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The challenge for today's bioethics: metals and their alloys as biodegradable material

Annotation: The author pays attention to the presentation of biomaterials and biodegradable materials, their properties and possibilities of use in regenerative medicine. It draws attention to the latest knowledge in this field and notes that with regard to metals and their alloys as biodegradable materials, they are completely out of the spotlight of current bioethics, although there are some ethical concerns about possible negative consequences for the human body due to their multiple properties. He formulates his comments in the context of existing concerns about the use of bioprinting in contemporary medicine.
Keywords: biomaterials, biodegradable materials, magnesium, magnesium alloys, bioprinting

Wyzwanie dla dzisiejszej bioetyki: metale i ich stopy jako materiał biodegradowalny
Streszczenie: Autor zwraca uwagę na właściwości biomateriałów i materiałów biodegradowalnych, ich możliwości wykorzystania w medycynie regeneracyjnej. Zwraca uwagę na najnowszą wiedzę w tej dziedzinie i zauważa, że w odniesieniu do metali i ich stopów, jako materiałów biodegradowalnych, są one całkowicie poza centrum zainteresowania współczesnej bioetyki, chociaż istnieją pewne obawy etyczne dotyczące możliwych negatywnych konsekwencji dla organizmu ludzkiego ze względu na ich właściwości. Swoje uwagi formułuje w kontekście istniejących obaw dotyczących wykorzystania biodruku we współczesnej medycynie.
Słowa kluczowe: biomateriały, materiały biodegradowalne, magnez, stopy magnezu, biodruk

Thanks to the rapid development of biomedicine and biomedical technologies, bioethics has become the most dynamically developing field of ethics, and especially applied ethics, since the 1990s. In addition to classical medical ethics and its topics, completely new problems come to the fore, which are the result of research and development in biology and medicine, but also in technical sciences, which also contribute to the development of new biotechnologies used in biomedicine. In this context, fundamental issues and values in bioethics are often discussed, for example as regards the place and importance of human dignity. Many authors point to the limitations of the classical understanding of the inviolability of human dignity for the current development of bioethics and biomedicine, including biomedical research. Answers are intensively sought on how to modify the concept of human dignity in the context of current discussions, which take place not only in bioethics but also in the context of philosophical ethics itself. On the other hand, so far, within bioethics, relatively less attention is paid to such areas of bioetechnology and biomedicine as, for example, bioprinting or the use of biomaterials, and biodegradable materials in medicine, especially in relation to the use of metals and metal alloys in tissue engineering.

Biomaterials and biodegradable materials

Sandip Bag is of the opinion that the main criterion in tissue engineering and regenerative medicine is the construction of a scaffold, which serves to supplement the regeneration process or to compensate for infected or damaged tissue. The replacement is a temporary matrix that provides space for cell attachment, proliferation, and reproduction. Another important factor when considering the use of scaffolds is their biodegradability, which is related to the mechanical properties of the scaffolds. After implantation, the scaffolds must gradually degrade to ensure proper tissue regeneration. In her opinion, highly porous scaffolds are crucial for cell infiltration, especially for coarse scaffolds, where diffusion is an obstacle. Porosity also plays an important role in providing a larger surface area for cell attachment. The ideal replacement, as Sandip Bag argues, is in balance between all these factors and must have excellent biocompatibility to ensure cell growth and a minimal immune response after implantation. Various biomaterials are available for the creation of scaffolds, and various techniques can be used to construct these scaffolds. As part of the preparation of the replacement, various physical and chemical changes can be made to them to increase their bioactivity. Cellular, skeletal and growth factors are the three key parameters for tissue engineering[1].

Rozlin Abdul Rahman and the team consider it very important that the biomaterials used in the construction of the skeleton must be biocompatible in vivo. Materials must have certain properties to be compatible with clinical use; biodegradable and aid in remodeling to help create new cartilage that will gradually replace the implant structure. They must also effectively promote cell adhesion and cell proliferation, which leads the cell to differentiate into a specific phenotype (cartilage formation). In addition, these substances must be non-toxic, non-immunogenic and non-stimulating inflammatory cells. According to them, by integrating more than one biomaterial, many properties of these replacements can be manipulated, such as the rate of biodegradation, cell attachment, proliferation and differentiation[2].

