Chapter 7

Biological Concepts on Bisphosphonate Treated Patients in the Context of Increasing Patient Life Quality and the Need for Oral Surgical Procedures

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Additional information is available at the end of the chapter

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Abstract

Bisphosphonates are used for treatment of different bone conditions, most frequently for increasing bone density in osteoporosis patients and for treatment of primary or metastatic bone tumor as well as intake for osteoporosis patients.

The pharmacokinetics of bisphosphonates is well described in order to clarify mechanisms of action of each sub-group according to the classification of these drugs.

Bisphosphonate-induced avascular osteonecrosis is described as phenomenon in the human bones especially observed in human jaws. From pathophysiological point of view this process is studied describing the osteoclast activity inhibition. Several studies and results are stated.

Having in mind that this process occurs in cases that do not include bisphosphonates intake, the American Association of Oral and Maxillofacial surgeons accept a new diagnostic and treatment strategies as well as new name of the disease - Medicine related osteonecrosis of the jaw.

By comprehensive analysis of all studies by now and cases from our practice, several important and significant protocols are introduced in this chapter, effecting diagnosis, treatment preparation, treatment and post-surgical behavior.

Keywords: Bisphosphonate-induced osteonecrosis of the jaw, dental implantology, medicine related osteonecrosis of the jaw

1. Introduction

Since it was first identified in 2003, bisphosphonate-induced osteonecrosis has been under growing control by medical and dental specialist alike because it affects cancer patients receiving intra-venous bisphosphonate therapy and osteoporosis patients receiving oral bisphosphonate therapy.

It is of significant importance to introduce the mechanism of action of this type of medications, way of distribution and risk of complication during or after treatment with them. A strategy of preparation, medication support and techniques before, during and after dental surgery procedures and especially placement of dental implants must be clarified in order to avoid bisphosphonate-induced osteonecrosis.

2. Indications for bisphosphonates

Even though they were founded in the 18th century, their real clinical usage began only a hundred years ago with the synthesis of the first bisphosphonate (BP)–etidronate. The birthplace of these medicines is considered to be the scientific institute in Davos, Switzerland, where a team headed by Herbert Fleisch, Sylvia Bisaz, and Roman Muhlbauer proved the role of bisphosphonates in bone metabolism and their importance in bone disorders treatment in 1967.

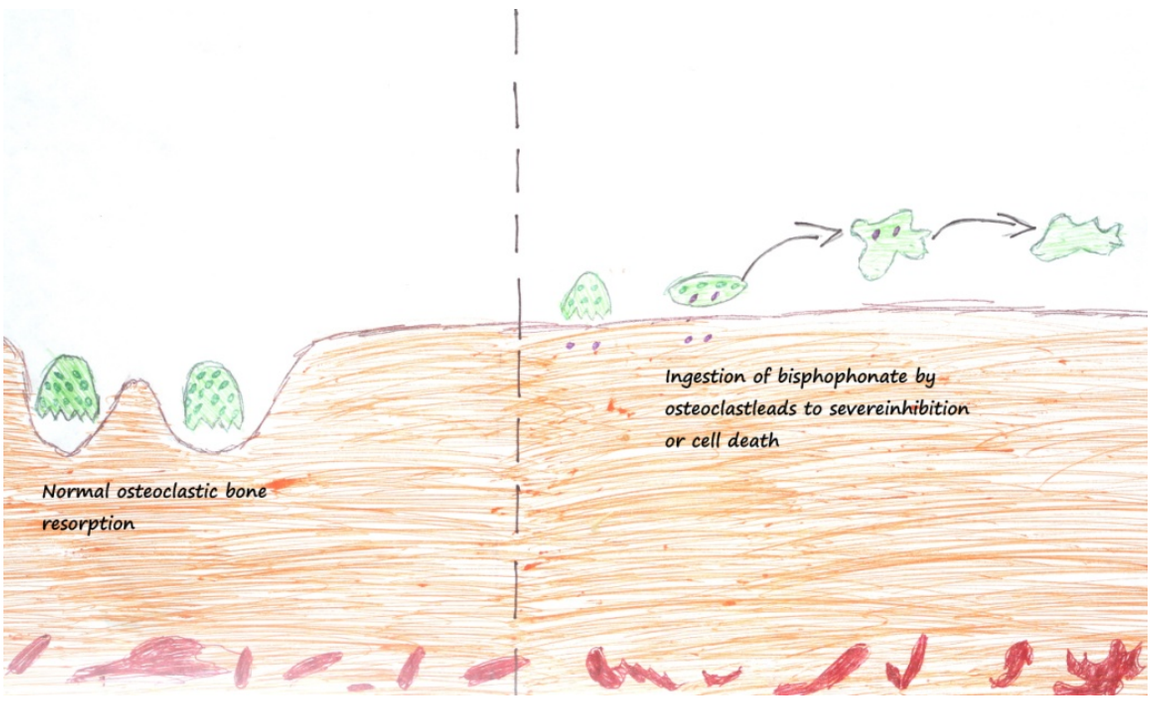

Figure 1. Normal osteoclast activity and osteoclasts death by bisphosphonate treatment (after R.E. Marx).

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Data concerning pharmacokinetics of diphosphonates, later called bisphosphonates, were published for the first time in 1969. Forty-five years of experience, including researches, has significantly manifested the advantages and disadvantages of this drug group.

Inventing and developing bisphosphonates for treatment of different bone conditions is immense progress in solving fine mechanisms of bone formation and a significant development in medicine as a whole.

Bisphosphonates treatment indications are mainly for increasing bone density in osteoporosis patients (e.g. alendronate and rizedronate), and intravenous (IV) with mouth intake dosage for patients with primary or metastatic bone tumor (e.g. pamidronate and zoledronate). Intravenous intake is also recently tolerated in osteoporosis patients.

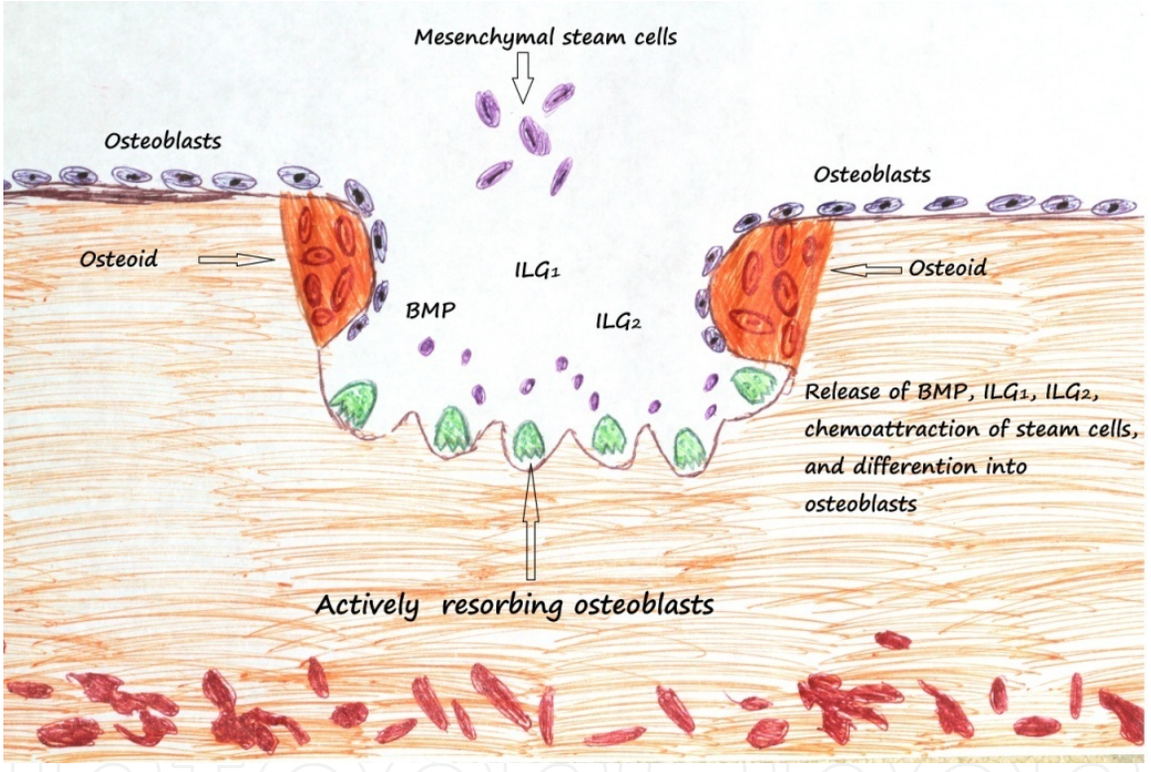

Figure 2. Scheme of bone metabolic unit (BMU) (after R.E. Marx).

3. Pharmacokinetics of the bisphosphonates

Bisphosphonates are chemically stable analogs of non-organic pyrophosphates (PPi) related to skeleton mineralization. Their development is related to inventing inhibitors of calcification in order to resist hydrolysis with alkaline phosphatase. PPi and BPs could not only slow down bone growth but also destroy hydroxyapatite crystals. BPs are remarkably efficient inhibitors to bone resorption during experiments in vitro and in vivo. During the process of their clinical application in the 1990s, it became clear that in order to clarify the chemical and physical

reactions, and explain the variety of their biological effects, it is necessary to study the cell to cell interactions. Bisphosphonates suppress bone resorption by selective absorption to mineralized bone surface where they counteract to osteoclasts.

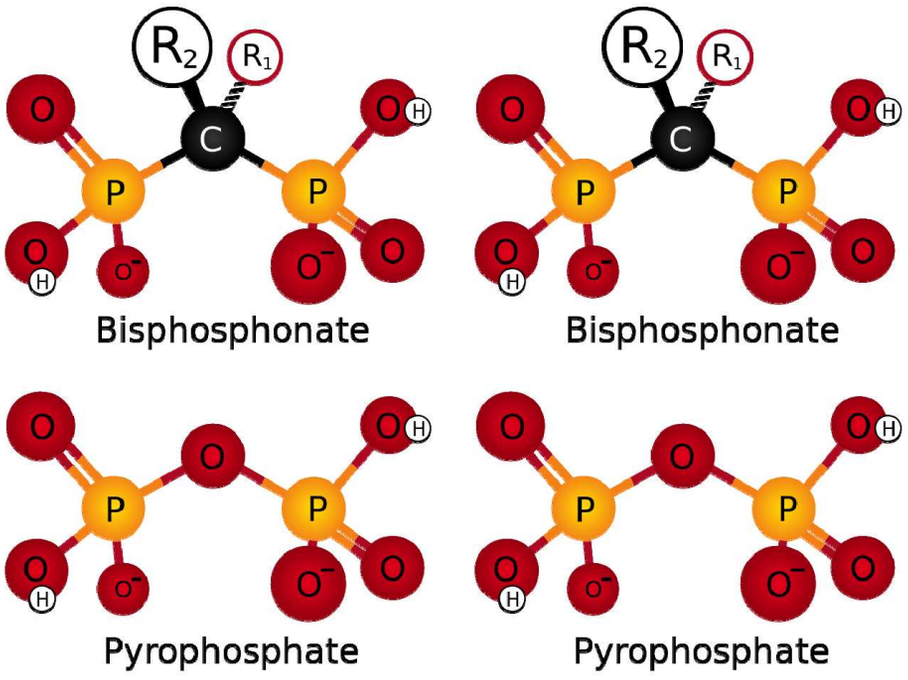

Figure 3. Basic molecular structure

Bisphosphonates couldcan be classified to at leastinto two groups with different molecular action mechanisms. The first one: is nitrogen free bisphosphonates (like etidronate and clodoronate) that interfere ATP-dependent intercellular ways. The second group is bisphosphonates with nitrogen, they that are more powerful (including pamidronate, alendronate, rizedronate, ibandronate, and zoledronate) they). They are metabolized differently, by inhibiting key enzymes of mevalonat/cholesterol biosynthetic way.

Precisely because of the obviously differentobvious biochemical and pharmacological differencedifferences and uneven intercellular interaction is important the division of, BPs in tohave been divided into separate groups and their specific usage according to a specific disease.

They are incorporated in skeletal bone without being degraded. Bisphosphonates are attached to Ca^{2+} in areas with increased bone resorption and stay integrated in the bone for 10 to 40 years – alendronate. For example, alendronate's half-life for example is 12 to 28 years. Once taken, BPs unlock cascade biochemical processes leading to loss of osteoclast ability to resorb bone or even to their apoptosis.

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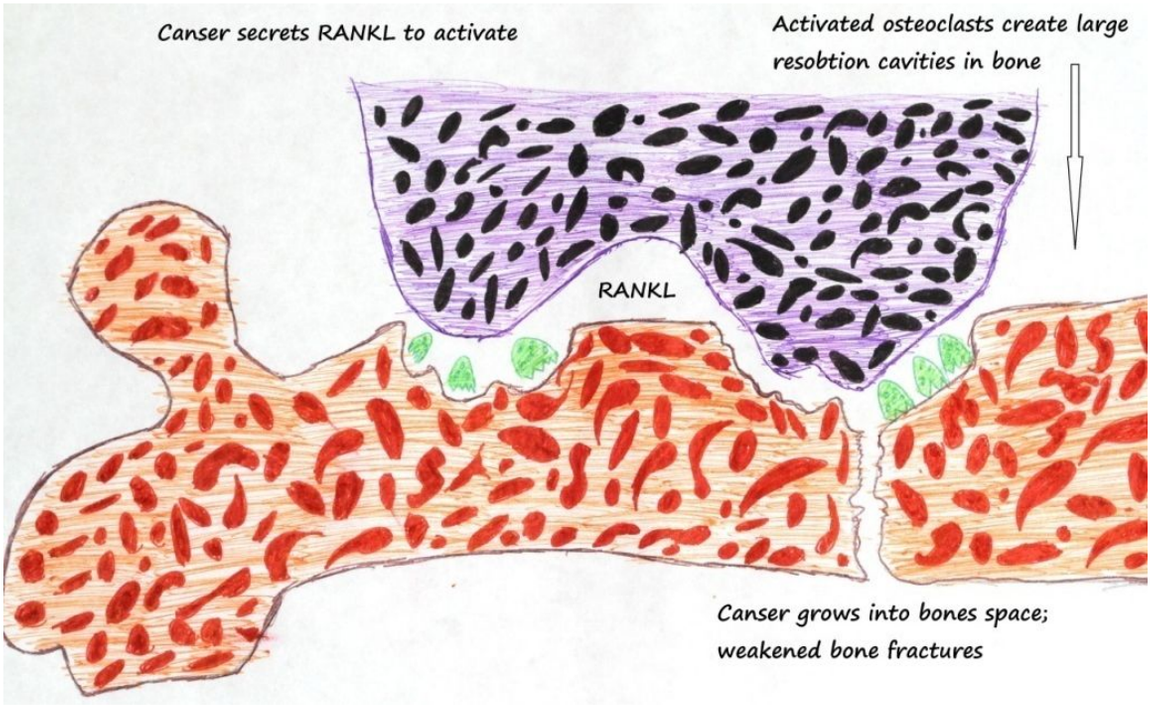

Figure 4. The way to bone fracture by solid bone tumors (after R.E. Marx).

