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Osseoperception following dental implant treatment: a systematic review

Running title: Review on osseoperception

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Authors contribution

Dandan Song worked on data collection and analysis, drafting manuscripts, critical revision and

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approval of manuscript. Sohaib Shujaat worked on critical revision and approval of manuscript and Prof. Kaan Orhan assisted on data analysis. Prof. Constantinus Politis and Prof. Reinhilde Jacobs contributed to study design.

Abstract

Objectives: Osseoperception is defined as the ability to perceive tactile sensation via mechanoreception in the peri-implant environment. The objective was to systematically review the available literature on the osseoperception phenomenon following dental implant placement and to explore potential factors which might improve the perception capacity.

Material and methods: A literature search was performed using PubMed, Cochrane, Embase, and Web of Science databases up to June 2021. Both human and animal studies assessing sensory capacity or innervation following implant placement were included in this review. Two reviewers independently performed the study selection, data extraction and quality assessment of the included studies. The methodological quality of the included papers was assessed using Cochrane risk of bias for human studies and SYRCLE's risk of bias tool for animal studies.

Results: The electronic search of databases yielded 1667 results. Following removal of duplicates,

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title and abstract screening and full-text reading, 22 publications were eligible to be included in the review. Psychophysical evidence from 14 studies indicated a lower tactile function of implants, where active and passive threshold level were found to be 5 and 50 times higher for implants compared to natural teeth, respectively. The neurophysiological evidence from 3 studies indicated cortical plasticity following dental implant placement, measured via trigeminal nerve evoked potentials and functional magnetic resonance imaging. Histological evidence from 5 studies demonstrated the presence of myelinated nerve fibres in the peri-implant tissues. Additionally, immediate implant placement and loading showed beneficial effect on peri-implant tissue (re)innervation, however, no other biological or physiological factors could be identified influencing osseoperception.

Conclusions: The reported evidence supported the existence of so-called osseoperception phenomenon for restoring the sensory feedback pathway following oral implant rehabilitation. Further studies are required to identify factors that might further assist physiological integration of the oral implants in the human body as such to approach natural oral function.

KEYWORDS: Dental implant, osseoperception, tactile function, neurosensory innervation

1 | INTRODUCTION

Natural teeth are surrounded by an abundant number of periodontal mechanoreceptors, responsible for controlling oral motor functions such as mastication and speech. Most of these receptors are found in the periodontal ligaments (PDLs). Following tooth extraction, the PDLs get damaged which could lead to an irreversible damage of these functional mechanoreceptors. Thereby, deteriorating the sensory feedback pathway and sensory-motor interaction, which in turn might lead to the impairment of oral motor functions.

Implant-supported prostheses seem to offer an improved tactile function and fine-tuning of natural oral motor behavior compared to conventional fixed and/or removable prostheses[1-3]. Previous studies suggested that bone-anchored prostheses have the ability to improve the (re)innervation pattern in the peri-implant region by transmitting mechanical stimuli directly to the bone[4,5]. However, multiple factors, such as low nerve fibre density and lack of PDL receptors following implant placement make it difficult for patients to perceive chewing forces and passive

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occlusal loading. Consequently, the high chewing forces might cause an implant overload which in turn can lead to bone resorption and eventually implant failure[4,6,7]. Thus, a proper function is required to maintain implant longevity and global physiological integration of dental implant in the human body.

Osseoperception refers to the sensory response following mechanical loading evoked by peri-implant mechanoreceptors in the absence of a functional PDL mechanoreceptive input[8]. Primarily, the (osseo)mechanoreceptive function is evoked from the bone, yet it might also be derived from joint, muscle, mucosa and periosteal tissue which provide mechanosensory information in relation to jaw function and occlusal contacts of artificial teeth (Figure 1) [9-11].

Although, the concept of osseoperception initially originated from the studies focusing on the restoration of tactile perception in patients with osseointegrated orthopedic artificial limbs following amputation[1,12]. However, the term "osseoperception" was coined by Prof. P-I Brånemark and colleagues, who pioneered the research on osseoperception in patients with dental implants.

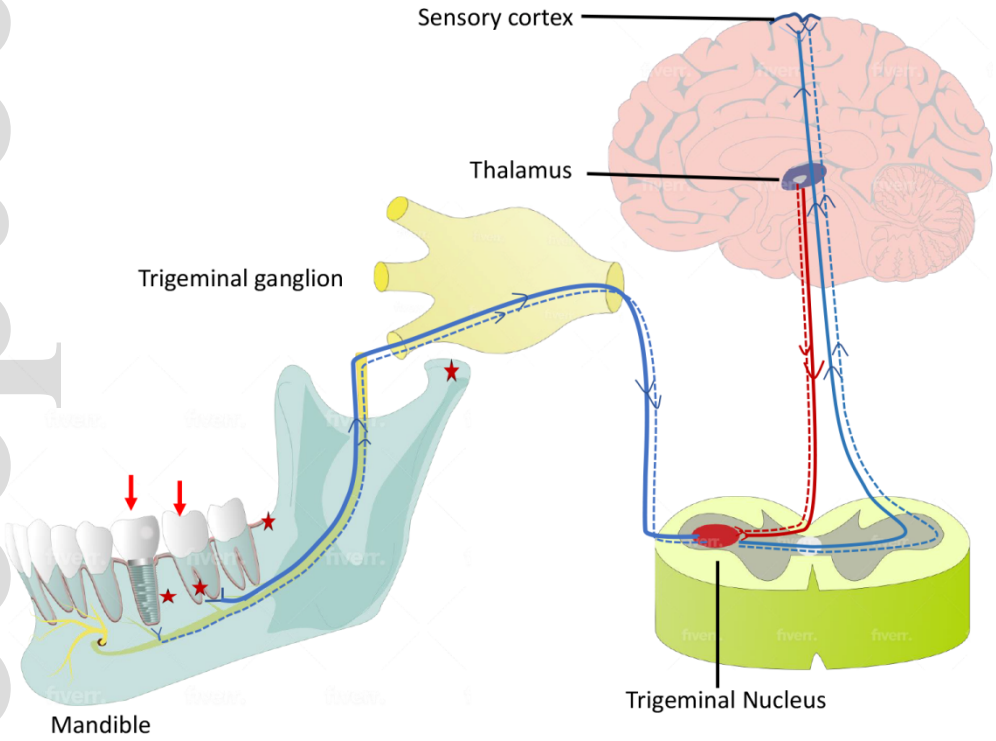


FIGURE 1 Sensory pathway for tooth/implant stimuli. Activation of periodontal sensory endings

