Bisphosphonates in improving the osseointegration of dental implants

Alyssa Golden, University of Minnesota Duluth
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Abstract

Dental implants have become a commonly used restorative option for tooth replacement, and with this common option comes the need of methods that ensure quick initial healing and long-term stability. One area of study addressing this need has been in the use of bisphosphonates, a class of medications commonly taken for osteoporosis treatment. This review primarily focuses on the effects of two of the most common bisphosphonates (alendronate and zoledronic acid) and differing methods of delivery. Most studies focusing on bone growth and bisphosphonates are similar in their test organism of rats and placement of implants in the leg bones, but vary on the dosage and duration of medication. Overall, the effect of alendronate and zoledronic acid show improvement of bone regrowth and implant stability. There are some exceptions, with studies of very high dosage and intravenous usage instead of local delivery showing negative effects on the bone regrowth. More study is required on the effects of bisphosphonates, especially as only a handful of the published research utilize maxillary or mandibular implant placement, but the use of these medications seems to be mostly beneficial.

Introduction

Over the years, the popularity of dental implants has increased throughout the world, with over 450,000 implants placed yearly in the US, matching the number of hip and knee replacements (Gaviria et al. 2014). One of the most important factors in ensuring that an implant will last as long as possible is osseointegration. Osseointegration is the growth of new bone tissue around an implant, so that no movement between the two is possible, except with likely breakage of the bone (Manolea et al. 2017). The medical profession has been increasingly recognizing importance of osseointegration not only regarding dental implants, but also regarding arm and leg implants (to replace external prosthetics).

Osseointegration is achieved by a natural process called bone remodeling, which is how all bones of the body are replaced with new bone tissue over time. Bone remodeling is carried out by two different types of cells present in the medullary cavity of bones, osteoclasts and osteoblasts. Osteoclasts break down the old bone tissue while osteoblasts replace it with new tissue (Bart 2008). However, as people age, a disease of the bone sometimes occurs, osteoporosis. In this disease, the breakdown of bone happens at a faster rate than the rebuilding, so there is an overall decrease in the amount of bone tissue present and an increased risk of fracture (Frizzera et al. 2019).

Dental implants are typically composed of titanium screws, often chosen because of their low maintenance needs and their ability to withstand higher force. When placing implants, a hole into the bone is drilled, the implant placed and then left to heal for bone growth and osseointegration. Once the implant is adequately anchored, an abutment is added to the top of the implant, which is what the crown attaches to. Since stability is one of the most important factors affecting the longevity of the implant, the initial osseointegration is crucial. Research methods exploring the improvement and quickening of osseointegration have focused on many different factors, from implant surface acid etching to medications. One of the most common experimental methods that can contribute to the success or failure of this initial osseointegration is the use of bisphosphonates, a type of drug commonly used to treat osteoporosis. Bisphosphonates are anticatabolic, meaning they prevent the breakdown of bone tissue. They work by disrupting osteoclast differentiation and signaling, and they can even lead to apoptosis of the cells (AbuMoussa et al. 2018). They are typically taken orally, for osteoporosis treatment, or intravenously, for cancer treatment (Oliveira et al. 2015).

Over the years, as the use of bisphosphonates and implants have crossed paths, some side effects have occurred. Bisphosphonate related osteonecrosis of the jaw, or BRONJ for short, has been observed in patients taking some types bisphosphonates around the time when they get an implant. Osteonecrosis is a reduction of blood flow to a bone, leading to the eventual death of the bone tissue. Fortunately, this is not very common in people taking bisphosphonates for osteoporosis and is more likely to happen in people who are taking the medication intravenously. Still, it is an issue that needs to be investigated since researchers do not understand the reasons why this drug causes this reduction (Khojasteh et al. 2018).

There are also different types of bisphosphonates, falling into two different categories: non-nitrogenous and nitrogenous. Non-nitrogenous aren't as commonly used as are the nitrogenous, partly because nitrogenous bisphosphonates are more powerful and effective (Oliveira et al. 2015). The most common nitrogenous bisphosphonates are alendronate, pamidronate, and zoledronic acid. Alendronate and pamidronate are commonly taken orally for osteoporosis, and zoledronic acid intravenously for cancer treatment (Mayo Clinic 2019). This review will be focusing on the effects of different bisphosphonates and the delivery methods on dental implant osseointegration.

