MSc Biomedical Science Literature Thesis:

A Critical look at Fatty Degenerative Osteonecrosis of the jawbone: A Controversy in Modern Dentistry

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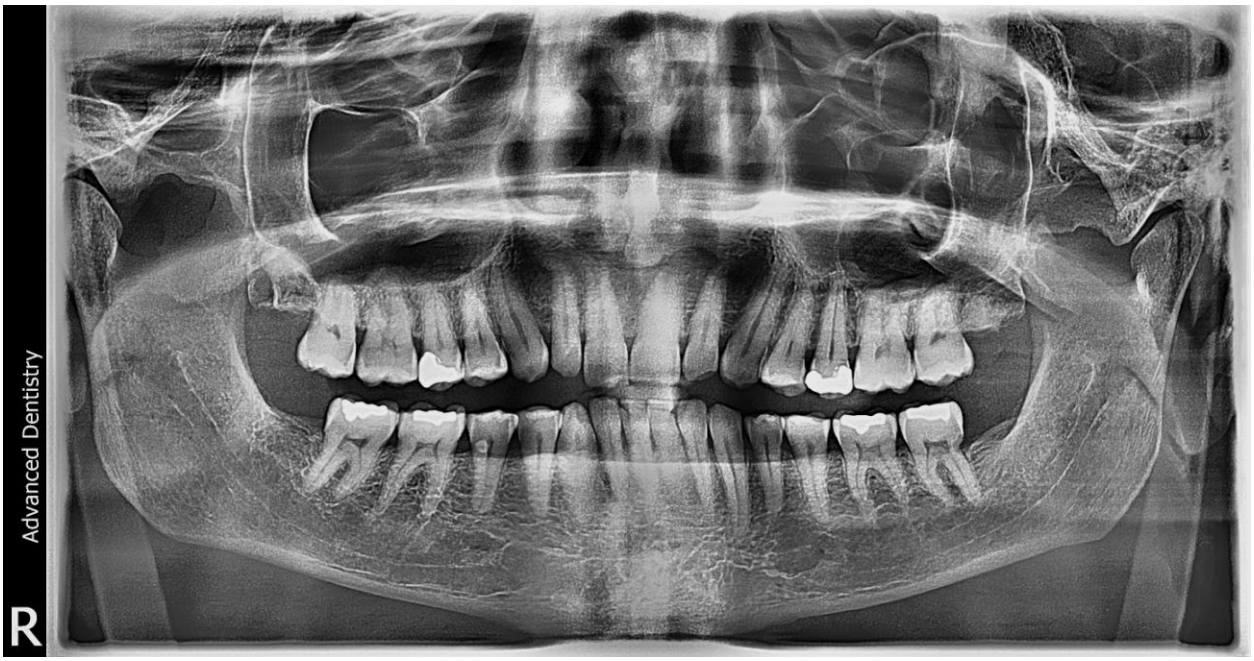
For my Father, family and every future “patient” of *Modern Medicine & Dentistry.*



“‘We won.’ But we knew we were going to win, because we had the truth and the best treatment. In medicine, the correct treatment, the correct strategy and the most efficient strategy will eventually win, whatever happens – but it may be delayed.”

-Barry Marshall, Noble Prize Winner in Physiology or Medicine 2005

Content

Abstract

Human jawbone represents a unique morphology due to its connection with the teeth, which are initiated by epithelial ingrowth that can form remnants and are crucial for proper bone persistence. Within this bone fatty degenerative osteonecrosis can occur and lead to inflammation and can persist with or without symptoms. Surprisingly, diagnosis and therapy of this condition are still a controversy in modern dentistry. In this review of the literature the history of this condition was redrawn. A multitude of names confused symptoms and pathophysiological ideas lead to communicative problems. Radiography is unfortunately not the most reliable imaging tool and therefore has to be supported by trans-alveolar ultrasonography. This novel method is now standardized and ready to be tested by larger groups. The most reasonable treatment is to remove the necrotic tissue. The numerous arguments and denial of the main dental community is not convincing, and the fatty degenerative osteonecrosis should be more in focus of clinical trials to improve the patients' needs and care.

Keywords: *Fatty degenerative osteonecrosis of the jawbone, neuralgia-inducing cavitational osteonecrosis, Bisphosphonate-related osteonecrosis of the jaw, Medication-related osteonecrosis of the jaw, Radiography, oral diseases, ultrasound sonography, epithelial remnants, RANTES/CCL5*

1 Introduction

1.1 Disease and cause are not synonyms

Pathology is the study of disease. The fundamental understanding of a disease is having any detrimental deviation from either the *normal* functional, structural, or psychological state of an organism[1, 2]. This deviation is often associated with distinct clinical appearance(s) and symptomatology. In order to understand whether any deviation might be detrimental, it is essential to elucidate what is considered to be *normal*. However, this might not always be apparent through simple observation. To understand any disease, one needs to determine the etiology (cause), structural and morphological changes (histopathology), pathogenesis (molecular and mechanistic understanding), and its potential detrimental deviation in relation to what is considered to be normal[3, 4].

The studying concept of causality, understanding a disease through the study of Etiology, the origin or cause of disease forms a great part in this elucidation. More importantly, the latter is of cardinal importance in disease and health research[4]. This can be achieved by conducting a Medical diagnosis through observation of the clinical appearance and making use of diagnostic testing, which involves studying Hematology, Imaging, Histopathology, etc.

Distinguishing *cause* from *disease* is not linear or often apparent to the observer. This is clearly illuminated by examples throughout history. For example, for many years it was not apparent what causes coronary heart disease (CHD). Factors such as high serum cholesterol, high blood pressure, lack of exercise, and smoking are all causally related and have been amply demonstrated to play a role in the development of CHD[5].

Understanding cause and effect rejection by the medical standard of care/consensus has a long history. New emerging evidence opposing the *consensus* is not always welcomed with open arms, but at times treated as an intrusion or lead to mockery. Rejection of the correlation between lung cancer and cigarette smoking was one of them. It took many years before there was clear consensus for elucidating this as (scientific) fact. The use of statistical analysis and evidence was the breakthrough that led to overcoming the opposing claims made by the Tobacco industry[5].

Another example, includes the case of *"Puerperal fever"* (childbed fever), which was common in mid-19th-century hospitals and often fatal. Ignaz Semmelweis proposed the practice of washing hands with chlorinated lime solutions in 1847 while working in Vienna General Hospital's First Obstetrical Clinic, where doctors' wards had three times the mortality of midwives' wards. At that time doctors thought that it was caused by *miasma*, poisonous gases in the air. Unfortunately, this practice only became widely appreciated after he was mocked, ridiculed, and eventually tricked into an insane Asylum where he passed[6].