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derived from temporomandibular joint, periosteum, gingiva, periodontal ligament (PDL), mucosa, and alveolar bone receptors (red stars) following stimuli exertion on tooth through the trigeminal neurons located in the trigeminal ganglion. Thereafter, signals are sent to the ventral posterior nucleus of thalamus and sensory cortex allowing the natural neurosensory pathway feedback (Blue and red solid lines). For the implant, PDL mechanoreceptive input is lacking, thereby hampering the peripheral feedback pathway (Blue and red dashed lines).

So far, multiple methodologies have been applied for evaluating osseoperception within the peri-implant region following dental implant placement in both humans and animals, which include, histological, psychophysical and neurophysiological assessment techniques. Histological methodologies include microscopic assessment of the quantity and quality of nerve fibres at the peri-implant region. Psychophysical techniques are mainly based on assessing either active tactile sensibility (ATS) or passive tactile sensibility (PTS). ATS assessment involves inter-occlusal placement of foils of varying thickness to detect the implant's ATS threshold level. PTS methodologies consist of applicatying manual or semi-automatic pressure onto the implant for detecting its maximal threshold level compared to natural teeth. Neurophysiological approaches comprise assessment of osseoperception either through recording trigeminal somatosensory evoked potential (TSEP) or generating activation maps of the brain' sensory cortex with functional magnetic resonance imaging (fMRI) following mechanical implant stimulation.

Although oral implants act as the most effective option for replacing missing teeth, their role in reactivating the sensory feedback pathway and restoring oral function remains a matter of debate[13-16]. Additionally, factors influencing the sensory feedback have received little attention. Therefore, the following systematic review was performed to accumulate and present the evidence justifying the concept of osseoperception by observing restoration of neurosensory function following osseointegrated implant treatment and to explore the potential factors which might improve the perception capacity.

2 | MATERIAL AND METHODS

2.1 | Protocol and registration

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This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines[17] and registered in the PROSPERO (Prospective Register of Systematic Reviews) database under the number CRD42018116167.

2.2 | PICO question

The PICO question was formulated as follows:

Patients (P): animals and humans,

Intervention (I): endosseous dental implant treatment,

Comparison (C): natural tooth or non-implant-supported prosthesis,

Outcome (O): sensory-motor function.

"Can neurosensory innervation restore following dental implant treatment and what factors may affect its restoration?"

2.3 | Information sources and search strategy

An electronic search was performed in PubMed, Embase, Web of Science and Cochrane Library up to the period of June 2021. Only English language publications were included. The search strategy consisted of a combination of controlled terms (Mesh and EMTREE terms, respectively) and keywords. The full search strategy is presented in Appendices 1. The identified publications were imported into Endnote 9 (Clarivate™Philadelphia, USA) and duplicates were removed electronically.

2.4 | Inclusion and exclusion criteria

Inclusion criteria: Human clinical studies (clinical controlled trials, cohort studies, observational clinical studies); Animal studies; Implant-supported prostheses in oral cavity; Studies evaluating innervation and sensory function within the peri-implant region.

Exclusion criteria: In vitro studies; Review articles; Case reports/case series; Letters to the editor; Guidelines reports; Questionnaires; Patients or animals with any other disease (systemic disease or dental disease); Non-English publications.

2.5 | Study selection and data extraction

Two reviewers (DS & KO) independently screened the titles and abstracts relevance based on the eligibility criteria using EndNote software. Thereafter, full-text articles were read by both

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reviewers for determining if the articles met the inclusion criteria and reasons for exclusion were recorded. Any disagreement between the two reviewers was solved by discussion. A third reviewer (RJ) was consulted if a consensus could not be reached. The extracted data consisted of information related to the study design, subject characteristics, surgical interventions and protocols, restorative procedures, assessment methodologies and study outcomes.

2.6 | Risk of bias assessment

The Cochrane Handbook for Systematic Reviews of Interventions[18] was utilized to assess the risk of bias for evaluating the methodological quality of human study and SYRCLE's risk of bias[19] tool for animal studies. Risk of bias was evaluated in six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias and others. Two reviewers (DS & KO) assessed the quality of included articles separately for judging the risk of bias to be low, high or unclear. When consensus could not be reached due to inconsistency, an experienced third author (RJ) was consulted.

3 | RESULTS

3.1 | Screening

The electronic search of 4 databases yielded 1667 results. In total, 421 duplicates and 1204 additional articles which did not meet the inclusion criteria based on titles and abstracts were excluded. The full text of the remaining 42 articles was read, out of which 20 were excluded. Ultimately, 22 studies were selected for inclusion in the qualitative synthesis (Figure 2).

