The Use of Bioactive Glass Integrated Telescoping Rods to Treat Osteogenesis Imperfecta

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Background and Introduction to Osteogenesis Imperfecta:

Osteogenesis Imperfecta (OI), commonly known as brittle bone disease, is a disorder in the genes that produce type I collagen, the type of collagen found in bone. This mutation makes bones extremely fragile and susceptible to fractures, deformities, and growth abnormalities. Osteogenesis Imperfecta is classified as a rare orthopedic disease and is diagnosed in approximately one in twenty-thousand to one in fifteen-thousand births [1]. It's usually classified into one of five different types [2]. Types I is the most mild case of Osteogenesis Imperfecta and Type II is lethal to the fetus that develops it. Types III and IV are types that are severe but where survival is possible post birth. Type V is Osteogenesis Imperfecta of any severity in which there is calcification of interosseous membranes. The more mild types of OI are occasionally not recognised until the patient reaches adulthood meaning that it can range from perinatal lethal to undetectable in children [3]. In more severe cases of OI, a prenatal ultrasound can be used to diagnose the fetus with the disease [3]. After being diagnosed by the ultrasound, it is then confirmed using genetic testing and other imaging systems.

Osteogenesis Imperfecta occurs when the genes involved in the production of type 1 collagen mutate [3]. This usually results in a reduced production rate of type I collagen or abnormal collagen synthesis [2]. Type I collagen is used to reinforce the bone matrix alongside the hydroxyapatite [1]. Reduced or abnormal collagen production will create less reinforced bone matrices which will mean the bone is weaker, brittle, and more susceptible to breaking.

Collagen I is created when three polypeptide chains are produced by ribosomes in the osteoblast and then folded together to form a triple helix [8]. The chains are a repetition of the amino acid pattern Gly-X-Y where X and Y are any amino acid [8]. X is typically Pro and Y is typically Lys but that isn't always the case. Gly is always in the center of the triple helix because it's the smallest amino acid and there isn't any space to house a larger amino acid. While the triple helix is being zipped up, Hydroxyl groups can attach to the Pro and Lys along the amino acid chain creating Hydroxyproline or Hydroxylysine depending on the amino acid it attaches to [8]. The sugar molecules Glucose and Galactose can then attach to the Hyl, forming Galactosyl-Hyl and Glucosyl-Galactosyl-Hyl. The attachment of the Hydroxyl groups and the sugar molecules are time-dependent meaning that the longer the zipping takes, the more attachments form.

Figure 1: [8] On the left side, a schematic view on the formation of collagen, both intracellular and extracellular. On the right side the same formation but with a mutation in one of the alpha chains as is seen in osteogenesis imperfecta (OI). Step 1: formation of three alpha chains by ribosomes (note the bigger amino acid in one of the chains in OI). Step 2: hydroxylation and glycosylation and the triple helix formation (note the slower folding in OI with increased hydroxylation and glycosylation: Glucose (Glc), Galactose (Gal), Lysine (Lys), Hydroxylysine (Hyl), Proline (Pro)). Step 3: extracellular cleavage of the C- and N-terminus. Step 4: quarter-staggered arrays (note the increased space between the molecules in OI). Step 5: the formation of cross-links which is unaffected in OI. Step 6: mineralization between the collagen molecules with an increased amount of mineral crystals of the same size in OI.

Osteogenesis Imperfecta interferes with this process in two ways: by delaying the folding of the triple helix and by substituting a larger amino acid for the Glycine in the first or second polypeptide chain [8]. Delaying the zipping creates more connections along the chain and substituting a larger amino acid in for Glycine creates a molecular deformation. Figure 1 shows the process by which collagen is formed. The left side of the image is the formation in a healthy individual and the right side of the image is the formation in an individual with Osteogenesis Imperfecta. In step 6 of the OI case, it can be seen that there is more mineralization between the collagen molecules because of the larger amino acid substituted for the Glyc.

The Current Standard of Care for Osteogenesis Imperfecta and Its Faults:

The current standard of care for Osteogenesis Imperfecta can vary significantly depending on the type of OI the patient has, the age at which it is discovered, and the symptoms they are exhibiting. Osteogenesis Imperfecta does not currently have a cure although there are many ways of treating it. The two most common ways are with medication and through preventive surgery [1]. Medication is helpful to increase bone strength and bone mineral density in patients with Osteogenesis Imperfecta, especially pediatric patients because they have a more rapid turn-over rate in their bones [1]. Preventive surgery is helpful to decrease the chance of fracture by adding an intramedullary rod to the bone to increase mechanical strength and decrease the load on the patient's bone [1].

The addition of an intramedullary rod is a crucial treatment for Osteogenesis Imperfecta because it significantly decreases the risk of fracture in patients with the disease. This is made more difficult, however, in pediatric patients because their bones are not a consistent size [1]. As the child grows, the bones grow as well meaning that the rod can not stay implanted for an extended period of time. As the bone grows, multiple revision surgeries are needed in order to appropriately size the implant to the bone. This makes the treatment more expensive and time consuming for the patient and their family. The solution to this problem is to use elongating rods that will grow alongside the patient [4]. These rods are typically made of stainless steel or titanium which provide enough mechanical strength to support and stabilize the bone. The rod is made up of two components, one male and one female, that connect together and overlap in such a way that the rod can extend as the male component retracts from the female component [5]. Each component is fixed with a screw on the end in order to connect it to the bone. The components are attached to the proximal and distal epiphyses and overlap in the center of the bone to form one continual rod along the length of the bone in question.

