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[WILL THERE EVER BE A CURE FOR OSTEOGENESIS IMPERFERCTA?]

Exploring the genetic condition of Osteogenesis Imperfecta and looking at the implications of the condition of an individual. Than taking a look at the current treatments and planned trials as well as looking to the future to see what is being done and why more isn't being done to find a cure for this condition.

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What is Osteogenesis Imperfecta?

Osteogenesis Imperfecta (OI) is a genetic bone disorder. The name is derived from Osteogenesis, meaning formation of bone[1] hence, the literal interpretation of the condition is the imperfect formation of bones. Currently the prevalence rate of OI according to the OI Foundation in America estimated the prevalence of OI was somewhere in the region of 20,000 to 50,000[2] out of a current population of 300 million and growing. Worldwide OI is estimated to affect 6 - 7 per 100,000 people[3].

The following is an account by Ute Wallentin, the president of the Osteogenesis Imperfecta Federation Europe, and her experience of OI as a child;

> "I had a very happy childhood with my family and friends and have wonderful memories. But in retrospect I know I felt quite lonely and sometimes even isolated because I was 'different'. I could not do the same things as all the others, had to be careful and was protected by the special precautions put in place by my parents or other adults. My parents did everything possible to enable me to do as many normal activities as possible, but still I sometimes felt excluded from 'normal life'.[4]"

From other cases this appears to be all too common of an experience, especially for OI sufferers at a young age. At the time of writing this report a definitive cure for OI has not been found but finding a cure would allow those individuals to lead a 'normal life' or an increasingly normal life that Ute talks about. Current treatment focuses on symptom management as well as trying to improve on the individual's quality of life.

Rauch and Glorieux were amongst the first to publish in the 20th century on OI and they concluded that the disorder caused sufferers to be born with defective connective tissue or without the ability to produce it which could be typically attributed to deficiencies in Type 1 collagen[5]. Furthermore, thirty per cent of the human body weight is Type 1 collagen[6] and it's found in tendon, bones and parts of the eye like the cornea and sclera. It is crucial for the tensile strength of bones; the distribution of this dictates the ultimate density of bones[7].

The reasons behind why mutations in collagen cause complications with OI sufferers are:

- The defective collagen rods caused by OI form around an abnormal mould of bone. Since the bone does not form correctly, the structure that forms outside the collagen rod is formed improperly.

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[1] Dorland's Medical Dictionary for Health Consumers. (2007). Osteogenesis. Available: http://medical-dictionary.thefreedictionary.com/osteogenesis. Last accessed 15/03/2013.
[2] The National Institutes of Health Osteoporosis and Related Bone Diseases. (2012). Fast Facts on Osteogenesis Imperfecta. Available: http://www.oif.org/site/PageServer?pagename=fastfacts. Last accessed 05/07/2012.
[3] NIH. (2013). Osteogenesis Imperfecta . Available: http://ghr.nlm.nih.gov/condition/osteogenesis-imperfecta. Last accessed 01/12/2012.
[4] Nathacha Appanah. (2010). Osteogenesis Imperfecta. Available: http://www.eurordis.org/content/osteogenesis-imperfecta-mother-and-daughter-experience-brittle-bone-disease. Last accessed 20/03/2013
[5] Rauch F, Glorieux FH. (2004). Osteogenesis imperfecta. The Lancet. 363 (1), 1377-85
[6] Horacio Plotkin, MD, FAAP. (2012). *Genetics of Osteogenesis Imperfecta - Background.* Available: http://emedicine.medscape.com/article/947588-overview. Last accessed 18/06/2012.
[7] Clifford R. Wheeless, III, MD. (2011). Type 1 Collagen. Available: http://wheelessonline.com/ortho/type_i_collagen. Last accessed 08/12/2012.

- The badly formed collagen rods are more susceptible to the body's normal process that detects and destroys broken molecules. Thus, the amount of bone, however imperfect, is reduced further by 'house cleaning' cells that remove defective collagen rods.
- The cells that form bone, the osteoblasts, are affected by the presence of bad collagen molecules. Osteoblasts have great difficulty making abnormal collagen fibres and transferring them outside the cell. Thus, the cells are filled with vast quantities of imperfect collagen fibres that cannot be moved outside. Consequently, these cells become very inefficient in the way they make additional bone proteins and are very slow to divide and make new cells. [8]

We will be taking a further look at the role of osteoblasts as well as osteoclasts later on. However, the body demands that the bone cells make more bone, particularly during childhood. This is when new bone is needed to carry the increased stature and weight of a growing child. Unfortunately, the only bone that it can make still contains the defective fibres, so the strength is never improved. This spiral of ineffective bone formation is never ending.

The ineffective bone formation specifically goes on to explain why sufferers of OI have such an extended healing period if they break or fracture a bone compared to an individual without the condition. This effect reduces following puberty[9] when the growth rate slows; leading to a reduced rate of fracture and a reduced rate at which these defective fibres are produced.

The brittleness of the bones of sufferers which is an indicative factor of OI varies on the different types of phenotypes that develop causing the condition to range from mild to severe and sometimes lethal versions of the condition. Phenotypes are the expression of a specific trait based on genetic and environmental influences[10] . In this case, it affects the symptoms of severity of the condition. The two different genes that encode for type 1 collagen are COL1A1 and COL1A2, found on chromosome 17 and 7 respectively[11]. The mild forms are usually caused by mutations which inactivate one allele of COL1A1 gene and result in a reduced amount of normal type I collagen, while the severe and lethal forms result from dominant negative mutations in COL1A1 or COL1A2 which produces structural defects in the collagen molecule. The most common mutations are substitutions of glycine residues, which are crucial to formation and function of the collagen triple helix, by larger amino acids.[12]

[8] David Rowe, M.D., University of Connecticut Health Center. (1997). Understanding the structure of Bones. Available: http://www.oif.org/site/PageServer?pagename=BoneStruct. Last accessed 05/07/2012.
[9] Joan Marini, MD, PhD. (2010). Chapter 16: Osteogenesis Imperfecta. Available: http://www.endotext.org/parathyroid/parathyroid17/parathyroid17.pdf. Last accessed 31/01/2013.
[10] Biology Online. (2008). Phenotypes. Available: http://www.biology-online.org/dictionary/Phenotype. Last accessed 20/03/2013.
[11] Washington Pathology. (2013). COL1A1 AND COL1A2 GENOMIC SEQUENCING TESTING FOR OSTEOGENESIS IMPERFECTA (OI). Available: http://www.pathology.washington.edu/clinical/collagen/index.php/available-tests-right-column/col-1a-1-2-gdna/. Last accessed 20/03/2013.
[12] Anna Gajko-Galicka. (2002). Mutations in type I collagen genes resulting in Osteogenesis Imperfecta in humans. Acta Biochimica Polonica. 49 (2), 433-441

The triple helix creates a strong structure and if the structures of collagen genes are compromised, as they are with OI, bone formation becomes affected. Collagen is made up of a triple helix with repetitious amino acids with a sequence of glycine – X – Y, in most cases X and Y are most commonly Proline and Hydroxyproline, as illustrated in figure 1 below. Hydroxyproline content can often be used as an indicator of collagen levels in the body as it's only found in very few other proteins including collagen. Whereas Proline is one of the twenty DNA encoded amino acids, while not an essential amino acid, its characteristics means that the human body can synthesize it[13].