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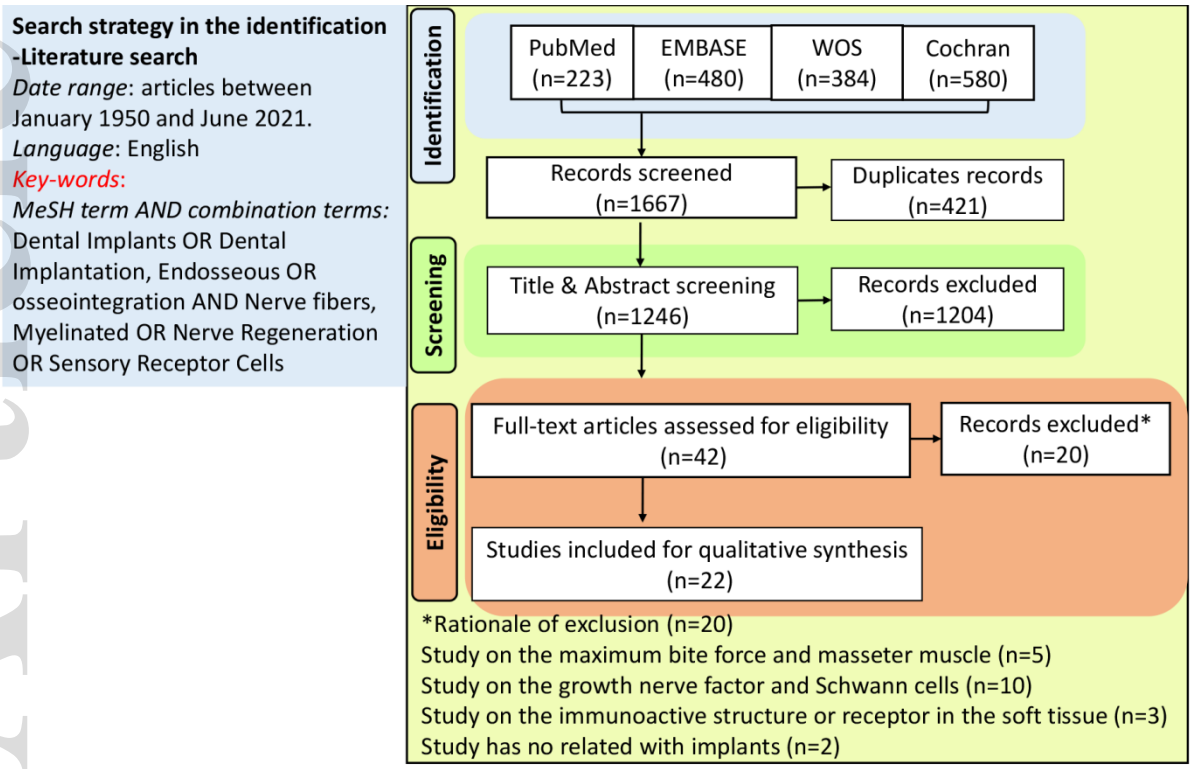


FIGURE 2 Flow diagram of the selection process. (PRISMA 2009 format).

3.2 | Study characteristics

All of the 22 selected articles retrospective in design and focused on the oral sensory function or peri-implant innervation following dental implant treatment. Fourteen articles performed psychophysical assessment of the active or passive tactile function, five articles[4,20-23] performed histological analysis for assessing myelinated nerve fibres within the peri-implant tissue, and three articles[24-26] assessed cortical plasticity through neurophysiological evaluation.

3.2.1 | Histological evidence

Table 1 describes the studies assessing osseoperception by observing nerve fibres in the peri-implant environment through histological evaluation. Out of the 5 studies, 4[4,20,22,23] assessed the presence of nerve fibres in peri-implant tissue using animal models (beagle and mongrel dogs), while one study was performed in humans. Two studies[20,23] found increased neurosensory fibre content following implant loading, particularly for immediate implant placement protocols. It was further suggested that immediate implant placement and loading protocols might have a

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positive impact on the peri-implant bone innervation[20,23]. The increased nerve fibre density following immediate implant placement and loading in the apical region compared to other protocols further reinforced this evidence[27,28].

The number of fibres increased over time with the presence of a higher number of fibres in the apical region compared to the middle or coronal area. Furthermore, only one human study[21] was performed for quantitation of nerve fibres in the peri-implant bone, where 12 mechanically failed implants were retrieved from 10 patients for histological analysis. The authors found both myelinated and unmyelinated nerve fibres within the peri-implant bone, thereby confirming the possibility of osseoperception. However, the exact origin and functionality of the nerve fibres could not be identified.

3.2.2 | Psychophysical evidence

Table 2 describes the studies assessing the tactile sensibility of the osseointegrated dental implants. Fourteen articles objectively evaluated the tactile sensibility by employing various psychophysical methodologies[2,29-40]. Seven articles evaluated the active tactile sensibility (ATS) by placing foils of varying material (steel[29], copper[34,41,42], aluminium[43] or gold[35,44]) and thickness inter-occlusally between the implant-supported prostheses (over-denture or single-implant-supported) and natural opposing teeth. The threshold level of ATS was recorded and ranged between 20-150 µm depending on the dental status, with a 2 to 5 times increased threshold for implants compared to natural teeth [29-31,33-35,43]. In another 6 articles[2,36-40], pressure was manually or semi-automatically exerted on natural teeth and implant-supported prostheses, and the threshold of passive tactile sensibility (PTS) revealed an up to 50 times higher threshold level for implants (force = 100 grams) compared to natural teeth (force= 2 gram). Overall, implant-supported prosthesis showed higher tactile force threshold level compared to natural teeth but remained more sensitive than the non-implant-supported prosthesis. Factors such as age, gender, time of implantation, implant properties and prosthetic period of function did not seem to influence the outcome.

3.2.3 | Neurophysiological evidence

Table 3 provides the details of studies assessing osseoperception through the neurophysiological

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capability of osseointegrated implants. Only 3 studies[24-26] provided neurophysiological evidence, where 2 studies delivered electrical stimuli to the implant abutment for analysing the trigeminal somatosensory evoked potential (TSEP) and 1 study performed brain functional magnetic resonance imaging (fMRI) for generating activation maps following punctate mechanical stimulation of the implant and natural teeth.

