REVIEW ARTICLE

G King

Biomedicine in orthodontics: from tooth movement to facial growth

Author's affiliation:
G. King, Department of Orthodontics, University of Washington, Seattle, WA, USA

Correspondence to:
Gregory King
Department of Orthodontics
University of Washington
Box 357446
Seattle
98195 WA
USA
E-mail: gking@u.washington.edu

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Structured Abstract

Author – King G

Biomedicine has the potential to improve orthodontic and dentofacial orthopedic treatment significantly. The importance of biomedicine has grown as the result of three trends that have experienced rapid development in recent years: the increased molecularization of biology; the rise of computer modeling; and the greater application of experimentation to clinical settings. Despite this, the translation of new biologic knowledge to clinical practice in orthodontics and dentofacial orthopedics has been slow. Notably promising areas of orthodontic biomedical research can be recognized in diagnosis, treatment rationales, therapeutics, and monitoring. Despite facing significant challenges in all of these areas, some innovations have been rapidly adopted with minimal understanding of their biologic fundamentals while others are slow to be implemented in clinical settings. Issues related to this disparity can be identified but solutions are often less clear. Two future challenges will be highlighted: 1) the inadequacy of infrastructure and systems organization to support translation of bench science to the clinic; and 2) the inherent differences in the logic and assumptions of efficacy vs. effectiveness research.

Key words: biomedicine; effectiveness; efficacy; implementation; research infrastructure

The gap between what we know and what we do

There is a disparity at the heart of biomedicine today that has increasingly become more evident. Advances in technology and the availability of funding opportunities have helped biomedical researchers to produce new data at an impressive rate; but the impact of all of this new information on the health and wellbeing of humans has been much more modest (1). The Institute of Medicine estimates that new knowledge generated by randomized clinical trials takes an average of 17 years to be incorporated into clinical practice, prompting the speculation that, in some extreme cases, deaths could be avoided. To illustrate, the 4-year survival rate for Hodgkin's disease was around 5–10% in 1970. That year, a clinical trial reported an 80% cure rate, but it took 11 years for that treatment approach to be disseminated and for that cure rate to be realized (2). Systematically documenting lives actually saved by the application of new biomedical knowledge strongly suggests that this example is not rare (3).

Dentistry has not been immune to this problem. In a recent survey, dentists report that they find scientific data valuable in selecting dental products only 42% of the time, while relying more or equally on the advice of peers and the opinions of experts. Organized dentistry is beginning to recognize the importance for oral health and wellbeing of accelerating the dissemination of biomedical knowledge to practice by establishing advisory board on evidence-based practice, facilitating systematic reviews, and implementing practice guidelines.

One frequently cited solution to the problem is translational research, a term hardly heard a decade ago. The National Institutes of Health (NIH) defines translational research as applying biomedical discoveries to human trials and studies aimed at enhancing best practices in the community. Although this approach has advantages, it also can present with its own set of problems. There are at least two problems that are noteworthy. 1) Translational research often dictates new and unfamiliar relationships between academic scientists and funding entities. With relation to NIH, this is manifested by specific announcements and requests for proposals in designated areas as well as the use of cooperative agreements in place of the more familiar research grants. Likewise, industry sponsors will recruit investigators to carry out specific projects on accelerated timelines that reflect financial and not necessarily scientific priorities. Investigator-initiated biomedical research projects without obvious immediate clinical relevance are becoming increasingly rare with the possible consequences of inhibiting creative inquiry and stifling serendipitous findings. 2) The commonly held view is that translational research travels one way: from the bench to the bedside. However, biomedical researchers are increasingly rejecting this concept, realizing that many important biomedical findings can originate from the clinical arena (e.g. distraction osteogenesis). Therefore, a robust dialog between clinicians and scientists, which does not exist today, needs to evolve. The NIDCR-sponsored centers designed to establish infrastructure for practice-based research networks may prove valuable in this regard (4).

