Dental implant treatment has become the treatment of choice for complete or partial edentulism for the past 40 years. Nevertheless, dental implant therapy has shown biologic complications and different clinical outcomes in terms of success and failure. To achieve more promising treatment outcomes with minimal complications, this article proposed conceptualizing osseointegration beyond its definition, understanding its history and determinants as a phenomenon via employing omics sciences in tandem with advanced bioengineering technologies. These scientific approaches are expected to improve current technologies, detect new biologic biomarkers, and identify genes with high specificity along with their signaling pathways involved in peri-implant bone healing.1,2 The amalgamation of advanced bioengineering in implant dentistry along with the genomes in favor of endosseous wound healing will engender enormous datasets as a basis of robust knowledge for osseointegration through a system-based biology. Further, omics sciences will deepen the understanding of osseointegration mechanisms and contribute in developing new diagnostic and treatment strategies in implantology. The founding of personalized dental implant therapy will enable clinicians and implant researchers to stratify patients according to their needs.3,4 It will also serve to individualize dental implants with therapeutic features, suit the patients’ status contingent on their stratifications, construct safe and predictable clinical protocols for healthy individuals and patients with compromised conditions, and shorten healing time post–implant insertion. Subsequently, entering the genomic era will enable both implant researchers and clinicians to transfer from phenotype to genotype and revamp patient outcomes. Table 1 shows some of the common terminologies used in the field of omics sciences and personalized medicine.

Harnessing Omics Sciences and Biotechnologies in Understanding Osseointegration—Personalized Dental Implant Therapy

Ali K. Refai, BDS, MSc, PhD1/ David L. Cochran, DDS, MS, PhD, MMSci2

Keywords: bioengineering, dentistry, implantogenomics, omics, osseointegration, personalized dental implant therapy

A number of significant advances (omics and bioengineering) now enable seamless stratification of patients according to their individual genotypes. This allows for more precise diagnoses coupled with patient phenotypes and improved treatment planning and predictable outcomes. Collectively, these advances are designated as “personalized dental medicine.” To become an essential part of personalized dental medicine, this term will have a robust impact on dental implant practice. This narrative review elucidates the importance of utilizing advanced bioengineering techniques and biotechnologies in the realm of dental implants, aiming to understand gene expression profiles controlling endosseous wound healing and promoting bone formation. Thus, the first objective of the review was to present the state of the art of conceptualizing osseointegration as a phenomenon. The second objective was to pave the way for personalized dental implant therapy and to introduce “implantogenomics” for the first time. Int J Oral Maxillofac Implants 2020;35:e27–e39. doi: 10.11607/jomi.7272

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assessments, including cost-effectiveness and benefit evaluation of treatment procedures; (3) well-characterized and different demographic patient groups, and (4) assessment of the effect of various training methods and an understanding of the training and skill of the clinician on treatment outcome. These will collectively raise awareness among researchers and clinicians to start communicating their knowledge regarding the emergence of omics sciences and inspiring personalized dental implant therapy as a novel treatment strategy in implant industry. Therefore, the main objectives of this narrative literature review were to summarize the molecular basis of endosseous wound healing and introduce implantogenomics based on understanding personalized dental implant therapy. It will then elucidate the importance of utilizing omics sciences along with advanced bioengineering in fostering bone formation and modulating osteogenesis processes via un-raveling osteogenesis-related signaling cascades. It will also point out the need for critical appraisal and validation of existing singular molecular approaches and genetic data, with reported assessment of the molecular basis of osseointegration.

**Summary of Endosseous Wound Healing**

Osseous wound healing around dental implants is similar to the concept of soft tissue wound healing. Both healing concepts share similar features: four phases (hemostasis, inflammatory, proliferative, and remodeling), temporal sequence (duration), and cellular, molecular, and overall biologic processes. Physiologically, the process of endosseous wound healing around dental implants mimics the healing of intramembranous ossification without cartilage formation. Although there are similarities between soft tissue healing and osseous wound healing, soft tissue healing results in fibrous tissue formation, whereas endosseous wound healing ends with bone apposition. The mechanism of shifting to bone formation at the proliferative stage was attributed to the presence of a mechanically stable environment resulting from an angiogenetic osteogenesis process at the bone-implant interface.

In 2011, Terheyden et al reviewed the scientific information of cell-cell communication, their secretions, crosstalk, and signaling pathways, at each stage of osseous healing around dental implants, leading to a holistic understanding of the osseointegration phenomenon. Briefly, the sequences of biologic events leading to osseointegration involved: (1) hemostasis, coagulum formation, and transient inflammation; (2) proliferation and granulation tissue formation; (3) bone formation (provisional matrix de novo bone, woven bone, parallel-fibered bone, and lamellar bone); and (4) bone remodeling. The principal factors that regulate endosseous wound healing are cells dominating the osteotomy site.