The analysis of TSEP was performed with a constant-current stimulator for delivering bipolar electrical square-wave stimuli onto the abutment of endosseous implants[24,25]. A variability in polarity, latency and number of waves was observed. Both studies confirmed the presence of trigeminal waves and activation of other neural structures in the peri-implant region. Based on the brain mapping of patients following dental implant treatment, a larger activation of primary and secondary somatosensory areas was observed compared to patients with a complete denture. Additionally, punctate tactile stimuli were capable of inducing cortical plasticity in subjects with implant-supported prostheses, with a somewhat weaker yet rather comparable signal as compared to a natural dentition. Based on age, gender, implant surface, geometry and position, no significant influence on tactile function was detected [29,30,32-36,39,40,45].

3.3 | Risk of bias

All clinical studies in the quantitative analysis were conducted by a non-randomized retrospective study design, hence showing a low level of evidence based on the evidenced-based medicine (EBM) scale. Table 4 and Figure 3 have shown the overview of outcomes and summarising plots of the risk of bias assessment. In 17 of 22 included studies, only patients with the implant-supported prosthesis were selected as the subjects into the analysis of neurosensory function, which induced a high risk of bias. While random designs were performed in 3 animal studies[20,22,23] and the animals were also randomly selective for assessment at different follow-up periods. All the participants were blinded to the test procedures and the outcome assessment. However, the variety of specimen and sample preparation techniques, as well as the different stimuli techniques and recording methods, can also have introduced bias. In 5 studies[24,25,32,36,45], the outcome data were not completed. One author performed the evaluation of the threshold of the passive sensory function via measuring RL and DL[36], yet in the results, the DL for the full fixed

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prostheses was omitted. While measuring TSEP[24,25], 15 patients were involved in total but only 3 or 5 subjects were analysed in the results. The differences among the partial/full implant-supported prostheses, complete denture and natural dentition in the threshold level of active and passive tactile function, and density of nerve fibres can be detected in all included studies, which is the main purpose of this review.

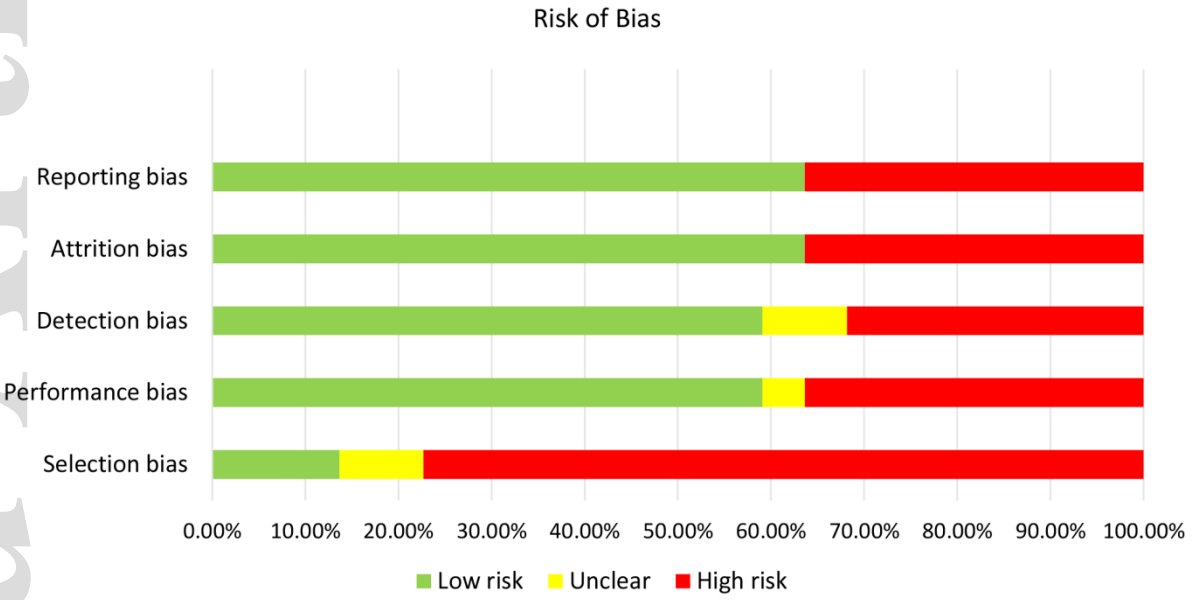


FIGURE 3 Risk of bias of included studies

4 | DISCUSSION

The present systematic review was conducted to update the scientific evidence for supporting the concept of osseoperception. The primary aim was to review the evidence related to the histological, psychophysical and neurophysiological aspect. The secondary aim involved evaluation of the potential factors influencing osseoperception.

4.1 | Histological evidence

For discovering the mechanism of osseoperception, histological studies were performed to investigate the pattern of nerve fibres and the function of mechanoreceptors or axons in the peri-implant tissue. Both myelinated and unmyelinated nerve fibres were observed in the peri-implant bone within a range of 200 - 1000 µm from the implant surface in both human and

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animal studies[4,20,21]. The presence of Ruffini mechanoreceptive terminals in peri-implant bone and/or epithelium demonstrates a link with the neurosensory myelinated nerve fibre content[4,46]. Previous animal studies exhibited dense peri-implant bone innervation around loaded implants, whereas a sparsity in innervation was detected around unloaded implants which might have resulted due to ankylosis with the surrounding bone[4,20,23]. Within a 200 - 500 µm perimeter of the peri-implant bone, the density of myelinated nerve fibres was larger around loaded implants as compared to unloaded ones.