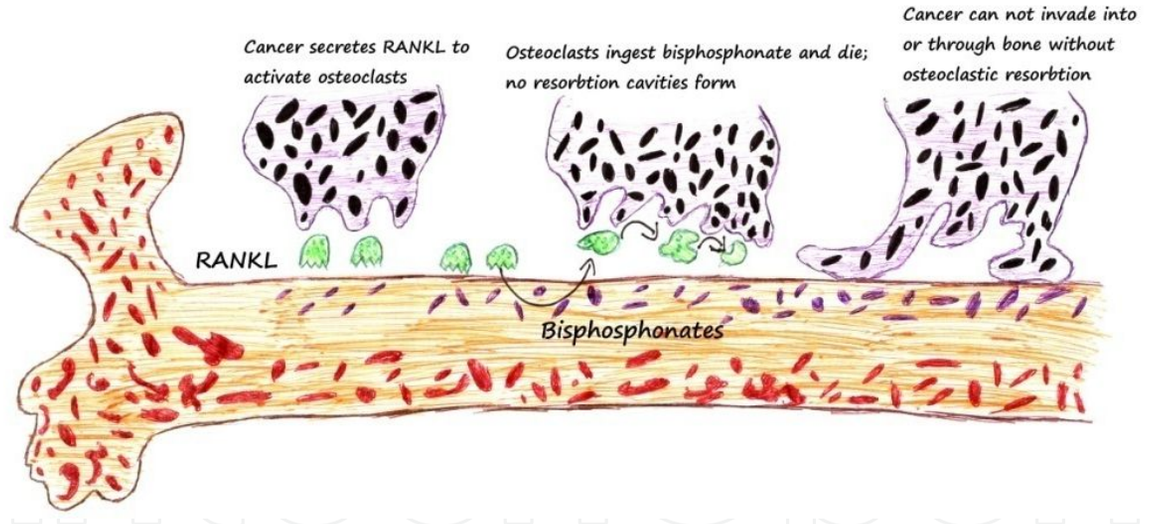

Figure 5. Prevention of bone resorption by bisphosphonate osteoclast inhibition (after R.E. Marx).

4. Bisphosphonate-induced osteonecrosis of the jaws

It is undoubtedly thatUndoubtedly, the intake increases the quality of life of the treated patients in general, but negative effecteffects should also be taken in tointo consideration. Stomach disorders, erosions of the esophagus, uveitis, flueflu-like conditions, muscle and joint pain, and severe necrosis in the maxillofacial area, known as BONJ – (bisphosphonate osteonecrosis of the jaw) could appear.

Recently inIn recent literature is found date for, a new type of complication associated with bisphosphonate intake –has been found, which is called avascular necrosis of the jaws. It is defined as necrosis associated with or without dental procedures, which could persist for more than 6-8 weeks with irresponsive to conservative treatment, found in patients without history of previous radiotherapy in the area affected but treated with nitrogen group bisphosphonates with nitrogen group, i.v. through IV for at least a year or per os for longer period, and associated with general condition withof bone resorption. Similar cases arewere published for the first time in 2003 by Marx with patients treated with pamidronate and zoledronate. Later, Carter and Gross, Ruggierro, Migliorati, and Wang reportalso reported similar cases. In 2005, Novartis (Aredia and Zometa48 producer) officially declaredeclared 475 cases of Bisphosphonate bisphosphonate-related osteonecrosis of the jaws. In nowadaysNowadays, the number of affected patients worldwide is unknown. Scientific literatures says the BONJ is from 1,.3% to 10%. More There are more than 5,.1 million patients are treated with bisphosphonates. More and more than 2 million acceptaccepted BPs as antimalignatanti-malignant therapy. The number of patients treated for osteoporosis with BPs is increasing rapidly. More than 10 million patients, mainly women in the USA has, have osteoporosis,. It and it is supposed that the number will increase to 12 million and 34. Thirty-four million patients older than 50 have decreased bone density and considered high risk for osteoporosis development. Oral BPs arewere prescribed to more than 70% of the patients diagnosed with osteoporosis in US during the USA in 2003- to 2006.((American association of Oral and Maxillofacial Surgeons)). More than 190 million prescriptions arewere issued in North America. In 2003 Alendronate, alendronate is 19th most prescribed medicine (17 million prescriptions) Risedronate), risedronate is 72nd (6 million prescriptions) zolendronate), while zoledronate is used from more than 300,000 sick people.

5. Pathophisiology of BONJ

Bisphosphonate-associated osteonecrosis of the jaws is a result of treatment with BPs, bone metabolism disorders and physiological micro damagemicrodamage of the jaws interferinginterfere their biomechanical properties. Oral cavity conditions, microtrauma, infections increase the efforts of the organism to bone recovery, exceeding the ability of the hipodynamic bone. Compared to all other bones maxilla and mandible are remodeled most frequently in the human body. This is the reason why BONJ is observed only in jaw-bones. Unlike to other bones in the human body, they are not enough protected enough. It is an important fact that only a thin mucosa and a periosteum are the only barriers protecting bone from injuries. From the other side teeth are prerequisite to easy microorganisms penetration and development of internal infections–caries and periodontal disease complications. It is interesting to mention that local factors like partial and full removable dentures are also factors that increase the risk of osteonecrosis. Smoking and continuous corticosteroid therapy are also risk factors.

According to Denn et al., all osteonecrosis cases describe todescribed in 2006 arewere associated with nitrogen containing bisphosphonates. In scientific literature, there is no single opinion which bisphosphonates exactly leads to more frequent BONJ development. The

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thought that Zoledroniczoledronic acid isis the most dangerous prevails. Most cases of BONJ are related with i.vIV intake.

In spite of the fact that for BONJ is has been here for a long period of time, factors that initiate the necrosis are still discussing.being discussed. It would be right to point out that for initiation of BONJ many factors are responsible with variable priority in different cases.

OnIn the first place, this is the inhibition of osteoclast activity and bone remodeling. But only this factor is not enough, because similar osteonecrosis would be observed in the other bones. Bacterial invasion with consequent inflammation is a factor that distinguish the condition in oral cavity compared to other body parts. The existence of various biofilm in oral cavity is dictated by different periodonatlperiodontal diseases, caries and its complications and periapical inflammation. This is a prerequisite for microorganism invasion to the left open bone left (after extraction, for example). In necroticNecrotic bone fragments after tooth extraction in BPs treated patients arehave isolated mainly Actinomyces species but also viruses and fungus. Angiogenesis suppression could also be initiator of jaw osteonecrosis. Medicines that disturb growth, migration, and differentiation of endothelial cells for new vessel formation playsplay an important role in avascular osteonecrosis. In addition to these basic factors to pathogenesis of medication-related osteonecrosis of the jaw (MRONJ could be added), microtrauma of the jaw during masticatory action and supposed harmful or acquired immune deficiency could also be added.

6. Prophylaxis and treatment of BONJ

In literature, there is no solidarity concerning bisphosphonate therapy suspension after the appearance of jaw-osteonecrosis. Marx suggests bisphosphonate therapy in onco-patients to be discussed with an oncologist in order to define positive effect/risk ratio, having in mind bisphosphonatebisphosphonate's half-life (10 years).

In literature thereThere is prevalence of BONJ with prior dental procedures compared to the so called spontaneous osteonecrosis and 33%–86% of the BONJ in literature are described after different dental procedures.

Prevailing opinion is that with ageas one gets older the danger from bisphosphonate osteonecrosis increases withby 9%.

Behavior inof diagnosed osteonecrosis patients is dependent on the disease stage. It should be mentioned that American Association of Oral and Maxillofacial Surgeons proposeproposed a change in the disease nomenclature formfrom BONJ to Medicine medication-related osteonecrosis of the jaws (MRONJ). The reason is an increasing number of patients with osteonecrosis of the jaws have been diagnosed after other drug intake (denosumab). Due to this reason Hence, the AAOMS changeschanged the name, which was accepted in 2009, on. On their consensus conference in 2014, with a Position Paper and in addition to the new name accepts, they accepted new diagnostic and treatment strategies corresponding to the contemporary researches., as follows:

1. I.v.IV bisphosphonates for treatment of primary bone tumors and bone metastasis, multiple myeloma, and severe osteoporosis but with lower dosage.

2. Oral bisphosphonates mainly for osteoporosis and osteopenia treatment, as well as PagetPaget's disease and osteogenesis imperfectimperfecta.

3. DenozumabDenosumab–RANK ligand inhibitor–it inhibits bone resorption by inhibition of the function of osteoclasts and as an advantage could be mentioned that it is not connected to the bone so within 6 months after treatment the risk of complications is slightly noticeable.

4. Antiangiogenetic medications–it is used in different tumor conditions and is useful due to the fact that preventsto prevent formation of new blood vessels. It connects to signal molecules responsible for blood vessels formation and interfereinterferes the angiogenesis signaling cascade.

According to AAOMSAAOMS's Position Paper, it is possible to think about MRONJ if several characteristics are present:

1. Antiresorptive or atiangiogenicantiangiogenic treatment conducted before or in the past.,

2. Bone that is exposed in the maxillofacial region through intraoral or extraoral fistula(e) persisting for more than 8 weeks, and

3. Lack of radiation therapy in the oro-facial region or metastatic disease to the jaws.

It should be mentioned that, according to the AAOMS, risk for osteonecrosis development in patients with bone tumors treated with zoledronate is 0% to 1%. It is similar in patients treated with denozumab.denosumab. A bit lower is the valuepercentage risk in patients treated with antiangiognetic drugs, like bevacizumab –, which is 0.2%. The risk for patients with osteoporosis treated with denozumabdenosumab and zoledoronate is 0.04%. It should be noted that with increasingthe longer the period of time for treatment is increasingthe higher the risk for jaw osteonecrosis form, from 0.5% for one year of treatment to 1.1% for three year years of treatment. After all it is a matter ofThese are based on retrospective studies of treated patients, which who have not been treated surgically in the oral cavity but has develophave developed spontaneous osteonecrosis. As aA trigger factor could be underlined tooth or even multiple teeth extraction and placement of dental implants. In differentDifferent retrospective studies are shown showed that 1.6% to 14.8% of patients treated i.v.through IV with BPs for longer than a year period of time and have developed osteonecrosis developed after tooth extraction. According to a research done by Carlos Pigrau – –Serralach et al since 2014, BONJ reachescases have reached 30.2% Viridance since 2014. Viridans group Streptococcistreptococci are isolated in 83.3% formfrom the cases and AcctinomycesActinomyces spp in 39.0% from all bone histological samples.

According to other studies, between 52% and 61% from all cases described of osteonecrosis of patientscases treated with bisphosphonates are triggered after surgical treatment – –a percentage that is extremely high. Retrospective research done by Kunchur R,., Need A,., Hughes T,., et al. in 2009, says stated that from0.5% out of 194 patients treated with oral bisphospho-

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nates have developed osteonecrosis occurrence is 0.5% after tooth extraction. They assumeassumed that dental implant placement iswas with similar biological load as tooth extraction. Moreover, Donggeol Lee reportsreported that 77 patients treated with bisphosphonate undergounderwent implantology treatment, with 78 placed implants with 97.4% success equal to success in normal conditions. Sebastien Hoefert and Harald Eufinger report i.v.reported IV and per os antibiotic treatment in bisphosphonate treated patients before surgical treatment.

In 2009, P. Pechalova, A. Bakardjiev, B. Vladimirov, E. Poryazova, I. Angelova, and A. Jeleva publishpublished a case of a patient with bisphosphonate osteonecrosis of the mandible of a patient after consistent oral intake of 14 month consistent intake for fourteen months of FosamaxR (alendronate) (70mg per week dosage, taken once a week) and BonvivaR (ibadronate) (150mg month dosage, taken once a month) on the occasion ofdue to severe osteoporosis with pathological fractures of vertebras. The oddly think in the case published is bone sequester covered entirely with mucosa. Without fistula..

A group formfrom ITI (Bornstein, Cionca, Momblli)), based on a vast literature in 2009 differentiate, differentiated the surgeon behavior in patients with oral and i.v.IV bisphosphonate intake. They assumeassumed that, in addition to the way of intake there is, the duration of intake played an important role of the duration.. They saysaid that patients with osteoporosis/osteopenia take much lower dosage of bisphosphonate compared to cancer patients and, thus, the accumulation of the medicine should be several years. This is enough to conclude that In conclusion, patients who underwent oral surgical procedures are withhave significantly lower risk of necrosis in these patientscompared to those who had IV bisphosphonate intake.

Similar conclusions are were made by our team on the basis of 3 treatedthree patients in 3 yearswho underwent treatment for the period of three years. One of the patients were onhad an oral intake of bisphosphonates, one i.v.had IV, and one on DenozumabeDenosumabe (subcutaneous) As part of our). Our entire biological concept treatment include includes preliminary antibiotic treatment, irrigation with chlorxeidine solutions, general and local ozone therapy, hyperbaric chamber, PRGF usage, Er;Yag:YAG laser, photodynamic therapy, and minimally invasive surgical techniques.