Cells populate each stage of the healing process and are found to coordinate and communicate with each other by producing a myriad of cytokines, chemokines, growth factors, extracellular matrix proteins, hormones, and ions, which orchestrated the osseous healing process at the bone-implant microenvironment. (Table 2). It is well understood that the cells initiating the osteogenesis process are well controlled by sequential activation of typical genes. Activated cells along with their secretory profiles communicate with each other and the extracellular matrix through juxtacrine, paracrine, autocrine, and endocrine signaling mechanisms. Categorizing gene profiles and their signaling cascades in tandem with endosseous wound healing stages will allow implant dentistry to be individualized therapy to unique biomechanistic upregulating genes in favor of osseointegration. Consequently, this approach may result in a new concept for osseointegration known as “implantogenomics” and pave the way for personalized dental implant therapy and ultimately improve patient outcomes.

A myriad of obstacles must be overcome to achieve these goals. For example, high-throughput genetic and transcriptome data obtained via omics technologies reveal the cellular complexity of osseointegration. Such huge data must employ a powerful bioinformatics program to precisely determine which genes in each stage of endosseous wound healing will have a positive impact and which genes have a negative effect in the process of osteogenesis around dental implants. Thus, a broad spectrum of experimental and clinical studies is needed. A summary of the essential events that normally take place upon osseous wound healing is presented in Fig 1.

**Genomics Signature of Endosseous Wound Healing**

In tandem with the histologic observation of osseointegration around dental implants, molecular assessment was evaluated to depict a correlational illustration of both phenotype and genotype at the early stages of the osteogenic process. Cells dominate osseous healing stages and are regulated by an ample number of genes, and then, such activated cells secrete a myriad of proteins and hormones resulting from genes expressed during the process of osseointegration.

Early molecular assessment of osseous healing demonstrated that the placement of dental implants evokes a cascade of healing events associated with a gene expression profile shifting from genes upregulated at immunoinflammatory processes to gene expression upregulated in favor of angiogenesis, osteogenesis, and neurogenesis. The studies investigating the gene and protein profiles around dental implants showed that they emulate the gene profiles taking place upon
bone formation, bone wound healing, and repair and healing of extraction sockets.\textsuperscript{18,20} Normally, the mechanism of bone formation involving transcriptional factors regulates the osteoblast phenotype, which in turn modulates the genes that cipher for bone matrix proteins.\textsuperscript{28} Surface implant characteristics including topography and chemistry influence the pattern of gene expression for bone formation–associated proteins. The surface topography modulation of osteogenesis was found to be osteoinductive transcription factor–dependent (ie, Runx2/Cbfa1 and Osx/Sp7).\textsuperscript{33,34}

It is noteworthy that the genetic network in osseointegration is highly intricate.\textsuperscript{35} The actions of typical activated genes involved in osseous wound healing (Table 2) are partially specific and exert versatile functions on cells in the vicinity of wound healing.\textsuperscript{35,36} For optimal tissue reconstruction, the mediators must be accurately balanced to avoid mutilation and/or unwanted effects, an area that demands further research.

The last two decades have seen a plethora of studies investigating the genetic expression profiles and their mechanisms of upregulating and downregulating specific genes around the dental implant both in vitro and in vivo. Most of these studies relied on one singular molecular technique (ie, ELISA, qRT-PCR, etc). A few more recent studies have reviewed and employed omics technologies for understanding bone regeneration and osseointegration mechanisms around dental implants and how different molecules interact and crosstalk at the biomaterial interface. Although this is a narrative review, a thorough PubMed and MeSH search was carried out, aiming to identify studies that assessed the molecular basis of osseointegration and/or endosseous wound healing. Because of the breadth of the topics, Table 3 shows a summary of selected studies particularly focused on utilizing molecular technologies and omics sciences exploring gene expression profile of osseointegration.\textsuperscript{7,8,31,32,37–49}

Despite the recent advancement in the omics era, biotechnology and bioinformatics studies investigating the genetic basis of osseointegration have been limited to redundant genes and proteins and generally lack specificity, reproducibility, and validated genotyping accuracy.\textsuperscript{50–52} Moreover, there is a scarcity of useful systematic reviews and meta-analyses to understand the best evidence of genes expressed during endosseous wound healing involved in osseointegration, as well as a lack of profound bioinformatics tools integrating different genes and their signaling pathways. It is conceivable that advanced omics technologies may confer novel approaches for further understanding of cell-cell communication during osseous healing, as well as leveraging molecular assessment of genes profiling osseointegration both in vitro and in vivo. Such a study would (1) identify specific genes that promote osseointegration at each stage of peri-implant wound healing and (2) evolve new modalities and strategies in implant therapy with high efficiency and safety.
# Synopsis of Endosseous Wound Healing