Zoledronic Acid

Zoledronic acid is a nitrogenous bisphosphonate commonly used to treat skeletal issues involved with cancers like multiple myeloma, breast and prostate cancer (Oliveira et al. 2015). It is the most powerful type of bisphosphonates, including other nitrogenous bisphosphonates (Dikicier et al. 2017). Like other bisphosphonates, zoledronic acid limits the activity of osteoclasts and has a very long residence time (Dikicier et al. 2017). Many studies have outlined the use of zoledronic acid as an osseointegrative agent, as the effects can vary.

One of the beneficial effects of zoledronic acid is an increase of bone implant contact, or BIC, a measure of the percent of the dental implant that is in contact with bone (Kwon et al. 2017; Chen et al. 2013). Both Kwon et al. and Chen et al. found that with zoledronic acid, BIC increased significantly, with around double the BIC compared to the control in both cases. Zoledronic acid also impacts bone mineral density, which reflects the quality of the new bone formation. Research also found that the use of zoledronic acid resulted in increases in bone mineral density (BMD), with increases of 23% (Chen et al. 2013) to 200% (Ying et al. 2016). The ability of zoledronic acid to improve osseointegration was also demonstrated in rats that had their ovaries removed (OVX), to simulate an osteoporotic state. Despite the experimental group of rats having lower BMD compared to the control, those treated with zoledronic acid exhibited increased levels of BMD compared to the OVX rats with no treatment (Dikicier et al. 2017; Ying et al. 2016).

Another parameter measured was of the implants. Research has also measured the amount of force required to break the implant from the surrounding bone by either pushing or bending the implant, known as the removal torque. Kwon et al. 2017; Chen et al. 2013 found that the use of zoledronic acid nearly doubled the breakage force required compared to the control.

However, zoledronic acid also can have some negative side effects that contradict the beneficial effects already covered. Treatment with zoledronic acid decreased BIC, especially in IV delivery (Khojasteh et al. 2018). Cardemil et al. (2013), and Basso et al. (2018) also saw decreases in the amount of turnover markers present. Basso et al. in particular assessed initial cell adhesion to the implant surface and found that the treatment reduced that adhesion. This early adhesion can have a large impact on the overall osseointegration of implants. In most of these cases, the negative effects of the treatment could possibly be attributed to increased dosage and longer duration of treatment. Most of the doses were around 1 mg/kg weekly or less, but three of the studies had high doses, with Khojasteh (2018) at 3.5 mg/kg for 1 year. Such high dosage is also unusual because most prescriptions of bisphosphonates for osteoporosis are at a weekly dosage of 1 to 1.5 mg/kg.

The location of the implant also appears to have a considerable effect on the results. For example, Cardemil et al. (2013) saw increases of BIC in the tibia, but the opposite occurring in the mandible. Such difference could possibly be due to the varying turnover rates and density in different bones. Normal bone turnover rates for long bones like the leg bones is 3-5 % while the turnover rates of the mandible are much higher. The turnover rate of the basal mandibular bone is 7% a year, and the rate of the alveolar bone is 25% a year. The mandible is also denser than many of the other bones in the body, which could attribute to the varying effects (Khojasteh et al. 2018).

Alendronate

Alendronate is another type of bisphosphonate in the nitrogenous category. It has a similar mechanism and function to zoledronic acid, but it is not as potent as zoledronic acid. Like zoledronic acid, it also has varied and conflicting effects. Alendronate increases the BMD of bone surrounding implants (Verzola et al. 2015, Chen et al. 2013), in one case at almost a 60% increase. This increased BMD also contributed to the increased removal torque required in alendronate treated test animals. Two studies exhibited an increase in force, with one increasing 17% (Chen et al. 2013, Verzola et

al. 2015). Additionally, alendronate increased the BIC exhibited by 1.6 fold (Chen et al. 2013) and Verzola in particular depicted that the use of alendronate to improve osseointegration has long term benefits, of up to 60 days after implantation (Verzola et al. 2015).

Like zoledronic acid, alendronate also has negative effects associated with it. Some of these most important negative effects are the reduction in bone turnover/growth indicators. Basso (2018) and Frizzera (2019) studied the amount of growth, or turnover, factors present in test animals receiving treatments of alendronate and found that the use of the drug decreased the amount of growth factors present. Frizzera, in particular, highlighted the long-term effects. Frizzera studied bone growth at varying periods of alendronate withdrawal after implantation. The longest withdrawal period they performed was 45 days, and at that point growth factor levels still had not been restored to normal parameters (Frizzera et al. 2019). Removal torque was also decreased with this medication, in a study by Guimarães (2015) it was reduced by half.

