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RESEARCH ARTICLE

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The clinical use of bone graft substitutes in orthopedic surgery in Germany—A 10-years survey from 2008 to 2018 of 1,090,167 surgical interventions

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Abstract

Aim of the study was to evaluate (1) the overall use of bone graft substitutes, autografts and allografts, (2) of different types of bone graft substitutes (calcium sulfate, calcium phosphate, calcium phosphate ceramics or polymethyl methacrylate) and of different bone grafts (cancellous vs. cortical), and (3) the use of antibiotic-loading of bone graft substitutes in orthopedic surgery in Germany. Gross data were provided from the Federal Statistical Office of Germany and revealed an overall increase in bone defect reconstruction procedures using bone graft substitutes, autografts and allografts from 86,294 in 2008 to 99,863 cases in 2018 (+15.7%). The relative use of bone graft substitutes for these interventions strongly increased from 11.8% in 2008 (10,163 cases) to 23.9% in 2018 (23,838 cases) with an increase of +134.4%. Furthermore, antibiotic-loaded bone graft substitutes were implanted more frequently with an overall increase of +194% (2008: $n = 2,657$; 2018: $n = 7,811$). The work shows an increasing use of bone graft substitutes and antibiotic-loaded bone graft substitutes over the last 10 years in Germany.

KEYWORDS
allograft, autograft, biomaterials, bone graft, bone substitute

1 | INTRODUCTION

In orthopedic and trauma surgery, bone defects pose an increasing clinical problem in daily practice. These result from bone infections and tumors, which in most cases require surgical resection followed by bony reconstruction. In addition, fractures after high-energy trauma and osteoporotic fractures are frequently accompanied by bone defects necessitating bone augmentation procedures.[1] Osteoporotic fractures are the expected main driver for an increased number of bone defects. Numbers of individuals at high risk of osteoporotic fractures are estimated to double until 2040 in the Western World due to demographic aging.[2] Even today, half a million patients are reported to receive bone defect repairs per annum in the United States and Europe with an estimated cost exceeding US$ 3 billion.[3]

Bone defect reconstruction can be achieved by the use of autografts, allografts and, biomaterial-based bone graft substitutes containing ceramics, synthetic or natural polymers.[4,5] Hitherto, autogenous bone grafting has been considered the gold standard.

Autograft not only provides osteogenic but also osteoconductive and osteoinductive properties. However, drawbacks associated with the use of autologous bone grafts are limited availability, donor site morbidity and increased operation time. From the clinical perspective those shortcomings were the key drivers for advances in biomedical research to develop bone graft substitutes for bone defect reconstruction in the past.[6] Efforts in bone tissue engineering are based on the benchmark autograft: providing a biocompatible scaffold similar to natural bone, osteogenesis by cells in the osteoconductive scaffold, growth factors directing and promoting cell growth as well as development to improve bone ingrowth and remodeling, and finally, sufficient vascularization for nutrient supply and clearance needs.[7] Impaired vascularization entails an increased risk of foreign body infection. Application of local antibiotics evolved as one of the central tenets for prevention and treatment of bone infections. Thus, additional application of antibiotics in combination with allografts and synthetic bone graft, which are otherwise prone to bacterial infections, has been implied in recent years.[8,9] Despite efforts in basic research with progressively implementation of bone graft substitutes in the orthopedic biomaterial markets, no data are available, which demonstrate recent trends in use of bone graft substitutes and autologous as well as allogenic bone for bone defect reconstruction.

We therefore asked: What are the general trends for use of bone graft substitutes and bone grafts in the recent decade? What trends have been developed in use of different bone graft substitutes and bone grafts? Is there an increase in bone graft substitute use with additional antibiotics for local anti-infective treatment?

2 | MATERIALS AND METHODS

2.1 | Data source

Data were provided by the German Federal Statistical Office (Destatis). For our analysis, historical data from 2008 through 2018 were utilized. Since 2004 all somatic departments have to classify their cases according to the diagnosis related groups (DRG). Lump-sum payment is based on DRGs which are generated by diagnosis codes as well as surgery and procedure keys (Operation and Procedure Classification System [OPS] codes). Thus, procedure numbers for use of bone substitutes and bone grafts were available from all German hospitals for inpatient procedures within the analyzed period. All kinds of clinical applications including off-label use of bone graft substitutes were included in our analysis.

