Evidence-based Evaluation of Publications on Tissue Engineering and Regenerative Medicine

CHRISTIAN NAUJOKS¹, CHRISTIAN GERGES², ULRICH MEYER³, SAHAR FAZELI⁴, RITA A. DEPPRICH¹, NORBERT R. KÜBLER¹ and JÖRG HANDSCHEL¹

¹Department of Cranio- and Maxillofacial Surgery, Heinrich Heine University Düsseldorf, Düsseldorf, Germany; ²Department for Gastroenterology, Evangelic Hospital Düsseldorf, Düsseldorf, Germany; ³MKG-Muenster, Muenster, Germany; ⁴Department of Gastroenterology, University of Heidelberg, Heidelberg, Germany

Abstract. The performed study gives a literature review of preclinical and clinical publications on tissue engineering and regenerative medicine. Furthermore, an overview of the clinical application of these processes is given. The literature research was based on different electronic media, e.g. Medline of the National Library of Medicine. The quality assessment of this study was performed by standardized, evidence-based criteria. Studies were analyzed regarding the clinical area of application, organ systems, tissue types, level of evidence, cell types and release date. Since 1989, the number of publications in the field of tissue engineering has increased dramatically. The articles deal predominantly with three tissues (skin, bone or cartilage). Even if the number of clinical studies is increasing, there is still a lack of clinical studies with a high level of evidence. The research has moved from preclinical research to the field of applied medicine. There is a need for strategically planned clinical trials to establish clinical guidelines for this field.

Due to the achievements in research and progress in human medicine, the average life expectancy is about 80 years today in Germany and is rising (1). Therefore it is becoming more and more necessary to deal with degenerative processes that may be caused by hereditary, age or prosperity. The metabolic syndrome is one of the consequences of an affluent society, e.g. promoting degenerative changes of the vessels leading to coronary heart disease (CHD). In 2004, CHD was the most common cause of death in Germany (2). With increasing maturity, patients often suffer from different diseases affecting each other (multimorbidity). Almost 50% of all dialysis patients in Europe and the U.S. are diabetics because their kidneys have been damaged by diabetic nephropathy (3). So the question arises as to how we can treat or compensate for functional limitations or the failure of organs and organ systems. For instance, which options remain open at progressive cardiac insufficiency or kidney failure? Currently, the therapeutic options such as dialysis or the donation of an organ are often the only treatment options in progressive disease. In addition, such therapies are less effective compared to the original organs and do not restore the function of organs (4-6). Moreover, although in 2006 there were almost 4,000 organs transplanted in Germany, there are three times as many patients waiting for a kidney transplant as are transplants available (7-8).

Progress in regenerative medicine and tissue engineering may provide solutions to such problems of modern medicine. Within the scope of tissue engineering, tissue constructs can be generated extracorporeally by the use of cells, growth factors and scaffolds. These generated constructs can be transplanted into an organism and are supposed to restore the specific functions of a tissue. Even if we cannot engineer a complex organ system as yet, the techniques of tissue engineering and of regenerative medicine are being increasingly used in clinical practice. Autologous stem cell transplantation for the regeneration of blood vessels and contractile fibers is nowadays considered as a possible therapy for a myocardial infarction (9). It is not only soft tissue that can be regenerated by the use of tissue engineering. Pradel et al. were able to demonstrate that the therapy of cystic bony defects of the mandible with autologous stem cells results in a better ossification than treatment without any stem cells (10). Furthermore, skin and cartilage substitutes can already be successfully produced by tissue engineering (11). Regeneration of complex organ systems by the use of tissue engineering may be possible in the future and thus reduce need for donor organs.
Referring to PubMed, many articles about tissue engineering, with spectacular results, are available. The so-called Vacanti mouse with a tissue engineered human ear on its back (12), or the vision of a tissue-engineered heart (13) are only two examples. Unfortunately, it is not known in what ways these results are on evidence-based levels and when they were used as common therapeutic concepts. The aim of this study was to give a literature review of preclinical and clinical publications on tissue engineering and regenerative medicine. Furthermore, we wanted to present an overview of the application of these biomedical processes in various areas of medicine. We also determine the value of the various procedures under evidence-based criteria.