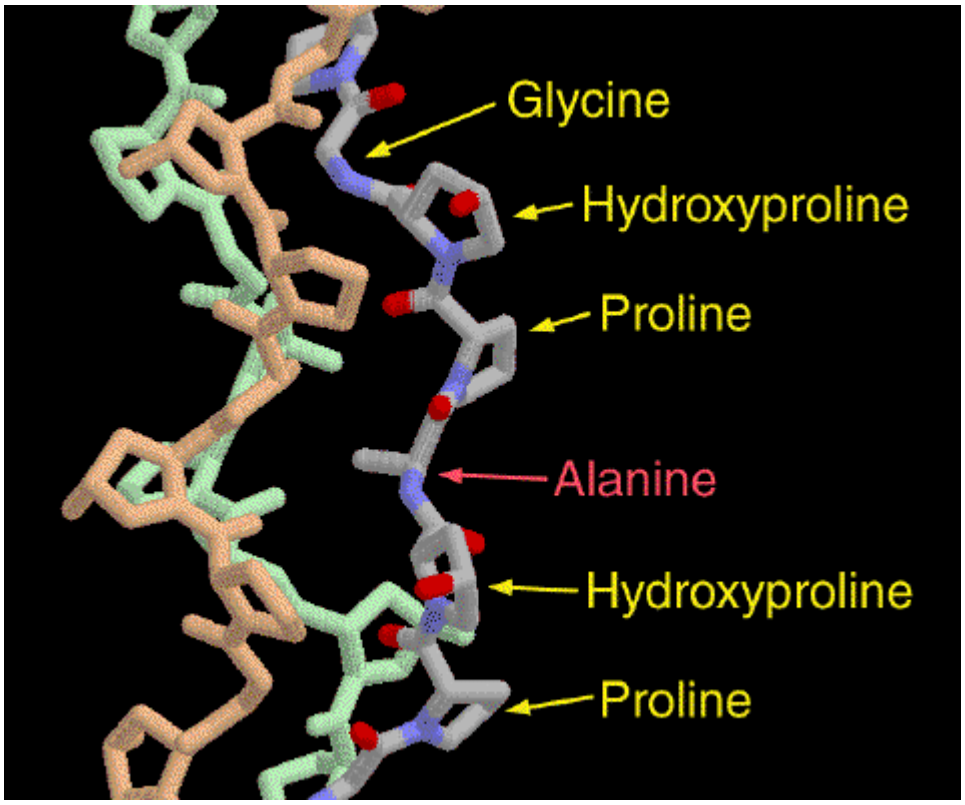

Figure 1 Collagen Triple Helix[14]

[13]NCBI. (2009). Proline - Compound Summary. Available: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=614&loc=ec_rcs. Last accessed 09/12/2012

[14] David Goodsell. (2000). Collagen. Available: http://www.rcsb.org/pdb/101/motm.do?momID=4. Last accessed 09/12/12.

Type	**Severity of Condition**	**Gene**	**Mode of Inheritance**	**Noteworthy/ Interesting Facts**
I	Mild	COL1A1	Dominant	Most common type of OI, with an occurrence level of 50% of all OI sufferers
II	Severe and usually lethal during neonatal (few weeks after birth) periods	COL1A1 & COL1A2	Dominant	Most severe type of OI
III	Progressive and deforming	COL1A1 & COL1A2	Dominant	Most severe for younger OI suffers who survive first few weeks after birth
IV	Deforming, but with normal sclerae	COL1A1 & COL1A2	Dominant	Diagnosis of this type is often not made until the child is walking.
V	Deforming, but with normal sclerae	IFITM5	Dominant	This makes up 5% of all moderate to severe OI cases
VI	Deforming, but with normal sclerae	Unknown	Unknown	Extremely rare
VII	Associated with cartilage associated protein	CRTAP	Recessive	Recessive inheritance of OI only counts for 10% of all recorded cases
VIII	Severe to lethal	LEPRE1	Recessive	Recessive

				inheritance of OI only counts for 10% of all recorded cases[15]

As you can see from the summary table above, up to this point there have been 8 types of OI which have been found, each with their own different symptoms, levels of severity and resulting from defects in different alleles and inherited in one of two ways; either through dominant or recessive alleles. Alleles are alternative forms of a gene, located at a specific region of a specific chromosome, which varies according to the mutation. The combination of these alleles on the gene form the DNA coding's which determine distinct traits to be passed from parents to the offspring[16]. With OI, the alleles which code for COL1A1, COL1A2, CRTAP, IFITM5 or LEPRE1 are pivotal as to whether the offspring inherits the condition.

As picked up in my summary table above, apart from mutations in COL1A1 and COL1A2 causing defective collagen to produce there are 3 other types of gene mutations which can occur causing the other types of OI. One of the other dominant mutations is caused by mutations to IFITM5. IFITM5 or Interferon induced transmembrane protein 5 is believed to play a role in bone mineralisation and formation[17]. Hence a mutation in this gene results in calluses and process of calcification to occur more than in an individual without OI[18]. The calluses, specifically hypertrophic calluses can occur spontaneously. Hypertrophic calluses are hard bony tissues which are produced during the healing phase after a fracture[19]. Increased calcification, especially in the region of the interosseous membrane, which is the tissue which separates many of the bones in the human body[20], between the radius and ulna can restrict forearm rotation leading to dislocation of the radial head.

[15] OI Foundation. (2012). Types of OI. Available: http://www.oif.org/site/PageServer?pagename=AOI_Types. Last accessed 15/03/2013.
[16] Regina Bailey . (2012). Allele - A Genetics Definition. Available: http://biology.about.com/od/geneticsglossary/g/alleles.htm. Last accessed 15/03/2013.
[17] NCBI. (2013). IFITM5 interferon induced transmembrane protein 5 [Homo sapiens(human)]. Available: http://www.ncbi.nlm.nih.gov/gene/387733. Last accessed 20/03/2013.
[18] OI Foundation. (2012). Types of OI. Available: http://www.oif.org/site/PageServer?pagename=AOI_Types. Last accessed 15/03/2013.
[19] The American Heritage Dictionary of the English Language. (2009). Callus. Available: http://www.thefreedictionary.com/hypertrophic+callus. Last accessed 20/03/2013.
[20] Merriam Webster Medical Dictionary. (2013).Interosseous Membrane. Available: http://www.merriam-webster.com/medical/interosseous%20membrane. Last accessed 20/03/2013.

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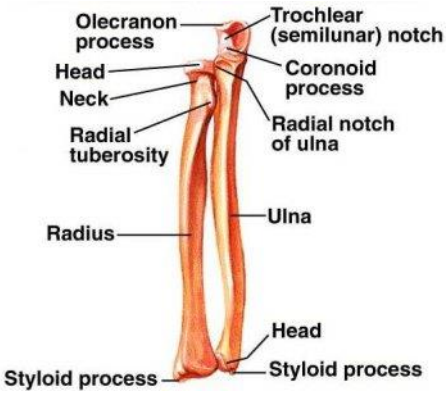

Figure 2 Radius and Ulna

Until very recently it had only been thought that OI could be contracted through dominant genes such as COL1A1, COL1A2 and IFITM5. This implied that if someone in the family had it then, it would be likely that offspring would inherit the condition. In 2006 however, the US National Institute of Heath, specifically the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) team headed by Dr Joan Marini found two recessive OI genes[22]. The National Institute found that type 7 and 8 are caused by the CTRAP (cartilage associated protein) and the P3H1 (Prolyl 3 – hydroxylation) genes[23]. Even though the full role of CTRAP is not yet known, the best understanding of it is that is that it is known to be part of a complex protein involved in the chemical formation of collagen from simple protein 'chains' into its final form.[24] Also it is the interaction between this and the enzymes of the P3H1 gene which allows collagen to be formed; in type 7 and 8 OI this collagen structure was found to be of an abnormal nature hence causing OI[25]. These types of OI are said to be lethal or the most severe.