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[1] S. Bag, *Biodegradable Composite Scaffold for Bone Tissue Regeneration*, [in:] *Biomedical Engineering and its Applications in Healthcare*, ed. S. Paul, Springer Nature, Singapore 2019, p. 660.

[2] R. A. Rahman, M. A. A. Radzi, N. M. Sukri, M. Md Nazir, M. Sha'ban, *Tissue Engineering of Articular Cartilage: From Bench to Bed-side*, "Tissue Engineering and Regenerative Medicine" vol. 12 No. 1, 2015, pp. 3-4

The decisive criteria for the selection of scaffolds in tissue engineering are their biocompatibility, biodegradability, their mechanical properties, the architecture of the scaffolds and the production technology used. In terms of biocompatibility, the properties of the replacement material, which allow the cells to adhere properly, function normally and reproduce, are primarily monitored. In the case of biodegradability it is crucial that the replacement creates the conditions for the formation and growth of the human body's own cells, which gradually replace the implant, while the replacement must not be toxic and degrade without damaging other parts of the human body. Another criterion is the mechanical properties of the biomaterial used as a substitute, which should resemble as closely as possible the parts of the human body that they are intended to replace. In the first place, it is a question of sufficient strength, this is especially important, for example, with bone implants, which are supposed to function for a long time as a replacement in the human body. Bag points out that the architecture of the restoration is one of the most challenging tasks in tissue engineering, as the implant is intended to ensure cell growth and sufficient diffusion of nutrients to the cells in the structure. On the other hand, it must allow the excretion of waste products from the diffusion replacement and the by-products of implant degradation must be able to be excreted from the body without damaging other tissues in the human body. Last but not least, an important criterion for the selection of biomaterials as replacements for damaged organs of the human body is the efficiency of the whole process from their development, through production to application in clinical practice[3].

Anna Julie Rasmussen and Mette Ebbesen state that the implant is responsible for defining the space that new tissue takes up and for helping in the process of developing new tissue. However, unlike Sandip Bag, biomaterials place emphasis on high mechanical strength, as well as good biocompatibility supporting cell adhesion, viability, proliferation, differentiation and their biodegradability. They especially emphasize the importance of biodegradability or biodegradability of the scaffolds used, because if the components of the implant are not biodegradable, there is a risk that these will accumulate in tissue or other parts of the body and cause adverse health effects[4].

Metals and their alloys as biodegradable materials

At present, among biomaterials, metals and their alloys are also increasingly appearing as biodegradable materials, magnesium alloys, which belong to progressive materials, are particularly common, so they are increasingly used not only in the transport, electronics and optical industries. In recent decades, a new application has also been found in the field of biomedicine. According to Pavel Doležal and his team, important advantages predetermining magnesium alloys for many uses, even in biomedicine and tissue engineering, are their low density, high specific strength, stiffness and high damping ability. The authors are of the opinion that magnesium alloys also have excellent biomechanical properties for many applications and biocompatibility, which allow their adoption as materials suitable for implants in orthopedics and traumatology therapy[5].

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[3] S. Bag, op. cit., pp. 660-662.

[4] A. J. Rasmussen, M. Ebbesen, *Characteristics, Properties and Ethical Issues of Carbon Nanotubes in Biomedical Applications*, "Nanoethics" vol. 8 No 1, 2014, p. 37

[5] P. Doležal, J. Zapletal, S. Fintová, Z. Trojanová, M. Greger, P. Roupcová, T. Podrábský, *Influence*

Similarly, Marián Vlček and his team state that magnesium alloys are suitable as biodegradable medical implants, which reduce the need for a second operation to remove scaffolds. According to them, yttrium in solid solution is an attractive alloying element because it improves mechanical properties and exhibits suitable corrosion properties. They consider silver to be very important, which has an antibacterial effect and can improve the mechanical properties of magnesium alloys[6]. Other important prerequisites for the use of magnesium and its alloys in biomaterials may include the adaptation of the properties of the material by changing its chemical composition, as well as its appropriate mechanical and chemical treatment. The advantage of magnesium is that it is non-toxic and biocompatible. According to Jakub Tkacz and his colleagues, magnesium ions have very important biological functions, for example, magnesium participates in bone and mineral homeostasis, supports DNA replication and transcription, and regulates the opening and closing of ion channels. Magnesium implants used to support bone also support bone growth[7].