General background on biomedicine

Biomedicine arose after World War II from the stunning success of three scientific trends: the molecularization of the life sciences; the use of computers to model extremely complex datasets; and the increasing use of experimentation in the clinic (5). Despite this success, much remains to be done in each of these areas before their full impact on human health and wellbeing will be felt. The molecular counterpart to the moonshot was the Human Genome Project. The promise of biomedical breakthroughs from this remarkable achievement, completed in 2001, has yet to be fully realized, however. Instead, it has lead to new lines of investigation designed to understand how genes work (i.e. genomic and proteomics). We now appreciate that these mechanisms can be exceedingly complex and, until they become clearer, the use of the human genome to diagnose, understand and treat human disease will not be fully realized. Likewise, the increased use of finite element modeling can serve to illustrate how increased computing power has influenced craniofacial biomedical research. However, the validity of this approach is dependent on accurate input variables. In orthodontics, this means more and better data on things like microanatomy, physical properties, and functional inputs. Similarly, we can take advantage of computing power to more easily access the literature and as a result the assessment of clinical evidence is on the rise with more meta-analyses and systematic reviews. Unfortunately, many of these studies are finding that our clinical evidence is often of low enough quality to be of minimal value in clinical decision-making. The solution seems to be the adoption of more robust clinical research designs (e.g. randomized clinical trials), but these can be logistically complex and expensive to conduct.

There are at least three conceptual models for biomedicine that are useful, but none are totally satisfying. Biomedicine can be viewed 1) as the confluence between biology and clinical medicine; 2) through the prism of reductionism; or 3) as a complex interaction between biologic, psychologic, and social realms. Biology and medicine can be construed as two distinct disciplines with a certain amount of commonality. Biomedicine then represents areas where the two overlap to form a third discipline. The extent of overlap can vary dependent on the disciplines. The idea that biomedicine arises from successive layers of biologic complexity leads to the concept of reductionism – human disease can be explained as arising from organs, cells, molecules, and ultimately genes (6). Although this

concept may eventually be realized on a biologic level, it does tend to ignore the impact of behavioral and social factors on the etiologies and manifestations of human disease (7).

Biomedicine in orthodontics and dentofacial orthopedics: status and challenges

Biomedical activity in craniofacial biology can be categorized under four broad topics: diagnosis and counseling, rationales for treatment, therapeutics, and monitoring. Considering progress in each of these areas, it becomes clear that the availability of good biomedical evidence has not always lead to adoption in clinical practice and, more often than not, approaches are embraced by clinicians on a pragmatic basis without much support from biomedical research.

Patterning of the human dentition, specifically hypodontia, can serve to illustrate the current status of biomedicine in craniofacial diagnosis (8). Although somewhat uncommon (4–5%), hypodontia has significant dental health, psychosocial, and financial consequences for the families and affected individuals. Several genotypes have been implicated in hypodontia with Msx1 and Pax9 linked to the phenotype in humans. However, the genetic basis for human tooth agenesis is complex and not well understood. Registries may ultimately prove useful for the application of these biomedical data in genetic counseling for hypodontia families.

The most common use of biomedical data in orthodontics and dentofacial orthopedics involves justifying treatment approaches that seem to be effective or have clinical appeal. There is no shortage of examples in this category: temporary anchorage devices (TADs), self-ligating bracket systems, and corticotomy-assisted orthodontic treatment are illustrative.

Successful orthodontic tooth movement requires an intact periodontal ligament (PDL). The PDL permits tooth displacement and the subsequent pathophysiology that characterizes orthodontic tooth movement. Also, the PDL is the repository of many of the cells responsible for this adaptive response. By virtue of their lack of a PDL, TADs can provide excellent orthodontic anchorage, a virtue that accounts for their appeal for clinicians. Despite their widespread implementation in clinical practice, our understanding of the biology of TADs is minimal (9).

Self-ligating bracket systems seem to be able to provide low-friction and low-force tooth movement. Biologic and clinical studies seem to suggest that low-force appliances are very efficient and carry minimal risk (10, 11). Based on this rationale, manufacturers claim that these approaches provide better office efficiency, more rapid tooth movement, and stable arch expansion with minimal risk of gingival recession. However, many of these claims are not well supported by clinical data and our understanding of the biologic consequences of force magnitude remains rudimentary.

Corticotomy-assisted orthodontic treatment is based on the knowledge that alveolar bone remodeling is necessary for tooth movement and the suggestion that enhancing bone remodeling can lead to more rapid tooth movement. Bone remodeling is a cyclical process designed to renew bone through a series of cellular steps characterized by activation of osteoclasts, removal of a packet of bone, reversal of that process, and replacement of the bone that was removed. The molecular mechanisms that control remodeling are not well understood, but we know that the process underlies tooth movement. Some have suggested that localized boney injuries can lead to a localized increase in remodeling, known as a regional acceleratory phenomenon. Boney injury seems to provide a temporary enhancement of remodeling that briefly facilitates the rate of tooth movement (12). However, it seem likely that the future of such approaches lies, not in producing non-specific tissue injuries, but in understanding the biologic mechanisms involved and then administering bioactive substances to control them.