This changed the perceptions of what OI was and how it should be treated. The implications of these two recessive OI genes being found was that even if there was no previous track record of anyone in the family who suffered from the disorder, if both parents were healthy carriers of the genetic defect, then there would be a one in four chance of the offspring having the condition.

[21] David Darling. (2012). Radius (of the arm). Available: http://www.daviddarling.info/encyclopedia/R/radius_arm.html. Last accessed 20/03/2013.
[22] BBC. (2007). 'Silent' brittle bone genes found. Available: http://news.bbc.co.uk/1/hi/health/6252988.stm. Last accessed 05/07/2012.
[23] BBC. (2007). 'Silent' brittle bone genes found. Available: http://news.bbc.co.uk/1/hi/health/6252988.stm. Last accessed 05/07/2012.
[24] BBC. (2006). Fatal brittle bone gene is found. Available: http://news.bbc.co.uk/1/hi/health/6212103.stm. Last accessed 05/07/2012.
[25] Howard Hughes Medical Institute. (2006). Genetic Mutation Explains Form of Brittle Bone Disease. Available: http://www.hhmi.org/news/pdf/lee20061019.pdf. Last accessed 01/12/2012.

		Parent 1	
		F	**f**
Parent 2	**F**	FF	Ff
	f	Ff	ff

This is illustrated in the punnet square above, where F is a healthy copy of the dominant allele and f being the recessive allele with a defect. If the child has two FF alleles, then the child will be healthy and not a carrier of the disorder. If the child has Ff then the child would be a carrier of the defect like the parents but still healthy. Ultimately, if the child had ff alleles, then the child will have OI.

Diagnosis and Prognosis

In order to fully understand the impact of OI, it is essential to understand the difficulty in reaching a diagnosis of it because without a correct diagnosis treating it is clearly very difficult. This difficulty arises from the varying genetic mutations which can occur causing the condition as outlined previous. Even with the current method of diagnosis available as Tulane University found:

"Because [genetic] mutations have not been detected in every patient with a clinical diagnosis of OI, these tests can *not* be used to conclude that an individual does not have OI"
Matrix DNA Diagnostics Website (Tulane University)[26]

In attempts to cure the condition, researchers need to have individuals with the condition on whom they are able to trial some of these treatments out on. However, not all individuals with OI are identified. As aforementioned, in America the estimated prevalence of OI is somewhere in the region of 20,000 to 50,000[27] out of a current population of 300 million and growing but that number is merely an estimate; a more accurate method of identifying the best method of diagnoses is required in order to make real head way in reaching a cure. Someone with OI has a 50% chance of passing on the condition to their offspring, while the gene that causes the mutation will be the same in the child, the symptoms presented may be milder or more severe. Also there is a chance that the offspring may have a completely new gene mutation but the chances of that occurring have been reported to be no greater than that happening to any member of the general population[28]. Diagnosis of OI can be done prenatally; these procedures are typically carried if one of the parents is a sufferer of OI.

1) Ultrasound is used to examine the foetus for bowing of legs or arm, shorting or any other bone anomalies which are consistent with OI. This method is most helpful

[26] OI Foundation. (2012). Diagnosis and Testing. Available: http://www.oif.org/site/PageServer?pagename=DiagTest . Last accessed 05/02/2013.
[27] The National Institutes of Health Osteoporosis and Related Bone Diseases. (2012). Fast Facts on Osteogenesis Imperfecta. Available: http://www.oif.org/site/PageServer?pagename=fastfacts. Last accessed 05/07/2012.
[28] Dr. Deborah Krakow. (2002). OI Issues: Pregnancy Considerations for women with OI. Available: http://www.oif.org/site/PageServer?pagename=PregOI. Last accessed 05/02/2013.

when trying to diagnose more severe forms of OI. Foetuses with mild OI show very little evidence of fractures or deformity before birth. Ultrasound is a non – invasive, low risk procedure. Ultrasound can typically pick up if a foetus is displaying symptoms of OI between 13 to 16 weeks of conception.

2) Chorionic villus sampling (CVS) is a test carried out during pregnancy to detect specific abnormalities in a foetus. A sample of cells is taken from the placenta and tested for genetic defects. It is carried out between 10 to 13 weeks of conception. This method of diagnosis carries the risk of miscarriage or birth defects in the baby; this risk is heightened if this procedure is carried out before week 10 of the pregnancy[29].
3) Amniocentesis is a diagnosis test carried out to assess whether the foetus could develop, or has developed, an abnormality or serious health condition. This process is usually carried out between weeks 15 to 20 of the pregnancy. A needle is used to extract a sample of the amniotic fluid. Amniotic fluid contains cells shed from the foetus that can be examined and tested for a number of conditions. As with CVS, this is an invasive procedure and has an estimated miscarriage rate of 1/100[30].

If however a child starts to display symptoms after birth than there are a few methods of diagnosis which can be carried out.

First, is a Collagen Biochemical Test, this procedure is sometimes referred to as a 'Skin Punch Biopsy' test. This looks at the collagen proteins made by skins cells (fibroblasts) and requires a dermal punch biopsy sample, a small circle of skin. This test looks for evidence of abnormalities in the folding of the collagen. Moreover, the test does not come up with the specific mutation which causes the condition and would require collagen molecular testing[31].

Secondly, there is Collagen Molecular Testing also referred to as DNA Analysis which looks directly for the mutation in collagen by sequencing at the gene level. This requires either a blood sample or skin sample.

Finally, there are ways for testing for recessive OI which look for defects in the genes controlling CRTAP or P3H1, which requires a skin biopsy. To achieve this biochemical and molecular tests are used but, when testing for recessive OI the tests look for different characteristics. The biochemical test examines indirectly for the biochemical effects of mutations in CRTAP and LEPRE1 on collagen. The absence of either of these proteins again leads to over-modification of collagen synthesized by skin cells in culture. Molecular testing in this context determines the specific gene mutations by direct sequencing of the coding regions of the two genes and the adjacent non –coding regions[32]. Regulation of other genes produces protein called repressive protein which will turn off or turn on another gene with protein.

[29] NHS. (2012). Chorionic villus sampling . Available: http://www.nhs.uk/Conditions/Chorionic-Villus-Sampling/Pages/Introduction.aspx. Last accessed 05/02/2013.
[30] NHS. (2012). Amniocentesis. Available: http://www.nhs.uk/Conditions/amniocentesis/Pages/Introduction.aspx. Last accessed 05/02/2013.
[31] NICHD. (2012). Dominant OI. Available: http://www.oiprogram.nichd.nih.gov/dominant.html . Last accessed 05/02/2013.
[32] NHID. (2012). Recessive Parental Status. Available: http://www.oifprogram.nichd.nih.gov/recessive.html#parentalstatus. Last accessed 05/02/2013.

What are the current treatments in place for sufferers of Osteogenesis Imperfecta?

As of yet a cure for OI has not been discovered and as such, the treatments currently being administered focus on managing the symptoms of OI, preventing further complications and developing and maintaining bones mass and muscle strength[33].

Surgical Treatments

Before the introduction of pharmaceutical intervention into OI, surgical intervention was routinely used to manage symptoms. This came as a result of failures of initial attempts carried out by Leon Root MD in 1969 who was the principal investigator in some of the first clinical studies into children with OI. Some of his first attempts involved attempts to strengthen the bones of those with OI by administering magnesium sulphate, which was felt would alter the action of enzymes OI patients produce which he believed to be part of the disease process[34]. Following clinical trials, however, Magnesium Sulphate was ruled out as a treatment for this condition as it had several side effects ranging from general side effects to metabolic and respiratory issues[35]. Other therapies which failed to yield any effective therapies from this era include hormone therapy, steroids and high doses of Vitamin C and Calcium. The surgical methods which Dr Root and his colleagues looked into involved a procedure which segmented bones and then inserted long rods through the segments.