7. Conclusions

During an surgical, respectively a surgery, such as implantology treatment, especially in bisphosphonate treated patients it is vital antibiotics preparation and is vital for the primary healing process to be guaranteed, especially in bisphosphonate treated patients. Usage of Clindamycin as osteotopicosteotropic antibiotics is a gold standard assuring lackto ensure absence of post-operation infection and prevention of complications. LackThe absence of dehiscence assureensures us smooth osteointegration process and lack of bone lose. That is whyFor this purpose, the common requirements for soft tissue management, include suitable implantology system, proper operation technique, atraumatic preparation, and last but not least proper suturing materials and technique. Implantology has extra sources like PRP, PRF,, PRGF, which could be applied with great success if it's needed. The high concentration of

platelets rich in growth factors (PRGF) in the operation field contributecontributes to a light and with lack of troublestrouble-free post-operative process, guaranteeing perfect conditions for the osteointegration process. In cases of post-operative complications MethronidazoleMetronidazole is a matter of choice.

8. Clinical cases

8.1. Case 1

The patient has arrived at our clinic for the first time in 2009 with pain syndrome, periodontal abscess in the 47, 44, 31, 32, 41, and 42 area due to periodontitis developed formfrom the plaque with periodontal pockets form 6from 6mm to 8mm.,combined with chronic occlusal trauma from iatrogenic sharp edges of metal-ceramic constructions made years ago (X-ray, Fig. 1). Based on the anamnesis, a treatment with medicines was found–6 months treatment with Bonviva medicine–3mg once a month parenteral, associated with diagnosed osteopenia in 2007 with quantitative osteometry over tibia bone with T-score 2,9. It was considered that due to the short-term treatment with the bisphosphonate medicine and the 5five-year period after it by keepingto keep certain protocol for preparation and implantation, an implantology treatment could be initiated. A multiple extraction of 47, 44, 42, 41, 31, and 32 was undertaken after antibiotic protection, initial ultrasonic and sand-blasting therapy divided in tointo several appointments, high-intensity and low intensity laser therapy, local and general ozone therapy and hyperbaric therapy. Extraction sockets were filled with PRGF and sutured with PTFE. As an additional prophylaxis measure from bisphosphonates induced osteonecrosis, photodynamic therapy was used. The healing process was without any complications.

The treatment plane includesplan included the entire sanitation of the mouth, periodontal and endodontic preparation, and placement of 11 pieces titanium screwed implants. After uncovering of the implants, tooth 43 was planplanned for extraction despite the exact root-canal treatment, due theto long term prognosis and high risk of root fracture. TillUntil that time, this particular tooth was used for temporary fixed construction abutment. Because of the short clinical crowns, crown-lengthening was planplanned and performed with Er:YAG laser, based on the preliminary analysis of the size and shape of future prosthetic crowns and attached gingiva available. X-ray surgical guide was made, along with a prototype of the future prosthetic constructions, and was used for the CT. Due to the fact of previous bisphosphonate usage, a certain surgical protocol was used again including: antibiotic prophylaxis, high-intensity and low intensity laser therapy, local and general ozone therapy, hyperbaric therapy, PRGF, precise soft-tissue management and photodynamic therapy. One implant was placed in 15 area. Due to the lack of complications it was proceeded to, the placement of the rest of the planned implants proceeded. Bone type was D4 for the maxilla and D3 for the mandible. Bone spreaders were used for bone condensation. The primary stability of the implants was 15 up to 30 N/cm. Osteotomic implant beds were shaped by the usage of the existing surgical guide. Existing bone doesdid not demandeddemand additional augmentative procedures. Suture material was 4/0 PTFE. On the both jaws, fixed long-term temporary constructions

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waswere provided. After longer than usual period of waiting (more than ana year)), implants were uncovered by half-thickness flaps moved apically. All 11 implants were osteointegrated. After open-tray, impression technique with transfers zirconium abutments with titanium base were made. CAD-CAM zirconium constructions were madmade directly on the same model. In the frontal area constructions were made by blend-ceramic and distally full anatomy zirconium.

Complete functional rehabilitation of the masticatory apparatus was achieved. Aesthetic demands of the patient was covered completely.

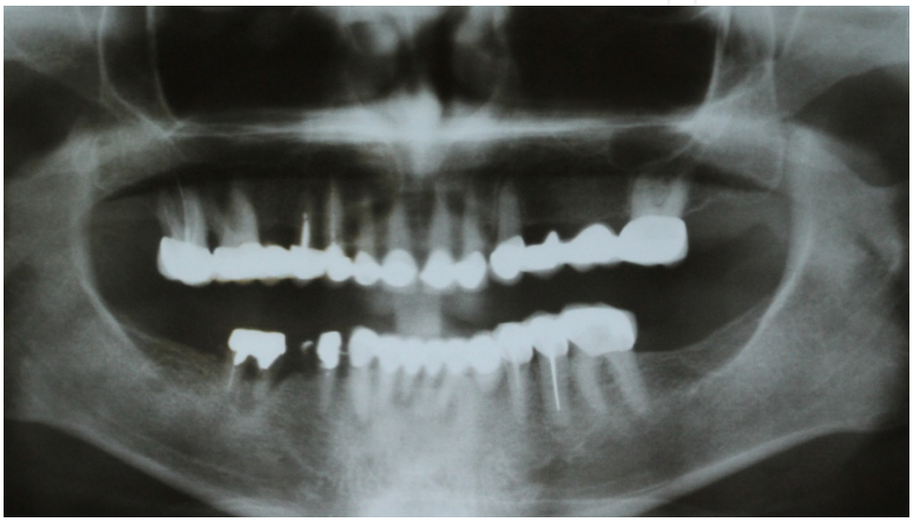

Figure 6. Basic X-ray

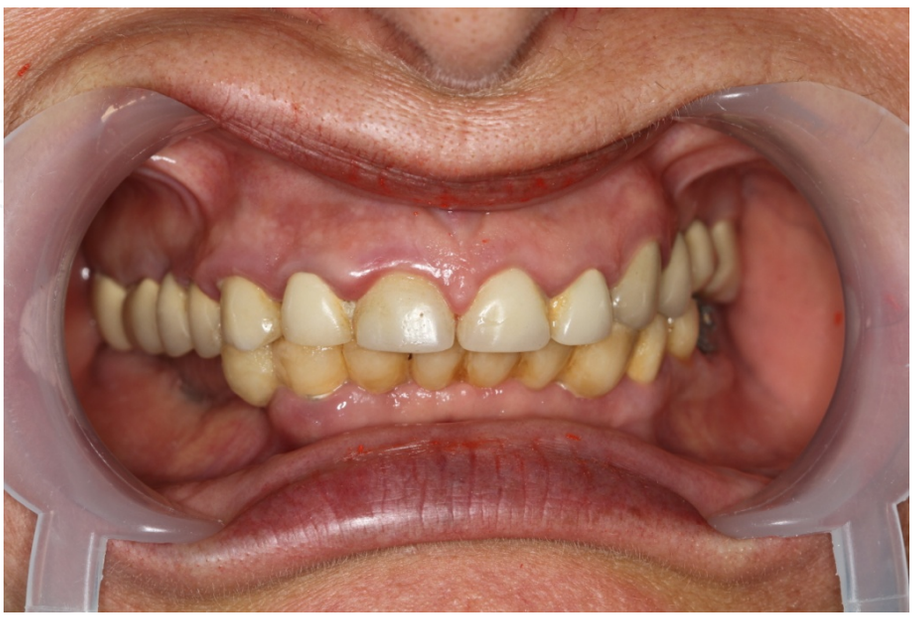

Figure 7. Intraoral situation after preliminary treatment

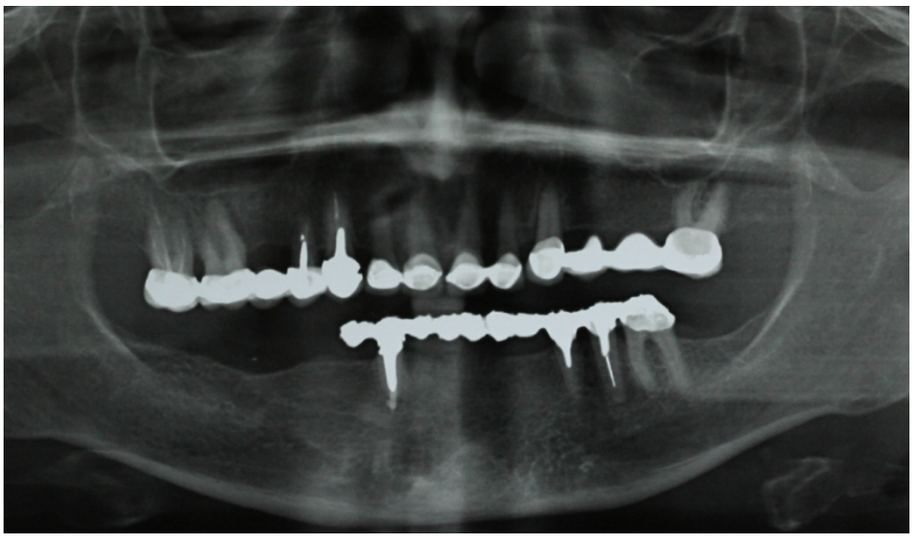

Figure 8. X-ray- before implant insertion

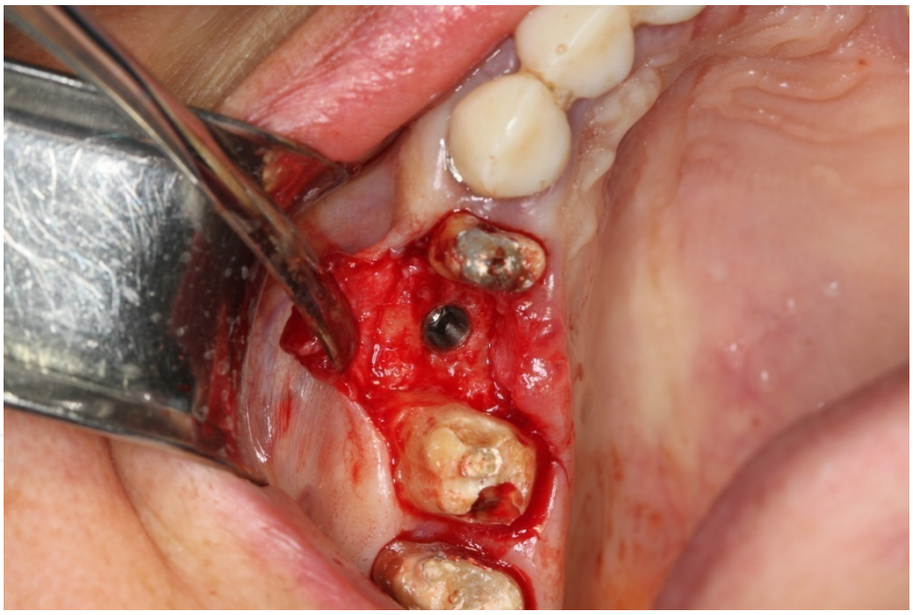

Figure 9. Minimal invasive insertion of the first implant

After preliminary treatment, the patient receivereceived one implnantimplant in the area of the second upper right premolar (15) accompanied with clindamycin prophylaxis, PRGF activation of the implant surface and covered by PRFG fibrin membrane, combined with postimplantationpost implantation photodynamic therapy using PhotoSan® for 4 minutes, two timetimes a day tilluntil the suture removal, and ozone therapy in the first three days combined with hyperbaric-chambers.

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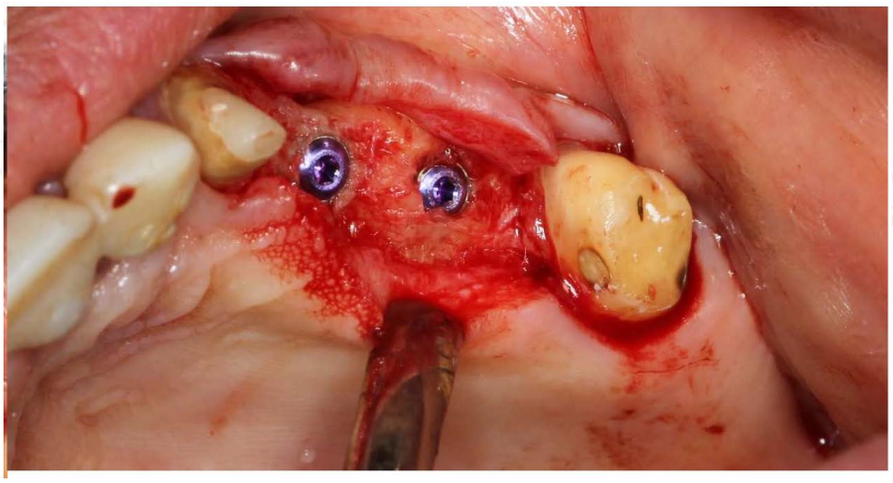