Other authors consider magnesium and its alloys as a better alternative than stainless steel or titanium in the case of use as a biomaterial, or biodegradable material because it has a better stress protection effect with a longer implant duration inside the body[8]. In addition, magnesium is responsible for more than 300 host-tissue enzymatic interactions in the body, including DNA and RNA synthesis. Therefore, they claim that it is a necessary nutritional supplement for the body. Magnesium alloys also show positive results in terms of corrosion resistance and biocompatibility, which in their opinion can be achieved by adding alloying additives, microstructure modifications and chemical surface treatments. The authors even claim that the antibacterial properties of magnesium alloys for clinical applications in medical practice are improved by rare earth and zinc alloying[9].

In general, scientists agree that these biomaterials offer opportunities for a complete reassessment of the implant concept and are a great hope for their use in orthopedic surgery. The rationale for the use of biodegradable materials stems from their ability to serve as a support for the treated bone, which allows the newly formed healthy tissue to stably replace the implant and, if possible, even promote the formation of new tissue. This eliminates the need for further surgery to remove the implant after tissue healing, as well as the risk of problems posed by permanent implants, such as long-term dysfunction, physical irritation, or chronic inflammatory local reactions[10]. According to authors, implant degradation must be balanced by new tissue formation

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of Processing Techniques on Microstructure and Mechanical Properties of a Biodegradable Mg-3Zn-2Ca Alloy, "Materials", vol. 9, 2016,, p. 880.

[6] M. Vlček, F. Lukáč, H. Kudrnová, B. Smola, I. Stulíková, M. Luczak, G. Szakács, N. Hort, R. Willumeit-Römer, *Microhardness and in Vitro Corrosion of Heat-Treated Mg–Y–Ag Biodegradable Alloy*, "Materials" vol. 10, 2017, p. 55.

[7] J. Tkacz, J. Minda, S. Fintová, J. Wasserbauer, *Comparison of Electrochemical Methods for the Evaluation of Cast AZ91 Magnesium Alloy*, "Materials" vol. 9, 2016, p. 925.

[8] E. P. S. Nidadavolu, F. Feyerabend, T. Ebel, R. Willumeit-Römer, M. Dahms, *On the Determination of Magnesium Degradation Rates under Physiological Conditions*, "Materials" vol. 9, 2016, p. 625.

[9] Ibidem, p. 625.

[10] A. Turyanskaya, M. Rauwolf, T.A. Grünewald, M. Meischel, S. Stanzl-Tschegg, J.F. Löffler, P. Wobrauschek, A.M. Weinberg, H.C. Lichtenegger, Ch. Streli, *XRF Elemental Mapping of Bioresorbable Magnesium-Based Implants in Bone*, "Materials" vol. 9, 2016, p. 811.

in order to maintain mechanical integrity, so controlling the rate of degradation in the body remains a key challenge in current approaches to implant design. The addition of rare earth elements such as yttrium may, in their view, improve the performance of magnesium-based alloys in terms of strength, ductility and corrosion rate[11].

On the other hand, in addition to these clearly positive properties of magnesium and its alloys in the case of use as a biomaterial or biodegradable material, they are also aware of the shortcomings or risks associated with their use in clinical medical practice. Pavel Doležal and his colleagues point out that the biggest disadvantage of magnesium and its alloys is poor formability and limited ductility at room temperature, which is a consequence of their structure. Another disadvantage, in their view, is the lack of corrosion resistance. However, the authors argue that this disadvantage may turn into an advantage when using this material for biomedical applications, such as temporary implants[12]. On the problem of corrosion of magnesium and its alloys when used as biomaterials or biodegradable materials are also pointed out by other scientists. The reason is the rate of corrosion of magnesium in body fluid, which is said to be too high for magnesium-based implants to be able to maintain mechanical strength during the treatment of injured bone (at least three months). The rate of corrosion of magnesium, in their view, also leads to the release of a significant amount of hydrogen gas in the body fluid, which is harmful to the host tissue in the human body. Alloying is a suitable and effective method to increase magnesium corrosion resistance[13].