Materials and Methods

On the basis of electronic media, a detailed literature research was carried out regarding published studies in the field of tissue engineering and regenerative medicine. The period of interest was assessed from 1984 until 12/2009. The research was performed with: Hard copy publications of the library of the University of Düsseldorf and different electronic media: Medline of National Library of Medicine (http://www.ncbi.nlm.nih.gov/), The Cochrane Library (http://www.cochrane.de/de/index.htm), The deutsche Ärztelrblatt (http://www.aerzteblatt.de), The Fraunhofer Institut (http://www.fraunhofer.de), The International Technology Research Institute (http://www.wtec.org/loyola/itri/).

The literature research was performed by the use of the keywords “tissue engineering” or “regenerative medicine”, leading to two main groups of articles. Afterwards, we added the term “and stem cells” to both groups. To specify the results of the literature research, the articles found were categorized into tissues and organs that the articles deal with and the clinical area of application. In addition, a subdivision regarding the type of article, the date of publication, the used cell types and the level of evidence was made. After the literature research was performed in all of the above mentioned libraries, the articles were analyzed for redundancies and false-positive results. From the numerous studies, the clinical trials have been intensively analyzed and summarized in tabular form according to their level of evidence. The quality assessment of this study was performed by standardized, evidence-based criteria (Table I). Adequate randomized controlled trials were classified as high quality; descriptive or retrospective studies were assigned a lower level of evidence.

Results

Because tissue engineering and regenerative medicine are not clearly separated from each other, it is difficult to assign an article exclusively to one of both areas. Hence we focused our analysis on the field of tissue engineering. The performed literature research incorporating publications since 1984 gave 16370 articles dealing with the key word “tissue engineering”. Only 3115 of these 16370 articles were reviews (Figure 1). The first article dealing with tissue engineering or regenerative medicine was published in 1984. This does not mean that there was no research in this field before 1984, but then it was called “stem cell research”. In these articles, tissue engineering is often equated with stem cell research. There is no precise separation between the concept of tissue engineering and regenerative medicine. Almost 90% of published studies in the field of tissue engineering or regenerative medicine do not use stem cells. When we look at the development of publications dealing with tissue engineering over the time, we can see that between 1984 and 1990, only three further articles were published. Between 1986 and 1988, there was a complete lack of publications. Until 1998, the number of publications increased very slowly and remained below 100 articles per year. For the first time, a three-digit number of published articles was reached in 1998. Since then the number of publications has increased rapidly. In 2001, there were almost 500 articles, in 2003 already more than 1000 articles and in 2009, more than 3,000 publications were published (Figure 2).

When we analyzed our data, we paid particularly attention to articles reporting clinical trials. These clinical trials reflect the latest research in the field of tissue engineering and mirror the state of integration of the results into clinical treatment. In comparison to the entire research field, research in tissue engineering started very late with clinical trials. It took 13 years from the first publication dealing with tissue engineering for the first clinical study to be published. From 1997 to 2003, very irregular and only limited clinical studies were performed. Except for a small decline in 2005, the number of clinical studies has been rising continuously since 2003. Especially in recent years, the proportion of clinical trials on the published articles has increased (Figure 3).

Only 84 clinical studies had been published up to December 2009 including four meta-analysis, with evidence level Ia. As randomized, controlled trials, 23 articles achieved evidence level Ib. When we compare these 23 articles to the entire 16370 articles dealing with tissue engineering, the level Ib-studies comprise only a small proportion (0.15%) of all
published results so far. This highlights the lack of clinical studies with a high level of evidence. The majority of publications reach only evidence level III, for example well-designed case control studies (Figure 4). Therefore over half of all clinical trials cannot be used to establish clinical guidelines. This is a result of the short time of clinical research in this field and reflects the difficulties in arranging and carrying out these clinical studies.