Figure 10. Implant insertion in second quadrant

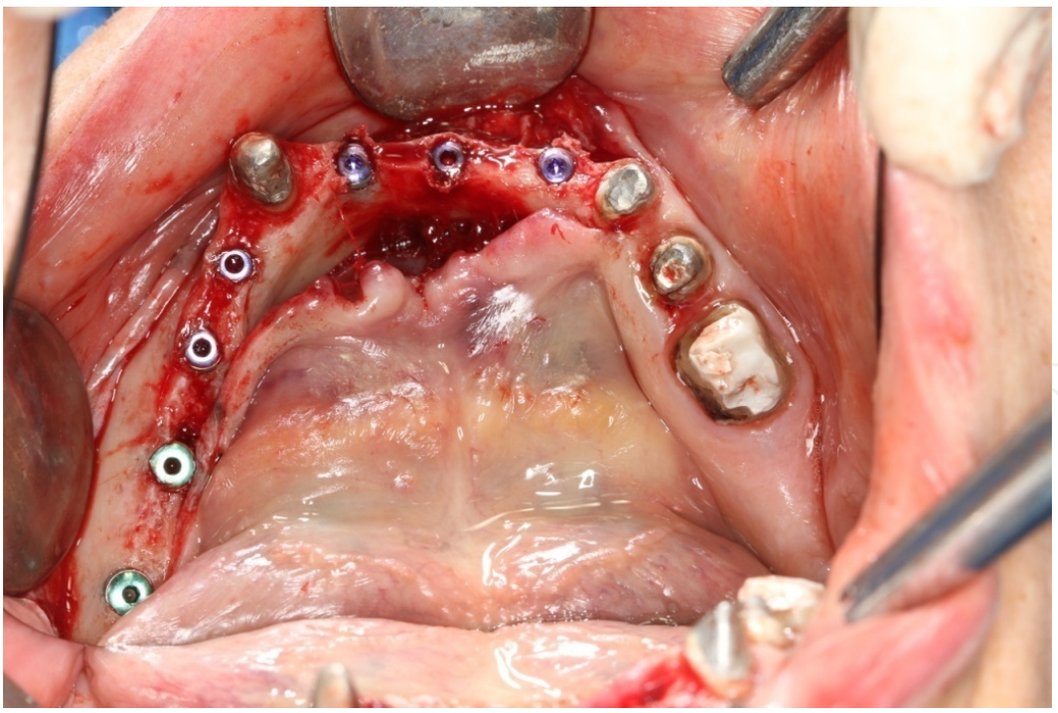

Figure 11. Implant insertion in lower jowjaw

Figure 12. Activation of implant surface with PRGF

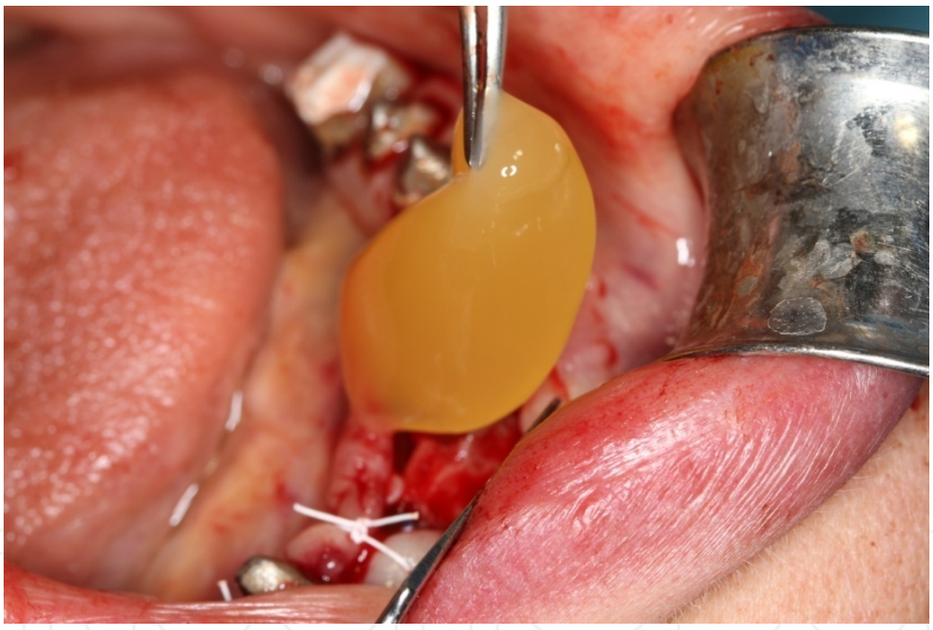

Figure 13. PRGF membrane for covering of the implants

The high concentration of platelets rich in growth factors (PRGF) in the operation field contributecontributes to a light and with lack of troubles trouble-free post-operative process, guaranteeing perfect conditions for the osteointegration process.

The process of tissue repair iswas based on a complex cascade of biological events controlled by a long list of biologically active growth factors and proteins. The spatial and temporal action of this family of mediators on the tissue-damaged area regulates the mechanisms and phases that govern tissue repair and regeneration

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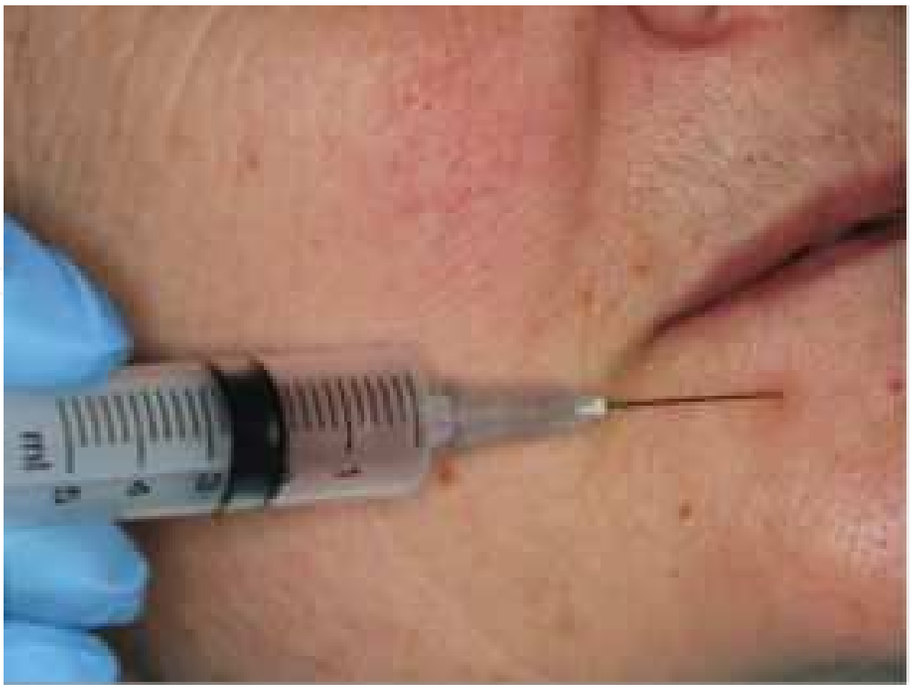

Figure 14. Pure ozone injected subcutaneously in the manipulation area

Another method used in our biological concept is ozone therapy. There are several known actions of ozone onin the human body, such as anti-microbial, immunostimulating, antihipoxyc, analgesic, detoxicating, bioenergetics and biosynthetic (activation of the metabolism of carbohydrates, proteins and lipids)), etc. Ozone is a relatively rare and unstable molecule composed of three oxygen atoms O_3. The normal oxygen molecule has two oxygen atoms O_2. Stratospheric ozone is important in the earth system because it absorbs ultraviolet radiation from the sun, protecting life on earth. The beneficial biological effects of ozone, is its antimicrobialantimicrobial activity. How we can derive ozon?the ozone? Using a simple electric arc, we can produce ozone. In case, for example, of bone regeneration, for example, the purpose of ozone using ozone is the initial local growth factor expression and stimulatetion stimulate the migration of osteoprogenitor cells to the wound site and subsequentlyand subsequently, in a controlled fashion, to direct their differentiation to the osteogenic cell line. Throughout this process, another set of factors will regulate the dynamic equilibrium between cell inhibition and proliferation, as well as angiogenesis and extracellular matrix formation. Ozonegenerator can introduce pure ozone in saline. Ozone infusion is also precious for the fact that it generates a therapeutic effect on faster post op wound healing and preliminary preparation of the patient by avoiding further complications and assuring on 99% smooth primary closure. Anti-microbial effect of ozone asis a result of its action on cells by damaging its cytoplasmatic membrane due to ozonolysis of dual bonds and also ozone-induced modification of intercellular contents because of secondary oxidants effects. This action is non-specific and selective to microbial cells, it does not dameagedamage human cells because of their major antioxidative ability. Ozone is very efficient in antibiotics resistant strains. Its anti-microbial activity increases in liquid environment of acidic pH. In viral infections, the ozone action lies in the

intolerance of infected cells to peroxides and change of activity of reverse transcriptase, which takes part in synthesis of viral proteins.

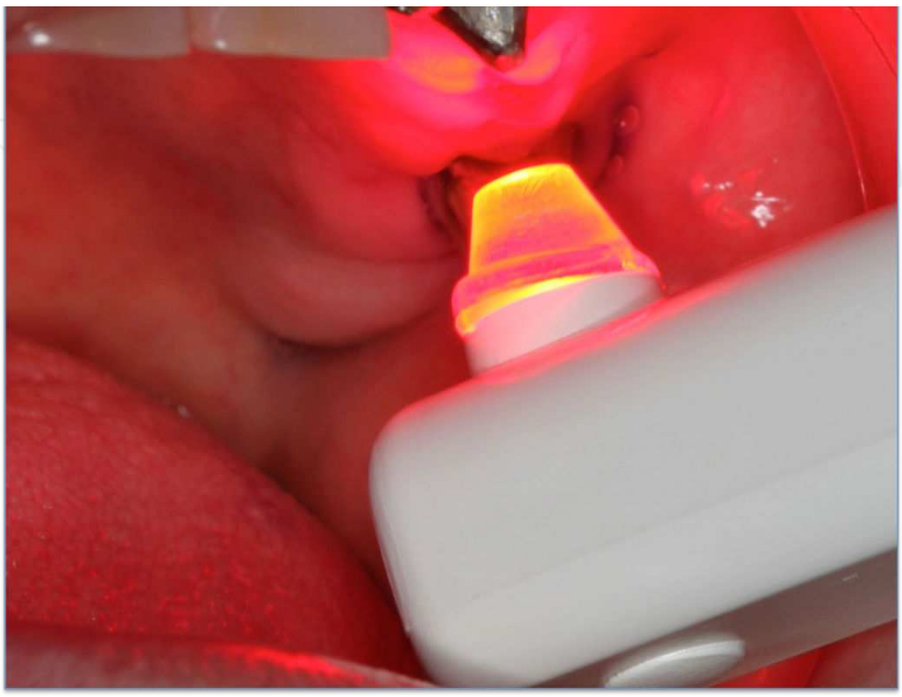

Figure 15. Usage of photodynamic therapy contributecontributes to cell destruction of the microorganisms and preventprevents complications and accelerateaccelerates wound healing

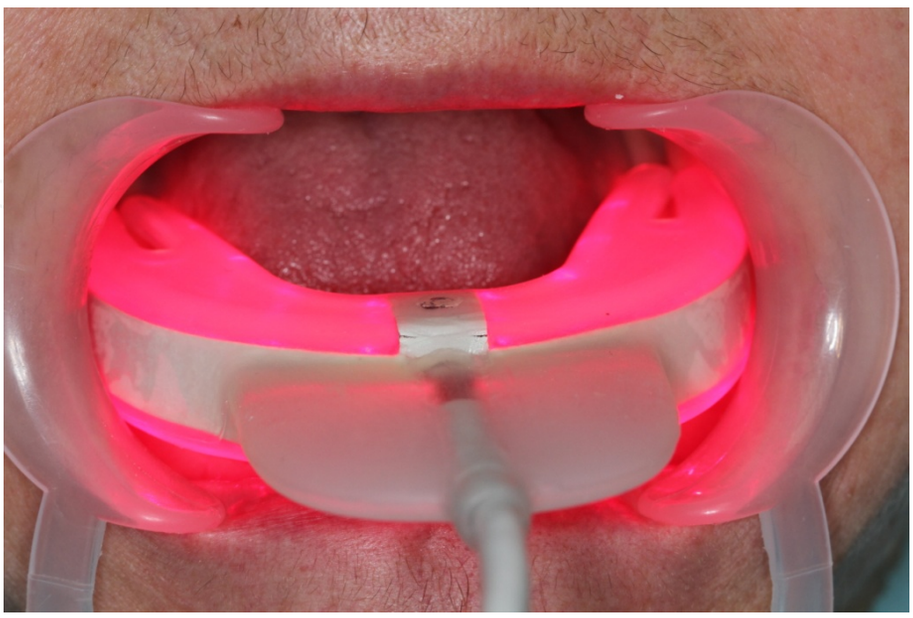

Figure 16. Photodynamic therapy with photodynamic intraoral tray

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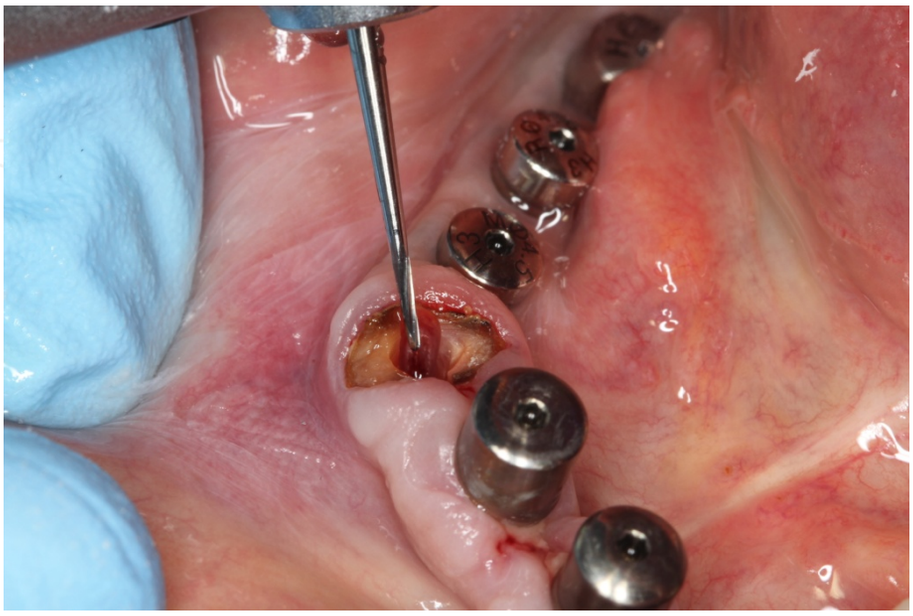