2.2 | Data processing

Surgery and procedure keys (OPS codes) were used to identify all procedures being performed using bone substitutes or bone grafts. We focused on OPS codes for usage of bone grafts and their substitutes treating bone defects at the extremities and pelvis, which are summarized under the OPS codes 5–785 and 5–784. These include all types of bone grafting and transplantation (5–784), but also exclude the closure or filling of iatrogenically created or access-related bone defects with local tissue.

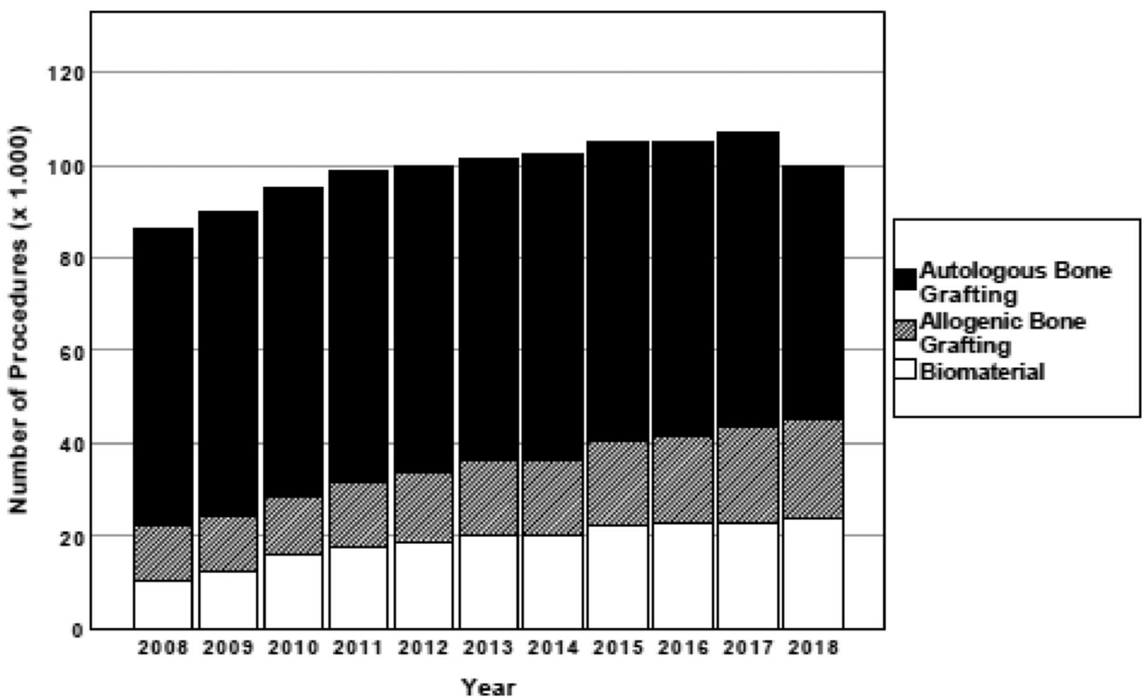

FIGURE 1 Total use of biomaterials, autologous and allogenic bone grafts in orthopedic surgery in Germany from 2008 to 2018. Total numbers increase over time peaking in 2017. The distribution of used biomaterials, autologous or allogenic bone grafts remain roughly the same over the 11-year period

TABLE 1 Comparison of absolute and relative numbers of bone graft and biomaterial procedures between 2008 and 2018

	2008		2018		Percentage changes from 2008 through 2018
	Absolute numbers	Percentage share	Absolute numbers	Percentage share	
Total procedures	86,294	100%	99,863	100%	+15.7%
Autologous bone graft	63,929	74.1%	54,784	54.9%	−14.3%
Allogenic bone graft	12,202	14.1%	21,241	21.3%	+74.1%
Biomaterials	10,163	11.8%	23,838	23.9%	+134.4%