<table>
<thead>
<tr>
<th>Hemostasis</th>
<th>Inflammation</th>
<th>Proliferation</th>
<th>Remodeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding and serum adsorption</td>
<td>Transient</td>
<td>Fibroplasia</td>
<td>ECM synthesis and degradation</td>
</tr>
<tr>
<td>Fibrin coagulum</td>
<td>Activate innate immunity</td>
<td>Angiogenesis</td>
<td>Persistent bone modeling and remodeling</td>
</tr>
<tr>
<td>Platelet activation</td>
<td>Elaboration of growth factors</td>
<td>Reepithelization</td>
<td>Removal of woven bone (CO)</td>
</tr>
<tr>
<td>Complement activation</td>
<td>Wound debridement</td>
<td>ECM synthesis</td>
<td>INC tensile strength</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>Angiogenic</td>
<td>Granulation tissue formation</td>
<td>DEC cellularity and vascularity</td>
</tr>
<tr>
<td>Blood born cells and platelets</td>
<td>Fibrinogenic</td>
<td>Woven bone formation</td>
<td>OB + OC act interdependently bone hemostasis</td>
</tr>
<tr>
<td>Platelets neutrophils</td>
<td>Cells recruitment</td>
<td>Formation of lamellar bone (DO)</td>
<td></td>
</tr>
<tr>
<td>Monocyte macrophages (M1)</td>
<td>Fibroblast activation</td>
<td>Osteoclast, osteoblast</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>Evidence of bone formation (CO)</td>
<td>Resident macrophage (M2)</td>
<td></td>
</tr>
<tr>
<td>Complement C5, EGF, TGFβ, PDGF, IL1, IL6, TNFa, bFGF, IL8, PAF, and PF4</td>
<td>Hours to days</td>
<td>RANK, RANKL, MCSF, BMPs, osteoproteoglycans and secretion from OB and OC</td>
<td></td>
</tr>
<tr>
<td>Osteoblast osteoclast FGF, MMPs, TGFβ, bFGF, c-TGF, PDGF, VEGF, TNFa, BMPs, IGF, IL1, and IL6.</td>
<td>Weeks to months to years</td>
<td>How do OCs control and activate OBs? Are Macrophages present as preregeneration?</td>
<td></td>
</tr>
</tbody>
</table>

**Fig 1** Summary of the essential events normally takes place upon osseous wound healing. CO = contact osteogenesis; DO = distance osteogenesis; OB = osteoblast; OC = osteoclast.
Dental Implant Surface Modifications: Achievements, Limitations, and Future

The success of dental implants depends on an optimal direct contact between the living bone and implant, a phenomenon known as osseointegration. Since the foundation of osseointegration, dental implant characteristics (chemical, physical, mechanical, and topographic) were substantially advancing and developing to engineer implant surfaces in favor of speeding biologic responses and technically promoting osseointegration. There is an immense number of published works distinctly showing that implant surface properties are able to modulate osseous healing by influencing the cells at the bone-implant interface to proliferate and differentiate and then produce several genes and proteins that serve as key regulators to inflamo-immuno-angio-neuro-osteogenesis processes.

Several means have been implemented to advance surface modifications on dental implants to improve the biologic surface properties and to exert a decisive modulation of the osteogenesis process (ie, nanostructures, biomimetic coating technology, etc). However, implant failures still existed and were estimated to be between 19% and 65%. Dental implant failure was attributed to persistent infections surrounding the dental implant (peri-implant mucositis and peri-implantitis), which were considered to be major biologic complications of dental implant therapy, threatening its longevity. In addition to that, the presence of patients with medically complex diseases may have quantitative and qualitative compromised osseous wound healing and may dramatically affect the osseointegration process.

Studies coupling omics sciences and advanced engineering may thus have a positive influence in developing the realm of implant dentistry by resolving the following: (1) patient selection (healthy vs disease), (2) assimilating gene expression profiles (stratification of population), and (3) identifying genetic networks of osseointegration linked to endosseous wound healing stages with more specification. Therefore, an advanced dental implant design envisages, as a single tailored implant, functioning as bioreactors (synthesis of useful substances) and bioactivators (optimizing biologic functions). Such individualized dental implants will grant the periodontist, surgeon, prosthodontist, and oral implantologist a way to foster osseointegration, optimize success and survival rate of their dental implant therapy, and overcome challenging conditions.