[36]

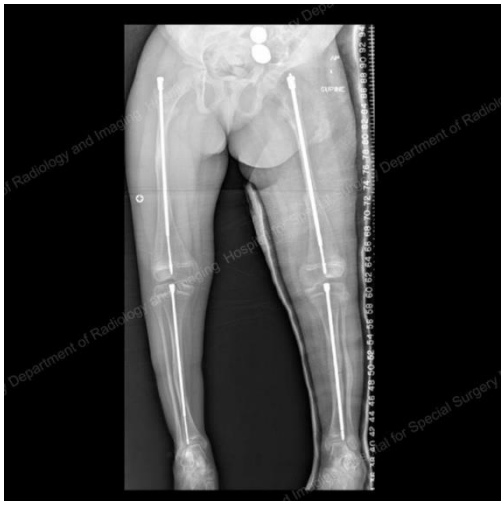

Figure 3 Example of rodding

[33] Campbell M Gold. (2004). Osteogenesis Imperfecta: An Overview. Available: http://campbellmgold.com/archive_health/osteogenesis_imperfecta.pdf. Last accessed 05/07/2012.

[34] Daniel W. Green, MD, MS, FAAP, FACS. (2011). Osteogenesis Imperfecta: A Multidisciplinary Approach to Treatment in Children. Available: http://www.hss.edu/conditions_osteogenesis-imperfecta-approach-to-treatment.asp. Last accessed 05/07/2012.

[35] Medha Godbole. (2011). Magnesium Sulfate Side Effects. Available: http://www.buzzle.com/articles/magnesium-sulfate-side-effects.html. Last accessed 05/03/2013.

[36] HSS. (2012). Fassier Duval Rods. Available: http://www.hss.edu/images/articles/fassier_duval_rods_OI_3_original.jpg . Last accessed 09/02/2013.

The process is not recommended to all individuals with OI; it is not normally a procedure to be carried out on those who have mild forms of OI. It is typically used in situations where either the individual has:

- Curved bones
- Broken certain bones repeatedly over a period of time

People with more severe types of OI may opt for this treatment if they were to have consistent fractures, as they may feel it to be a way of increasing their quality of life rather than being treated by screws and plates. This also reduces the treatment time for the individual as rodding will reduce number of fracture as it will provide support and strength to bones. Also, this will reduce the time of recovery when compared to plates and screws as you have to factor in the time for them being put in and the period of recovery after their removal.

When going in for rodding procedures there are two main types of rod which can be used:

1) Non Telescopic rods – These rods are used in children who have short and thin bones and they support the full length of the long bones. This method comes with the disadvantage of the length of the rod being fixed therefore, as the child grows up it could mean that further surgery would be needed to adjust the rod or to replace the rod.

[37]

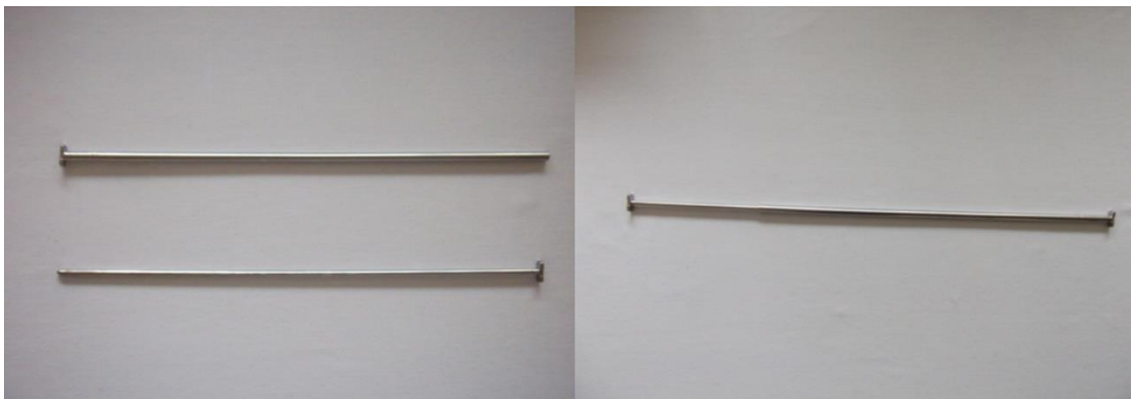

Figure 4 Non - Telescopic Rod

2) Telescopic rods – These types of rods are more adjustable as they grow as the bone grows, this takes away the need for surgery as often. With telescopic rods they are essentially smaller rods within a larger hollowed rod. However due to this fact they are larger than the non-telescopic rods and are therefore only used in individuals with larger bones i.e. teenagers and adults who have more developed bones. [38]

[37] The Journal of Bone and Joint Surgery. (2011). Non - Telescopic Rods. Available: http://jbjs.org/data/Journals/JBJS/4342/1994fig1.jpg. Last accessed 09/02/2013.
[38] Peter Smith, M.D. (2011). Rodding Surgery. Available: http://www.oif.org/site/PageServer?pagename=Rodding. Last accessed 15/01/2013.

[39]

Figure 5 Telescopic Rods

As times have progressed a newer type of rod is being used, the Fassier Duval rod system; it was approved in the US in 2005 and it was designed and developed by orthopaedic consultants who had extensive experience with treating individuals with OI. This has shown signs of being a less invasive type of surgery compared to the aforementioned types of rodding, as it provides quicker recovery times as well.

[40]

Figure 6 Fassier Duval Rods

The Fassier – Duval rodding system is more effective than the other two types of rodding previously mentioned as it can be seen as a longer term implant. And, it has been said to have a lower failure rate and hence, replacement is said to be less frequent and can be replaced in the event of a fracture, bending of the rod, in case of other complications or when the OI sufferer has reached skeletal maturity[41].

All these surgical interventions came from a core belief that the most important goal in the orthopaedic arsenal in treating OI was best directed to minimise deformities and encouraging normal function[42] of individuals with OI. Additionally, rodding is certainly one of the best methods in achieving both of these goals; in the first instance rodding does indeed minimise deformities as through surgery, the rod encourages bone to grow more in line than without it. Furthermore, rodding provides more structure and strength to the

[39] Orthopaedic Implants. (2010). Telescopic Rods. Available: http://www.orthopaedic-implants.com/external-fixators/external-fixation-system/images/239.010_telescopic-rod_SS.jpg . Last accessed 15/01/2013.
[40] CA. (2011). Fassier Duval Telescopic IM System. Available: http://www.ca.all.biz/img/ca/catalog/11858.png. Last accessed 15/01/2013.
[41] Pega Medical. (2006). Fassier Duval Telescopic IM System FAQ. Available: http://www.pegamedical.com/pdf/fassier-faq-surgeons-en.pdf. Last accessed 12/03/2013.
[42] Primorac et al. (2001). Osteogenesis Imperfecta. Croatian Medical Journal. 42 (1), 393-415.

affected bones which allows the individual to have a higher chance to achieve greater mobility and independence.