Figure 17. Minimal invasive extraction of 43- root separation

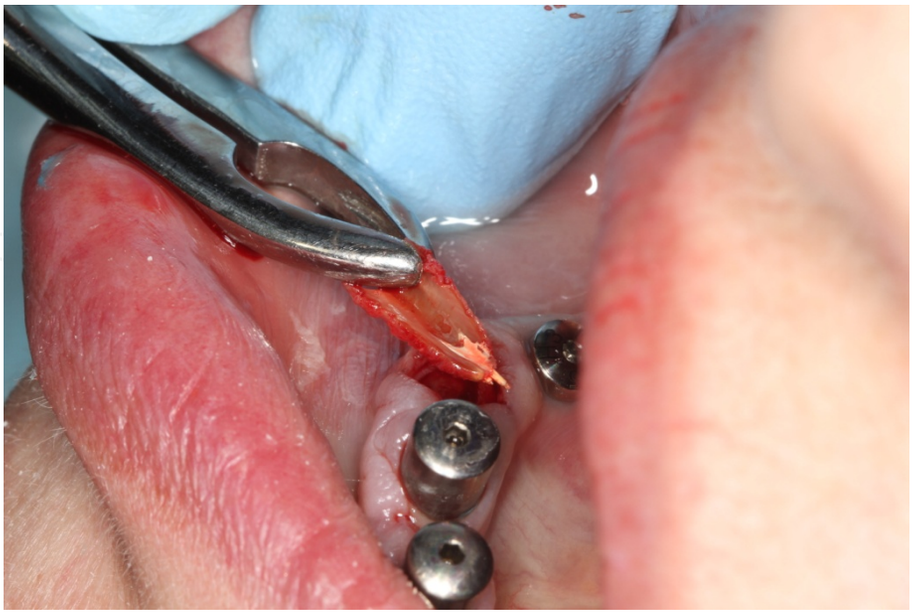

Figure 18. Minimal invasive extraction of 43

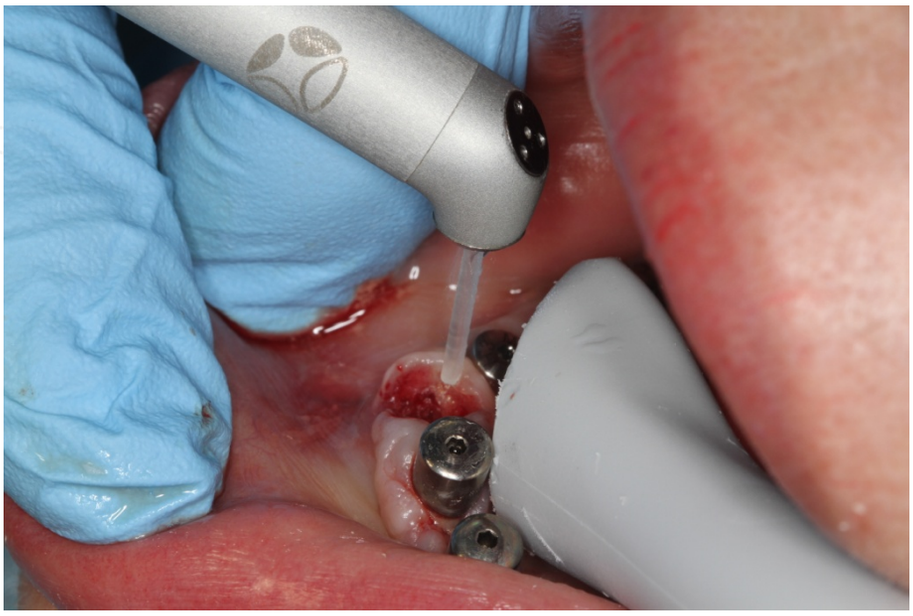

Figure 19. Granulation tissue ablation with Er:YagYAG laser

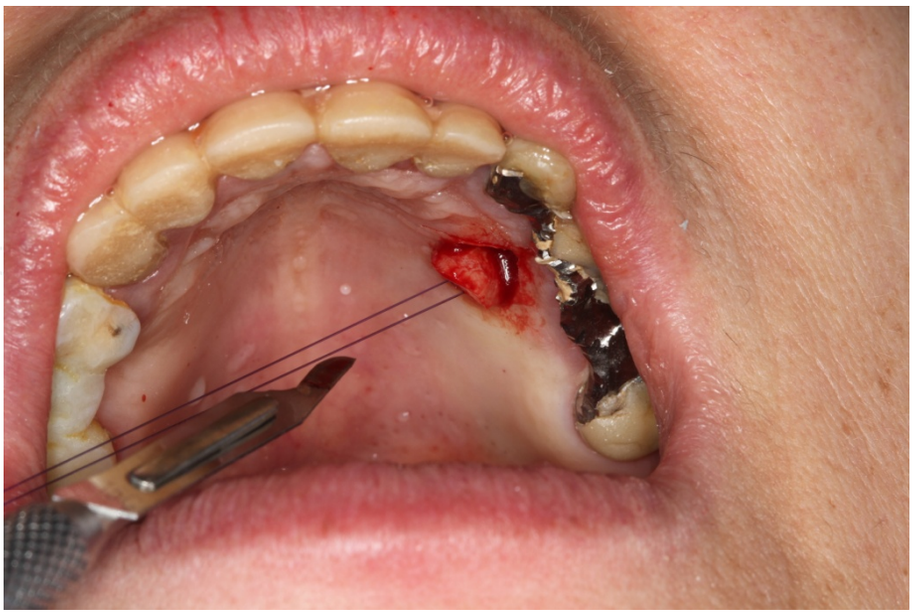

Figure 20. Palatal connective tissue graft

http://dx.doi.org/10.5772/61731

Figure 21. Palatal connective tissue graft in PRGF

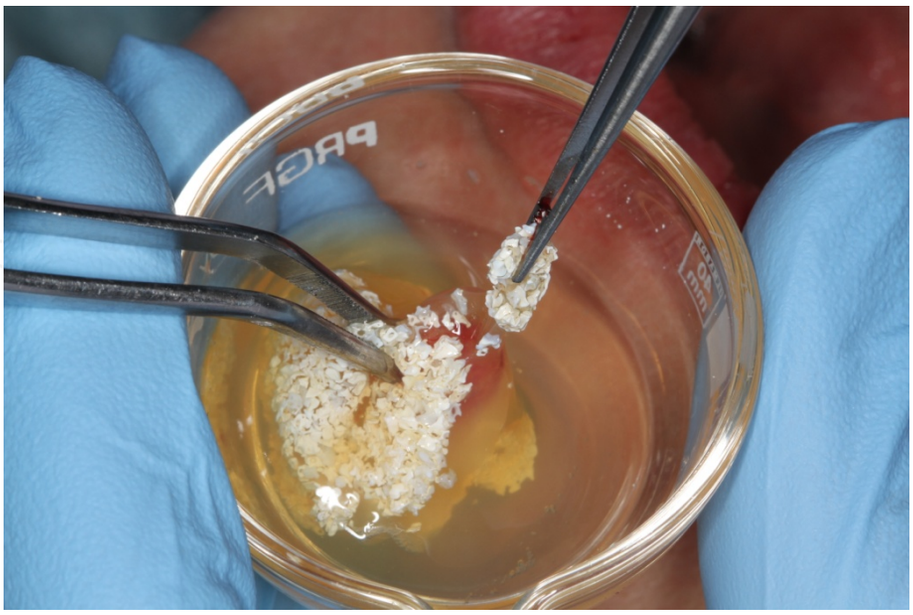

Figure 22. Bone graft material mixed with PRGF

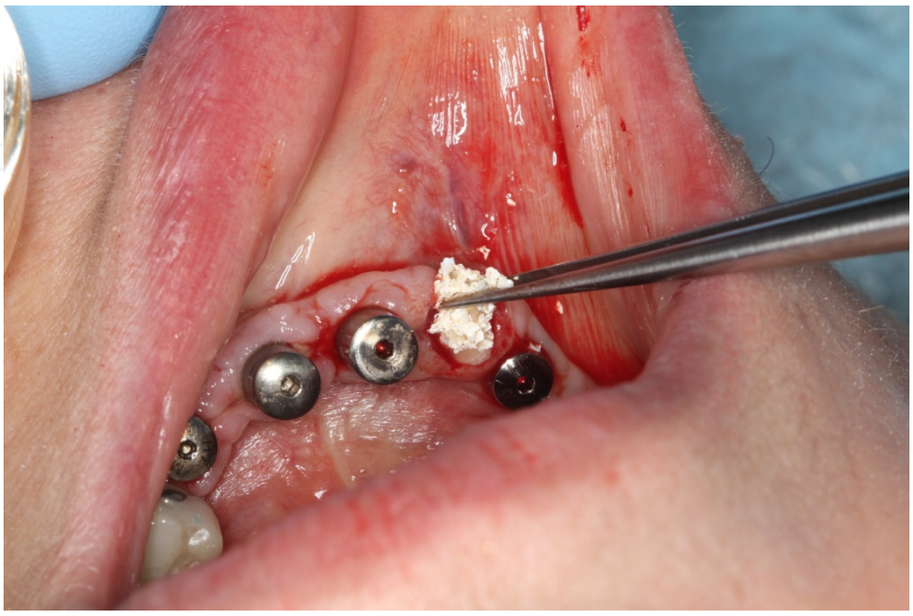

Figure 23. Bone graft material mixed with PRGF in postextractionpost-extraction socket

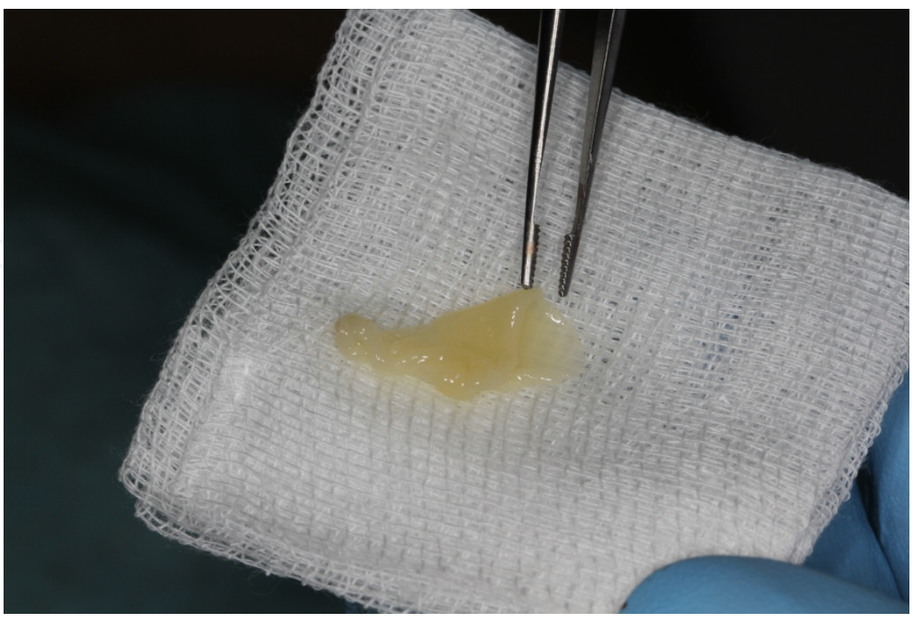

Figure 24. PRGF-clot cloth

http://dx.doi.org/10.5772/61731

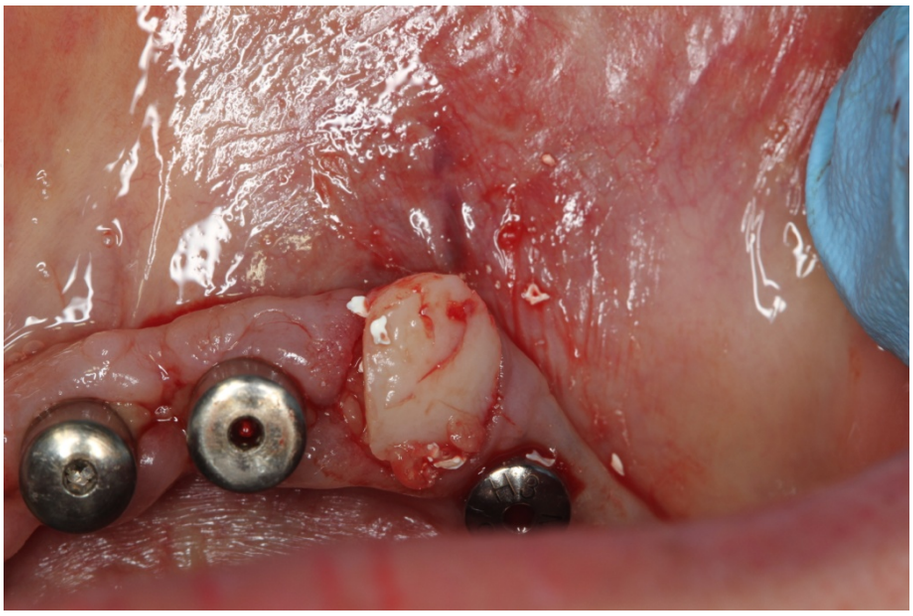

Figure 25. Covering of bone graft material with the PRGF clotcloth

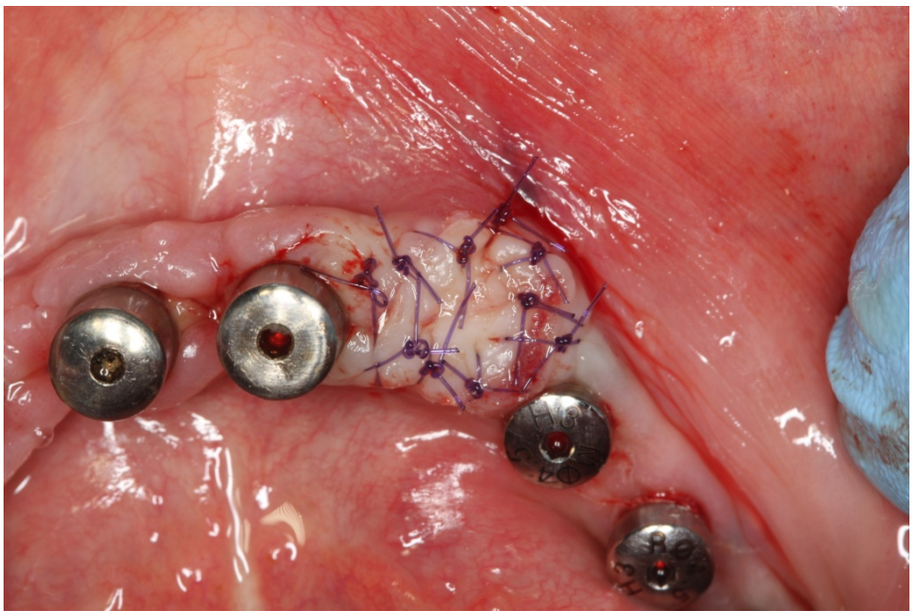

Figure 26. Suturing of the palatal connective tissue graft over the postextracted socetpost-extracted socket