Table 2  Summary of Essential Cytokines, Chemokines, Growth Factors, ECM Proteins, and Transcription Factors Involved in Wound Healing Stages

<table>
<thead>
<tr>
<th>Cytokines and chemokines</th>
<th>Growth factors</th>
<th>ECM proteins</th>
<th>Transcription factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokines:</td>
<td>Transforming growth factors</td>
<td>Structural proteins: 1-Collagens: bone and cartilage</td>
<td>Runx2: Runx2, (Cbfal/PEBP2aA/AML-3/Osf2), central control gene within the osteoblast phenotype</td>
</tr>
<tr>
<td>Interleukin 1, 6, 8, and 2</td>
<td>Bone morphogenetic proteins and BMP receptors</td>
<td>2-Elastin</td>
<td>Bone formation markers: ALP, Coll I, OCN, ONC, OPN, BSP, and MMP1</td>
</tr>
<tr>
<td>Interleukin 4, 13, 10, 18, and 27</td>
<td>Platelet-derived growth factors</td>
<td>3-Albumin</td>
<td>Osterix (Osx/Sp7): Characterized osteoblast-specific genes</td>
</tr>
<tr>
<td>Interleukin – 1ra</td>
<td>Vascular endothelial growth factor</td>
<td>Glycosaminoglycans and proteoglycans: Hyaluronic acid, dermatan sulfate, chondroitin sulfate heparin, heparan sulfate, and keratan sulfate</td>
<td></td>
</tr>
<tr>
<td>Chemokines: CCL2 (MCP1), (CCL3) MIP 1 alpha, CX3CL1, CXCL10 and CXCL11, CXCL8 or IL-8 and CXCL12</td>
<td>Epidermal growth factor</td>
<td>CX3CL1, CXCL10 and CXCL11,</td>
<td>Dlx5: Differentiation and maturation of the osteoblast phenotype</td>
</tr>
<tr>
<td>Colony-stimulating factors: (cytokine immunostimulators) GM-CSF, M-CSF, and G-CSF</td>
<td>Heparin-binding epidermal growth factor</td>
<td>CXCL8 or IL-8 and CXCL12</td>
<td>Alkaline phosphatase: Indicator of cellular activity and differentiation</td>
</tr>
<tr>
<td></td>
<td>Keratinocyte growth factor (known as FGF-7)</td>
<td>Matrix-cellular proteins: Thrombospondins, osteopontin, tenascins, periostin (POSTN), alkaline phosphatase, osteonectin, bone sialoproteins, and osteocalcin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fibroblast growth factor FGF-1</td>
<td>Proteases: Tissue remodeling and ECM degradation (MMPs and TIMPs)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insulin-like growth factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatocyte growth factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Connective tissue growth factor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The International Journal of Oral & Maxillofacial Implants
<table>
<thead>
<tr>
<th>Studies</th>
<th>Study model Technique Time</th>
<th>Surfaces Target genes</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schneider et al,37 2003</td>
<td>In vitro RT-PCR 72 h</td>
<td>Grooved and sandblasted Cbfa1 and BSP II</td>
<td>Surface topographies modulated gene expression of key osteogenic factors.</td>
</tr>
<tr>
<td>Schneider et al,38 2004</td>
<td>In vitro RT-PCR 3 wk</td>
<td>Grooved and sandblasted Runx2/Cbfa1 and OCN</td>
<td>Surface topographies increased Runx2 and OCN expression.</td>
</tr>
<tr>
<td>Masaki et al,39 2005</td>
<td>In vitro qRT-PCR 72 h</td>
<td>Tioblast, Osseospeed SLA-1 and SLA-2</td>
<td>Implant surface topographies modulated expression of transcriptor factors involved in osteogenesis.</td>
</tr>
<tr>
<td>Kojima et al,41 2011</td>
<td>DNA microarray 1, 2, and 4 wk</td>
<td>Cp-Ti with chamber Genes associated with ECM and bone resorption</td>
<td>86 genes upregulated in the implant healing group in at least one time point of healing required for osseointegration.</td>
</tr>
<tr>
<td>Donos et al,32 2011</td>
<td>Microarray hybridization 4, 7, and 14 d</td>
<td>SLA and SLActive Genes associated with osteogenesis process</td>
<td>SLActive exerted a positive regenerative response enhancing endosseous wound healing process.</td>
</tr>
<tr>
<td>Ivanovski et al,33 2011</td>
<td>Microarray hybridization 4, 7, and 14 d</td>
<td>SLActive Genes associated with early and late osseointegration and signaling points</td>
<td>Early osseointegration regulated via I-kB kinase/NF-kB pt, whereas later stage regulated by TGF-b/BMP, Notch, and Wnt signaling.</td>
</tr>
<tr>
<td>Mamalis and Silvestros,43 2011</td>
<td>DNA microarray 24 h</td>
<td>SLA, SLActive, and smooth genes control and regulate ECM and bone formation</td>
<td>SLActive enhanced an earlier osteogenic response than the SLA surface itself.</td>
</tr>
<tr>
<td>Lin et al,44 2011</td>
<td>qRT-PCR 3, 7, 10, and 14 d</td>
<td>Cp-Ti treated with hydroxylation/hydration 17 p genes linked to wound repair</td>
<td>Peri-implant healing process mimics the dynamics of the healing alveolus (with minor variation).</td>
</tr>
<tr>
<td>Thalji et al,45 2013</td>
<td>Whole-genome microarray 2 and 4 d</td>
<td>Microroughened (AT-II) and nano surface implant (AT-I) Genes involved in biologic bone formation process</td>
<td>Nano-implant AT-I modulated bone formation more prominent than AT-II at D 4 vs D 2.</td>
</tr>
<tr>
<td>Bryington et al,46 2014</td>
<td>RT-PCR and PCR arrays 1, 3, and 7 d</td>
<td>Microroughened Nanotopography Osteogenesis-associated genes Cytokine-associated genes</td>
<td>Osteogenesis genes upregulated on both surfaces at 3 and 7 d Nanotopography-induced genes that regulate the early phases of osseointegration.</td>
</tr>
<tr>
<td>Thalji et al,47 2014</td>
<td>Whole-genome microarray 3 and 7 d</td>
<td>Roughened surface Nanoscale surface Genes associated with endosseous wound healing stages</td>
<td>Osteogenesis genes upregulated at 7 d vs 3 d for both implant surfaces. Markers for “M2” macrophage were observed.</td>
</tr>
<tr>
<td>Thalji et al,48 2015</td>
<td>Whole-genome microarray 3 and 7 d</td>
<td>Tioblast (roughened) Osseospeed (nanoscaled) Genes related to osteogenesis processes</td>
<td>Similar trends in gene expression were noted in implant-adherent cells regardless of implant surface and smoking status at early time point.</td>
</tr>
<tr>
<td>Altmann et al,49 2017</td>
<td>qRT-PCR 1 and 7 d</td>
<td>Zirconia-based implant: microroughened and smooth 90 genes associated with osteoblast and fibroblast</td>
<td>Zirconia implant modulated genes involved in biologic processes of bone repairing. Gene modulation was dual dependent on time and biomaterial.</td>
</tr>
<tr>
<td>Sartori et al,50 2018</td>
<td>qPCR, NGS, and Western Blot 3, 7, and 14 d</td>
<td>Nanotopography Osteogenic gene markers</td>
<td>Nanotopography surfaces affected MSC differentiation to osteoblast. miRNAs expressed regulation of osteogenic genes, and they are topographic dependent.</td>
</tr>
</tbody>
</table>
Moreover, bio and/or multi-functionalization of the implant surface will modulate osteogenesis based on individualized scientific evidence and technically will strive to improve the future of the dental implant industry.