Pharmaceutical Treatments

In line with new surgical techniques as a way of managing OI, current management revolves around the use of pharmaceutical intervention to try and reduce the symptoms of OI. One of the main pharmaceutical treatments of OI is the administration of Bisphosphonates. Bisphosphonates are used to prevent the loss of bone mass and typically are used to treat diseases such as Osteoporosis[43]. The name Bisphosphonates comes from the fact that they have two phosphonates and assist is the increased coordination of calcium ions. The administration of bisphosphonates bind calcium molecules together and as the largest store of calcium is accumulated and stored in the bones it results in higher concentration of calcium in the bones[44]. There are various different types of Bisphosphonates which have been trialled and eventually put in place to treat patients with OI. One of the most commonly used Bisphosphonate drug is known as Pamidronate. Pamidronate is a drug administered intravenously and it is designed to inhibit bone resorption, which is the natural, on-going process of bones being destroyed by osteoclasts in order to get rid of tissues which no longer function well.

Bone resorption happens as a part of a process known as bone remodelling, which is basically the building, the breaking down of and the rebuilding of dynamic bone tissues. Osteoclasts are multi nucleated cells originating from bone marrow and break down bone tissue; they liberate minerals and other molecules stored within the bone matrix. The bone tissue acts as a repository for vital minerals such as Calcium Phosphate. Cells, known as Osteoblasts, are responsible for building new bone tissues that are associated with blood vessels. Once these osteoblasts are activated they produce they produce the organic compound of bone which is known as osteoid, which is predominately made of collagen. Minerals then start to crystalize around the collagen structure and form hydroxyapatite, which is the major inorganic component of bone and contains Calcium Phosphate[45].

Studies of bones of patients with OI have suggested that abnormal activity of osteoclasts and osteoblasts contribute towards greater bone fragility. Imperfect bones are more susceptible to the osteoclasts, so OI bone is resorbed more quickly than new bone. Additionally when the osteoblasts begin to reform new bones, they also produce imperfect bones. As a result, the mutation in the collagen causes the osteoblasts to become less efficient and produce less bone. This leads to the fragile bones which are the characteristics of OI[46].

Through inhibiting bone resorption, it allows the individuals bones not to be forming newer and greater imperfect bones and therefore allowing the individual a better chance to

[43] NOS. (2013). Drug Treatment - Bisphosphonates. Available: http://www.nos.org.uk/page.aspx?pid=264&srcid=234. Last accessed 15/03/2013.
[44] Dr Tim Kenny. (2011). Bisphosphonates. Available: http://www.patient.co.uk/health/bisphosphonates. Last accessed 15/03/2013.
[45] Amgen. (2012). Osteoblasts and Osteoclasts. Available: http://www.youtube.com/watch?v=78RBpWSOl08. Last accessed 09/02/2013.
[46] OI Foundation. (1998). Results of Study on Pamidronate Use in Children with OI. Available: http://www.oif.org/site/PageServer?pagename=Pamidronate. Last accessed 05/07/2012.

reduce their fragility. In addition, as the bone resorption rate reduces, it also slows down the rate at which the osteoblasts become less efficient at what they do therefore, again slowing down the rate at which the individuals' bones are becoming increasingly fragile.

The use of Pamidronate to treat patients has shown fracture incidence decreasing as well as showing increases in Bone Mineral Density[47] and in OI patients with more severe types of OI, it has shown to assist in subsiding bone pain which is often experienced. This subsidence of bone pain has led to increased mobility and improvement in muscle strength. Also, this medication has also been noted as contributing to an increase in quality of life experienced by those with OI after having the medication. There have also been cases where after receiving the treatment, those previously completely dependent on the use of a wheelchair were becoming increasingly more mobile with the aid of walking aids[48].

This was backed up by Glorieux's group in 2001 that were treating children with severe OI with this treatment regime. In analysing data of their first 30 cases who were treated for a time period of between 1-4 years and were having the treatment administered in 4-6 month cycles firstly showed a reduction of an average of 1.7 fractures per year in these children confirmed by x – rays. Furthermore, in 16 of the 30 children their dependence on mobility aids such as walkers and crutches were reduced and all of the children reported that they experience relief in their chronic pain and fatigue levels.[49] This study also came to the conclusion that the response to Pamidronate showed a faster and more pronounced effect on children under the age of 2 than on older children[50]. Finally, it was shown that not only did the Pamidronate increase lumbar Bone Mineral Density like expected, it also seemed to protect bone integrity.

However, there has been some speculation over the long term effects of Pamidronate on the OI patients, concerns have been raised over the quality of bones being affected by the prolonged use of it. This has arisen from the knowledge that Pamidronate suppresses bone turnover during the length of the treatment, leading to concerns this decreased remodelling may prevent repair of micro damage to the bone. Essentially, any small injuries or hairline fractures which are experienced by OI sufferers will not recover as a result of prolonged use of the drug. It has also been put forward that the continued use of bisphosphonate pamidronate can impair the bone modelling process associated with fracture healing[51]. There have also been concerns over individuals receiving this drug may develop Osteonecrosis of the jaw[52] which is can cause lesions (a wound or injury[53]) to

[47] Primorac et al. (2001). Osteogenesis Imperfecta. Croatian Medical Journal. 42 (1), 393-415.
[48] P.J Roughley, F Rauch, F.H Glorieux. (2003). Osteogenesis Imperfecta – Clinical and Molecular Diversity. European Cells and Materials. 5 (1), 41-47.
[49] Primorac et al. (2001). Osteogenesis Imperfecta. Croatian Medical Journal. 42 (1), 393-415.
[50] Plotkin H, Rauch F, Bishop NJ, Montpetit K, Ruck – Gibis J, Travers R, et al. (2000). Pamidronate Treatment of severe Osteogenesis Imperfecta in children under three years of age. The Journal of Clinical Endocrinology and Metabolism. 85 (1), 1846-50.
[51] Burr, 2002; Parfitt *et al,* 1996; Srivastava and Alon, 1999
[52] WebMD. (2005). Drugs & Medications - Pamidronate. Available: http://www.webmd.com/drugs/drug-11598-Pamidronate+IV.aspx?drugid=11598&drugname=Pamidronate+IV. Last accessed 20/03/2013.
[53] The American Heritage® Medical Dictionary. (2007). Lesions . Available: http://medical-dictionary.thefreedictionary.com/lesion. Last accessed 20/03/2013.

develop exposing bone[54]. The chances of this occurring are exacerbated if there is poor dental hygiene, or the individual has poorly fitted dentures or certain dental procedures[55]. All these increase risks of the individual getting osteonecrosis of the jaw as the bacteria forming and infections coming as a result of this which causes lesions to occur and the osteonecrosis reduces the chances of this healing. As a way of trying to minimise these long term impacts of receiving Pamidronate, the patient receiving the course of treatment has DEXA scans yearly to monitor the bone density and the treatment will be stopped once the consultant in charge decides the bone density is at a suitable level for the individual's age and condition[56].

Growth Hormone to augment growth and collagen production

Another approach to therapy of OI is through using growth hormones. Growth hormones, according to Joan Marini reports that it increases stature, increase volume in the thorax and abdomen, as well as increases in bone quality. She also reported that children with type 4 were the best respondents to this treatment with 50% having a strong, sustained response over 2 years. In adult trials with growth hormones, the greatest improvement occurred after several years of treatment[57].