Although tooth extraction leads to the damage of myelinated nerve fibres, nevertheless, the remaining functional nerve fibres and their endings in the PDL residue might be able to regenerate and partially recover the sensory feedback. This theory can be backed up by the evidence related to limb amputation, where axons in the proximal stump of the nerves randomly produce a large number of collateral and terminal sprouts which advance distally within the initial days or weeks following transection of the nerve trunk[47]. Afterwards, some of these sprouts approach Schwann cell proliferation in the distal segment or grow as connective tissue in the nerve trunk, while other terminal endings degenerate. Thus, it can be assumed that the contact between axons and Schwann cells is particularly important for regeneration of nerve fibres also in case of restoration with dental implants[47]. Previous studies suggested that the stimulation of functional implants resulted in an accelerated proliferation of adjacent Schwann cells, and the loading pressure on regenerated nerve fibres surrounding the implants allowed axons differentiation and guided sprouting to connect with Schwann cells[48,49].

The potential to improve this sensory function by boosting restoration or regeneration of nerve fibres following implant placement has received growing attention. Various methods have been proposed to improve nerve restoration, such as changing the type of implant placement and loading protocol [4,20] and modifying implant surface structure[4]. A preliminary study in cats demonstrated that periodontal mechanoreceptors might remain within the bone after tooth extraction, enabling successful immediate stimulation of the nerve fibres in the healed extraction socket[50]. These findings coincide with the studies involved in the review, where immediate implant placement and loading resulted in a higher sensory nerve fibre density in the

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peri-implant region compared to delayed protocols[20]. Hypothetically this concept could allow the damaged nerves to be stimulated and activated by immediate loading, preventing retrograde degeneration of nerve tissue after tooth extraction. However, it remains unclear whether restored or regenerated nerve fibres might have a sensory function. Additionally, there is not enough evidence proving that modification of implant surface structure and application of growth factors increase the amount of nerve fibres. Histological evidence associated with peri-implant innervation is scarce. Further studies are required with a standardized methodology to evaluate osseoperception within the peri-implant region. Furthermore, techniques for enhancing regeneration of nerve fibres following implant placement need to be developed, thus potentially improving osseoperception.

4.2 | Psychophysical evidence

Psychophysical evidence has been mainly derived from the evaluation of either ATS [30,32,34-36] or PTS[2,36,38-40,45]. The threshold level of ATS and PTS were found to be 5 and 50 times higher for implants compared to natural teeth, respectively. This large discrepancy could be attributed to the fact that during active occluding threshold determination, various mechanoreceptors are activated (periodontal, muscular, mucosal periosteal, joint-related), while for PTS only low-threshold cutaneous mechanoreceptors (bony and periosteal) are activated by the tactile touch stimuli. Overall, patients seem to function well after rehabilitation with an implant-supported bone-anchored prosthesis, and surely better than with removable mucosa-borne prosthesis where tactile function would need to rely on mucosal mechanoreceptors.

Tactile function is known to be higher for posterior teeth, considering the larger number of PDLs and thicker nerve bundles. Thus, one might argue that osseoperception might be higher in the posterior region following implant therapy[34]. Yet, a variety of study designs with a wide range of force intensity, uncontrollable experimental design, unsubstantial sample sizes and a critical influence of the psychophysical set-up could have led to inconsistent findings.

4.3 | Neurophysiological evidence

The damage of PDLs after tooth extraction and implant placement induce loss of

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mechanoreceptors and free nerve endings, resulting in disruption of sensory feedback pathway (Figure 1). Evidence from TSEP in the cortex by electrical stimulation of oral implants showed that the sensory feedback pathway remained functional following osseointegration of implants and healthy periodontal mechanoreceptors showed projections on cortical somatosensory areas. The fMRI-based analysis demonstrated activated areas of primary and secondary sensory-motor cortex in patients with implant-supported prostheses. This activation was found to be less compared to natural teeth but fairly higher than non-implant-supported complete dentures[26]. Additionally, the activated function of a single implant remained close to that of natural teeth, with some ipsilateral as well as bilateral and contralateral sensory cortex activations, thereby, illustrating cortical plasticity. However, discrepancy in brain cortical plasticity during fMRI recordings with various types of implant-supported prostheses was observed, which could have resulted from triggering different groups of adjacent and remote receptors in the peri-implant region and oral cavity. Considering the limited number of studies and the small sample size, more convincing evidence is needed regarding the functional mechanoreceptors in the peri-implant bone.

Based on the aforementioned evidence[3,51], the following clinical implications can be withdrawn: i. A failure to achieve optimal osseoperception might cause implant overloading and failure due to maximal occluding force, which a patient is unable to properly perceive if the neurosensory function is not restored; ii. Oral parafunctional activities such as grinding or clenching of the teeth might negatively influence the implant healing phase and osseoperception, thereby leading to implant failure if the eccentric function is not managed.

5 | CONCLUSIONS

The reported evidence supported the existence of so-called osseoperception phenomenon for restoring the sensory feedback pathway following oral implant rehabilitation. The presence of remaining natural teeth impacted the outcome, hence assisting the recovery of sensory function. Furthermore, a positive impact on neurosensory fibre content was also observed following immediate implant placement and loading protocol, with some studies confirming the influence of implant placement protocol on the tactile sensibility. Periosteal receptors seem to

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compensate for the loss of PDL mechanoreceptors following tooth extraction and implant placement. Other mechanoreceptors in the peri-implant vicinity together with cortical plasticity following an adaptation period after implant placement might further reinforce the osseoperception phenomenon. Further studies are needed to identify factors that might further assist physiological integration of the oral implants in the human body as such to approach natural oral function.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figure Legends

FIGURE 1 Sensory pathway for tooth/implant stimuli. Activation of periodontal sensory endings derived from temporomandibular joint, periosteum, gingiva, periodontal ligament (PDL), mucosa, and alveolar bone receptors (red stars) following stimuli exertion on tooth through the trigeminal neurons located in the trigeminal ganglion. Thereafter, signals are sent to the ventral posterior nucleus of thalamus and sensory cortex allowing the natural neurosensory pathway feedback (Blue and red solid lines). For the implant, PDL mechanoreceptive input is lacking, thereby hampering the peripheral feedback pathway (Blue and red dashed lines).