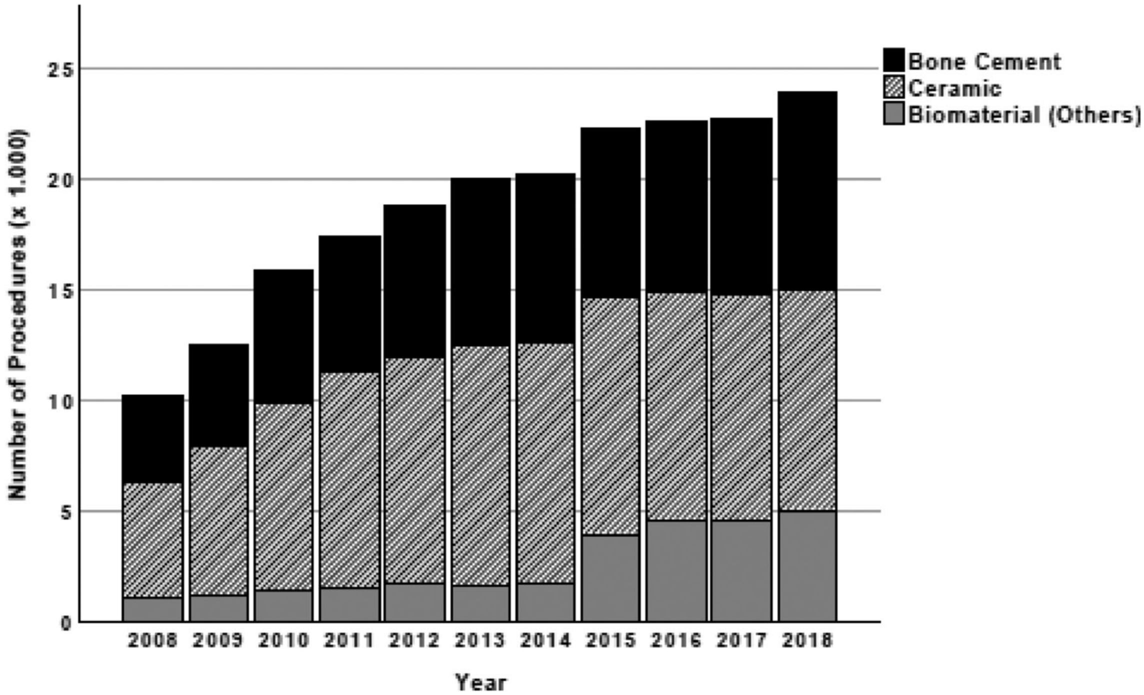

FIGURE 2 Illustration of the application of biomaterials for bone defect reconstruction. Bone cements were used slightly more frequently than ceramics for bone defect reconstruction in extremities and pelvis

The implantation of bone substitutes (5–785) excludes all interventions for endoprosthetic joint and bone replacement. For bone substitutes, the OPS codes were used to distinguish between bone cements without (5–785.0) and with added antibiotics (5–785.1). For ceramics a distinction was made between ceramics with additional antibiotics (5–785.5) and those without (5–785.2 and 5–785.3). Other codes such as metallic bone graft substitutes (5–785.4) and other alloplastic bone graft substitutes without (5–785.6) and with (5–785.7) antibiotics were also included in the analysis. Autologous bone transplantation was discriminated as follows: autologous cancellous bone (5–784.0, 5–784.c), autologous cortical bone graft (5–784.1, 5–784.2, 5–784.d), other autologous bone grafts (5–784.3, 5–784.4, 5–784. 5, 5–784.a); allogenic procedures: allogenic cancellous bone (5–784.7, 5–784.9, 5–784.e), allogenic cortical bone grafts (5–784.8, 5–784.f), demineralized bone matrix (5–784.b), allogenic bone grafts (5–784.6).

2.3 | Data analysis

Data was analyzed and graphically displayed using the statistical software SPSS Version 26.0 (IBM, SPSS Inc. Armonk, New York).

3 | RESULTS

3.1 | Overview of 1,090,167 cases—high increase in the use of bone graft substitutes

This works relies on the analysis of a total of 1,090,167 procedures in orthopedic surgery in Germany from 2008 through 2018.