Therapeutic interventions in orthodontics should focus on the signals and the responses. Orthodontic signals today are exclusively biomechanical and there are two pre-requisites for their biomedical application: accurately measuring them and modeling their nature. Biomedical research suggests that altering the biologic response to orthodontic signals is feasible. There are promising developments waiting in the wings: bioactive molecules, innovative approaches to delivery and scaffolds. However, we have yet to see much work on implementing these approaches in a clinical setting.

Convenient devices for measuring biologically relevant processes are common in medicine. These include

things like dosage counters and glucose monitoring devices. These can provide patients with biofeedback as well as motivation. The 2-min toothbrush timer can be viewed in this category. Clinical measurement of biomechanical signals in orthodontics has focused exclusively on the headgear, using various timing devices. These have not been implemented for various reasons including validity, complexity, and expense. A new timer promises to address some of these problems with a simple inexpensive temperature device that can be attached to off-the-shelf headgear straps and can download data to hand-held devices. A more complicated device that can be calibrated for loads has also been developed. Using these two devices in combination, the extreme variability in data on headgear 'dose' collected on a series of patients challenges some of our clinical assumptions about biomechanical signals and suggests that they may need to be re-examined once biomechanical measurement becomes reliable, inexpensive, and convenient. We can gain a glimpse of what may be possible from implantable transducers designed for use in animal studies. One of these involves microsonometry, where a small piezoelectric device can send sonic pings to receiver arrays. The distance that the sound travels can be precisely calculated and tissue deformations determined in three-dimensions (3D) (13).

Biomechanical data gathered in clinical settings also need to be processed before they can be used in clinical settings. Clinicians today have several simple biomechanical operational assumptions that may not be entirely valid: teeth behave like free-bodies, compressive, and tensile strains can be predictably generated, and normal function has minimal impact on orthodontic biomechanics. Conversely, bioengineers recognize that the PDL has a nonlinear response to force, which is anisotropic and 3D; that this varies with load frequency and force magnitude and that conditioning from functional variation will alter these responses (14).

Biomedical research on the control of tissue turnover has emphasized the importance of several molecules that would be potential candidates as bioactive agents in altering responses. Most of those studies emphasize the importance of the osteoclast in tooth movement and suggest that by controlling osteoclastogenesis and osteoclast function we can alter the clinical response. Research implicating RANK/RANKL, OPG, and CSF in orthodontic tooth movement promises to bring biomedical control of response to the forefront of therapeutic thinking (15). Likewise, the development of osteogenic agents in combination with distraction osteogenesis also is beginning to emerge.

Despite these promising developments, there are some significant challenges that face us in orthodontic therapeutics. Many of the most promising bioactive agents are not yet commercially available. Also root resorption and alveolar bone loss may be difficult to prevent using agents that stimulate osteoclasts. Another important challenge will be to develop methods to deliver agents to specific sites, retain them there and clear them when required. These problems are not trivial and will require significant multidisciplinary collaboration. Finally, the use of bioactive agents will be subject to closer regulatory scrutiny than we have previously been accustomed to because historically most orthodontic innovations have been devices, which are subject to much looser regulations than drugs.

The use of stem cells, scaffolds, and genetic engineering will probably not impact orthodontic biomedicine, but will definitely play important roles in craniofacial treatment and the regeneration of lost or injured structures. One of the more exciting and challenging uses for these technologies will be in tooth regeneration, a process that will require the marriage of multiple tissues with complex and varied forms (16).

Monitoring treatment is another key prerequisite for orthodontic and dentofacial biomedicine. The elements that need to be monitored involve process and outcome. Specific biomarkers and sampling sites that provide valid information about orthodontic process need to be identified. The primary outcomes are tooth movement and craniofacial change.