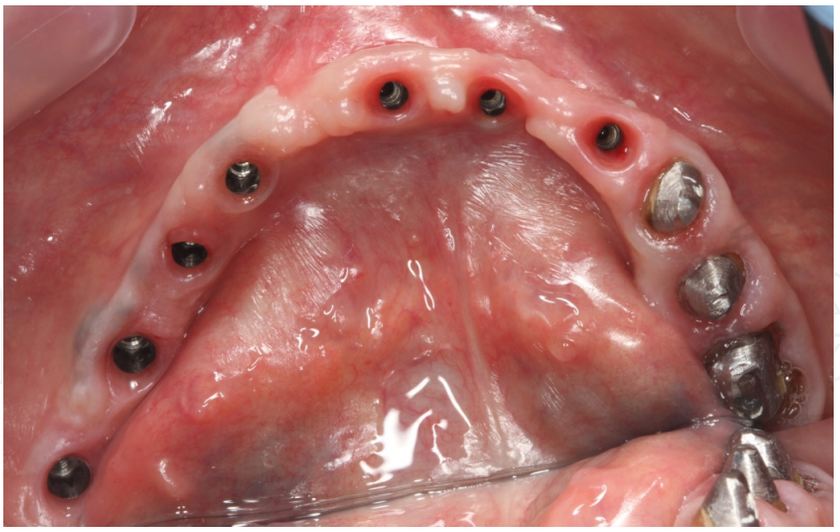

Figure 27. Soft healing process

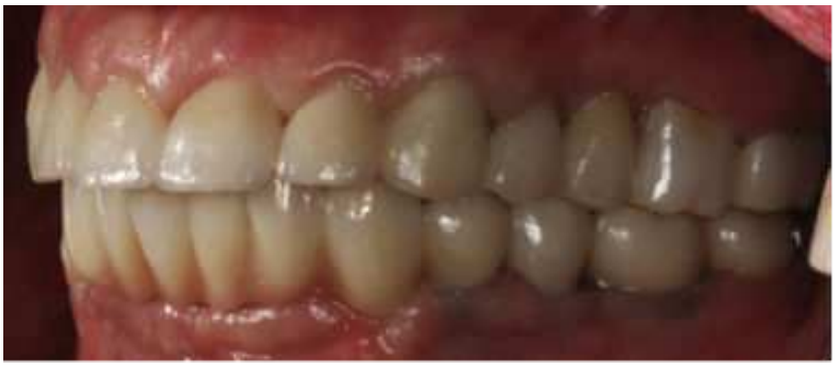

Figure 28. The end result

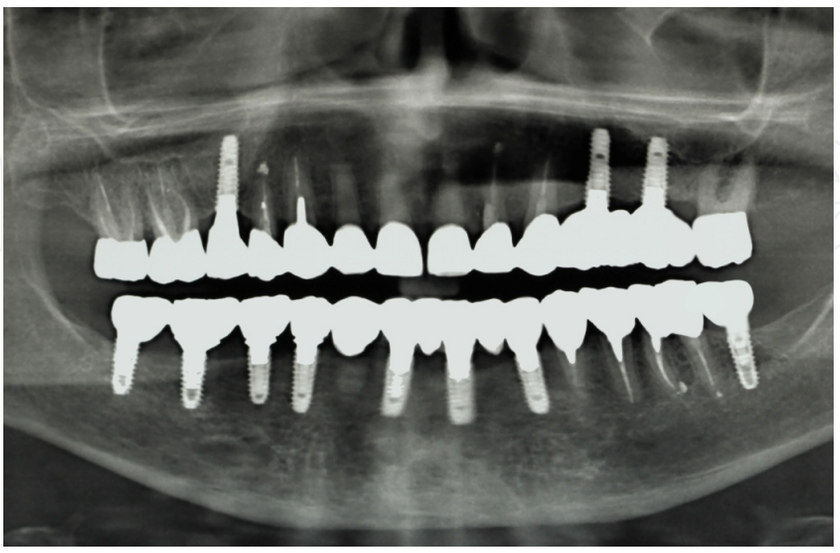

Figure 29. End result after treatment

http://dx.doi.org/10.5772/61731

8.2. Case 2

A female patient, 57 years old, S. H. in good general good health, non-smoker, was received at the clinic with complainscomplaints of mobility of the entire upper jaw prosthetic fixed construction, accompanied with pain and inability to eat, dating back to 3 months earlier. Clinical exam findfound out significant mobility (4th degree by Miller) of metal-ceramic fixed one-piece bridge prosthetic construction of the upper jaw. (Fig. 2). On the X-ray (Fig.1), 4 screwing dental implants arewere observed, "Tramonte design" and 4four residual roots were in terminal stage. There iswas a significant bone resorption around the implants visible on the x-ray (proven lack of osteointegration.). From the patient histori ispatient's history, it was known that these implants arewere placed 5five years ago. AnA year later, patient beginsbegan treatment with Fozamax per os once a week withfor the duration 2of two years because of osteoporosis diagnosediagnosis (T-scorscore-2.9%).

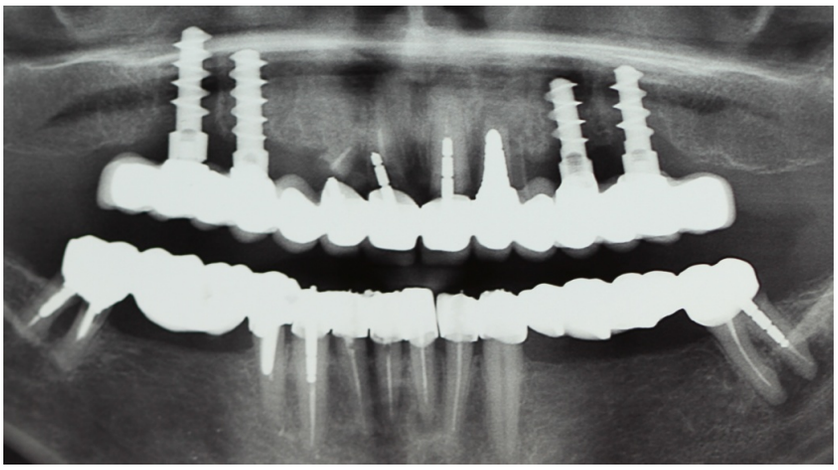

Figure 30. Initial X-ray

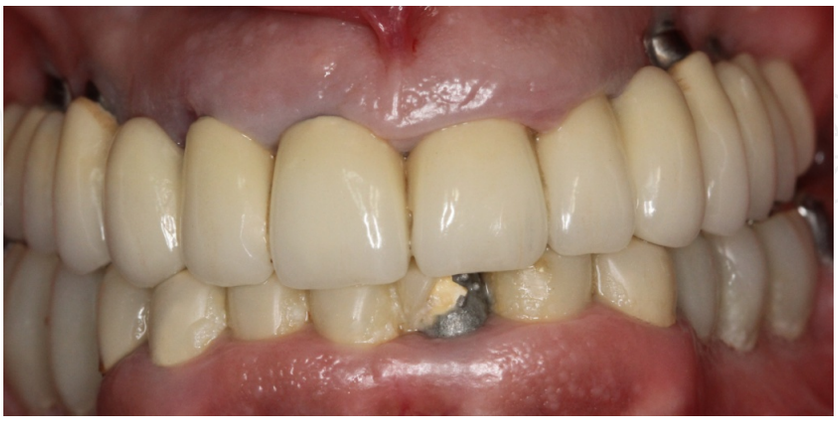

Figure 31. Intraoral view

After initial periodontal therapy, with ultrasonic device and highintensityhigh intensity laser, under antibiotic cover (clindamycin 600mg. /./8h per os), 2two times hyperbaric chamber

before and three times after the dental procedures, saline enriched with ozone 9nine times and three were locally applied subcutaneously, photodynamic therapy tilluntil the 10th den after the dental procedure of removing all residual roots and implants. In the extraction sockets were placed PRGF cloth, collagen sponge and the wound were sutured. Post-operative period was smooth without any pain or complications. The patientspatient was given an immediate fabricated total removable dentures.