FIGURE 2 Flow diagram of the selection process. (PRISMA 2009 format).

FIGURE 3 Risk of bias of included studies

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Appendices

Equations for the search strategy

Pubmed

Concept 1:

"Dental Implants"[Mesh] OR dental-implant*[tiab] OR oral-implant*[tiab] OR Surgical-Dental-Prosthes*[tiab] OR implant-supported-prosthes*[tiab] OR peri-implant-bone*[tiab] OR single-tooth-implant*[tiab] OR "Dental Implantation, Endosseous"[Mesh] OR endosseous-dental-implant*[tiab] OR endosseous-implant*[tiab] OR osseointegrated-dental-implant*[tiab] "osseointegration" [Mesh] OR osseointegrat*[tiab] OR peri-implant-endosseous-healing*[tiab]

Concept 2:

"Nerve fibers, Myelinated"[Mesh] OR myelinated-nerve-fib*[tiab] OR innervation[tiab] OR "sensation"[Mesh] OR sensation*[tiab] OR sensory-function* OR perception* [tiab] OR osseoperception[tiab] OR "Nerve Regeneration"[Mesh] OR nerve-regeneration*[tiab] OR "Nerve Endings"[Mesh] OR nerve-ending*[tiab] OR "Sensory Receptor Cells"[Mesh] OR sensory-neuron*[tiab] OR sensory-receptor*[tiab] OR neural-receptor*[tiab] OR neuroreceptor*[tiab] OR neuroplasticit*[tiab] OR sensory-nerve-ending*[tiab]

Embase

Concept 1:

'dental implants'/exp OR 'dental implant*':ti,ab,kw OR 'oral implant*':ti,ab,kw OR 'Surgical Dental Prosthes*':ti,ab,kw OR 'implant supported prosthes*':ti,ab,kw OR 'peri-implant bone*':ti,ab,kw OR 'single tooth implant*':ti,ab,kw OR 'dental implantation, endosseous'/exp OR 'endosseous dental implant*':ti,ab,kw OR 'endosseous implant*':ti,ab,kw OR 'osseointegrated dental implant*':ti,ab,kw OR 'osseointegration'/exp OR 'osseointegrat*':ti,ab,kw OR 'peri-implant endosseous healing*':ti,ab,kw

Concept 2:

'myelinated nerve'/exp OR 'myelinated nerve fib*':ti,ab,kw OR 'innervation':ti,ab,kw OR 'sensation'/exp OR 'sensation*':ti,ab,kw OR 'sensory function*':ti,ab,kw OR 'perception*':ti,ab,kw OR 'osseoperception':ti,ab,kw OR 'Nerve Regeneration'/exp OR 'nerve regeneration*':ti,ab,kw OR 'Nerve Endings'/exp OR 'nerve ending*':ti,ab,kw OR 'Sensory Receptor Cells'/exp OR 'sensory neuron*':ti,ab,kw OR 'sensory receptor*':ti,ab,kw OR 'neural receptor*':ti,ab,kw OR 'neuroreceptor*':ti,ab,kw OR 'neuroplasticit*':ti,ab,kw OR

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'sensory nerve ending*':ti,ab,kw

Web of Science

Concept 1:

"dental implant*" OR "oral implant*" OR "Surgical Dental Prosthes*" OR "implant supported prosthes*" OR "peri-implant bone*" OR "single tooth implant*" OR "endosseous dental implant*" OR "endosseous implant*" OR "osseointegrated dental implant*" OR "osseointegrat*" OR "peri-implant endosseous healing*"

Concept 2:

"myelinated-nerve-fib*" OR "innervation" OR "sensation*" OR "sensory function*" OR "perception*" OR "osseoperception" OR "nerve regeneration*" OR "nerve ending*" OR "sensory neuron*" OR "sensory receptor*" OR "neural receptor*" OR "neuroreceptor*" OR "neuroplasticit*" OR "sensory nerve ending*"

Cochran

Concept 1:

#1: [mh "dental implant"]

#2: ((dental NEXT implant*) OR (oral NEXT implant*) OR (surgical NEXT dental NEXT prosthes*) OR (implant NEXT supported NEXT prosthes) OR (peri-implant NEXT bone) OR (single-tooth Next implant*)):ti,ab,kw

#3: #1 OR #2

#4: [mh "dental implantation, endosseous"]

#5: ((endosseous NEXT dental NEXT implant*) OR (endosseous NEXT implant*) OR (osseointegrated NEXT dental NEXT implant*)):ti,ab,kw

#6: #4 OR #5

#7: [mh "osseointegration"]

#8: ((osseointegrat*) OR (peri-implant NEXT endosseous NEXT healing)):ti,ab,kw

#9: #7 OR #8

#10: #3 OR #6 OR #9

Concept 2:

#11: [mh "nerve fibre,myelinated"]

#12: ((myelinated NEXT nerve NEXT fib*) OR (innervation)):ti,ab,kw

#13: #11 OR #12

#14: [mh "sensation"]

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#15: ((sensation*) OR (sensory NEXT function*) OR (perception*) OR (osseoperception)):ti,ab,kw

#16: #14 OR #15

#17: [mh “Nerve Regenearation”]

#18: ((nerve NEXT regeneration*)):ti,ab,kw

#19: #17 OR # 18

#20: [mh “nerve endings”]

#21: ((nerve NEXT ending*)):ti,ab,kw

#22: #20 OR #21

#23: [mh “sensory receptor cells”]

#24: ((sensory neuron*) OR (sensory NEXT receptor*) OR (neural NEXT receptor*) OR (neuroreceptor*) OR (neuroplasticit*) OR (sensory NEXT nerve NEXT ending*)):ti,ab,kw

#25: #23 OR #24

#26: #13 OR #16 OR #19 OR #22 OR #25

#27: #10 AND #26

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TABLE 1 Histological evidence for presence of osseoperception through observing nerve fibres in the peri-implant environment.