A third example is the discovery of the causal relationship between *Helicobacter pylori* and its role in peptic ulcers and gastritis. It took Barry Marshall and his colleague 10 years to show the causation. Marshall had to go to the extent of drinking the bacterium and develop ulcers himself to prove this point. In the end, vindication led them to win the Nobel Prize[7]. These examples make it apparent that presenting the etiology of a disease is not easy and apparent by any means. Furthermore, it proves how performing Clinical diagnosis alone is insufficient. Nonetheless, it may serve as a conclusion for further research and technology to develop that does aid in proving etiology. This fact should not be

underestimated in current times, as technology is rapidly improving, we should remain vigilant of the fact that we (may) still know little.

1.2 Peculiarities of the jaw bone

The jaw bone consists of the maxilla (upper jawbone) and mandible (lower jawbone). What is critical to acknowledge is that the ridges of these specific regions have a unique interconnection between bone and teeth nowhere else found throughout the human body. During embryonic development, tooth development is a complex regulated series of processes and interactions between surface epithelium and the neural crest-derived dental ectomesenchyme[8, 9]. Upon completion of the dental developmental phase, specifically the root formation, the Hertwig's epithelial root sheath (HERS) undergoes apoptosis and forms epithelial cell remnants of Malassez (ERM) that are situated in the periodontal ligament (PDL) (See Fig.1)[10]. Only most recently has ERM become increasingly acknowledged for its implications in research, dental pathology and regeneration of PDL[11].

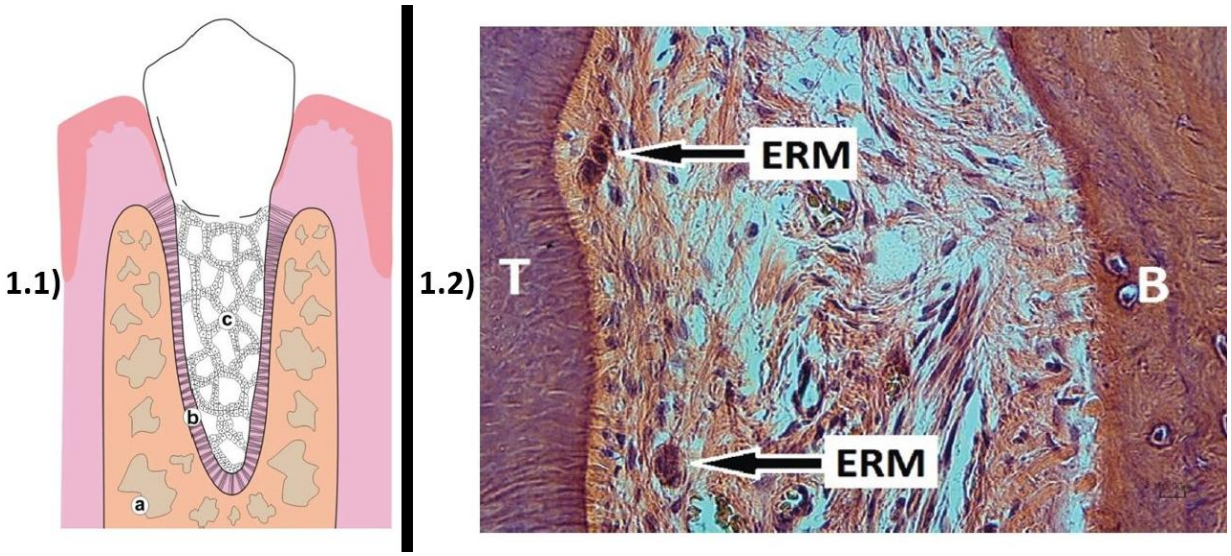


Figure 1. Epthelial remnants of Malassez. **(1.1)** Drawing depicting epithelial cell remants' network (c) distribution across the root within the periodontal ligament (PDL) (b); located in the alveolar bone (a). **(1.2)** 400x magnification photomicrograph of the PDL indicating cluster formation of epithelial remnants (black arrow) adjacent to tooth surface (T) and further away from alveolar bone (B)[*Ref.: Miniggio & Raubenheimer, 2016].*

The jawbones are subjected to more functional alterations in comparison to any other bone structure in the human organism. The latter is supported by the fact that there is a radical change in the structural skull bone development from the newborn to geriatric (See Fig.2)[12]. Alterations within this structure itself, such as tooth loss alone can often lead to disruption of the normal mechanical function of the masticatory system. This disruption is further exhibited by the amount of pressure-stress evoked upon the jawbone, which could be considered essential for the maintenance of the structure. Thus, the lack or insufficient pressure causes a disruption of the *homeobalance* of the bone structures and could lead to a process called "inactivity atrophy". Other factors include mechanical (e.g., trauma and surgical interventions) and biological factors (e.g., neoplasia, bone metabolism, gender, disease, etc.). The maxilla and mandible are structurally different from each other. This difference is exemplified by the difference in atrophy, as the maxilla is subjected primarily to horizontal atrophy and the mandible subjected to vertical atrophy[12, 13].

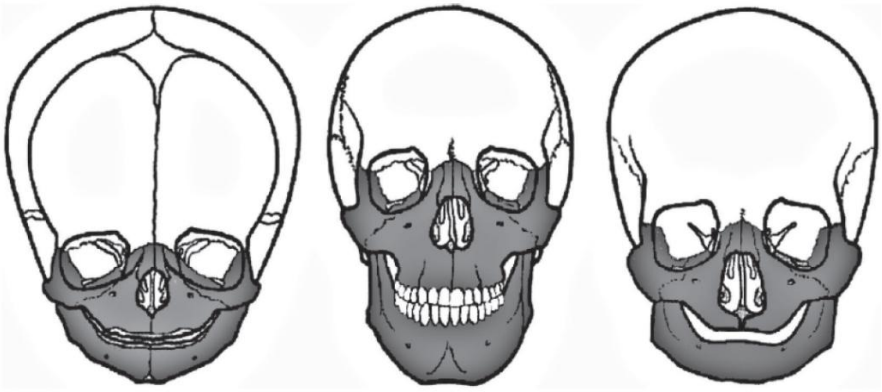


Fig.2 Radical structural change of the aging human skull
[Ref.: Fanghänel et al., 2006].

1.3 Identification of a modern dentistry controversy

In the field of modern dentistry there has been a controversy around an observable anomaly, osteonecrosis of the jaw bone. The observable anomaly is widely acknowledged among cases with bisphosphonate/medication-related osteonecrosis of the jaw (BRONJ/MRONJ), which is associated with the use of e.g., bisphosphonates, denosumab, corticosteroids, antiangiogenic drugs, chemotherapy, etc [14]. Other associations include certain cancers, infections (bacterial, viral and /or mycotic infections), rheumatological-, metabolic-, hematological disorders, exogenous substance use and / or by ionizing radiation[15-19]. The exact cause of osteonecrosis of the jawbone remains to be unknown and speculative. It is widely acknowledged that these associations are correlated with an increase of occurrence when surgery, root-canal, and / or tooth-extraction are involved.