Bone Marrow Transplantation

Bone marrow transplantation was a method suggested to treat suffers with severe OI, specifically type 3. This was trialled in St. Jude Research Hospital, Memphis and Horowitz (1999) published the results of the trial and reported that:

> "The authors transplanted bone marrow, taken from siblings, into three children who had suffered multiple bone fractures and deformity from this heritable disease. They describe improvements in bone mineral density, better growth and fewer fractures, all occurring during a relatively brief period after marrow transplantation"[58]

Bone marrow is "a substance found in the cavities of bones, especially the long bones and the sternum (breast bone). The bone marrow contains those cells that are responsible for the production of the blood cells (red blood cells, white blood cells, and platelets).[59]" So, by replacing bone marrow from the same gene pool, the hope was that it

[54] Sundeep Khosla,David Burr, Jane Cauley. (2007). Bisphosphonate-Associated Osteonecrosis of the Jaw: Report of a Task Force of the American Society for Bone and Mineral Research. Journal of Bone and Mineral Research. 22 (1), 1479-91.
[55] WebMD. (2005). Drugs & Medications – Pamidronate IV Precautions. Available: http://www.webmd.com/drugs/drug-11598-Pamidronate+IV.aspx?drugid=11598&drugname=Pamidronate+IV. Last accessed 20/03/2013.
[56] Oxford Paediatric and Adolescent Rheumatology Centre. (2007). Pamidronate Treatment - Parents Information Sheet. Available: http://www.noc.nhs.uk/oxparc/information/documents/pamidronate.pdf. Last accessed 25/03/2013.
[57] Joan Marini, MD, PhD. (2006). New Research and Clinical Strategies in OI. Available: http://www.oif.org/site/DocServer/2006sciencemeetingsummary.pdf?docID=3441. Last accessed 30/01/2013.
[58] Edwin M Horwitz et al. (2001). Clinical responses to bone marrow transplantation in children with severe osteogenesis imperfecta. Blood. 97 (5), 1227-1231.
[59] The Gale Group. (2008). Bone Marrow. Available: http://medical-dictionary.thefreedictionary.com/bone+marrow. Last accessed 08/03/2013.

would reduce fracture rate and the other benefits mentioned. Statistical association has shown links between between poor bone density and higher probability of fracture and as people with OI have relatively low bone density the transplant should increase it.

The three participants in the study all showed accelerated growth rates prior to the treatment, as before they were below the average height for their respective ages. Secondly, they all demonstrated increases in their total body bone mineral count showing that the treatment had increased density of their bones increasing the strength of them. Finally their fracture rates all went down from a median of 10 during a period of 6 months prior to the treatment to a consistent median of 2 which carried on for years after the initial treatment.

However due to the nature of this treatment there are risks the patients who participated in the trial developed sepsis, transient pulmonary insufficiencies, hygroma (a build - up of fluid in parts of the body) as well as GVHD (Graft Versus Host Disease). GVHD is a common complication in treatments which involve tissue transplants like in bone marrow transplant. The problem with this is that the immune cells, the white blood cells, from the tissue, i.e. the bone marrow, recognise the host as 'foreign' and tries to attack the host's body cells to try and get rid of it[60]. While the chances of this happening with this process should be reduced as they are from the same gene pool, the complications are still there. While there were all treated without complications it does have more side effects than Pamidronate.

This trial was merely a pilot and has provided solid foundation for future trials to be carried out on the subject and the authors of this paper concluded that more complete knowledge of mesenchymal cell biology is needed.

[60] Lee SJ, Vogelsang G, Flowers ME. (2003). Chronic graft-versus-host disease. Biology of Blood and Marrow Transplantation. 9 (4), 215-33.

What are the current research trials being conducted for those with Osteogenesis Imperfecta?

There are numerous current trials being conducted in attempts to try and find a cure or better manage the symptoms of OI. Whole Body Vibrations is one of the techniques currently being trialled.

Whole Body Vibrations

Whole Body Vibrations is something which consultants at Birmingham Children's Hospital are attempting. The study aims to see whether this technique works in making muscles stronger. There is muscle deterioration in people with OI as due to their fracture rate they never have time to rebuild muscle mass and also during immobilization after surgery or during recovery phase leads to depletion of muscle mass[61] and as part of the condition the muscles they do develop are weaker than the average human. This technique has been shown to work in children and young people who have weak bones for other reasons but has never been tested on those with OI in the UK. This technique arose from the rather late realisation that beside surgical and pharmaceutical intervention, physiotherapy is felt to be the most important in achieving improvement of mobility and independence. As the writers of the "Results of a prospective pilot trial on mobility after whole body vibration in children and adolescents with Osteogenesis Imperfecta" (2007) commented that those two factors should be the endpoint of all therapeutic procedures in these patients[62] [63]. Whole Body Vibrations involve training on a machine known as a whole body vibrations platform.

[64]

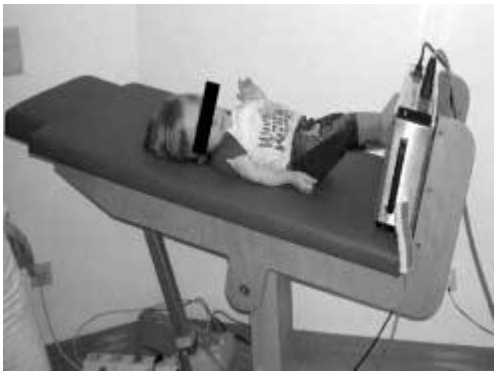

Figure 7 The Cologne Standing-and-Walking-Trainer powered by Galileo

[61] Oliver Semier, Oliver Fricke, Katharina Vezyroglou, Christina Stark, Angellka Stabrey, Eckhard Schoenau, Children's Hospital, University of Cologne. (2008). Results of a prospective pilot trial on mobility after whole body vibrations in children and adolescents with Osteogenesis Imperfecta. Clinical Rehabilitation . 22 (1), 387-394.

[62] Gerber L, Binder H, Weintrob J et al. . (1990). Rehabilitation of Children and Infants with Osteogenesis Imperfecta. A program for ambulation. Clinical Orthopaedics. 251 (1), 254-62.

[63] Binder H, Conway A, Hason S et al. (1993). Comprehensive rehabilitation of the child with Osteogenesis Imperfecta. American Journal of Medical Genetics. 45 (1), 265-69.

[64] O. Semler, O. Fricke, K. Vezyroglou, C. Stark, E. Schoenau. (2007). Preliminary results on the mobility after whole body vibration in immobilized children and adolescents. Journal of Musculoskeletal and Neuronal Interactions. 7 (1), 77-81.

The principle behind whole body vibrations is that the vibrations at low frequencies will activate and induce changes in the muscular system[65], this is hoped to increase the muscle force and due to the link between muscle force and bone strength[66] it is hoped that this method will allow the symptoms of OI to be reduced. The participants are asked to stand on the vibrating platform twice a day for nine minutes at a time and this test would last for 6 months[67]. Dr Hogler commented the medical outcomes his team wanted to observe from this technique is in the first instance improved mobility as well as improve bone structure, mass and density[68]. This will be measured by a 6 minute walk test and by measuring on a force platform. Force platforms are measuring instruments like the one below and they measure the ground reaction force that is, the force exerted by the ground to the individual who is standing on it, in order to assess the individuals balance, gait and other measurements needed for test[69].