**Personalized Medicine and Dentistry**

There is no one uniform definition of personalized medicine. Generally, personalized medicine concentrates on the development of new individualized therapies and diagnostic tests in order to optimize patient health. Personalized medicine has been extensively reviewed in the pharmacogenomics and pharmacogenetics disciplines. Several domains are used to describe the concept of personalized medicine, including customization of health care, integrating genomics-based medicine, tailoring therapy to meet the need of stratified individuals based on the characteristics genotype and phenotype, burdening epigenetic-environmental alteration factors, and employing bio-health informatics. Overall, the completion of the human genome project and advances in biotechnologies foster the concept of personalized medicine and accelerate its transition to both medical and dental clinical practice.

In tandem with prospective health care, both personalized medicine and personalized dental medicine aim to pave the way to shift the old paradigm from disease management to disease prevention and health care promotion. Personalized dentistry, as suggested, adopts the genomic medicine information coupled with advanced biotechnology to usher development of tailored therapy for craniofacial-oro-dental health needs. Understanding the genetic basis of diseases along with their environmental factors supports the concept of shifting from phenotype to genotype and eventually maintaining long-term disease prevention. Meanwhile, recognizing the genetic details of biologic responses (ie, system biology) to dental therapeutics (ie, drugs, implants, bone regenerative materials, etc) in the era of omics technologies will fuel the fields of medicine and dentistry with novel diagnostic and therapeutic strategies. Personalized medicine and dentistry will then assist health care providers in selection of the proper therapy, integrating the best treatment protocols suited for a stratified subpopulation, reducing unwanted side effects, and boosting patient success outcomes.