It is currently claimed that this pathology is exceedingly rare to non-existent in normal healthy individuals and may be suggested by some to occur only predominantly through idiopathic and / or iatrogenic means[20-24]. This is an assumption that still needs to be proven. The majority claims that cases outside (normal healthy individuals) do not exist. The main controversy is the doubt and / or refusal to acknowledge that osteonecrosis of the jaw occurs in the alveolar processes of the human jawbone mandible and / or maxilla beyond strictly idiopathic and iatrogenic origins[25].

In the most recent published review article from Sekundo et al., 2021 gives an overview of where the opposing group is still having difficulty accepting the pathology. Efforts made to propose (non-) scientific arguments to disprove and/or question the pathology include: 1) confusion observed due to continuous change in etiologic concepts and/or shifting opinions among advocators; 2) lack of properly designed research studies; 3) poor quality of research (which includes lack of Randomized (placebo) controlled trials, (anecdotal) case reports, and mainly observational studies that are (highly) subjected to bias (e.g. clinician/personal bias, non-blinded, lack of controls); 4) lack of acceptance and/or approval by institutional review panels; and 5) lack of any gold standard diagnostic tool(s) (include claims of its “invisibility” using radiography)[20-24]. The opposing majority even denies its existence entirely and like previous controversies in history, there are cases of mockery and ridicule observed. By opposing, ignoring, and not accepting this controversy, patients are not provided with the best of care. Is history repeating itself? Haven’t we learned from our mistakes?

2 Methods

To critically investigate, understand, and challenge a controversy, it is essential to critically assess the entirety of the data available. Relevant databases included were NCBI Pubmed (Central), MEDLINE, Cochrane Library, Web of Science, and Google scholar. The methodology used for searching included (research) articles in English. Publications in foreign language that included a full-text manuscript translated in English were considered to be useful in the investigation. Publications with abstract only were excluded. A combination of methodological and *grey literature strategy search* was utilized to find anything that would disprove or support FDOJ's existence, acknowledgement, and / or discussion. Moreover, all facets of pathology were considered, which includes evidence of the clinical observation, case reports, comparative study, validation study, etiology, histopathology, morphological, structural, diagnostic tools, and tests were of interest. Other "less" scientific papers were also considered, such as discussion papers, position papers, historical evidence, textbooks, anecdotal evidence, opinion and commentary papers. Specific systematical searches were made using the following MeSH terms: Neuralgia-Inducing Osteonecrosis of the jaw (NICO), (jawbone) cavitations, osteonecrosis of the jaw (bone), with both inclusion and/or exclusion of MRONJ (medical-related osteonecrosis) or BRONJ (bisphosphonate-related osteonecrosis), osteomyelitis, aseptic osteonecrosis (of the jaw), fatty degenerative osteonecrosis (FDOJ) and osteomyelitis of the jawbone. Additional search terms include: epithelial remnants (rests) of Malassez, odontogenic epithelial cells, RANTES(/CCL5), (immune)histochemistry, cytokine (profile), immune modulation, (acute/chronic) inflammatory response, (peri)apical (radicular)cysts.

For clarification purposes, the term FDOJ (fatty degenerative osteonecrosis of the jawbone) will be used exclusively to account for the subjected controversy.

(Selected) MeSH term	Search Interval	Number of hits	Inclusion emphasis
FDOJ	2017 - 2022	3	N.a.
Jawbone cavitations	1992 - 2022	13	N.a.
NICO	1992 - 2022	19	N.a.
Bisphosphonate Osteonecrosis Jaw	2001 - 2022	2.734	Quality of data, recency,
Medication Osteonecrosis Jaw	1956 - 2022	6.046	Quality of data, recency,
RANTES/CCL5 & Periodontitis	2001 - 2022	6	N.a.
RANTES/CCL5 & Jawbone	2017 - 2022	15	N.a.
RANTES/CCL5	1988 - 2022	6.459	Quality of data, recency,

Table 1. Overview of MeSH searched with number of hits (NCBI Pubmed Central).

3 Results

3.1 Clinical appearance of Fatty degenerative osteonecrosis

The clinical appearance of FDOJ presents itself in a myriad of ways. In 1860's Barret and Noel provided the first description of noticeable defects in the jawbone[26, 27]. In a 1920 G. V. Black textbook, the author being one of the founders of modern- and operative dentistry, there is an entire section dedicated to necrosis of the jaw, describing *"necrosis of the maxilla"* (as an acute necrotic process) and *"chronic osteitis of the maxilla"* (as a slow, often painless, chronic necrotic process)[28]. In the years afterwards there were limited publications on the subject matter. Until Ratner et al. 1979 first published

and described a predominantly chronic inflammatory and infectious process in the jaw bone, which can be observed by radiographic imaging (See Fig.3)[29]. It was noted that the observed *"cavitations"* were difficult to observe through the imaging technique and was almost considered to be *"invisible".*

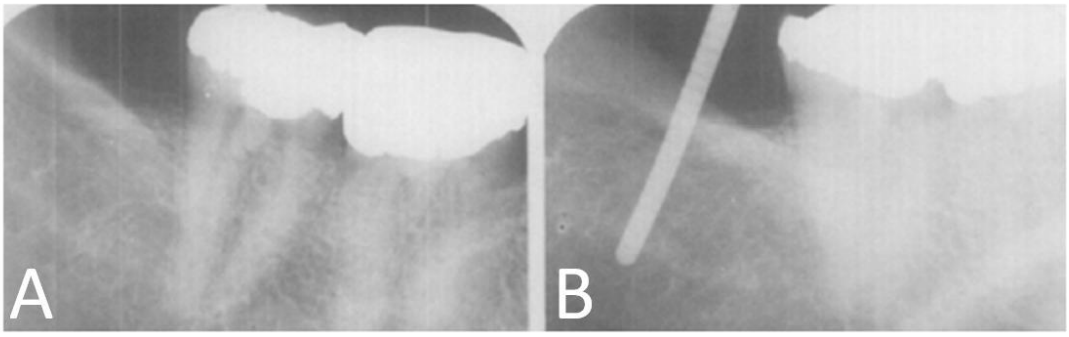


Figure 3. Radiographic image of the lower left posterior mandibular region, from a case of atypical facial neuralgia. As noted in the left image(A), there is no visible indication of an abnormality. However, the right image shows the same the area after a metal probe had been inserted into an existing bone cavity to a depth of 14 mm(B)*[Ref.: Ratner et al., 1979).*

3.2 Confusion in FDOJ terminology

After this first publication, many reviewers and papers note that Bouquot et al., 1992, introduced the highly controversial concept of *Neuralgia-Inducing Cavitational Osteonecrosis (NICO)*[30]. Since then, the presumed pathology has undergone 75 name changes[31, 32]. In strictly observable clinical pathophysiological context, terms attempted to describe FDOJ include: *alveolar cavitational osteopathosis*[33], *necrotizing ischemic chronic osteitis*[34], *aseptic-avascular osteonecrosis*[35], *chronic fibrosing osteomyelitis of the jaws*[36], *focal osteoporotic bone marrow defects and aseptic ischemic osteonecrosis of jawbone*[37, 38]. The most recent term proposed is *fatty degenerative osteonecrosis of the jaw* (FDOJ), which aims at describing both the morphological and pathohistological characteristics synonymously, and emphasizing to not include its associated symptomatology (See fig.4)[39, 40].