70

Figure 8 Force Platform

A similar test was run in Cologne, Germany in 2007. This pilot test had 14 children participants with a range of individuals with Type 1, 3 and 4 Osteogenesis Imperfecta and the results from their participants are summarised in the table below:

[65] Rittweger J, Mutschelknaus M, Felsenberg D. (2003). Acute changes in neuromuscular excitability after exhaustive whole body vibration. Clinical Physiological Function Imaging. 23 (1) 81-86.
[66] Rauch F, Sceonau E. (2001). The developing bone: slave or master of its cells and molecules?. Paediatric Research, 3 (1), 309-14.
[67] Wellcome Trust Clinical Research Facility. (2011). Information Sheet for Children ages 13-18 years with Osteogenesis Imperfecta - Whole body vibrations as an osteogenic treatment for children with Osteogenesis Imperfecta with limited mobility: A randomized controlled pilot trial. Available: https://mail-attachment.googleusercontent.com/attachment/u/0/?ui=2&ik=e694424af3&view=att&th=13b1cda3862658a1&attid=0.1&disp=inline&safe=1&zw&saduie=AG9B_P8V7vzQKNNJkXBLgyXURJBu&sadet=1363788456450&sa. Last accessed 19/11/2012.
[68] Dr Wolfgang Hogler, Clinical Lead, Dept of Endocrinology & Diabetes, Consultant Paediatric Endocrinologist, Birmingham Children Hospital
[69] Flemming Bonde-Petersen. (1975). A simple force platform. European Journal of Applied Physiology. 34 (1), 51-54.
[70] A - Tech Instruments Ltd. (2008). Force Platform. Available: http://www.a-tech.ca/series.php?id=848. Last accessed 15/03/2013.

Test Case	Initials	Results
1	R.J	Independent transfer from and in wheelchair, start walking with crutches.
2	Ö.E	Able to reach standing position on her own.
3	L.M	Increase of walking distance.
4	M.A	Increase of walking distance with walker.
5	M.E	Transfers independently from lying to sitting.
6	P.C	More trunk rotation while sitting.
7	H.J	Getting dressed and undressed independently.
8	Sch.M	Increase of walking distance (7.5m -> 20m).
9	vH.J	Reaches standing position without help.
10	N.B	Independent transfer sitting and standing increased handgrip.
11	D.A	Walking becoming safer and more symmetrical.
12	H.T	Increase of walking distance.
13	L.N	Transfer from dorsal position to sitting position without support.
14	F.J	Takes more support on his forearms. [71][72]

Although this is a fairly small test sample, the results are relatively encouraging as all the participants showed signs of improvements, even if they were relatively small changes. Obviously as most individuals' experienced different benefits, it is difficult to say what the definitive effects of the vibrations technique is but it is an encouraging finding and hopefully the results from the Birmingham trial will develop the picture more.

[71] O Semler, B Mueller, J Bartylla, E Schoenau. (2007). Whole Body Vibrations In Children With Osteogenesis Imperfecta. Journal of Musculoskeletal and Neuronal Interaction. 7 (1), 77-81.
[72] O Semler, B Mueller, J Bartylla, E Schoenau. (2007). O29: Whole Body Vibrations in Children with Osteogenesis Imperfecta – Oral Abstracts. Available: http://amplitudevibration.com/images/uploads/O29_Whole_Body_Vibration_In_Children_With_Osteogenesis_Imperfecta.pdf. Last accessed 20/03/2013.

What are future plans for research trials for those with Osteogenesis Imperfecta?

Joan Marini outlined three main types of Gene therapy as a way of trying to manage a condition such as OI in her book on Osteogenesis Imperfecta[73];

1) Mutation Suppression – As type 1 is the least severe type of OI, mutation suppression endeavours to supress the mutant gene in the other types through the use of hammerhead ribozymes to make the individual have biochemically type 1 OI[74]. This reduces symptoms and greatly improves life quality but this method of therapy is still in development using animal models and is yet to be trialled on patients with OI.
2) Replication of natural example of mosaic carriers – Mosaic carriers are individuals who have the condition but are clinically normal due to the proportionality of normal collagen and defective collagen cells they have[75]. This method was trialled in a human foetus in utero using foetal mesenchymal stem cells but the clinical outcomes of this were complicated as the during infancy the child was treated with bisphosphonates, but there was some claimed improvements in growth and in total body bone mineral content[7677]. More research is to be carried out into this type of genetic therapy.
3) Cell Transplantation – This method involves the targeting of the COL1A1 and COL1A2 gene, typically the defective gene in type 1-4 of OI, using Adeno – associated vectors in adult mesenchymal cells. This method at the time of her writing was found to only have a success rate of less than half of 1%, where success if defined as normal collagen being produced by the targeted cells. This is the method is being developed and looked at by Ali and Hasan below and I explore the detail further[7879].

[73] Joan Marini, MD, PhD. (2010). Chapter 16: Osteogenesis Imperfecta. Available: http://www.endotext.org/parathyroid/parathyroid17/parathyroid17.pdf. Last accessed 31/01/2013.
[74] Dawson PA, Marini JC . (2000). Hammerhead ribozymes selectively suppress mutant type 1 collagen mRNA in osteogenesis imperfecta fibroblasts. Nucleic Acids Research. 28 (1), 4013-20.
[75] Cabral WA, Marini JC . (2004). High proportion of mutant osteoblasts is compatible with normal skeletal function in mosaic carriers of osteogenesis imperfecta. The American Journal of Human Genetics. 74 (1), 752-60.
[76] Le Blanc K, Gotherstrom C, Ringden O, Hassan M, McMahon R, Horwitz E, Anneren G, Axelsson O, Nunn J, Ewald U, Norden - Lindeberg S, Jansson M, Dalton A, Astrom E, Westgren M. (2005). Fetal mesenchymal stem - cell engraftment in bone after in utero transplantation in a patient with severe osteogenesis imperfecta. Transplantation. 79 (1), 1607-14.
[77] Horwitz EM, Gordon PL, Koo WK, Marx JC, Neel MD, McNall RY, Mull L, Hofmann T. (2002). Isolated allogeneic bone marrow derived mesenchymal cells engraft and stimulate growth in children with osteogenesis imperfecta: implications for cell therapy of bones. Proceedings of the National Academy of Science USA. 99 (1), 8932-37.
[78] Chamberlain JR, Deyle DR, Schwarze U, Wang P, Hirata RK, Li Y, Byers PH, Russell DW. (2008). Gene targeting of mutant COL1A2 alleles in mesenchymal stem cells from individuals with osteogenesis imperfecta. Molecular Therapy. 16 (1), 187-93.

Phlorotannin – Incorporated Mesenchymal Stem Cells

In 2012 Tehseen Fatima Ali and Tabinda Hasan made the next step in trying to find a cure for OI. Ali and Hasan took the gene therapy plan which involved bone marrow stem cells used by Horwitz and his colleagues from 1999 – 2000 and developed upon this initial idea and came up with the idea of utilising Phlorotannin – incorporated mesenchymal cells as a way of boosting cellular differentiation into becoming healthy bone forming cells[80]. Horwitz bone marrow stem cell treatment at the time was not backed by clinical support. Although the initially trials of this showed improvements in all the patients it was tried in, with patients showing an improvement in total bone mineral content and there was an increase in their respective growth velocity as well as reducing their fracture rates[81]. Ali and Hasan's thesis was also put forward by the *molecular therapy journal*, in which they stated the workings of the planned treatment as being:

"Isolating the mesenchymal cells from OI patients and inactivating their mutant collagen gene by adeno-associated virus (AVV) – mediated gene targeting, and deriving induced pluripotent stem cells (IPSCs) that were expanded and differentiated into mesenchymal stem cells (iMSCs). Gene –targeted iMSCs produced normal collagen and formed bone in vivo, but were less senescent and proliferated more than bone – derived MSCs……. These results demonstrate that the combination of gene targeting and iPSC derivation can be used to produce potentially therapeutic cells from patients with genetic diseases."[82]

83

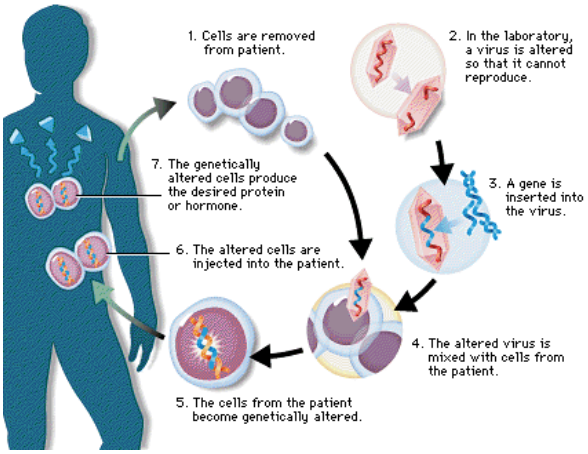

Figure 9 Main steps of Gene Therapy

[79] Chamberlain JR, Schwarze U, Wang PR, Hirata RK, Hankenson KD, Pace JM, Underwood RA, Song KM, Sussman M, Byers PH, Russell DW. (2004). Gene targeting in stem cells from individuals with osteogenesis imperfecta. Science. 303 (1), 1198-1201.