Although personalizing medicine and dentistry takes advantage of understanding the genomic basis of systemic and oral diseases derived from “omics sciences,” most of the human diseases and disorders conducive to early diagnosis and prevention remain under investigation and in their infancy.

Personalized dental implant therapy was suggested previously, focusing solely on bone turnover and remodeling upon immediate loading of a dental implant. Studies were more generalized, and patient stratification and genotype-phenotype correlation were not reported. For example, it has been hypothesized that residual ridge resorption (RRR) may have a genetic association resulting from genome sequence variations among individuals in terms of single nucleotide polymorphisms (SNPs). The presence of SNPs may yield genetic diagnostic tests, which could identify patients at risk of jaw resorption and allow for stratification of elderly individuals.

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**Table 3  Example of Studies (In Vitro and In Vivo) Evaluating Gene Expression Profiles of Peri-implant Osseous Healing (continued)**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Study model</th>
<th>Technique</th>
<th>Time</th>
<th>Surfaces</th>
<th>Target genes</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Araújo-Gomes et al, 2018</td>
<td>In vitro (genomics) and in vivo (proteomics)</td>
<td>qRT-PCR for genomic Nano ACQUITY UPLC system for proteomic</td>
<td>7 and 14 d: Genomic 2 and 4 wk: Proteomic</td>
<td>SAE-Ti surface 70M30T-coated implants Genomic: bone markers Proteomic: 113 proteins involved in cellular, biologic processes regulation</td>
<td>Osseointegration achieved on both surfaces. Coated implants displayed osteoinductivity and uncoated implants demonstrated osteoconductivity.</td>
<td></td>
</tr>
<tr>
<td>Calciolari et al, 2018</td>
<td>In vivo: genomics (human) and proteomics (animal) For Genomics: Microarray hybridization For proteomics: Liquid chromatography</td>
<td>4, 7 and 14 Ds</td>
<td>SLA and SLA-active Genes and proteins specific to bone formation-related signaling pathways.</td>
<td>Correlation between genes and proteins expression around dental implant for the first time. Genomic and proteomic data showed that the osteogenesis process takes place mainly at 7 and 14 d of healing on both SLA and SLActive surfaces. SLActive modulates bone formation and the crosstalk of pathways at multiple levels of healing processes.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Today, health care professionals are advised to be versed in emerging research of genome and bio-health informatics and their applications. They also must be knowledgeable about the power and limitation of the advanced genomic technologies and strategies. As research and discovery advance, personalized dentistry, along with its transformational driver to clinical practice, continue to illuminate the understanding with novel therapeutic approaches to establish rapid and effective health care. To be successful, it has been advised that clinicians, dentists, scientists, educators, and allied health science professionals should be incentivized for personalized medicine and personalized dentistry via a continual process of education and changing educational practice environment.95,96

Personalized Dental Implant Therapy: Introducing “Implantogenomics” (Implantomics)

Research innovation as a biologic and digital revolution will continue to augment orofacial health care advancement and assert the future of precision medicine and dentistry emphatically.90 Accordingly, the proper investment of tool kits available on biotechnologies will have a promising future for tissue engineering, including the replacement of missing organs and the regeneration of damaged tissue (ie, teeth and hip replacement and bony defect). Dental implants are a therapeutic approach that have both positive effects and biologic complications on certain occasions. Thus, mirroring pharmacogenomics, an “implantogenomics” (implantomics) concept is proposed to help pave the way for personalized dental implant therapy. To the best of the authors’ knowledge, this is the first time that the concept of implantogenomics (implantomics) has been introduced in the literature.

The deciphering of the genomics basis for endosseous wound healing will further expand the knowledge of the precise mechanisms of bone formation around dental implants and improve the selection of the proper biomaterials for healthy individuals as well as for those patients with compromised bone and challenging conditions. It will also unravel how genomes and their tangent signaling pathways are arranged to accelerate tissue repair and regeneration. Overall, this will impact the future of implant technology as a promising treatment modality that serves different types of stratified patients.