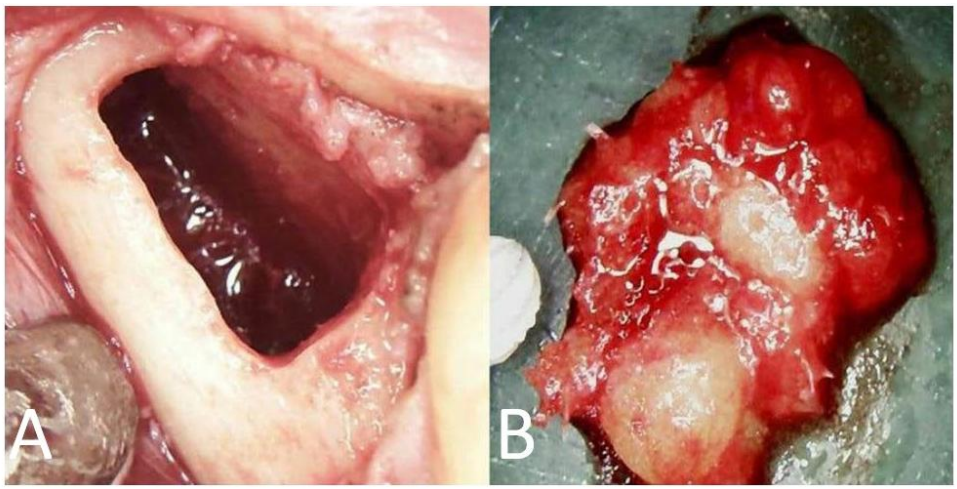


Figure 4. Visibly observable jawbone "cavitation"(A) with corresponding extracted fatty tissue(B) *[Ref.: Lechner et al., 2021].*

The most basic understanding of FDOJ includes necrosis of the (jaw)bone tissue[41]. However, the continuous change in terminology, especially among proponents of FDOJ, is often used as a justification to dismiss its legitimacy[42, 43]. However, this change in terminology and / or clinical (sub-)categorization is attributed to the diversity of its manifestation and attempts to associate it with categorical terminology in pathology. FDOJ may present itself clinically with or without exposed bone as local affected area, intra-orally, and / or subcutaneous, either with or without infection and / or pain [14]. On the basis of this alone, one can assume to classify these clinical observations as being a myriad of diseases.

The failed attempt of its terminology is not limited to its symptomatology. As previously mentioned, FDOJ is a *cause* and not a *disease*, but can manifest itself into presenting itself synonymously to a *disease.* FDOJ can be considered to be the cause, form part of a set of causes, or form as a manner of disease causation. Evidence suggests it plays a causative role in inducing Neuralgia[29, 44-47]. At present it is associated with local (to systemic) chronic inflammatory diseases, through increased RANTES/CCL5 chemokine levels[35, 48, 49]. Which has the potential to be directly causal for myriad of diseases and conditions, which is not currently accepted or possible the dismiss either. And lastly, FDOJ forms part in the determination of how prior causes (e.g., teeth extraction without removal of periodontal ligament, root canals, poor oral health, infection, medication use etc.) may lead to (a myriad of) disease.

3.3 (Potential) Risk factors influencing pathological progression

Risk factors posed in the literature that increase the likelihood of developing and / or accelerate the pathological progression include the following: 1) (dental alveolar-, periodontal-, periapical-) surgery, extractions, or placement of dental implant have been associated with an increased likelihood in comparison to patients who do not undergo surgery BRONJ/MRONJ; 2) Medication potency and or duration of the therapy play a role; 3) Anatomical/Location dependent. The predominant affected areas for the mandible include the lingual tori, mylohyoid ridge, and for the maxilla the palatal tori. The region that has an increased susceptibility are the 3rd and 2nd molar of each quadrant. Worldwide prevalence of (partially) failed impacted (erupted) wisdom teeth is around 24%. Conversely, almost 50% of modern humans experience problems with their 3rd molars**.** It is known that this process can often lead to partly and / or failed eruption of the 3rd molar. Consequently, this may impact the teeth directly in front. This process can go without signs symptomatology, and with or without development of dental disease; 4) Concomitant (dental) diseases include osteoporosis, cancer diagnosis, diabetes, inflammatory disease such as periodontal disease, and dental abscesses may cause an increase in occurrence; 5) Additional demographic factors such as age, sex, race. Caucasian women between 40-60 are more prone; 6) Additional factors include smoking, alcohol, and poor oral health[50-52]. The latter purposed risk factors are mostly from acknowledged from BRONJ/MRONJ cases; the question remains whether the same can be concluded. However, it is feasible to assume there is a biological rationale.

3.4 Current diagnostic “gold standard” fails to acknowledge FDOJ

It is apparent that based on symptomatology and clinical observation alone it is insufficient to make a proper assessment. A critical part in this assessment is making use of the proper diagnostic modalities. As this has been a challenge that preceded for many years until the present day. More importantly, this may be considered one of the major *bottle-necks* for FDOJ acknowledgment, understanding, and development in the field.

The American Association of Oral and Maxillofacial Surgeons (AAOMS) advocates the use of diverse imaging modalities when detecting cases of BRONJ/MRONJ[50, 52]. However, in modern clinical dentistry, imaging of routine cases to assess the condition of the jawbone is often limited to the *gold standard,* which is Radiographic imaging (a.k.a. Panoramic X-rays, Orthopantograms, (2D-)OPG)[53-55]. Similarly, it is often the preferred technique for diagnosing bone pathology in other areas of the body[56-58]. However, this technique performs inadequately to provide clear noticeable pathological changes, and provides insufficient diagnostic representation. This incapacity to use radiography to assess bone destruction was already noted by Adrian in 1951, stating *"routine radiography may not exclude the presence of secondary neoplasms or inflammation causing bone destruction"*[59].