From 2008 through 2018, an increased number of interventions in orthopedic surgery using bone graft substitutes and bone grafts were recorded. While a total of 86,294 procedures were

TABLE 2 Comparison of biomaterial applications in extremities and pelvis between 2008 and 2018

	2008		2018		Percentage changes from 2008 through 2018
	Absolute numbers	Percentage share	Absolute numbers	Percentage share	
Total numbers	10,163	100%	23,838	100%	+134.4%
Ceramics	5,202	51.2%	9,981	41.9%	+91.9%
Bone cements	3,884	38.2%	8,843	37.1%	+127.7%
Others	1,077	10.6%	5,014	21.0%	+365.6%

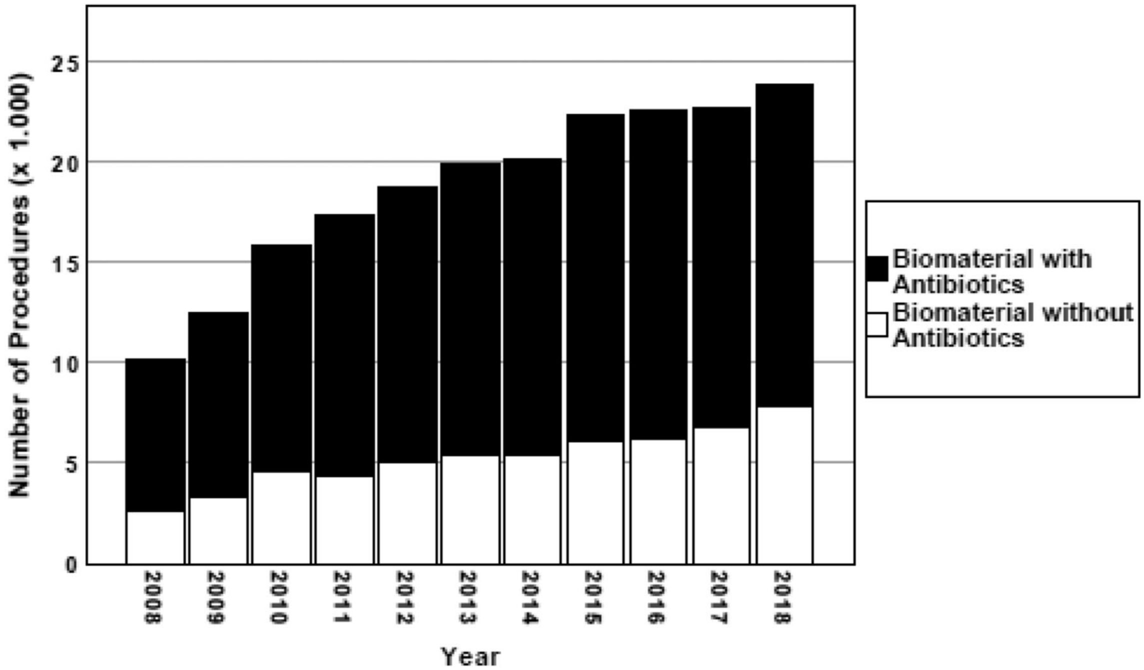

FIGURE 3 Total numbers of biomaterial application with and without additional local antibiotics. The share of supplemental antibiotics in biomaterials increases from 2008 through 2018

performed in 2008, 99,863 procedures were carried out in 2018 (+15.7%) (Figure 1). The largest number of bone defect reconstruction procedures was identified in 2017 (106,953 procedures). The percentage of bone graft substitutes increased over the years. While bone graft substitutes accounted for 11.8% of all bone replacement procedures in 2008 (10,163 procedures), this number has risen to 23.8% in 2018 (23,838 procedures). This represents an increase of 134.4% (Table 1).

3.2 | Analysis of the use of bone graft substitutes—growing use of all type of materials, particularly for ceramics

The increasing use of bone graft substitutes results from a growth of absolute numbers of all analyzed subgroups such as bone cements, ceramics, and other biomaterials. Similar to the increase in the total amount of bone graft substitute applications, an increase in clinical use was observed for bone cements (2008: 3,884 procedures; 2018: 8,843 procedures, +127.7%) and ceramics (2008: 5,202 procedures; 2018: 9,981 procedures, +91.9%) (Figure 2). The bone substitutes included under "other biomaterials" such as metallic replacement materials or bioactive glass have also been increasingly used over the years. While 1,077 procedures were coded in 2008, a total of 5,014 coded procedures with "other biomaterials" for defect reconstruction of extremities and pelvis were registered in 2018 (+365.8%). Looking at the percentage weighting of the individual years, it is remarkable that the specific use of ceramics accounted for 51.2% of all bone graft substitutes in 2008, decreasing to 41.9% of all bone graft substitutes in 2018. In contrast, the proportion of bone cements remained constant (2008: 38.2% vs. 2018: 37.1%). Other biomaterials were used much more frequently over the observed 11-year period (2008: 10.6% vs. 2018: 21%) (Table 2).