To achieve success and increase innovation, the scientific integration module of developing technologies must be established. Examples of advanced biotechnologies include omics sciences, biomimetic approaches, drug therapy (protein and peptide), systems biology (ie, stem cell biology, bio-root replacing dental implants), nanotechnology, phenomics (phenotypes on a genome-wide scale, three-dimensional [3D] printing and digitalization), and contemporary bioinformatics. The emergence of substantial datasets along with powerful bioinformatics from developing regenerative technologies will be spurring evolution of the dental implant industry.97–115 The ideal integration of interdisciplinary regenerative approaches will then feasibly leverage coining of personalized dental implant therapy as well as its new concept “implantogenomics” (implantomics) (Fig 2).

Taken together, personalized dental implant therapy is a branch of science emerging from personalized dental medicine, which descended originally from personalized medicine. Its main objective is to improve dental implant therapy to be an effective, reliable, and safe therapy individualized to a person’s genetic makeup. The future of personalized dental implant therapy will be founded by gaining consistent and specific information from advanced biotechnologies and employing omics tools. It will assist the implantologist in selecting the right implant, right patient, right position, and right time. In analogy with pharmacogenomics, which is part of the field of personalized medicine, does dental implant therapy, which is part of the field of personalized dentistry, follow the same path? The answer will be a breakthrough in the realm of implant dentistry and open the door for the main question: Can personalized dental implant therapy be established?

In summary, personalized dental implant therapy can be conceived as follows:

1. Selecting proper omics tools
2. Identifying growth factors and their signaling pathways with high specificity
3. Integrating and handling biologic and environmental information carefully
4. Establishing contemporary bioinformatics tools
5. Integrating different omics data along with their signaling pathways
6. Establishing proper guidance for patient selection and stratification
7. Modifying dental implant surfaces in favor of accelerating endosseous wound healing
8. Individualizing dental implants to each bracket of stratified patients to an unprecedented degree

(Four Rs):

- Right treatment → Implant design and legitimate protocols
- Right patient → Stratification and minimal biologic complication outcome
- Right time → Biophysiologic events.
- Right position → Jaw size and status
CONCEPTUALIZING OSSEOINTEGRATION
A MODEL FOR GENETIC BASIS OF ENDOSSEOUS WOUND HEALING:
STATE OF THE ART

BIOENGINEERING
- Biomaterial resources
- Biomaterial bank
- Featured implant
- Electrochemical anodization
- Self-assembly tools system
- Computer science
- 3D printing
- Stem cells and scaffolding
- Biomimetic approach to dental implants

OMICS
- Bioinformatics
- Biostatistics
- Analysis
- Data filtering
- Data acquisition and stratification
- Specific genes identification via signaling cascade
- Patient stratification
- Implant embellishment via several means
- Treatment prognostication
- Patient-centered outcomes

OMICS
- Genome
- Transcriptome
- Proteome
- Microbiome
- Metabolome
- Lipidome
- Epigenome
- History and clinical Ehealth record

BIOENGINEERING
- Experimental and clinical research
- Cellular and molecular mechanism
- Biologic validation
- Target validation

OMICS
- Sequence
- Structure
- Expression
- Pathway
- Regulation
- Network

Figs 2  Integration of omic sciences and bioengineering techniques and bioinformatics for personalized dental implants and introducing implantogenomics “implantomics.”
Table 4  Summary of Challenges and Unanswered Questions

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Unanswered questions in osseointegration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Obtaining a detailed understanding of the heritable variations within human genome</td>
<td>Q1: Is osseointegration independent from normal wound healing?</td>
</tr>
<tr>
<td>2. Characterizing these genetic variations among individuals and populations</td>
<td>Q2: If endosseous wound healing has many similarities with the general wound healing mechanism, what will be the turning point signals of osseous implant healing without noticeable formation of fibrous tissue?</td>
</tr>
<tr>
<td>3. Characterizing these genetic variations based on sources of origin (body fluids vs tissue sample)</td>
<td>Q3: Where do the BMP first signals come from (platelets, bone debris, ECM deposited, OsteoMac concept, or summation of biologic events initiate osteogenesis)?</td>
</tr>
<tr>
<td>4. Considering patient health (ie, patients with systemic diseases associated with existing genetic variations vs healthy individual)</td>
<td>Q4: Are osteoblasts differentiated from pericytes?</td>
</tr>
<tr>
<td>5. Considering ethnicity, gender biology, environmental factors (epigenetic), and their effect on gene expression profiles, as well as patient stratification</td>
<td>Q5: Are inflammation, angiogenesis, neurogenesis, and skeletogenesis mechanisms of endosseous wound healing poorly understood and do they warrant comprehensive studies?</td>
</tr>
<tr>
<td>6. Establishing a working knowledgeable representation model</td>
<td>Q6: Are the roles of growth factors, cytokines, ions, hormones, and others fully understood in both scales (micro vs nano) of implant surfaces?</td>
</tr>
<tr>
<td>7. Facilitating reasoning on high-dimensional heterogeneous data, using probabilistic graphical models (ie, Bayesian Networks)</td>
<td>Q7: What are the crosstalks between mesenchymal and nonmesenchymal cells, as well as their products in regulating osteogenesis within the microenvironment at bone-implant interfaces?</td>
</tr>
<tr>
<td>8. Eliminating noise biologic signals by filtering irrelevant genes and identified the one on target</td>
<td>Q8: Does robust understanding of genetic basis of osseointegration with high specificity guarantee a significant impact in terms of therapeutic application (mimicry pharmacogenomics) as well as accelerating healing time?</td>
</tr>
</tbody>
</table>