Alternative Methods of Delivery

Bisphosphonates are almost always delivered in a way that has a systemic effect, meaning that bisphosphonates can have side effects on unintended areas of the body. In almost all of the previous studies covered, such side effects existed, so researchers have explored other methods to limit the exposure to only the area of implantation. With varying success, two studies injected the medication directly into the site of implantation to better contain the spread. For example, Guimarães et al. (2015) injected alendronate into the implantation site as a gel. The dose was a very high concentration, and the implant was left to heal for 28 days before removal for testing. This treatment decreased the BIC and reduced the removal torque by a large margin. Similarly, AbuMoussa (2018) used an injection of zoledronic acid into the cavity of the bone. After implantation, a low dose of the medication was injected into the medullary cavity. In this instance, there was a general improvement of BIC and pushout force. These two studies emphasized that even local application of alendronate in high, rather than low, doses can be detrimental to osseointegration.

Another method of delivery was through the use of TiO2 nanotubes in the implant. In this method, Kwon (2017) utilized nanotubes in the surface of the implant that were loaded with zoledronic acid before being screwed into place. This method is very useful, as the size and depth of the tubes can be changed to fit the needs of the situation. In this instance, the amount of new bone present increased, nearly doubling the amount of removal torque required. Overall, this method was beneficial and also included hardly any of the typical side effects associated with delivering bisphosphonates systemically.

Lastly, Abhati (2016) used a layering of fibrinogen to deliver the drugs. The fibrinogen, a type of protein, was bonded to the implant, and small amounts of ibandronate and pamidronate were absorbed into the layering. The implant was placed in the upper jaw and evaluated at 2, 6, 18, and 60 months. This method exhibited a decreased amount of bone loss compared to the control, .7mm CTL and .2mm BP after 5 years. Also, most of the change in the bone was observed in the first in 6 months, and after that point the change was not significant. This study especially highlighted the

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importance of early healing and the ability of bisphosphonates to have a beneficial effect on the osseointegration and on the longevity of the implant over very long periods of time.

All in all, the local delivery of treatment seemed to be beneficial, with the single outlier of the alendronate gel. The reason for the negative effect of the local delivery on the osseointegration could be the high dosage used, 1 mL of 10,000 mg/kg alendronate. Other studies have reflected the negative impact of high doses of bisphosphonates (AbuMoussa et al. 2018), so clearly there is a point at which the medication begins to cause problems. In any case, local application is more desirable, as it provides more control over how much of the drug the body is exposed to, and what areas will be affected.

Conclusion

Overall, many studies have shown the benefits of bisphosphonates as they are used indirectly for osteoporosis. Different bisphosphonates have varying strength, but--for the most part--all cause similar effects. At low doses around 1 mg/kg and over longer periods of time, the effects have been largely beneficial and useful to the improvement of osseointegration, as shown by Abhati (2016) and Verzola (2015). Conversely, other studies have observed the opposite effects using the same drugs. Most of the time the more negative results resulted from the use of higher doses of the medication (greater than 3 mg/kg), but that wasn't always the case. Two studies compared zoledronic acid and alendronate with both showing zoledronic acid with overall stronger effects on osseointegration than alendronate. One study showed improvement and the other a negative effect, but in both cases zoledronic acid was more potent (Chen et al. 2013; Basso et al. 2018). Alternative methods of delivery, especially those that are more local, seemed to be beneficial without the possible side effects sometimes associated with systemic delivery like fever, flu like symptoms, muscle and bone pain, and anemia (Oliveira et al. 2015).

With these conflicting results, several aspects of these studies should be tested further for more clarity. For example, utilization of more implant sites in the maxilla or mandible would be important to consider, as clearly there can be large differences in the effect bisphosphonates can have on different bones of the body (Cardemil et al. 2013). Also, some of the studies used doses for the test animals that were far beyond what would actually be prescribed for people with osteoporosis, and this dosing could greatly affect the results. Despite the varying and sometimes conflicting results caused by bisphosphonates, research supports that the overall benefits of their usage outweigh the negative effects they can cause.

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