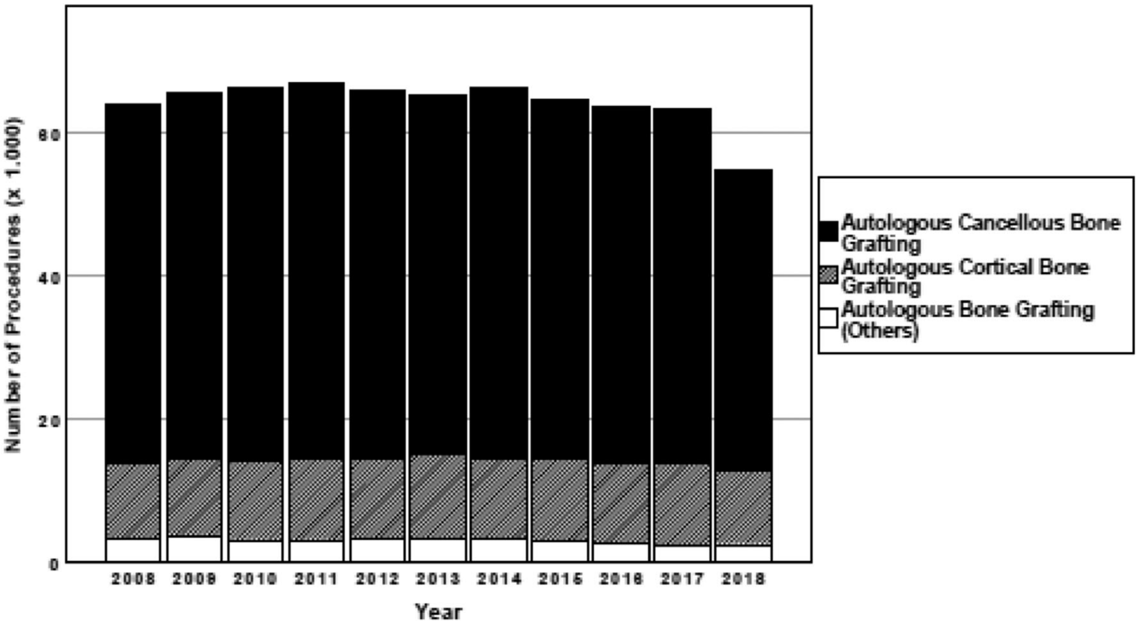

FIGURE 4 Overview of clinical application of autologous bone grafts from 2008 through 2018. Total numbers decrease over time. Percentage share of cancellous or cortical grafts as well as other autologous transplant procedures remains roughly the same over the 11-year period