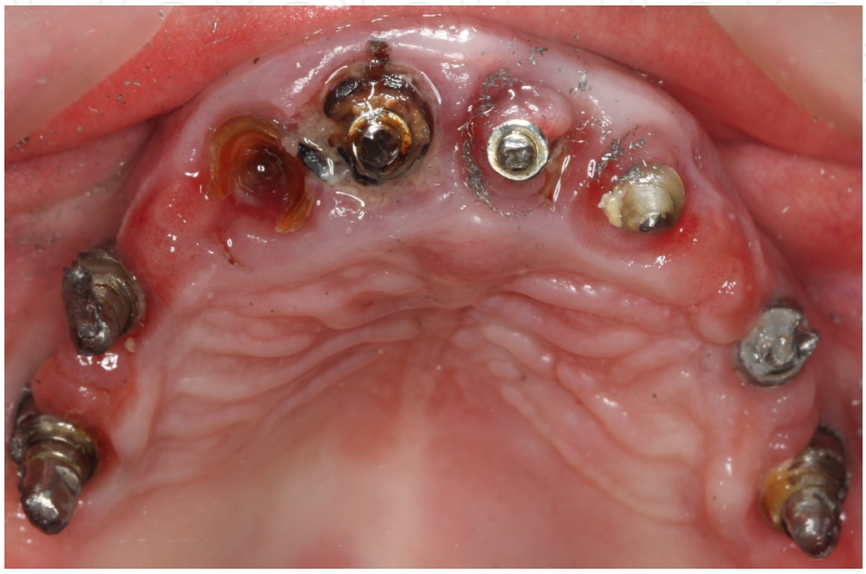

Figure 32. Intraoral view after bridge removal

Figure 33. All implants, teeth and bridge after removal

http://dx.doi.org/10.5772/61731

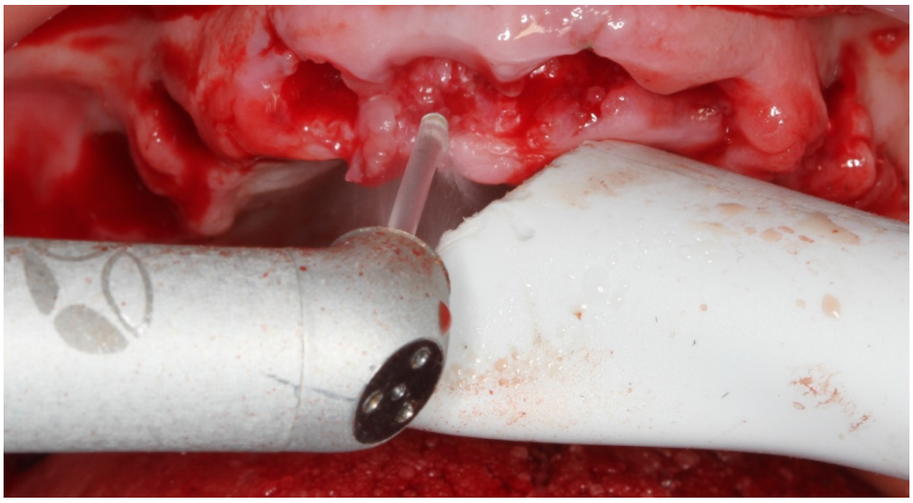

Figure 34. Granulation tissue ablation with Er:YagYAG laser

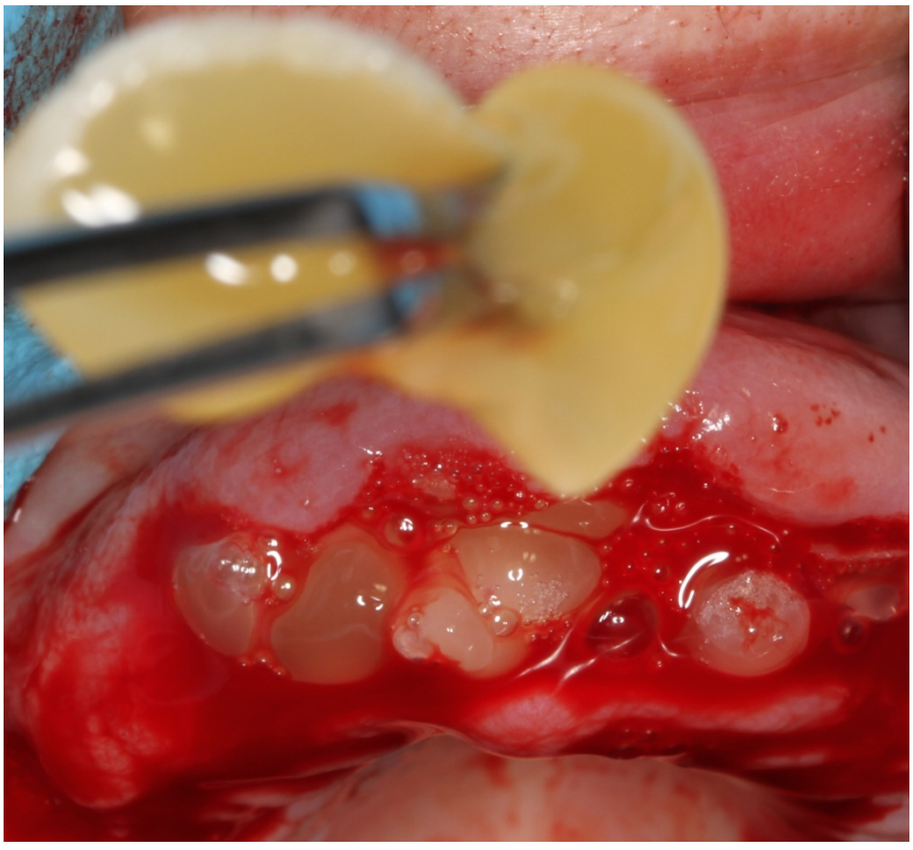

Figure 35. PRGF – cloth

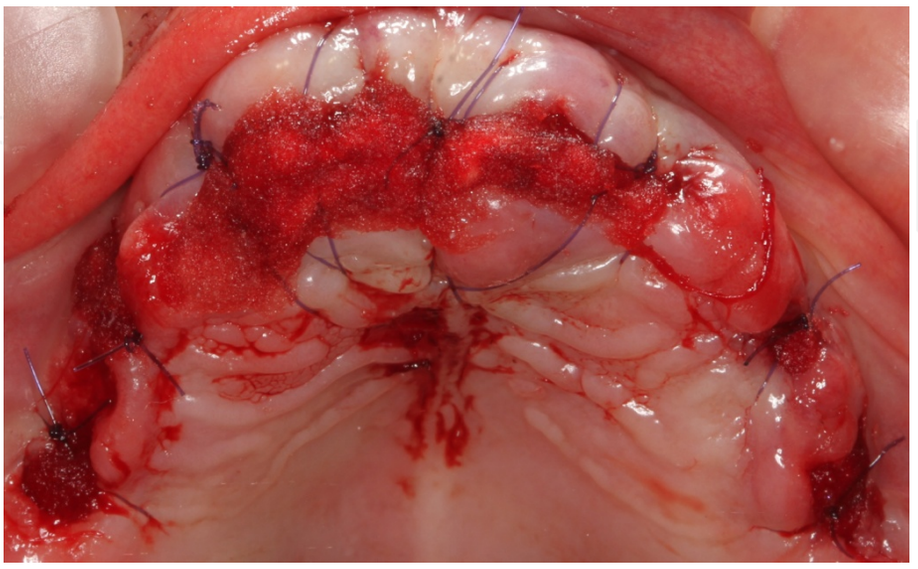

Figure 36. Covering with collagen sponge and suturing

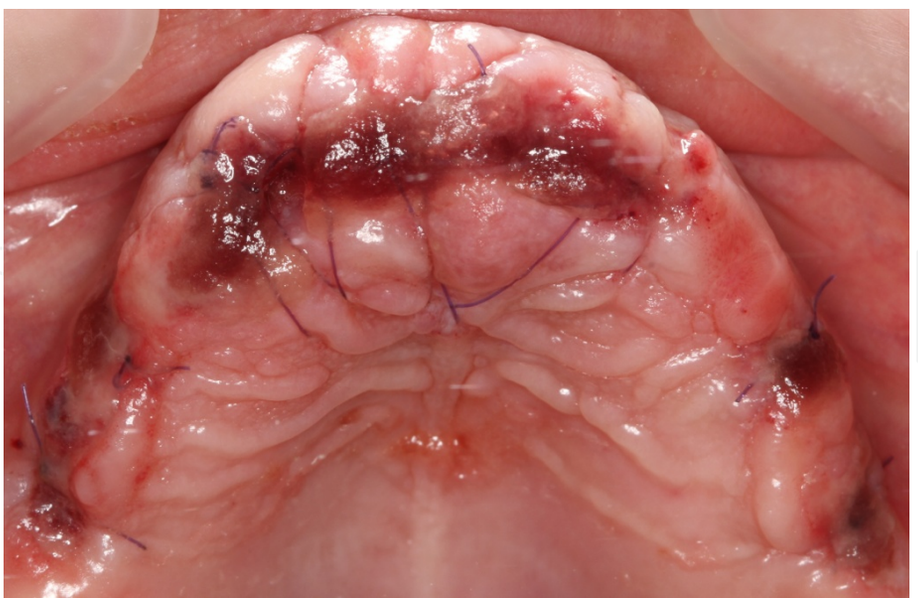

Figure 37. Day after surgery

http://dx.doi.org/10.5772/61731

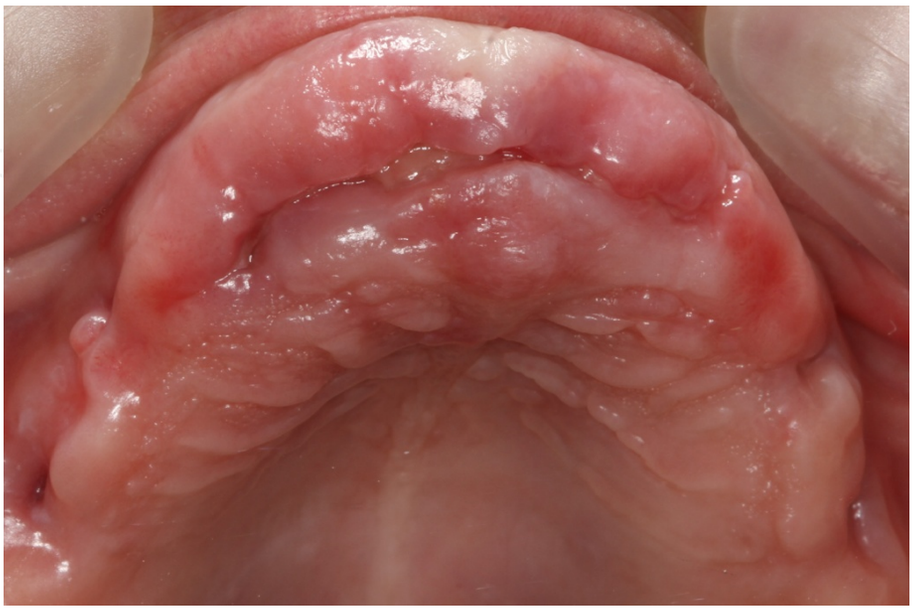

Figure 38. Ten days after surgery

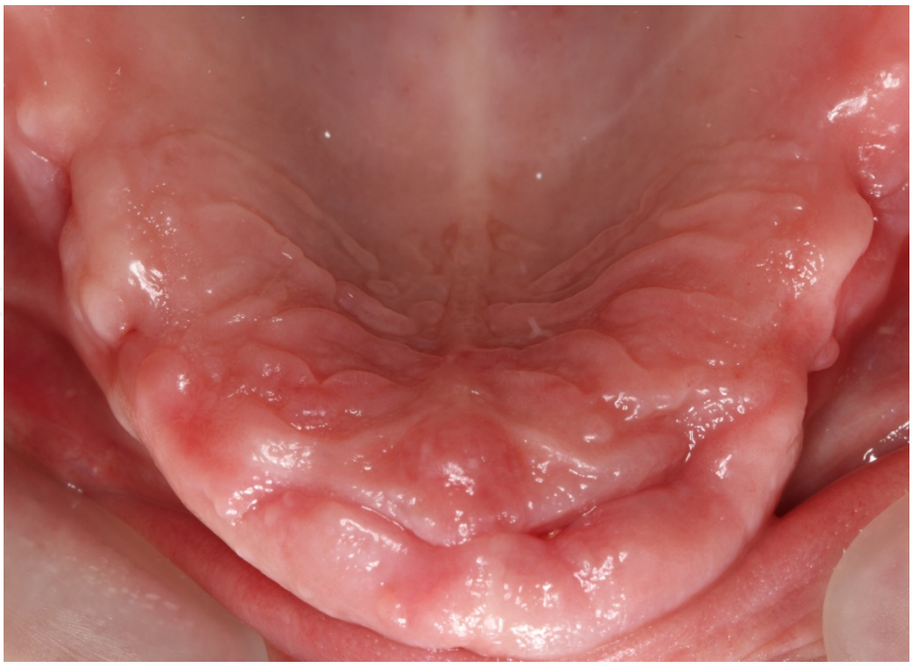

Figure 39. Three weeks after surgery

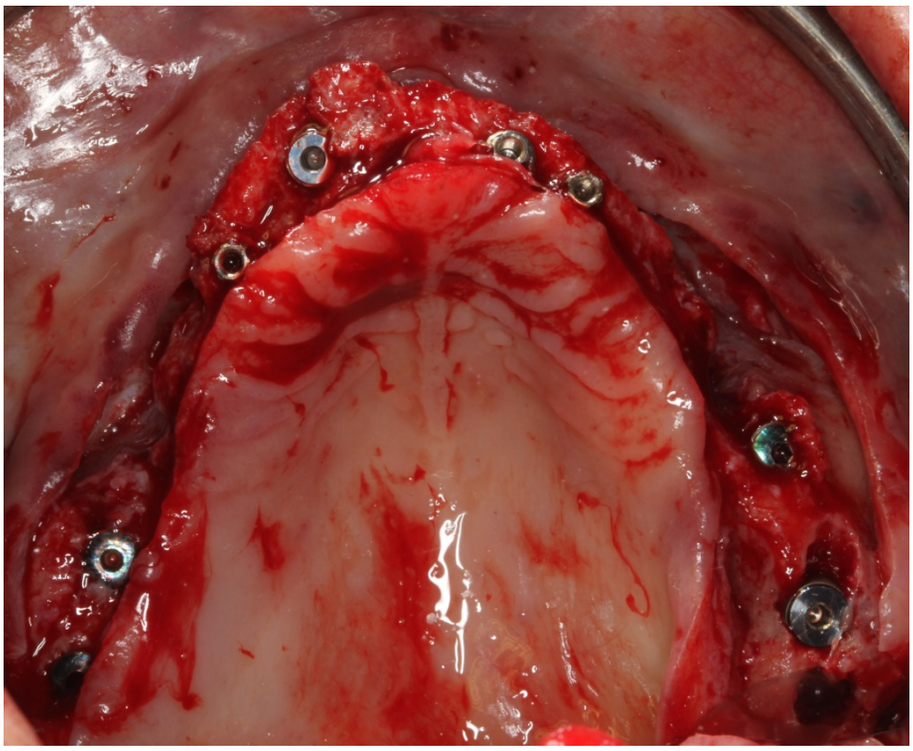

Figure 40. Intraoral view after implant insertion

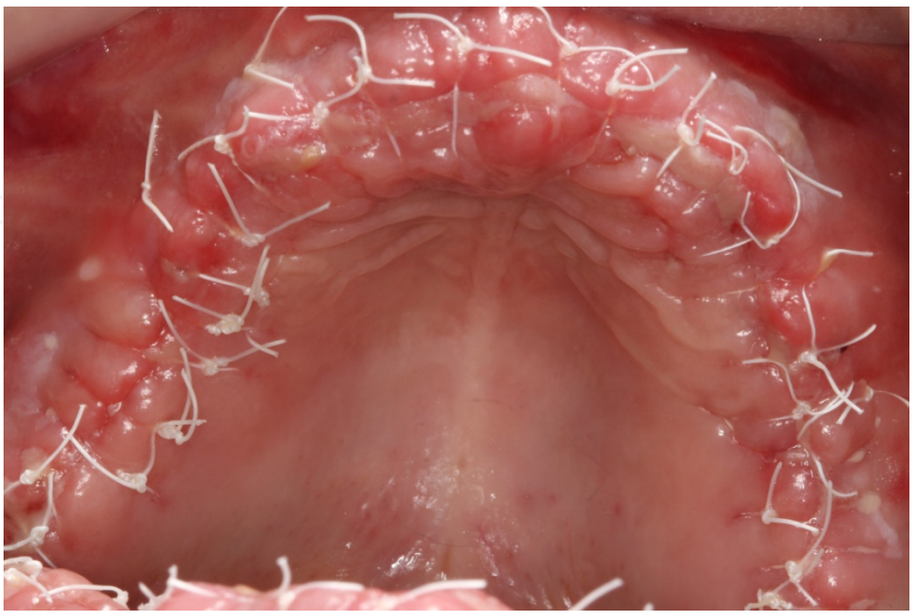

Figure 41. Intraoral view after suturing

http://dx.doi.org/10.5772/61731

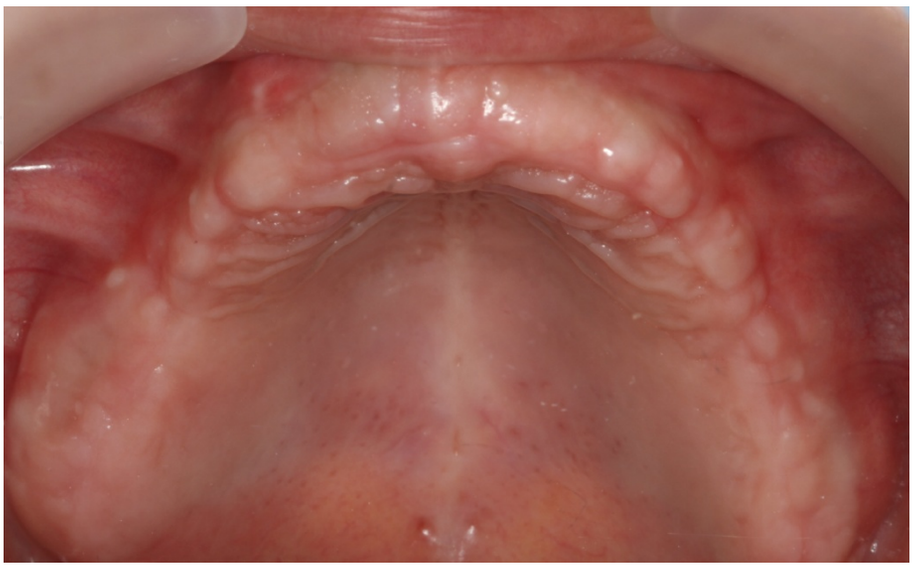

Figure 42. Two weeks after surgery

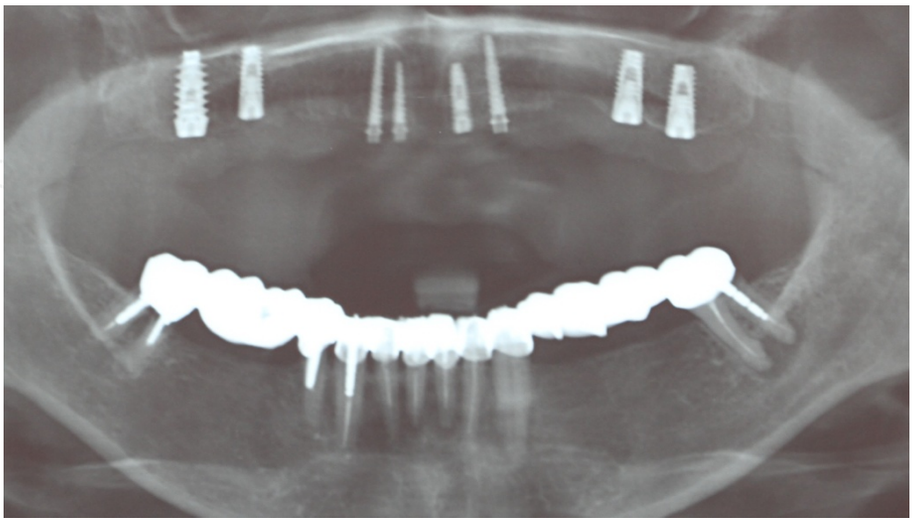

Figure 43. Panoramic X-ray after surgery

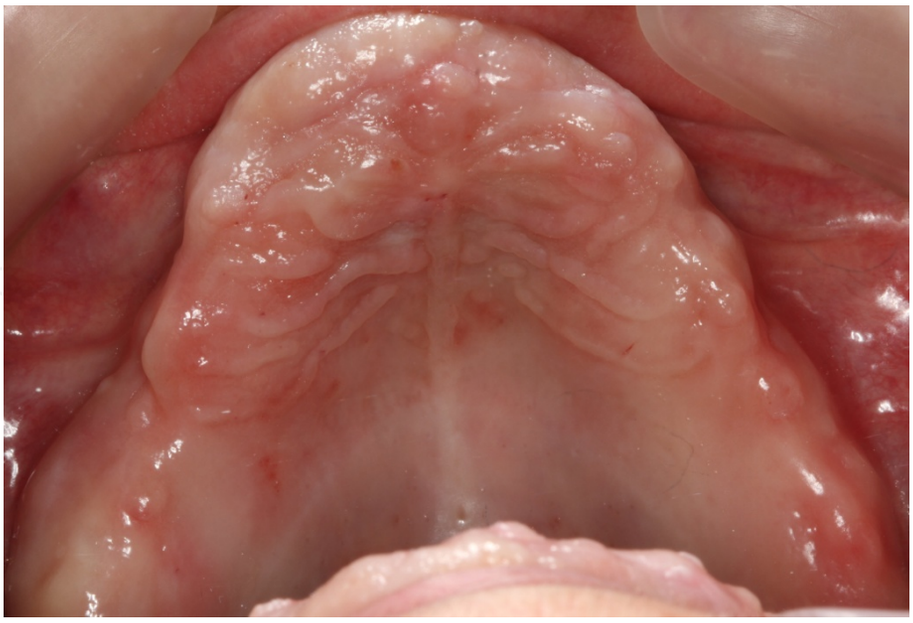

Figure 44. Four weeks after surgery

8.3. Case 3

A female patient, 54 years old, in good general health condition, smoker (over 10 cigarettes per day), was received at the clinic with complainscomplaints from fixed prosthetic construction mobility on the upper jaw, poor aesthetics, and inability to eat normally. X-ray proves anand aggressive periodntoalperiodontal disease with more than 9-10mm910mm bone resorption of interdental bone. PatientPatient's history sayssaid that she is was on Denosumabdenosumab (subcutaneously every 6 months) during for the last 3three years –in treatment for osteoporosis diagnose. The treatment plan was similar with case N2 and the healing process went smoothsmoothly.