FDOJ is often difficult to detect and was considered to be an *"invisible"* entity[29]. Due to this fact alone, there was a reason for increased skepticism around it even existing. However, later published articles solved this issue, as it was not meant through literal means but rather figuratively[37]. This is supported by Lee et al., 2014, showing radiography assessment in osteonecrosis cases to be unsatisfactory and non-uniform[60]. This fact becomes more evident when comparing its performance against other modalities such as Computed tomography (CT), 3D-cone beam, Nuclear Imaging, Fluorescence-Guided Bone Resection, Magnetic Resonance Imaging (MRI), PET scan, and more recently a novel trans-*alveolar ultrasonography*[61-65].

One of the main challenges of using radiographic images is the expectation of trying to observe the 3D-bone-structure using a 2D-based image, also noted as "*anatomical noise"*[66]. Detecting affected jawbone areas through radiography is limited to the outer ridge of the jaw, alveolar socket. On the contrary, it may be less apparent to detect when there is a "cavitation" present in the cortical/medullary location of the jaw bone (See Fig.5A). This can however be made visible by injecting a contrast agent (See Fig.5B)[39]. Nonetheless, this is only limited for its usability for assessing an (already) suspicious area. In the case of BRONJ/MRONJ, it is indicated that the image modality chosen depends on the availability (e.g., due to cost-saving) and the preferred method of choice. Nonetheless, it is apparent and most desirable to assess any bone aberration using a 3D-imaging modality[65, 67].

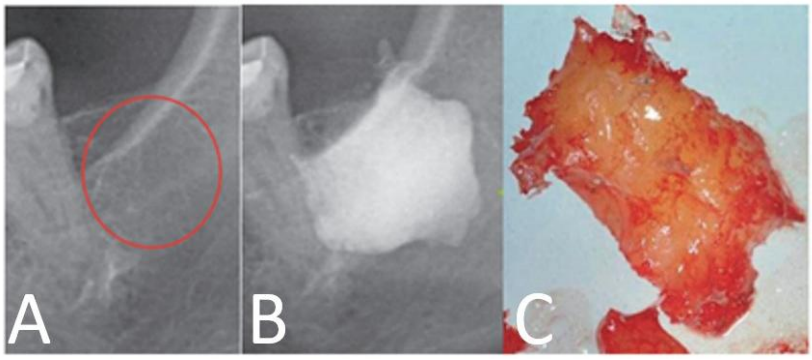


Figure 5. Radiographic inconspicuous FDOJ affected area(A,C) made visible with contrast agent(B) *[Ref.:Lechner et al., 2018].*

Additionally, the severity of the affected jawbone plays a role in detectability. This is mirrored by the experience in BRONJ/MRONJ cases[50, 52, 68]. The AAOMS 2009 presented 3 characteristic requirements needed to diagnose patients to with BRONJ/MRONJ, which includes; "*1) exposed bone in the maxillofacial (upper jaw) region that does not heal within 8 weeks (from identification by a*

healthcare provider); 2) in a patient that is currently or has been on bisphosphonates; and 3) who does not have a history of radiation therapy in the craniofacial region"[50, 69]. However, the first criteria were flawed and eventually revised, as it became apparent that emphasizing exposed bone strictly would limit detection of prior stages of the disease and lead to under-diagnosis. Subsequently, after critical assessment a revised 4-stage progression was purposed (stage 1-3 being "at risk"). Stage 0 cases are of particular interest, as a noticeable revision has been proposed by Patel et al., 2012 and subsequently implemented in 2014, suggesting an "Unexposed Bone Variant"[50, 66]. This variant includes radiographic detectable aberrations in the jawbone[70-72]. Yet, for optimal radiographic detectability a significant loss of bone (30-50%) must have occurred[68].

3.5 Trans-alveolar Ultrasonography – a promising new imaging tool

For many years ultrasonography was posed as a potential diagnostic candidate to solve the issues and limitations of radiography, as its benefits include low cost, painlessness, non-invasiveness, and it does not involve detrimental ionizing radiation[73, 74]. However, its usefulness was dismissed due to its lack of validation, standardization, low efficiency, and reproducibility[75, 76].

In 2021, a novel ultrasound, *trans-alveolar ultrasonic pulses*, device was put to the test in a validation and comparative study[37]. Ultrasound has reported to be superior to radiography, and has a high reproducibility compared to other traditional imaging techniques modalities (such as CT and cone-beam computed tomography (CBCT)) [74]. Its utilization is based on the fact that each designated structure has a highly distinct (biological) fluctuation, which allows one to discern pathological (See Fig.6). Which has evidently shown promising results for assessing cases of FDOJ, detection, and assessing early stage of jawbone aberrations[37].

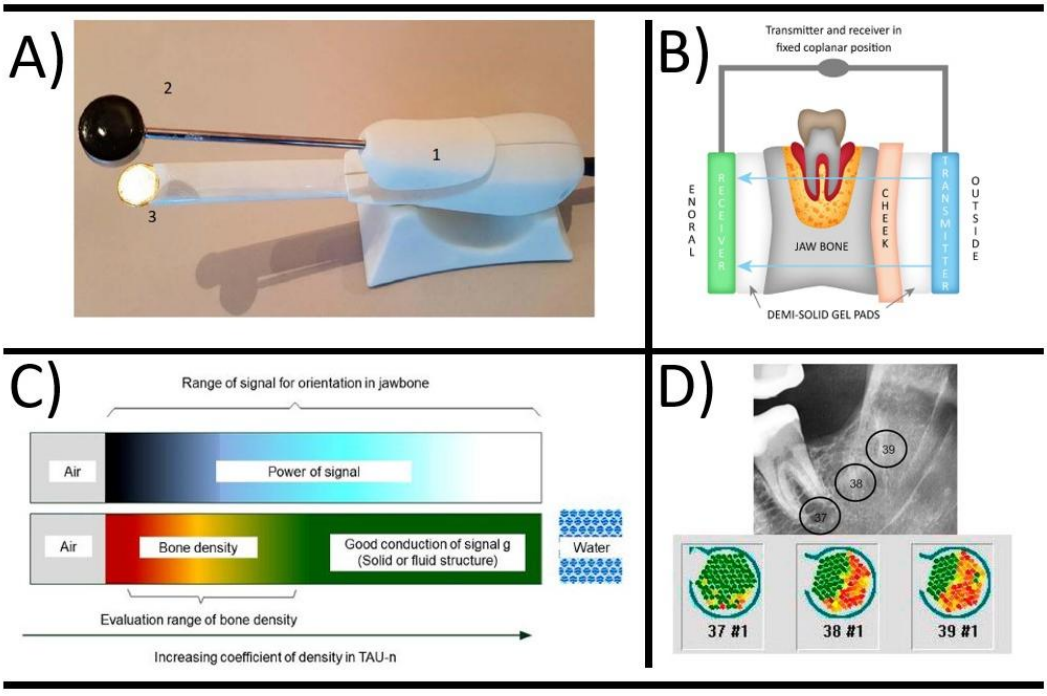


Figure 6. Trans-alveolar Ultrasonography. 6A) Hand piece with ultrasound receiver and transmitter(1), ultrasound transmitter(2), and ultrasound receiver. 6B) Illustration of positioning. 6C) Schematic overview of the ultrasonography principle indicating bone density based on a color scale. 6D) Case example showing bone density

at teeth position 37,38, and 39. Green indicates solid bone and red indicates reduced bone density. Abbreviation: TAU-n= new through-transmission alveolar ultrasonography*[Ref.:Lechner et al., 2021].*