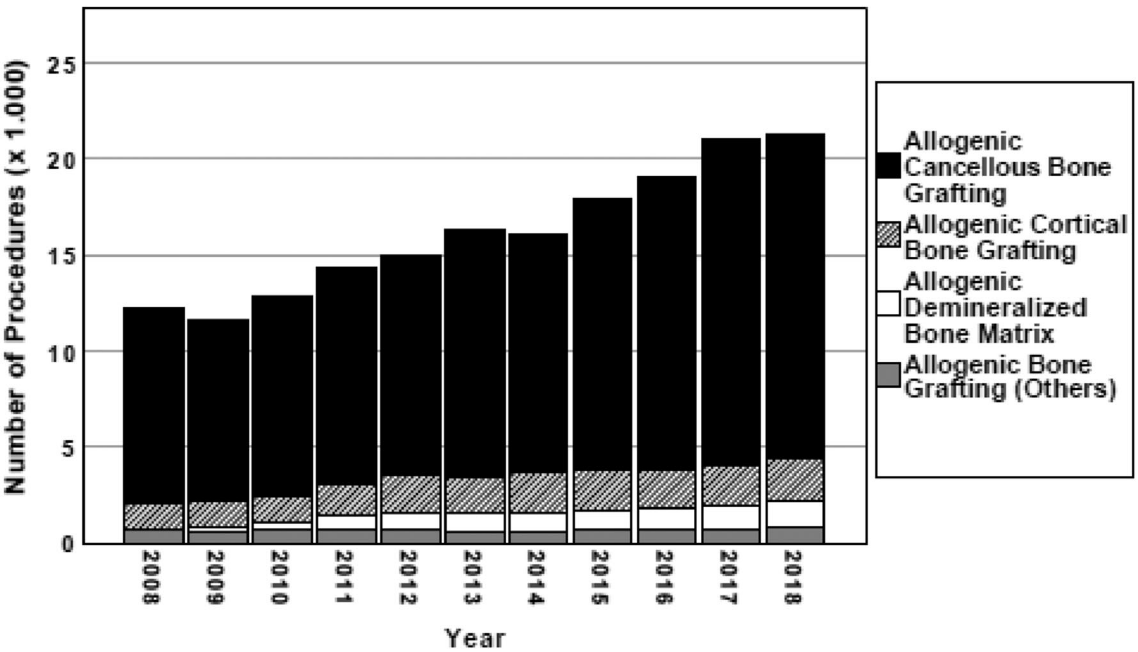

FIGURE 5 Illustration of absolute numbers of allogenic bone transplantations from 2008 through 2018 in Germany. Total numbers increase over time

3.3 | Antibiotic-loaded bone graft substitutes—increasing use

Regarding the use of bone graft substitutes containing antibiotics, an increase in absolute numbers and an increased relative use can be observed over the investigation period. In 2008, there were 2,657 procedures, for which the use of bone graft substitutes with added antibiotics was coded. In 2018, there were 7,811 procedures (+194%). The proportion of bone graft substitutes with added antibiotics increased over the observational period (2008: 2,657 cases, 25%; 2018: 7,811 cases, 32.8%) (Figure 3).

3.4 | Autograft and allograft procedures—decreasing autograft and increasing allograft procedures

The proportion of allografts has also increased in absolute and relative terms over the years. Between 2008 and 2018 the number of transplanted allografts in Germany rose from 12,202 to 21,241 (+74.1%). At the same time, the number of autologous bone transplants has decreased slightly over the 11-year period. From 63,929 procedures with autologous bone transplantation in 2008, 54,784 interventions could still be identified in 2018 (−14.3%). The proportion of autologous bone grafts has also decreased over time. Autologous bone transplants accounted for 74.1% of all bone defect reconstructions in the extremities and pelvis in 2008, whereas autografts were still used in 55% of all bone defect reconstructions in 2018.

Looking at autologous and allogeneic bone transplantation, cancellous bone grafting is by far the most common procedure over the years for both different types of bone grafting. Autologous cancellous bone grafting was performed 50,104 times in 2008 (78.4%). In 2018, there were still 41,988 autologous cancellous bone-grafting procedures (76.6%) (Figure 4). The situation is similar for allogeneic bone transplantation. Cancellous bone grafting accounted for the majority of procedures in allogenic bone grafting in all years (2008: 83.7%, 10,212 procedures; 2018: 79.0%, 16,774 procedures) (Figure 5). Although rarely used, a considerable increase in the application of demineralized bone matrix can be observed from 2009 to 2018. Whereas 288 procedures using demineralized bone matrix were registered in 2009, the number has increased continuously over the observed period. In 2018, 1,355 procedures with demineralized bone matrix were coded. This corresponds to a proportion of allografts of 6.4% in 2018.

4 | DISCUSSION

Between 2008 and 2018, the total number of procedures involving the use of bone graft substitutes, autografts, and allografts for bone defect reconstruction in extremities and pelvis increased (2008: 86,294 procedures; 2018: 99,863 procedures, +15.7%). Interestingly, the prevalence of bone graft substitutes and allograft application increased over the 11-year period, while autografts showed a decrease in absolute numbers (2008: $n = 63{,}929$, 2018: $n = 54{,}784$, −14.3%). This reflects a considerable decrease in percentage for autologous bone grafts (2008: 74.1%; 2018: 55%). An increase of allograft usage of 74.1% (2008: $n = 12{,}202$; 2018: $n = 21{,}241$) and an even larger increase of bone substitute applications of 134.4% (2008: $n = 10{,}163$; 2018: $n = 23{,}838$) has been demonstrated. As far as these data can be compared to the only available study dealing with numbers of bone graft and bone substitutes in the United States, our findings contradict those results reporting a decrease in bone graft use and even a slighter decrease in application of bone graft substitutes.[10] Although Kinaci and co-workers examined the trends from 1992 to 2007 in the US and described a proportion of bone substitute procedures of 17%, which is similar to our data, the different examined time period and countries as well as inclusion of additional spine procedures limit the comparability of both studies.[10] Market analyses predict a global compound annual growth rate of 5.2% and a total market of 4.4 billion US-Dollars for bone grafts and bone substitutes in 2027. Those projections are similar to the observed overall increase in bone defect reconstruction procedures reported in our study.[11]

