga P, Ganesh K: Effect of hafnium coating on osseointegration of titanium implants: A split mouth animal study. J Nanomater. 2021, 2021:1–9.
29. Matsuno H, Yokoyama A, Watari F, Uo M, Kawasaki T: Biocompatibility and osteogenesis of refractory metal implants, titanium, hafnium, niobium, tantalum and rhenium. Biomaterials. 2001, 22:1253–62.