3.6 Diagnosis beyond Imaging: Histopathology and Immunohistochemistry

Beyond the imaging *bottle-neck,* other diagnostic tools to support FDOJ detection include histopathology and immunohistochemical assessment. Histopathological assessment of the affected area can further help as a diagnostic means, but should be utilized in combination with imaging modalities and *vice versa*[77]. According to a commentary letter by Bouquot 2021, to address a recent review of Sekundo et al. 2021, noted the lack of mentioning the importance of known histopathological similarities between hip osteonecrosis compared to jaw lesions found in FDOJ. Specific pathohistological features can be repeatedly observed such as distinct immune cell infiltration patterns, variable size of fat cells, oil cysts, (abundant) fatty degeneration, air-filled space(s) or cavitations, loose to moderately dense fibrous connective tissue (marrow fibrosis), dystrophic calcification (See Fig.7)[30, 39, 41, 78].

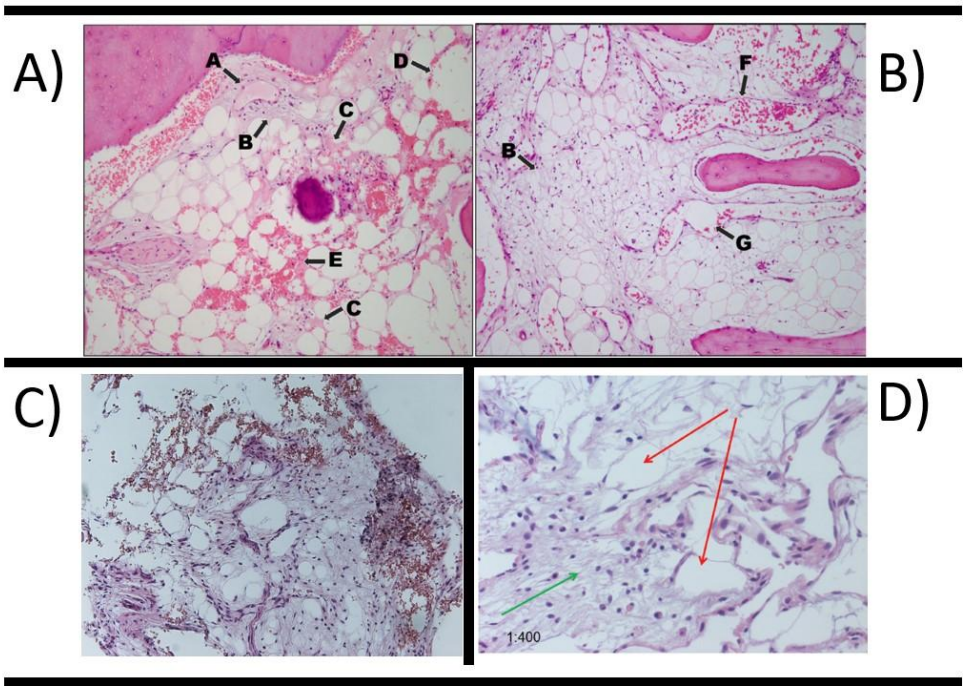


Figure 7. Pathohistopathological (microscopic) assessment from extracted fatty degenerative tissue depicting typical features. 7A and 7B *"Aggregated fibrin plugging a dilated capillary (a); ischemic myelofibrosis, with small numbers of lymphocytes and mast cells(b); plasmostasis (serous ooze)(c); oil cyst (bubble of liquified fat from previous fat necrosis)(d); focal hemorrhage (consistent with microinfarction)(e); greatly dilated marrow capillary (medullary congestion)(f); fat embolus plugging dilated capillary(g)".* 7C and 7D showing similar fatty/oil cysts and embolus, (limited) dispersed pattern of lymphocytes *[Ref.: Bouquot, 2021(7A,7B), Lechner & Volker, 2013(7C), Lechner & Volker, 2014(7D)].*

Additional immunohistochemical examination of this fatty degenerative tissue has recently provided ample understanding for the type of immune response evoked[39, 41, 79]. Until recently there is a cross-disciplinary field, called ("maxillomandibular") Osteoimmunology, that has started to demonstrate the dynamic interplay between immune and bone systems, of which much is still unknown and being uncovered[80, 81]. Distinct pattern of immune response can be observed across necrotic jawbone diseases, such as BRONJ/MRONJ, osteoradionecrosis, infectious bone diseases, etc.[82, 83]. Implicated

immunological factors include cytokines, interleukins, and chemokines. Differences in (Inflammatory) mediators have been observed such as interleukin (IL)-6, IL-1, tumor necrosis factor (TNF)-α, RANKL, FGF-2, and RANTES/CCL5 (See Fig.8)[84]. These mediators have a role in (dysfunctional) bone resorption and turnover, influencing osteoclast, osteoblast, and osteocyte communication networks.

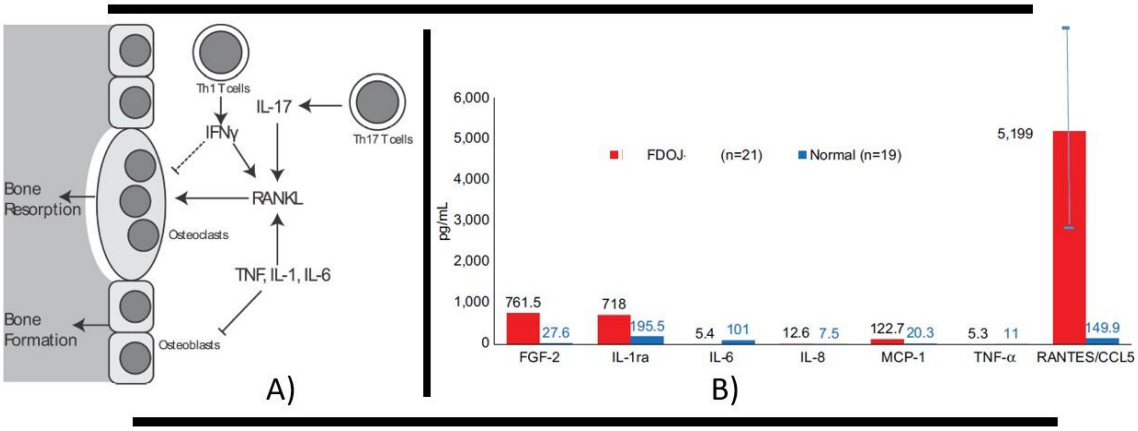


Figure 8.Osteoimmunology of the jawbone. 8.A) Overview of osteoimmunological molecular pathway influencing osteoclasts and osteoblasts. 8.B) Multiplex analysis measuring immunological factors of (n=21) patients with FDOJ compared with (n=19) healthy control. *[Ref.:Greenblatt 2013, Lechner et al., 2018].*