Anna Turyanskaya and her team also pointed out that, for example, when using rare earths for the alloying of magnesium alloys, there is a certain risk of damage to the health or other tissues of the human body. The problem is that yttrium does not normally occur in the human body and therefore has no known biological role and is considered a potentially toxic element that may adversely affect metabolism, especially in children. Yttrium, like other rare earth elements, may, according to these authors, act as a calcium antagonist. Indeed, yttrium has shown inhibitory activity in calcium ion neural channels. Research has revealed some toxicity of some human tissues after the use of yttrium in implants[14].

Ethical and bioethical aspects of the usability of metals and their alloys as biomaterials and biodegradable materials

So, on the one hand, we have the remarkable efforts of scientists who are developing new materials that can also be used as biomaterials or biodegradable materials that resemble the structural and morphological organization of the original bone. Given all aspects, according to S. Bag, the ideal implant design is a constant challenge for tissue engineering and regenerative medicine. Different cell types with a specific arrangement limit the combination of different replacements with the exact structures that encounter the original tissue. Thus, according to her, there is a great future for the improvement of current biomaterials and the development of advanced implants suitable for bone

[11] Ibidem, p. 812

[12] P. Doležal P. et al., op.cit., p. 880

[13] Y. Yang, P. Wu, Q. Wang, H. Wu, Y. Liu, Y. Deng, Y. Zhou, C. Shuai, *The Enhancement of Mg Corrosion Resistance by Alloying Mn and Laser-Melting*, "Materials" vol. 9, 2016, p. 216

[14] A. Turyanskaya et al., op.cit., p. 812.

regeneration[15]. On the other hand, there are also problems or risks that have either already been revealed by research, but possibly also hitherto unknown and unforeseen negative consequences of the use of these biomaterials and biodegradable materials in clinical medical practice. It is very interesting that these issues concerning the use of biodegradable materials in medicine and especially in the case of metals and their alloys are still almost completely out of the attention of bioethics, not only in the countries of Central Europe, but all over the world. Not to mention that scientists themselves pay very little, if any, attention to these issues, especially their ethical or bioethical aspects.

Alternatively, they will be limited to the general statement that doctors or bioengineers also face ethical issues in their day-to-day work in the hospital and laboratory. They have to think about ethical issues, even if they are trying to submit a publication of articles in a journal. Last but not least, the ethical debate can hopefully bridge the gap between the auditorium and the hospital bed in the near future. Similarly, scientists state very generally that clinical trials must undergo very strict regulation before they can be introduced into the public community. Ethical aspects should not hinder the development of research, but should be used as an additional tool to enable tissue engineering to reach its full potential as long as it is within accepted limits[16].

As bioethicists do not yet pay much attention to the issue of biodegradable materials made of metals and their alloys used in clinical medicine practice, I will use the approach chosen by the Australian bioethics team to bioprinting as a starting point for my reflections on this issue and its ethical or bioethical aspects. Frederick Gilbert and his colleagues point out that the use of biodegradable materials in the substitution increases the risk of harm to the recipient because the degradation produces by-products that can then move through the bloodstream. Therefore, according to them, the materials must be designed to pass through the renal system without damaging the body. Risks associated with biodegradation by-products include cytotoxicity, coagulation, ineffective excretion, which results in the accumulation of toxins in the body, and migration of by-products, resulting in disruption of another organ[17], mentioned also higher in relation to scientists' considerations of the risks associated with the use of, for example, yttrium in magnesium alloys.