Although the elongating rod treatment is functional and an improvement to the stationary rod, there are several complications that can arise due to its implantation. These complications include migration from their designated position, failure to telescope or elongate as the bone grows, fractures occurring along the rod, lesions occurring in the growth plate, the bending of the rod, issues in the rotational functionality of the rod, and possible infections [5]. A common failure to occur in these rods is a complication in the nail fixation component of the rod. This complication causes the nail fixation component to migrate into the surrounding muscle and assorted tissue. This complication can also cause failure to grow alongside the patient's native bone. The most likely next step in developing the elongating rod to be the most effective treatment for Osteogenesis Imperfecta lies in the locking mechanism to the epiphysis [7]. Improving this mechanism would reduce the amount that the threads of the screws could be pushed or pulled and therefore increase mechanical stability. This would lead to less complications and an overall better treatment.

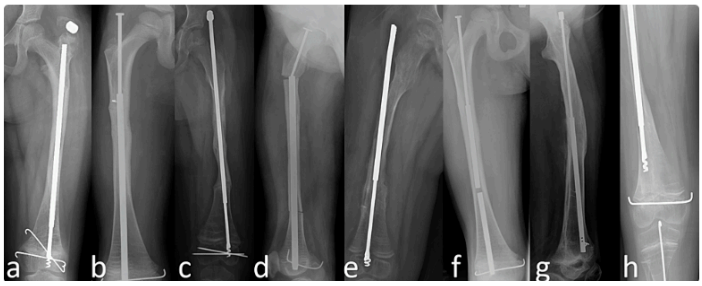

Figure 2: Complications seen in telescopic implant group. [6]
(a) Dislocation of the proximal locking screw; (b-c) migration into the abductor muscles; (d) fracture of the obturator part of the nail; (e) nail extraosseous; (f) fracture of the sleeve part of the nail; (g) limited telescoping of the implant with the locking hole system with K-wire; (h) limited telescoping of the corkscrew-tipped implant

Innovation for the Care of Osteogenesis Imperfecta:

Currently, the telescoping rod used to treat Osteogenesis Imperfecta has some complications associated with it. One complication that arises frequently is the migration of the nail fixation component. The next step in innovating this device is to focus on the locking mechanism in order to circumvent the migration of the screw [7]. Adding a layer of bioactive glass to the connection point of the telescoping rod would increase the tissue integration of the material and hopefully increase the stability and mechanical strength of the device [9].

Bioactive glass was originally created as a bone grafting material [10]. It was made for this purpose because of its ability to not induce fibrous capsule formations around it. Foreign material that the body does not integrate with has a tendency to form a fibrous capsule as the body tries to push it out, but bioglass integrates with the tissue so it doesn't form a fibrous capsule. This is what gives it the ability to anchor so well into the tissue. It integrates directly with the native material meaning the connection is far more secure than a standard bone screw.

Bioglass utilizes elements that already have high concentrations within the body so that the body does not reject the foreign material [10]. Bioglass also breaks down easily in slight basic solutions meaning that as soon the bioglass comes into contact with blood plasma, which has a pH of 7.35-7.45, it begins to break down and form bonds with the native tissue [10]. The glass begins rapid ion exchange with the hydrogen cations from the bodily fluids. This exchange of ions increases the pH of the solution. As the pH increases, attack on the silica network once again starts and the silica is released as $Si(OH)_4$ into the bodily fluids which then forms silanols, Si-OH on the surface of the glass [10]. After the silanols forms, it condensates and re-polymerizes on the surface of the glass. This creates a silica-rich layer on the surface of the bioactive glass. The Calcium and Phosphate from the blood migrate to the bioactive glass surface and first form amorphous hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$, then crystallizes as a HA layer on the bioactive glass. This HA layer is compatible with the native tissue and induces interfacial bonding between the native tissue and the foreign material [10].

The more integration between the body and the implant, the stronger the implant will be and the more mechanical load it will be able to accommodate. In cases where the implant is fully integrated into the body and with the native tissue, new bone structures form and fill the space in between the threads of the implant screw [10]. The new bone structure allows the implant to undergo significantly more stress without failure since the weakest part of the implant, the threads, become filled in.

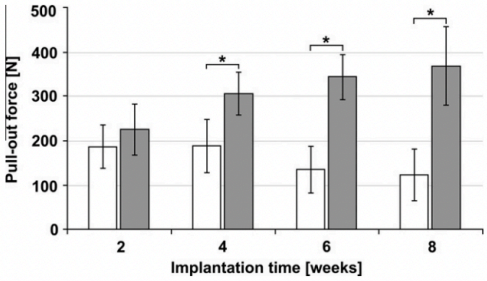

Figure 3: Pull-out testing results [11]
Mean peak pull-out force of standard stainless steel(white bars) and bioglass coated(grey bars) rods and standard deviation at different implantation periods. (* indicates a significant difference P<0.05)

Figure 3 shows a collection of data gathered from experimentation of Osteogenesis Imperfecta telescoping rod treatments both with and without the bioglass [11]. The gray blocks are the blocks that are coated in the bioactive glass material which promotes further tissue integration while the white ones have no bioactive glass attached to them. The gray bars have a significantly higher pull-out force than the white bars because they are more integrated into the tissue so they're harder to remove. This experimentally shows that coating a biomaterial in bioactive glass improves mechanical properties and increases the force needed to pull out of its connection.

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