Here we aim to focus solely on (proinflammatory) chemokine RANTES/CCL5, as this mediator has been the most noticeably implicated in influencing many biological processes beyond strictly immunological. However, its chemotactic activity has shown to recruit dendritic, T-cells, NK cells, eosinophils, basophils, and mast cells to sites of infection, injury, and inflammation[85, 86]. Until recently, through *multiplex analysis* of the fatty degenerative tissue it was shown that cases of FDOJ had a significant high-fold increase of RANTES/CCL5 compared to control samples(See Fig.8B and Fig.9). This was further supported by histological findings[40].

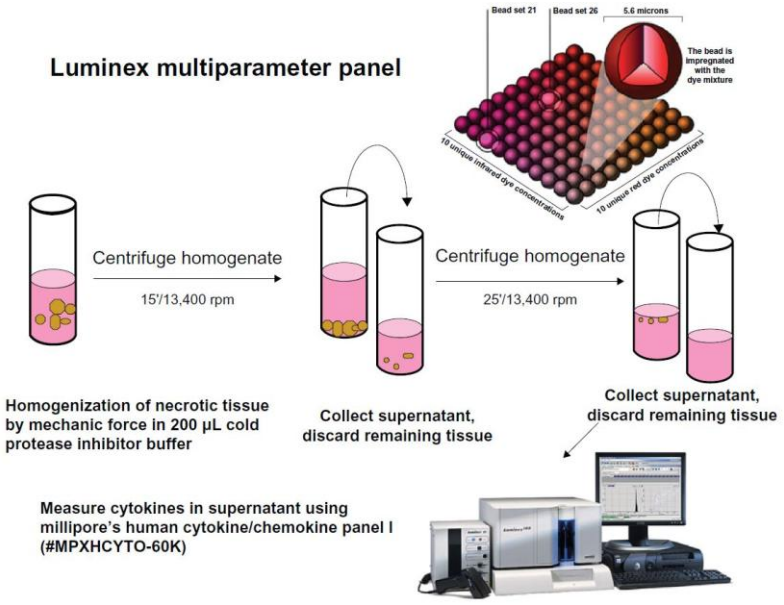


Figure 9. Methodological processing of FDOJ samples using multiplex analysis *[Ref.: Lechner & Volker 2013].*

3.7 Potential connection between Epithelial remnants of Malassez and FDOJ

The maxilla and mandible are the only human bones that have a distinct physiological connection with teeth, as there are no epithelial barriers against inflammatory of infectious agents upon necrosis and infection of the dental pulp. Consequently, illustrating the importance of immunological- and tissue responses in this area[87]. After the developmental stage of the teeth there are cell remnants that prevail upon apoptosis of HERS, amongst them are ERM or epithelial *rests* of Malassez (*pax epithelialis pediodontii*). For many years ERM were thought to be regarded as quiescent remnants of HERS with limited physiological importance[11]. ERM have a protective and reparative role in maintaining PDL integrity. Through expression of epidermal growth factor root resorption, calcification, and ankylosis of the PDL is prevented from occurring[9, 88, 89]. ERM have been widely disregarded and poorly described in context of periodontal research[90].

Until recently it has been shown that ERM form an intricate part of the PDL, as they play an essential to central role in both dental both pathology and regeneration[11]. These cells form a barrier for preventing periapical infections from spreading further into the PDL[91]. More recently it became evident that they have the ability to undergo multi-lineage epithelial mesenchymal transitioning, which allows them to differentiate into a broad range of cells types of both ectodermal and mesodermal origin, including adipocytes, chondrocytes, osteoblasts (i.o.w. fat, cartilage, and bone)[92, 93].

Currently, it remains speculative to assume that ERM stem-cell differentiation into adipocytes are central to the fat formation observed in FDOJ (See Fig. 4 and 5). However, it is acknowledged that chronic inflammatory responses cause ERM differentiation and proliferation, which may result into formation of dental (peri)apical (radicular) cysts, odontogenic cyst (or granuloma), cystic cavity, induce pocket formation, apical granulomatous tissue, and tumors. This response can be evoked by e.g., nonvital teeth caused by endodontic treatment, (surgical) trauma, dental caries, or infection)[94-97]. Additionally, differentiated ERM-cells have shown the ability to express 29 out of 120 cytokines in significant amounts (including growth factors, cytokines, chemokines, and other related proteins). Interestingly, RANTES/CCL5 was amongst the highly expressed chemokines. Furthermore, high levels of RANTES have been implicated in the formation of (peri)apical cysts[90, 98]. Even though there are familiar characteristics between (peri)apical cysts and FDOJ, it remains inconclusive and poorly understood how many molecular and cellular processes are (in)directly relatable.

3.8 Obligatory surgical treatment of FDOJ

Treatment of FDOJ consists of local anesthesia, incision of the gingiva, and drilling or piercing of the maxillary/mandibular periosteum (membrane that covers the outer surface of most bones). This process will expose the “cavitation or hole” (See Fig.4), which can be observed as fatty, mushy, semi-Liquid/gel-like, osteonecrotic tissue. The hole is cleaned out, and the sides are deburred to reintroduce optimal blood flow. In order to sterilize the area anti-microbial treatment and / or ozone is used[99, 100]. Lastly, bone-remodeling inducing strategies such as Leukocyte platelet-rich fibrin (L-PRF) might be introduced [51, 101, 102].

Improper removal of a tooth without curettage of apical (cystic) tissues, can result in formation of *residual cysts.* Central to this pathology are ERM. Noticeably, they can grow to large dimensions without any symptomatology[95, 97]. The amount of ERM cells reduces with age, as they undergo apoptosis[8, 89]. The consequences of this subsequent reduction remains unknown in dental pathology and regeneration.

3.9 Justification for FDOJ treatment

Beyond the controversial acknowledgement and inherent difficulty of proper diagnosis, treatment is even more disregarded and considered medically unnecessary. From opposing statements that claim FDOJ treatment to be anecdotal, experimental, disregarded as being expensive, (largely) ineffective, invasive, and carries significant risk[43]. Even if FDOJ would exist and / or acknowledged according to the skeptics, treatment is considered by many to be an unnecessary surgical procedure, especially when local symptomatology is lacking. This statement assumes that the current published studies do not prove its necessity and / or abides by the supposed low quality of evidence (e.g., lacking prospective and or Randomized control trials (RCTs). This is further supported by the notion that FDOJ is not an acknowledged clinical picture according to the ICD11 codes (most recently revised in January 2022) of disease listed[103]. Therefore, is it claimed that there is no medical need to perform diagnostics and treatment[104].