Our data demonstrate different trends for use of autografts, allogenic bone and bone substitutes. The decreased use of autografts and increased use of allografts and bone graft substitutes suggests that risks and benefits are weighed differently in clinical routine over time. Reasons for this development are manifold. Harvesting of autologous bone graft entails different downsides. Beside longer operation time those are subsumed under the term donor site morbidity, which includes persistent pelvic pain, postoperative hematoma, nerve injury or fracture of the pelvic bone. Those complications are reported to be up to 20%. Alternatives to iliac crest bone graft harvesting such as the reamer irrigator aspirator (RIA) technique also poses a risk for donor site morbidity of about 6% in the long bones.[6] Despite this less risky harvesting alternative, other choices for bone grafting are made by the treating surgeons. A decrease of drawbacks for allograft use such as a minimal infection risk for hepatitis and HIV nowadays, confers allografts a better acceptance among patients and users.[12] In addition, downsides reported after allograft use such as sensitization of the immune system seem not to be considered negative for bone defect reconstruction.[13] Furthermore, promoted use of bone graft substitutes by the industry might account for the changes observed in the study. Besides, treating surgeons could have recognized improvements being made in developing better biomaterials for bone graft substitutes in the last decade.[14] Thus, bone substitutes could have found their way in clinical practice more and more. Monetary reasons for use of bone graft substitutes and an increased DRG reimbursement rate by coding bone graft substitutes could be another cause for further increase of bone substitute use during the last years. However, since reimbursement of additional bone substitute application depends on localization of the treated bone defect, monetary reasons for increasing use of bone graft substitutes cannot be assessed conclusively by this study.

The use of cancellous bone grafts for both autologous and allogenic bone transplantation remained on a high level over the complete observation period. More than three quarters of all autologous and allogenic bone-grafting procedures were performed using cancellous bone for each year between 2008 through 2018. Defect size, morphology and anatomical location are crucial parameters for selection of bone graft materials. While in general, small defects with cortical support are amenable for cancellous bone grafting procedures, larger and sometimes segmental defects are often treated by cortical bone grafting, which promises additional biomechanical stability. Depending on anatomic location favorable results have been reported for segmental bone defects with a size between 2.5 and 6 cm.[1,15] In addition, newer procedures such as the Masquelet technique have been developed over the last years, demonstrating consolidation of cancellous bone grafting in major defects up to 26 cm. An induced membrane which supplies the bone defect zone with blood and thus with osteoinductive growth factors is held responsible for good results even in larger bone defects.[16,17] The need for osteoinductive potential in bone defect healing has been realized early in 1965 by Marshall R. Urist.[18] Based on the present results improved allograft materials, however, which contain additional osteoinductive growth factors such as demineralized bone matrix, seem to have entered the focus of clinical application only over the last decade.[19] From 2008 through 2018 the use of demineralized bone matrix increased from 288 to 1,355 procedures which corresponds to an increase of 370.5%.

The use of bone graft substitutes experienced the largest increase over the observed 11-year period compared to autologous and allogenic bone grafting. Based on the data provided by Destatis, it was possible to discriminate between ceramics, cements and other biomaterials. During the observed period ceramics were the largest group of used bone graft substitutes. Bone cements were a little less often used. For both biomaterial groups a large increase could be observed over time (ceramics +127.7%, cements +91.9%). For other biomaterials, an even larger increase of 365.8% could be observed from 2008 through 2018. This might be due to development of metallic bone augments such as trabecular tantalum based components or bioactive glass, which emerged as bone substitute material for bone defect reconstruction in the 1990s and experienced optimization of material properties since then.[20]

When analyzing total numbers and trends in use of various bone grafting materials by orthopedic surgeons in Germany, it has to be mentioned, that biomaterial sciences is not covered and taught in medical school. In contrast to pharmacology, which is a core course in all medical school curricula, biomaterial sciences, which often deal with materials and devices intended for permanent implantation as well as the interaction of materials and living tissues, is not taught in the context of medical school education or orthopedic residency. As a result, a thorough understanding of the importance of material properties with regard to cell and tissue responses and ultimately clinical outcomes is often not generated during medical and surgical training. Improving this knowledge base may have major potential for a more enlightened use of biomaterials in clinical practice. The present data underline the need to overthink current medical education curricula since a further increase in use of artificial bone grafts and other biomaterials has to be expected.