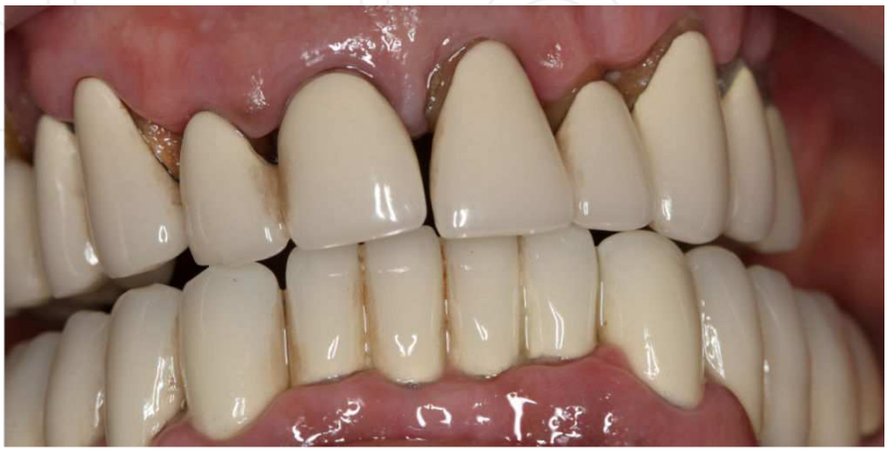

Figure 45. Intraoral view

http://dx.doi.org/10.5772/61731

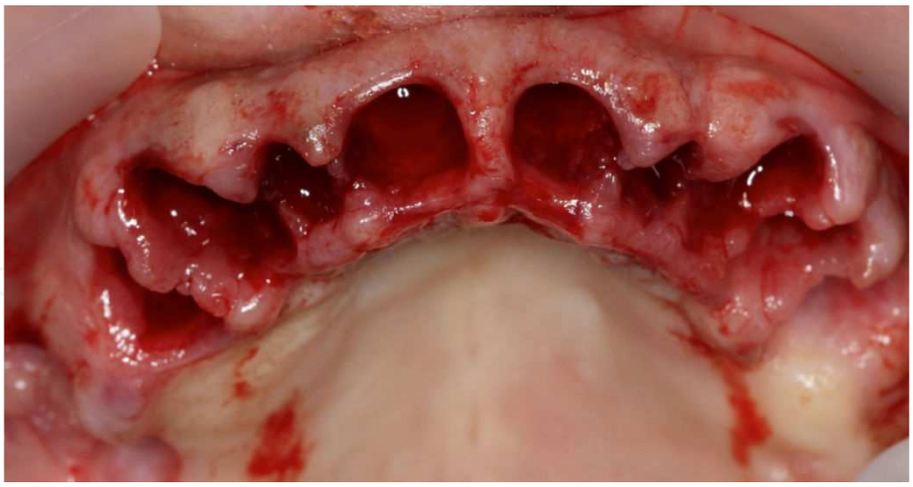

Figure 46. Postextracted sockets

Figure 47. The extracted teeth

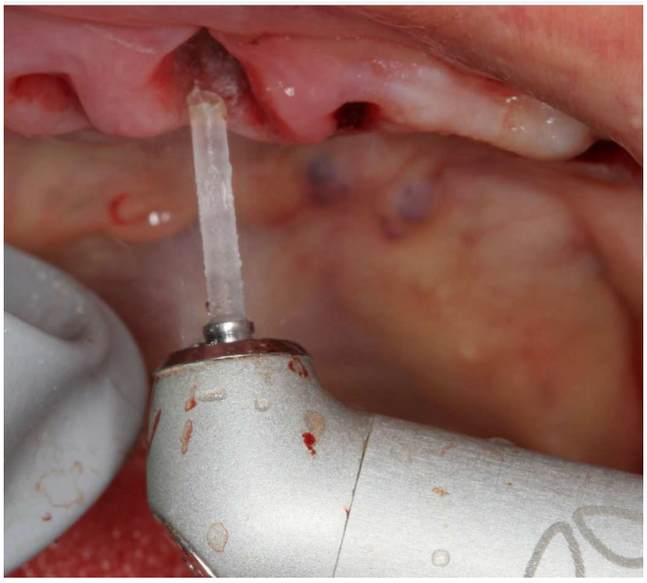

Figure 48. Granulation tissue ablation with Er:YagYAG laser

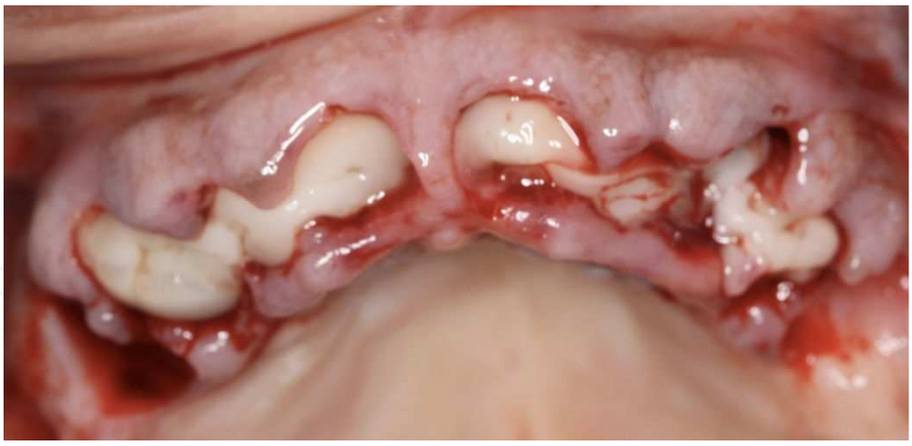

Figure 49. PRGF clotcloth

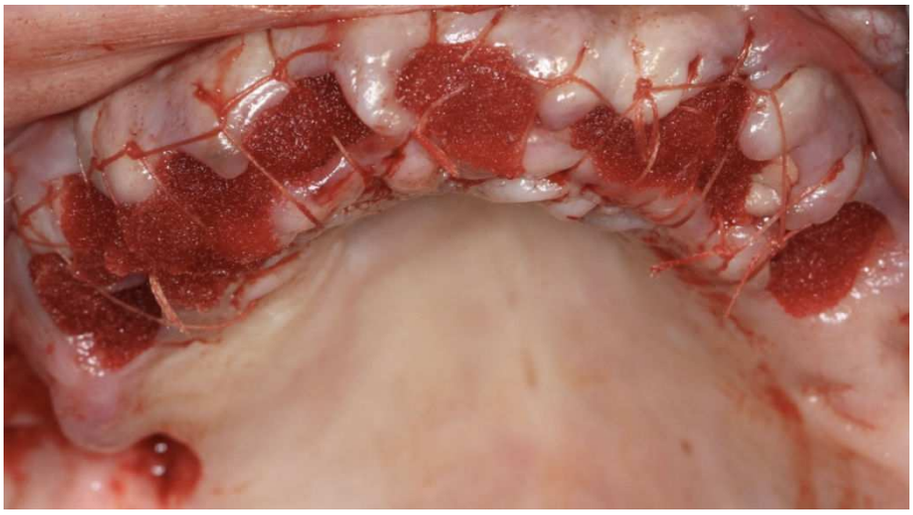

Figure 50. Covering with collagen sponge and suturing

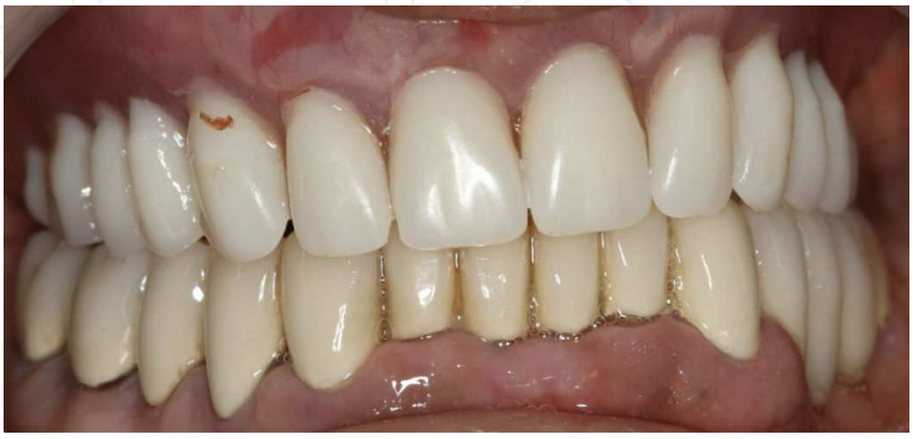

Figure 51. The immediate denture

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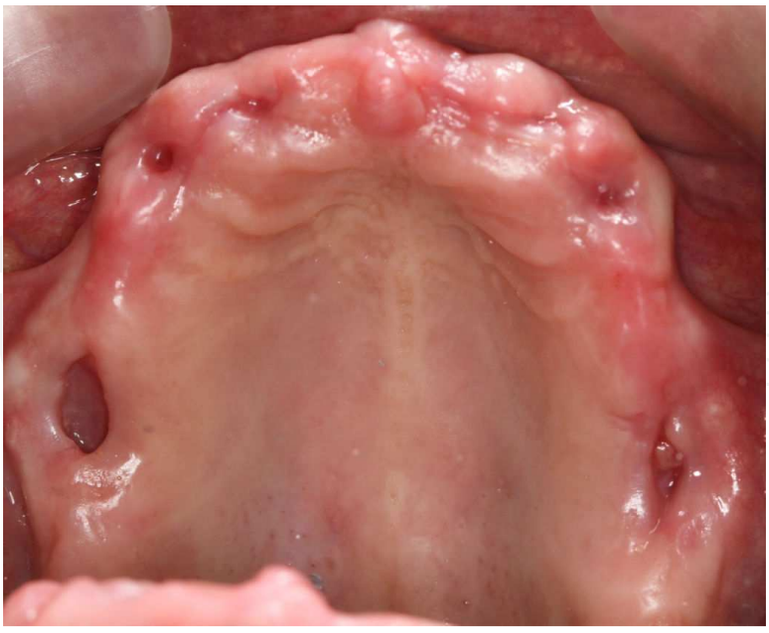

Figure 52. Three weeks after extraction

*All case-pictures are Dr. Abadzhiev's private practice patiens.

	Primary Indication	Nitrogen Containing	Dose	Route	Relative Potency**
Etidronate (Didronel)	Paget's Disease	No	300 -750 mg daily for 6 months	Oral	1
Tiludronate (Skelid)	Paget's Disease	No	400 mg daily for 3 months	Oral	50
Alendronate (Fosamax)	Osteoporosis	Yes	10 mg/day 70 mg/week	Oral	1,000
Risedronate (Actonel)	Osteoporosis	Yes	5 mg/day 35 mg/week	Oral	1,000
Ibandronate (Boniva)	Osteoporosis	Yes	2.5 mg/day 150 mg/month	Oral	1,000
Pamidronate (Aredia)	Bone Metastases	Yes	90 mg/3 weeks	IV	1,000 – 5,000
Zoledronate (Zometa)	Bone Metastases	Yes	4 mg/3 weeks	IV	10,000 +

Table 1. Usage and dosage of the bisphosphonates

After R.E. Marx

MRONJ† Staging	Treatment Strategies‡
At risk category No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates	· No treatment indicated · Patient education
Stage 0 No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes and symptoms	· Systemic management, including the use of pain medication and antibiotics
Stage 1 Exposed and necrotic bone, or fistulae that probes to bone, in patients who are asymptomatic and have no evidence of infection	· Antibacterial mouth rinse · Clinical follow-up on a quarterly basis · Patient education and review of indications for continued bisphosphonate therapy
Stage 2 Exposed and necrotic bone, or fistulae that probes to bone, associated with infection as evidenced by pain and ery- themaerythema in the region of the exposed bone with or without purulent drainage	· Symptomatic treatment with oral antibiotics · Oral antibacterial mouth rinse · Pain control · Debridement to relieve soft tissue irritation and infection control
Stage 3 Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one or more of the fol- lowingfollowing: exposed and necrotic bone extending beyond the region of alveolar bone,(, (i.e.,. inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extra-oral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible of sinus floor	· Antibacterial mouth rinse · Antibiotic therapy and pain control · Surgical debridement/resection for longer term palliation of infection and pain

Table 2. Staging and Treatment Strategies

Position Paper of American Association of Oral and Maxillofacial Surgeons (2014)

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