First, in order to address statements that disprove or question treatment efficacy is reductive in essence. To therefore, attribute the effectiveness exclusively to its treatment is fallible. As this may indeed remain probable, it is however least likely given the context of the innumerable amount of risk factors and variables influencing the outcome. What is evident is that there is a potential lack of improvement, relapses, and dangers. However, these should not be the reasons to not treat a patient, as every surgery performed has its potential complications and dangers.

Additionally, how would one dismiss its justification for treatment (entirely), especially when acknowledging that other (inflammatory) jawbone disease encourage treatment and / or surgery. In the latter case it is suggested that it's more likely beneficial for a patient to undergo surgery than to leave the affected area run its course[67, 102, 105]. It would be hypocritical to assume FDOJ to be of less significance to treat given the evidence.

And finally, these statements would fundamentally violate the nature of FDOJ, as it does not suffice the criteria for a disease. Yet, critical assessment shows it to be distinctive as a (manner of) cause and not a disease per se, as explained prior in the introduction. More importantly, if all of the above is critically considered (its etiology, clinical observation/appearance, immunohistochemistry, histopathology, and imaging modalities are confirmed), then there is enough (scientific) justification to opt for treatment and further research is warranted.

4 Discussion

4.1 Arguments posed against acknowledging FDOJ

The widespread confusion and denial that currently prevails can mainly be attributed to (the lack of) understanding its etiology and diagnosability. The reason for affirming this fact lies in the quality of arguments made by the opposing group. Most contra arguments, if not all, assume to be scientific in essence, yet lack any (systematic) scientific evidence (e.g., biological-, diagnostic-, experimental-, rationale, mechanistic-, anatomical-, functional rationale) to disprove and falsify the primary concept of FDOJ. Attempts are made to substantiate critically raised evidence on the quality of the presented data, emphasizing the value of performing RCTs. Even though the latter is of importance, it should not be considered to be a (sole) criteria for appreciating “lower quality” research. The latter being supported by

the fundamental principles of the Scientific Method, as performs at its best when the entirety of the data is considered, until factually proven otherwise.

An example to illustrate this point can be found in a review by Sekundo et al., 2021, where it was noted that most professional associations remain silent on the subject. Yet, the American Association of Endodontics (AAE) have stated that the practice of recommending the extraction of endodontically treated teeth for the prevention of NICO was claimed to be unethical and should be reported to the authorities[104]. However, when carefully assessing this position paper, it becomes evident that these recommendations are based on *consensus decision*, without critical assessment and consideration of the presented evidence regarding the issues of diagnosis and etiology[106].

Additionally, surgical interventions were deemed to be unethical for the lack of evaluation in RCTs. The presumable demand of RCTs itself is unethical to perform, as noted by Bouquot 2021[31]. As performing such a surgical procedure on healthy subjects would not be feasible. In this case, the *highest* (possible) quality of evidence would be derived from observational studies. The majority of the current evidence includes case studies and retrospective studies. Considering surgical intervention unethical seems unreasonable, particularly when disregarding its potential benefits to improve severe conditions perpetrated by FDOJ, such as Trigeminal Neuralgia, also known as *Suicide Disease.* Especially when conventional therapies often tend to fail.

Given the limitation of not being able to perform RCTs, future publications should focus on acquiring observational prospective studies, which ideally would include a longitudinal cohort study with a multi-center and / or third-party assessment. This would be feasible for testing the reproducibility of the findings found in the diagnostic tools (e.g., trans-alveolar ultrasound, and RANTES/CCL5), and treatment strategies. Eligible study cases would include any surgical procedure, which involves (wisdom)teeth removal and /or root-canal treatment, however not exhaustive to these variables.

4.2 Diagnostic limitation to understanding FDOJ's incidence

An argument often used is FDOJ's supposedly low rarity (to non-existence) in comparison to BRONJ/MRONJ very low incidence. A minor contributor to explaining the rarity of BRONJ/MRONJ is the *criteria for diagnosing* itself. As one of the 3 criteria for diagnosing a case involves exposed bone that does not heal within 8 weeks. Subsequently, in recent years 4 stages have been proposed. More importantly, the major contributing factor for its underreporting may stem from the limitations posed by the *gold standard,* radiography, currently used. As this technique has shown to be very limited at determining the different stages of BRONJ/MRONJ. A recent paper by Lechner et al., 2020, addresses this point, showing the necessity to introduce new standardized measures for imaging. Not opting to implement novel standardized technologies (such as trans-alveolar ultrasonography), will hamper the specialists' ability to properly diagnose and may cause to overlook FDOJ entirely. Proposing the hypothesis that FDOJ may be the (major) contributor to BRONJ/MRONJ pathogenesis.

4.3 Limitations

Limitations of this literature thesis would include the limitations of a "grey-search strategy", as there was a limited systematic approach to finding information. However, systematic search approaches both

have their benefits and limitations. Such an approach would potentially reduce the risk of personal bias and prevent subjected “cherry-picking”, yet it may confine the ability to critically assess the entirety of the data, especially within the context of a controversy. The writer’s own personal bias towards the subject includes having witnessed discussions in the field with dentists and researchers, and interviewing patients that have undergone FDOJ surgical interventions, and obtaining their anecdotal evidence. Despite these constraints, it remains a challenge for both the writer and reader to judge the argumentation in face of the evidence.

4.4 Conclusion

Many key questions remain to be answered in the future, which includes: 1) What do we want to achieve in the (near) future?; 2) Which symptomatology correlates to which state of the presumed (myriad of) disease, where FDOJ plays a causal role?; 3) What are the distinct (un)known risk factors (in)directly associated that lead to these diseases?; 4) What is the role of ERM in FDOJ?; 5) Is treatment required for all stages of (disease) development?; 6) What is the goal of treatment? Is it only restricted to symptom reduction?; 7) Can treatment improve inflammatory factors (e.g. RANTES/CCL5)? What would reduction mean for local to systemic chronic inflammatory diseases? 8) Do all patients benefit from treatment? Are there alternatives to treatment?; 9) How can (prospective) clinical trials be best conducted within the ethical limitation?; 10) How can this knowledge best be implemented through an interdisciplinary approach between specialists in the field of dentistry, medicine, research, and beyond?

In conclusion, the acceptance of FDOJ through clinical observation and using proper diagnostic modalities is only the beginning of its acknowledgment. Its causal role in local and systemic chronic inflammatory diseases should not be underestimated and overlooked. Failure to ameliorating this insidious hidden infection will only foster detrimental consequences for a patient’s health.

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