Intriguingly, application of antibiotic-loaded biomaterials increased considerable (+194%) between 2008 and 2018. Beside absolute numbers the proportion of antibiotic-loaded bone graft substitutes increased as well (2008: 25% vs. 2018: 32.8%). The relevance of local application of antibiotics for prophylaxis of infection in open fractures as well as crucial treatment element in bone infections has become increasingly evident in recent years.[8,21] This might be the reason for the observed trend of increased use of bone substitutes with antibiotic supplement. The well-known beneficial effect of antibiotic-loaded polymethyl methacrylate (PMMA) in arthroplasty might be another reason.[22,23] Additionally, commercially available and market approved antibiotic-loaded ceramic composites and further improved treatment concepts render a routinely clinical use.[24]

Even if the described trends of increasing use of artificial bone graft substitutes is impressive, this trend cannot simply be projected to the coming years. Beside events such as the COVID-19 pandemic, new regulatory requirements, such as the introduction of the medical device regulation (MDR), challenge biomaterial manufacturers within the European Union. Especially smaller companies might not be able to fulfill the demanded requirements which include recertification of medical devices including bone grafting materials every five years for every given application. Companies consecutively might withdraw their bone graft substitute products from the market. Besides, cost intensive investments in research and development are likely to be reduced due to regulatory and financial requirements for a market launch of a new bone graft substitute.[25] Although those regulations possibly hinder market introduction of new promising bone graft substitutes, improved demands on manufacturers to achieve patient safety are likely to achieve trust in health care providers. In the 1970s, 1980s and 1990s numerous bone grafting materials were introduced into the market based on equivalence to existing materials without detailed data from preclinical large animal studies as well as prospective clinical studies for the given application.[26] Clinical outcomes of various bone graft materials for various procedures have not been sufficiently followed-up. New regulations leading to well-documented safety and positive results in terms of bone reconstruction achieved by bone graft substitutes, however, might improve surgeons' confidence in the application of artificial bone graft substitutes. Thusly, an increase in clinical application would also be conceivable.

Our study has several limitations. The analyzed data provided by the Federal Statistical Office covers all inpatient hospital cases. Thus, it can be assumed that all usually complicated cases requiring inpatient treatment for bony defect reconstruction were assessed. The large sample of annual 86,294 (2008) to 106,953 procedures (2017) comes along with possible coding errors which might lead to distortion of the presented results. DRG coding specialists who are usually available in all hospitals might minimize such a bias. Nevertheless, specialists in the field of accounting might not overview the chemical compositions of different bone substitutes and correct classification of the correct OPS codes. For example, confusion of calcium phosphate cements with PMMA-based cements cannot be excluded. Even if the presented trend over the last 11 years provides an excellent overview for the stated research questions, it is not possible to derive a projection for future clinical use from the presented data. New insights in the field of biomaterials research, price development and product availability may influence future trends and each of them cannot be foreseen. Beside economic factors, which are known to play a pivotal role for the health care systems, remuneration in the DRG system is a decisive factor for future treatment decisions for or against application of bone grafts or bone substitutes in clinical practice. Those trends cannot be derived for the future from the present data analysis.

5 | CONCLUSION

Bone graft substitutes as well as allogenic bone graft procedures gain more and more importance for bone defect reconstruction in clinical practice. They are the key drivers for an increase in total numbers of bone graft and bone substitute applications from 2008 through 2018. Absolute and relative numbers of the gold standard autologous bone graft decreased in recent years, despite being the preferred choice in more than half of the cases for bone defect reconstruction. A further increase in use of bone graft substitutes can be expected if further improvements in materials are made, as it can be seen in the local application of antibiotics.

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DATA AVAILABILITY STATEMENT

The raw/processed data required to reproduce these findings cannot be shared at this time due to legal or ethical reasons.

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