When we analyzed the articles regarding the tissue of interest, it appears that different disciplines deal with the same tissue. For instance, the orthopedic surgery and dentists often deal with tissue engineering of bone. When we classified the articles found regarding the tissue they deal with, it emerges that most of the clinical studies concentrate on three different tissues (Figure 5). These studies deal with the tissue engineering of skin, cartilage and bone. The skin is one of the major tissues of interest for the research in tissue engineering. Hence, most of the studies with a high level of evidence are in this field. We found 10 studies with level of evidence Ib in the skin group, reflecting the largest clinical experience in tissue engineering compared to other tissues. In addition, the clinical studies about skin tissue have the largest number of cases compared to the studies dealing with other tissues (14-15). The cartilage tissue is particularly strong in orthopedic research, especially with the aim of improving the treatment of degenerative damages of the joints. The published clinical studies do not reach a high level of evidence and most of these publications reach only evidence level III. There is a negative correlation between the number of cases and the level of evidence of the clinical trial, e.g. the clinical trial with the largest group of patients (more than 1000) only reaches level of evidence III (16). Until 2007, the only randomized, controlled study was carried out only with a collective of six patients (17). In 2008 at least one level Ib study with 118 patients appeared (18). The eight clinical studies found reaching level of evidence Ib classify bone tissue engineering as the tissue with the second most level Ib trials. In principal, these studies are randomized, controlled trials. It is interesting that in the 44 clinical trials found, only 1513 persons were examined. Furthermore, one third of these persons were linked to three of these studies. Only four out of these 44 clinical trials include more than 100 patients. Ninety percent of the above mentioned clinical trials were performed with fewer than 50 probands.

As we mentioned above, there are many overlaps regarding the tissue the article deals with and the different medical discipline the research was performed in. Hence we analyzed the articles regarding the medical discipline in which the research was performed. We saw that most of these studies deal with maxillofacial surgery and show promising results. Almost one third of all articles with evidence level Ib stem from maxillofacial surgery. Only studies that reach these high levels

Figure 1. Overview of articles about tissue engineering. Total articles (dark grey) and the reviews (light grey) are shown.

Figure 2. The number of publications in every single year from 1984 to the end of 2009.
of evidence may lead to new therapeutic options and an inclusion of these new therapeutic options into clinical routine. When we take a look at our data, it seems that clinical research with the aim of the development of new treatment options/guidelines is advancing.

**Discussion**

In the last few decades, the interest in research in the field of tissue engineering has been increasing and the number of the articles published is rising. Although there are many studies dealing with tissue engineering and regenerative medicine, there still exists no systematic study analyzing the current state of affairs. Hence it appeared necessary to perform a study analyzing the state of the affairs of the research, an overview, and so enable a reasonable and well-structured planning of further research.

So far the publications produced as part of commercial research in the United States reflect the major proportion of the publications dealing with tissue engineering and regenerative medicine (19). The purpose of this research is predominantly financial interest and the commercial use of the results of the research. On the contrary in Europe and Japan, the research is mainly performed by researchers at universities, targeting predominantly fundamental research as a precondition for the clinical use of the results (19). A possible reason for this distribution could be the complexity and tediousness of studies dealing with fundamental research. Furthermore, the results of the performed research are not predictable and may not always be transferred to the clinical application. These factors may restrain companies from investing in fundamental research of tissue engineering because these companies are financially interested in a contemporary clinical application of the new technologies.
As our results show, there are certain problems to integrate the achieved knowledge. This would be necessary to coordinate the different work-groups so as to perform sensible clinical studies based on each other, leading to a more efficient development of routine clinical procedures. In addition, this could prevent many patients from receiving unnecessary treatments with ineffective therapies. For these purposes, an international initiative was started by the Tissue Engineering and Regenerative Medicine International Society (TERMIS). This society established a register for clinical studies (http://www.termis.org) on regenerative medicine and tissue engineering. It remains to be seen if this instrument will be accepted be researchers.