Biomaterials selected for implants are traditionally biologically inert (e.g. stainless steel, titanium), as stated in several researchers' statements above. However, even biologically inert materials can have unexpected, possibly unpredictable consequences. Gilbert and his colleagues recall a case with an artificial lumbar implant developed by John Charnley in the 1960s, which went wrong, and it was subsequently found that the polymer coating disintegrated into a previously unknown mechanism of wear when implanted in patients. Inflammation due to these particles has caused a new "human-caused disease" known as periprosthetic osteolysis[18]. Therefore, in relation to bioprinting, the authors have formulated five areas of ethical or bioethical issues that they believe need to be addressed: (1) whether there is a limit to what should be appropriate in

[15] S. Bag, op.cit., pp. 674-675.

[16] R. A. Rahman, op.cit., p. 8

[17] F. Gilbert, C.D. O'Connell, T. Mladenovska, S. Dodd, *Print Me an Organ? Ethical and Regulatory Issues Emerging from 3D Bioprinting in Medicine*, "*Science* and *Engineering Ethics*", vol. 24 No 1, 2018,, p. 78

[18] Ibidem, p. 80.

bioprinting medicine; (2) the extent to which the key risks of significant human damage associated with testing 3D bioprinting in humans are being investigated; (3) what is the clinical trial paradigm used to test 3D bioprinting at all; (4) whether ethical issues of irreversibility, loss of treatment options, and replicability are analysed; (5) note the current lack of a specific framework for the regulation and testing of 3D bioprinting treatments[19].

The authors state that the implantation, vaccination or injection of biological 3D printed materials into humans for the sole purpose of determining whether a new technology causes adverse effects is likely to be unethical, as the risk of harm would outweigh the potential benefit to patients being tested. According to them, this is most important for irreversible damage in personalized medical trials, where the individual participant assumes all risks of testing and where participants may then have limited access to any potential future therapies[20].

There are credible short-term and long-term negative consequences for patients and society that the authors think should be considered, and these may require new approaches to the approval of therapeutic implants and treatments. They further state that the therapeutic potential to displace new organs, such as the kidneys, is an excellent, innovative health solution that could provide far-reaching benefits to the health of individuals and humanity as a whole. However, due to the novelty of these technologies, their uncertain benefits to patients and their unique risk profile as invasive physiological changes, 3D bioprinting requires an assessment of the ethical challenges that need to be overcome, especially in the experimental trials. Because 3D bioprinting tests require a single intervention to determine their safety and efficacy for a person for whom the procedure has been specifically designed, a patient waiting for a biofabricated organ would likely serve as a guinea pig for their own 3D printed organ. In this context, the moral commitment to protect patients and society from potential harm associated with this technology means, according to the authors, the obligation to clearly formulate and communicate adequate information on the nature and objectives of 3D bioprinting and the risks involved for all concerned[21].

Similarly, according to the authors, the transfer of 3D bioprint research from the laboratory to the clinic brings with it already known ethical concerns discussed in the bioethics literature, as well as emerging ethical concerns regarding specific properties of new treatments that go beyond cell engineering or new medical implants. On the other hand, although they may find it difficult to establish and apply a consistent framework for research and development in the field of biomedicine, including bioprinting, it is urgent to outline consistent rules to fill this regulatory gap. An important area for development will be to create a clear ethical basis for regulation to control development and limit 3D bioprinting applications. Specific regulation of bioprinting with effective enforcement can prevent or mitigate some of the negative impacts in a given field of biotechnology[22].

[19] Ibidem, p. 73.
[20] Ibidem, p. 83.
[21] Ibidem, p. 87.
[22] Ibidem, p. 87.

Conclusion

I think that all five ethical and bioethical areas of problems that the authors present in connection with bioprinting are also relevant in relation to the topic of biodegradable materials. The goal can in no case be to stop or limit research and development in a given area of knowledge, because it is primarily an effort to help the patient alleviate his/her pain or problems associated with the disease. On the other hand, it is also necessary to consider the current or expected negative consequences resulting from new biomaterials, including biodegradable materials in their use in regenerative medicine. Not to mention that the possible unintended consequences for the human body, which may arise from the individual interaction of the human body and biomaterials, must also be borne in mind. These are all relevant ethical and bioethical issues that challenge today's ethics and bioethics.

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