Challenges and Unanswered Questions in Osseointegration

The co-evolution of innovation between omics sciences and advanced bioengineering will have a positive impact in resolving unanswered questions and conquering challenges. Further, expanding the foundation of personalized dental implant therapy and launching the concept of implantogenomics will significantly play a key role in overcoming the biologic problems yet to be understood in osseointegration and bone regeneration. Table 4 shows examples of the important challenges and questions associated with osseointegration.

Future Prospectus

An increase in genomic knowledge and its relevant emerging scientific approaches (ie, proteomic, transcriptomic, etc) will revamp the dental implant industry. It is conceivable that understanding the specific and validated genes that are involved in osseointegration, via employing advanced biotechnologies, will grant the foundation of holistic system biology of osseous wound healing (ie, genetically modified animals “transgenic and knockout,” reverse genetic approaches, etc). Thus, pursuing personalized dental implant therapy and its proposed concept “implantogenomics” as novel therapeutic strategies could serve stratified individuals with healthy and compromised bone and provide appropriate types of treatment.

Despite the throughput datasets from omics sciences, the emerging information is still limited and in its early stages. Medical and dental fields will clearly benefit from the omics technologies in both diagnostic and therapeutic aspects. Omics sciences are also promising technologies to investigate the holistic mechanisms of bone regeneration and osseointegration. Omics sciences will further assist in data mining, help in comparing different datasets, correlate genes and proteins to their pathways, and evaluate the existing loading protocols in regard to bone formation.

Currently, the major problems encountered among the publications of early molecular assessment for osseointegration can be categorized into two: first, general limitation of evidence from gene expression data, which will require conducting of ad hoc posttrial analysis as well as annotations; and second, a lack of coherent data, systematic reviews, and meta-analyses, because of scant data of genetics information linked to their signaling pathways and absence of their validation among published studies. Solving these problems warrants well-designed experimental and clinical investigations harnessing omics technologies in order to attain desirable outcomes of information. This information should explain the biologic process of bone formation around dental implants without data overlapping and variations at each stage of endosseous wound healing.

The eruption of huge information from omics technologies requires strict manipulation and validation of such datasets. To achieve such significant goals, it is advisable to take advantage of evidence-based and meta-analytic approaches reported previously, which tried to answer significant clinical questions using a systematic approach conducive to determining.
the state of science in implant dentistry. Meanwhile, unanswered and debatable biologic and molecular questions may follow to determine the state of the art of the genetic basis of osseointegration. These scientific approaches should enable the biologic and clinical outcome variables to be integrated and to ensure coherent data management and analysis.

CONCLUSIONS

Whole genome-wide profiling studies are widely carried out to unravel the genetic basis regulating the process of endosseous wound healing through its consecutive stages. Nevertheless, the process of osseointegration associated with micron and nano surfaces is poorly understood. Studies have shown that the genes expressed in relation to the biologic stages of wound healing were found to be implant surface–dependent. Thus, production of tailored bioactive dental implants that are able to modulate osteogenesis process as needed is more promising in the future.

At the present time, it is difficult to conceptualize implant osseointegration with its definite underlying biologic mechanisms. Limited evidence from transcriptome data and their signaling cascades have indicated the complexity of the genetic network associated with the osteogenesis process. The genetic pathways of osseointegration in individuals with relative risk factors of implant failure are yet to be investigated (ie, radiation, metabolic bone disease, etc.). Therefore, harnessing omics sciences and advanced bioengineering along with contemporary bioinformatics tools in understanding the mechanisms of osteogenesis and their specific genetics network should provide a more positive impact on patient care outcomes. Moreover, it will impart strategies in improving patient selection, optimizing bone-implant integration, shortening healing time, facilitating immediate loading, and yielding long-term clinical success of dental implant therapy. Finally, comprehension of osseointegration mechanisms based on employing omics sciences may serve as a stimulus toward personalized dental implant therapy and its conceptualized concept “implantogenomics.”

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REFERENCES