Since the WTEC Panel Report on Tissue Engineering Research was published in 2003 (19) the number of clinical studies has changed. There were only a few clinical studies published before 2003 and as can be seen, only 44 clinical studies exist overall. This increasing rate of clinical studies, mainly focusing on biocompatibility of biomaterials, reflects that there is a rising interest in tissue engineering research. Furthermore, these findings correlate with the increasing number of tissue engineering articles overall.

The main areas of application are dentistry (reconstruction of the bone of the jaws) and surgery (skin transfer to large wounds). Bone, cartilage and skin are the three tissues which are the focus of the interest and so most of the published articles deal with one of these tissues. One possible explanation for the high number of articles dealing with bony tissue engineering may be the fact that a multiple of disciplines are needed to reconstruct bony structures, e.g. Cranio- and Maxillofacial Surgery and Orthopedy, and are interested in the research in this field. In addition, the culturing in the laboratories of bone or skin is very fast and simple compared to that far other complex tissues. Thus, results can be obtained in a short period of time and failures can be compensated far better, leading to a higher number of publications in these fields.

When we reflect on all the publications dealing with bony research, we can see that there is still no established therapy for reconstruction of bone which is effective and long-lasting. Even if there are many promising approaches, often a reliable, reproducible and cost-effective in vitro cultivation of the tissue is not proven. Consequently there is a lack of clinical studies. When we take a look at the quantity of the existing clinical studies and their level of evidence it seems to be clear that it is not possible to establish a clinical guideline for the reconstruction of bone. Furthermore, the number of cases included in these studies is not sufficient. In summary, the number of existing clinical studies, the number of cases of each study and the level of evidence is too low. However, these studies can give evidence for which concepts should be analyzed further.

Dermatology mainly focuses on the skin tissue engineering. In contrast to the other tissues, e.g. bone and cartilage, clinical studies with a high level of evidence and a sufficient number of cases do exist. Almost one third of the overall numbers of cases are related to this area of interest. In spite of these promising facts, it is not possible to establish a clinical guideline for the reconstruction of the skin.

**Conclusion**

It was found that publications in the field of tissue engineering have been strongly increasing since 1989. The fact that clinical studies dealing with tissue engineering are present in a significant number only since 2002 highlights the fact that the
transfer to clinical routine has really only just started. There is still a lack of clinical studies. Of the 16370 publications by the end of 2009 with the key words “tissue engineering” and “regenerative medicine”, only 84 are clinical studies. The tissues most frequently used in clinical studies are skin, bone and cartilage, whereas all other tissues are used less frequently. The specialized branches which are dealing with this area most are dental/maxillofacial surgery and dermatology/general surgery. Studies with a high level of evidence are found only in small numbers (23 studies with evidence level Ia, one study with evidence level IIa, 10 studies with evidence level 2a, 44 studies with evidence level 3, 5 studies with evidence level 4, one study not specified). In fact there are only very few clinical studies on the use of stem cells, which reach a higher level of evidence. The literature analysis shows that the process of tissue engineering and regenerative medicine in recent years has moved from preclinical research to applied medicine. Unfortunately, there are still not enough studies with a high level of evidence-based study design. The high dynamics of dealing with this biomedical field lead us to expect more evidence-based clinical studies in the near future.

**Summary Points**

I. Publications in the field of tissue engineering have been dramatically increasing since 1989. II. Clinical studies on tissue engineering and regenerative medicine have been only present in a significant number since 2002. III. Of the 16370 publications by the end of 2009, only 84 are clinical studies. IV. Studies showing a higher level of evidence are found only in small numbers. V. The tissues most used clinically are skin, bone and cartilage. VI. There are actually only very few clinical studies with a high level of evidence on the use of stem cells.

**Competing Interests**

All Authors declare that there are no competing interests regarding the interpretation or presentation of the above mentioned data or results.

**References**