Abbreviation: No.: Number; T: Time; ?: Unclear; Y: Yes; AOT: Anode Oxidized Titanium; HAC: Hydroxyapatite-coating; PIB: Peri-implant bone; NPIS: Neurofilament protein immunostaining; TMB: Thionin methylene; MTS: Masson's trichrome; H&E: Hematoxylin and Eosin; MNF: Myelinated nerve fibres; DS: Density; Un-MNF: Unmyelinated nerve fibres; DM: Diameter; IAS: Immunoreactive structure, SISP: Single implant-supported prothesis, NE: Natural extraction socket.

Author (year)	Subjects (N)		Implant							Methodology			Outcome	
	Species	No.	Shape	Surface structure	Implant placement		Loading protocol			Region of interest	Staining	Parameter of testing	Primary	Secondary
					Delayed (T)	Immediate	Delayed (T)	Immediate	Unloaded					
Wada et al (2001)[4]	Mongrel dog	3	screw	AOT /HAC	Y (16 wks)	–	Y (10 wks)	–	Y	200µm (PIB)	NPIS	MNF (DS)	DS: Loaded > unloaded	No difference in surface structure
Huang et al (2015)[20]	Beagle dog	6	custom-made thread	machined surface	Y (8wks)	Y	Y (4 wks)	Y	–	300µm (PIB and gingival)	MTS/HIS (NF or NPY)	MNF (DS & DM)	DS: SISP > NE DM: NE > SISP	DS: IIP > DIP; IL > DL & gingival > apical > coronal > middle DM: IIP>DIP; DL >IL & middle > coronal > apical> gingival; No difference in regions
Corpas et al (2014)[21]	Human	10	?	?	Y (?)	–	Y (?)	Y	–	500-1000µm (PIB)	TMB	(Un) MNF (number)	MNF: 27 (5.13µm)	Un-MNF: 7
Song et al (2019)[22]	Beagle dog	9	screw	HA	Y (1 month)	-	Y (1 month)	-	-	500 µm (PIB)	MTS	MNF (DS & DM)	DS: PPP > control > PRP; DM: PRP > PPP > control	DS & DM different in period of prosthesis function
Song et al (2020)[23]	Beagle dog	10	screw	-	Y (3 months)	Y	Y (3 months)	Y	Y	500 µm (PIB)	H&M	MNF (DS)	IL > DL > UL IIP > DIP	Apical > middle > coronal & different in period prosthesis function (12 wks > 24 wks)

TABLE 2 Psychophysical evidence for presence of osseoperception through measurement of threshold level of sensory sensibility.

Author(year)	Population								Methodology			Outcome	
	Test				Control				Device	Method	Testing area	Primary	Secondary
	No.	Age (range)	Situation		No.	Age (range)	Situation						
			SISP (No.)	MISP (No.)			NT(No.)	NIPS (No.)					
Jacobs et al (1991)[29]	25	56.6 (29-77)	Y (19)	Y (6)	12	28 (18-49)	Y (12)	Y (6)	Foils (Steel)	RL: method of limits (↑&↓); DL: constant stimuli (thicker or thinner)	1st premolar	RL&DL CD/OD > SISP&MISP > SISP/NT > NT/NT	No difference in gender & jaw type
Jang et al (2001)[30]	30	50.8 (?)	-	Y (30)	20	45.6	Y (10)	Y (10)	Thickness threshold: Foil / Lateral pressure: tension meter	Method of limit (↑) Test 3x	Central incisor to the second molar / Labial or buccal surface	CD/CD > MISP/CD > MISP/MISP > NT/NT	No difference in regions
Enkling et al (2007)[41]	62	46 (19-86)	Y (62)	-	62	46 (19-86)	Y (62)	–	Foils (Copper)	Method of limits (↑&↓)	Anterior region/posterior region	50% value SISP/SISP > NT/NT	No difference in regions, surface structure, geometry, period of edentulism, period of prosthesis function & gender
Batista et al (2008)[32]	29	55.1 (?)	–	Y (29)	41	43.6	Y (24)	Y (17)	Foils (Aluminum)	Method of limits (↓)	Occlusal surface	50% value CD/CD > MISP/MISP > MISP/NT > NT/NT	No difference in age and period of prosthesis function
Enkling et al (2010)[42]	62	45.6 (?)	Y (62)	–	-	-	_	–	Foils (Copper)	Computer-assistant design random thickness (Test 10x)	Teeth or implant	50% value SISP/SISP (20.2 ± 10.9 μm)	Surface structure: TPS > Machined > SAE; No difference in age and gender
Enkling et al (2012)[34]	32	38.9 (25-63)	Y (32)	–	32	38.9 (25-63)	Y (32)	–	Foils (Copper)	Computer-assistant design random thickness (Test 10x)	Teeth or implant	50% value SISP/SISP (19.7 ± 11.1 μm) > NT/NT (16.1 ± 9.4 μm)	50% value anterior > posterior (significance in NT/NT but no in ISP/ISP)
Kazemi et al (2014)[35]	25	30.1 (21-66)	Y (50)	–	25	30.1 (21-66)	Y (50)	–	foils (Gold)	Computer-assistant design random thickness (Test 5x)	Maximum intercuspation (posterior) and edge-to-edge (anterior)	ATT: SISP/SISP (30.6 ± 9.15 μm) > NT/NT (21 ± 7.05 μm)	No difference in regions, surface structure & gender
Jacobs et al (1993)[36]	31	55.7 (24-88)	Y (5)	Y (26)	10	30 (20-51)	Y (10)	-	Solenoisd-driven stimulating	Method of limits (↑&↓)	Incisal edge of teeth or implant in both maxilla and mandible	RL: SISP > NT & OD > MISP > NT	No difference in period of prosthesis function & age
Jacobs et al (2001)[2]	24	51.7 (26-65)	Y (8)	Y (16)	16	53 (48-64)	Y (8)	Y (8)	LTS: Semmes-Weinstein monofilament sensory testing system; 2PD: Vibrotactile test-modified HC-200 hearing aid	Method of limits (↑&↓)	LTS & 2PD: buccal side of the alveolar mucosa; Vibrotactile: upper teeth or prosthesis	LTS: CD > SISP&MISP > NT; 2PD: CD > SISP&MISP = NT ; Vibrotactile: CD > SISP&MISP > NT	-
El-Sheikh et al (2004)[45]	20	65.1 (50-82)	–	Y (20)	20	65.1 (50-82)	–	Y (20)	Custom-made device	Method of limits (↑)	Impression copings	MISP 3.1-15.7N	No difference in period of implant placement, implant separation, geometry, age & gender
Habre-Hallage et al (2010)[39]	9	? (19-32)	Y (9)	–	9	? (19-32)	Y (9)	–	Von Frey filament	Method of limits (↑)	Gingival	LTS: SISP ≈ NT; 2PD: SISP > NT	No difference in period of implant placement and prosthesis function