The steps in the process of mechanotransduction are mechanosensing, transduction from a mechanical to a biochemical signal, transmission of the biochemical signal, and effector cell responses. Biomedical researchers are being unusually successful at illuminating these processes and identifying the molecules involved. Many of these have the potential for being useful biomarkers. The sampling site that has received the most attention in orthodontics has been the gingival crevice (17). Gingival crevicular fluid can be easily sampled in a clinical setting and at least one device is now commercially available to assay for fluid volume in a clinical setting. Biomedical research now available

suggests that valid information on the biologic status of orthodontic treatment can be obtained from this site. Several challenges remain, however. These relate to sampling variation and validity issues associated with contamination of the sites, location, and sequence of sampling. Most of these problems can be overcome by adhering to strict sampling protocols. The larger challenge will be to develop valid and reliable microassays that will adapt easily to a clinical environment. Likewise, 3D digital technology is rapidly approaching the point where tooth movement and craniofacial change will be monitored conveniently and precisely in the clinical setting.

The future of biomedicine in orthodontics and dentofacial orthopedics

There are several reasons for this gap between the generation of new biomedical knowledge and its implementation into clinical practice. Clinicians often have limited time and resources to incorporate new ideas into their routines. Also, innovations often require additional training. More importantly, incentives, infrastructure, and systems organizations do not exist. It is particularly noteworthy in this regard that some innovations with little biologic data do get rapidly implemented. This is the case primarily because they offer the incentives of greater efficiency and financial gain and this infrastructure is driven largely by manufacturers. A disparity in the logic and assumption of researchers and clinicians also emerges as a key barrier to implementation. These latter two points are particularly important and therefore bear closer scrutiny.

Infrastructure and systems organization that drive innovations into the clinical setting most often come from industry sponsors of the biomedical research. The usual path that technology takes in transferring to clinical practice is as follows: findings from biologic research or observations from the clinic are seen to have clinical value; their development is financed either by private investors or federal research grants; translational or pilot studies demonstrating 'proof of principle' are followed by clinical trials and finally governmental oversight and approval. This path is difficult and often requires a significant capital investment. As a result many worthy ideas can be abandoned.

The application of the hormone relaxin in orthodontics can serve to illustrate this point. Relaxin is a hormone occurring naturally in both men and women. It stimulates collagen remodeling and thereby relaxes ligaments. A start-up company recently acquired the rights to recombinant relaxin and obtained venture capital support. Several orthodontic researchers were involved in testing its potential as a bioactive molecule in orthodontic treatment. The most appealing use for relaxin might be to enhance stability following orthodontic treatment by stimulating turnover in the PDL. Histological and mechanical data were available suggesting that relaxin's effects on the PDL were characterized by decreased fiber organization and strength accompanied by greater tooth mobility. However, tooth movement studies in the rat and humans were not able to demonstrate any enhancement of the rate of tooth movement or short-term decrease in relapse (18). Many questions remain to be answered before this product can be totally eliminated from consideration as a potentially useful tool in enhancing orthodontic stability. However, the investment required to develop it further was too great and the idea was abandoned.

Another, potentially more challenging dissemination problem stems from the fundamental differences in the logic and assumptions of efficacy vs. effectiveness research. Efficacy studies test whether a treatment does more good than harm when delivered under optimal conditions. These are the types of studies that biomedical researchers strive to do. They are carefully controlled, use standardized designs and protocols, and have very narrowly defined inclusion criteria. Effectiveness studies, on the other hand, test whether a treatment does more good than harm under real world conditions. These are the studies that clinicians demand because they model the clinical setting. Studies done in these two very different settings rarely transfer easily. Studies specifically addressing dissemination and implementation are required. Dissemination studies involve the 'marketing' of biomedical knowledge to clinicians and implementation studies address the infrastructure and processes necessary to achieve adoption. The challenge for this type of research is to translate efficacy studies by considering means of reaching the target audience, assessing effectiveness in clinical settings, making allowances for reluctance to adopt, and identifying methods to facilitate implementation and maintenance of the innovation.

Conclusions

Biomedical research moves at a rapid pace. There is every indication that this will continue and even increase in the future. A tacit contract exists between researchers and the taxpayers who fund them that discovery will result in improved quality of life and wellbeing. While succeeding remarkably well in generating new knowledge, orthodontic research today is failing at implementing and disseminating biomedical findings to clinical practice. Specific strategies and approaches that are not commonly considered in efficacy studies are required to address this failing if biomedicine in orthodontics and dentofacial orthopedics is ever going to become reality.

Clinical relevance

Advances in biomedical research have the potential to transform clinical orthodontic practice. However, these are often slow to reach the patient. In contrast, clinicians often adopt promising approaches, in the absences of good data. This problem needs to be addressed with targeted research aimed at implementation of biomedical findings into the clinical setting.

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