Grieznis et al (2010)[40]	29	? (21-71)	Y (43)	–	29	? (21-71)	Y (81)	–	Computer-controlled custom-made pressure sensitive device	Method of limits (↑) Test 3x	Teeth or implant	PTT: SISP > NT	No difference in NT with or without ET & gender
Hsieh et al (2010)[52]	10	-	Y (10)	–	10	-	Y (10)	–	Vibrational transducer	Method of limits (↑)	Adjacent tooth and implant	VAS: SISP < NT	High intensity of vibration reduced the difference of ISP & NT
Negahdari et al (2019)[44]	45	-	Y (135)	-	45	-	Y (135)	-	Foils (gold)	Computer-assistant design random thickness (Test 5x)	Maximum intercuspation (posterior) and edge-to-edge (anterior)	ATT: Pontic > SISP > NT	-

Abbreviation: SISP: Single-implant-supported prosthesis; MISP: Multi-implant-supported prosthesis; NT: Natural tooth; NISP: Non-implanted-supported prosthesis; CD: Complete denture; OD: Overdenture; RL: Reiz Limen; DL: Difference Limen; LTS: Light-touch sensation; 2PD: 2-point discrimination; ATT: Active tactile threshold; PTT: Passive tactile threshold; Primary outcome: Implant(s)-supported prosthesis VS natural tooth (teeth) or non-implant-supported prosthesis; Secondary outcome: Involved outcome.

TABLE 3 Neurophysiological evidence for presence of osseoperception utilizing function magnetic resonance imaging (fMRI) & trigeminal somatosensory evoked potentials (TSEPs).

Author (year)	Subjects								Methodology			Outcome	
	Testing group				Control group				Device	Method	Testing area	Primary	Secondary
	No.	Age (range)	Situation		No.	Age (range)	Situation						
			SISP (No.)	MISP (No.)			NT	NISP (No.)					
Swinnen et al (2000)[24]	15	-	–	Y (15)	15	-	–	-	Constant-current stimulator	Square-wave stimuli (↑ 2Hz) 2X	Abutments	TSEP around teeth and implants	-
Van Loven et al (2000)[25]	15	58 (35-69)	–	Y (15)			–	-	Constant-current stimulator	Square-wave stimuli (↑ 2Hz)	Abutments	TSEP around teeth and implants	-
Habre-Hallage et al (2012)[26]	9	39.7 (?)	Y (9)	–	10	34.3	Y (10)	-	3.0 T fMRI & Von fray filaments & stimulation device with a constant frequency of 1 Hz	Fix force 9300g, 180g & 100g0	Brain	fMRI activation of sensory cortex for both teeth and implants, with the latter showing cortical plasticity	No difference in incisor and canine

Abbreviation: SISP: Single-implant-supported prosthesis; MISP: Multi-implant-supported prosthesis; NT: Nature tooth; NISP: Non-implanted-supported prosthesis; fMRI: function magnetic resonance imaging.

TABLE 4 Risk of bias of the included studies

	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective bias	
Jacob et al (1991)[29]	?	-	+	+	+	+	?
Jang et al (2001)[30]	-	-	-	?	+	+	+
Enkling et al (2007)[41]	-	-	+	+	+	+	?
Batista et al (2008)[43]	-	-	+	+	-	-	?
Enkling et al (2010)[42]	-	-	+	?	+	+	?
Enkling et al (2012)[34]	-	-	+	-	+	+	+
Kazemi et al (2014)[35]	-	-	+	+	+	+	+
Jacobs et al (1993)[36]	-	-	+	-	-	-	+
Jacobs et al (2001)[2]	-	-	+	+	+	+	+
El-Sheikh et al (2004)[45]	-	-	?	-	-	-	?
Habre-Hallage et al (2010)[39]	-	-	-	+	+	+	?
Habre-Hallage et al (2011)[38]	-	-	+	+	+	+	?
Grieznis et al (2010)[40]	?	?	-	-	+	-	?
Negahdari et al (2019)[44]	-	-	+	+	+	+	+

Van Loven et al (2000)[25]	-	-	-	-	-	-	?
Swinnen et al (2000)[24]	?	?	-	-	-	-	?
Habre-Hallage et al (2012)[26]	-	-	-	+	+	-	?
Corpas et al (2014)[21]	-	-	-	-	-	+	+
Wada et al (2001)[4]	-	+	-	+	-	+	?
Huang et al (2015)[20]	+	+	+	+	+	+	?
Song et al (2019)[22]	+	+	+	+	+	-	?
Song et al (2020)[23]	+	+	+	+	-	+	?

Legend: ?: Unclear risk of bias; -: High risk of bias; +: Low risk of bias