[80] Tehseen Fatima Ali, Tabinda Hasan . (2012). Phlorotannin-incorporated mesenchymal stem cells and their promising role in osteogenesis imperfecta. Journal of Medical Hypotheses and Ideas. 6 (2), 85-89.

[81] Horwitz E, Prockop D, Fitzpatrick L, Koo W, Gordon P, Neel M, Sussman M, Orchard P, Marx J, Pyeritz R, Brenner M. (1999). Transplantability and theraputic effects of bone marrow - derived stem mesenchymal cells in children with osteogenesis imperfecta. Nature Medicine . 5 (1), 309-13.

[82] Deyle DR, Khan IF, Ren G, Wang PR, Kho J, Schwarze U, Russell DW.. (2012). Normal Collagen and Bone Production by Gene Targeted Human Osteogenesis Imperfecta iPSCs. Molecular Therapy. 20 (1), 204.

[83] Human Genome Project. (2010). Gene Therapy. Available: http://dnainfo.wikispaces.com/Genetic+Therapy+(GT). Last accessed 20/03/2013.

The illustration above will help explain the process put forward by Ali and Hasan as well as by the *molecular therapy journal*:

1) Stage 1: The mesenchymal stems cells are extracted from the bone marrow of the individual with OI.
2) Stage 2: The virus which is used to stop the function of the extracted stem cells is known as Adeno Associated virus. This virus is used as it is a predictable virus and has the ability to integrate itself into the host cell at specific sites of the gene[8485]. Another attractive feature of using this virus in gene therapy is that it is a small virus which infects humans and is currently not shown to be responsible for causes any diseases and only causes a very mild response from the human immune system[86]. This makes is rather a favourable choice, as other methods of gene therapies have many undesired side effects as discussed previously and Ali and Hassan wanted to reduce the number of side effects.
3) Stage 3: This virus is combined with the gene for producing the defective collagen which inhibits the part of the gene which codes for the defect collagen and hence activating the gene for normal collagen production. In this step is where Ali and Hasan differ from Horwitz, as in this step they incorporated phlorotannins into the mesenchymal cells. Phlorotannins are found in brown algae and they say that it stimulates protein production, boosts calcification minerals and collagen synthesis[87]. Therefore not only in this process in the defective collagen corrected, there is a boost in the quality and quantity of collagen produced also increases in the strength of the bones of the patient.
4) Stage 4: This is then combined with the cells originally taken from the individual.
5) Stage 5: These cells are now genetically altered.
6) Stage 6: The altered cells are then injected back into the original patient into the bones.
7) Stage 7: The altered cells than starts producing normal collagen and starts creating more bone than the original mesenchymal stem cells were producing.

The reason for this working is that providing the affected host with the altered cells may allow a shift in the levels of balance between the synthesis of mutated and normal collagen

[84] Kotin RM, Siniscalco M, Samulski RJ, et al. (1990). Site-specific integration by adeno-associated virus. Proceedings of the National Academy of Sciences of the United States of America. 87 (6), 2211-5.

[85] Surosky RT, Urabe M, Godwin SG, et al. (1997). Adeno-associated virus Rep proteins target DNA sequences to a unique locus in the human genome. Journal of Virology. 71 (10), 7951-9.

[86] Grieger JC, Samulski RJ . (2005). Adeno-associated virus as a gene therapy vector: vector development, production and clinical applications. Advances in Biochemical Engineering/Biotechnology. 99 (1), 119-45.

[87] Tehseen Fatima Ali, Tabinda Hasan . (2012). Phlorotannin-incorporated mesenchymal stem cells and their promising role in osteogenesis imperfecta. Journal of Medical Hypotheses and Ideas. 6 (2), 85-89.

chains and thereby converting a severe OI phenotype into a less severe one[88]. A statement which was supported all the way back in 2001;

"Effects of OI cells can be neutralized by the presence of normal cells hence the introduction of normal cells into an individual with OI, the severity of bone disease would be reduced. The introduction of normal cells in such environment would rapidly populate the bone with cells having a normal proliferate rate and making a normal matrix, which would out produce the resident OI cells. OI bone cells can be engineered in vitro to correct the primary defect in type 1 collagen production and then reintroduced into the affected host.[89]"

- Primorac et al

The addition of phlorotannins assists in shifting this balance as it increases the levels of normal collagen produced and strengthens the bones of the individual. This also comes with less inherent risks as the phlorotannins are natural extracts and not man made, it should come with minimalistic side effects.

This method has only been shown to work in laboratories at present and is yet to be trialled on individuals with OI.

And finally, although gene therapy has the potential to increase the synthesis of type 1 collagen in mild variants and to correct mutations. Although in severe variants, there are a greater number of technical difficulties to overcome[90]

[88] Horwitz E, Prockop D, Fitzpatrick L, Koo W, Gordon P, Neel M, Sussman M, Orchard P, Marx J, Pyeritz R, Brenner M. (1999). Transplantability and theraputic effects of bone marrow - derived stem mesenchymal cells in children with osteogenesis imperfecta. Nature Medicine . 5 (1), 309-13.
[89] Primorac et al. (2001). Osteogenesis Imperfecta. Croatian Medical Journal. 42 (1), 393-415.
[90] Kocher M.S, F. Shapiro . (1998). Osteogenesis Imperfecta. Journal of the American Academy of Orthopaedic Surgeons. 6 (4), 225-36.

Conclusion

As my report has shown there are a few potential treatments and therapies for OI. Through looking at how treatment and therapies have developed, especially in the past two decades is a good indicator to the future of finding a definitive cure for OI. Whole Body Vibrations has shown marginal but positive effects in all the cases trialled in Cologne and the trial at Birmingham Children Hospital will hopefully reflect that.

Also the cell transplantation as proposed by Ali and Hasan is very hopeful and the theory behind it is very solid, while the success rate in humans is less than 1%, there is still time for it to be developed. In this report though I have only looked at treatments and therapies for the dominant type of OI, types 1-4, there are still treatments and therapies yet to be found for the recessive types such as type 7 and 8 caused by CTRAP and LEPRE1. We cannot definitively say a cure for OI has been found until all 8 types of OI can be treated and cured effectively.

Obviously in trying to achieve this goal there are a few barriers which need to be overcome. First of these barriers comes in the form of attracting funding into medical research for Children and Young people. Statistics have shown that there is a significantly less spent on children and young people research than there is on adult research. Currently, only 3% of all funding for research is being placed into children and young people research[91]. It is important to achieve a greater level of funding to be placed in children and young people research as my report has shown the majority of complications present themselves in childhood and as such it is ever more increasingly important that intervention is put in place as soon as possible in order to minimise symptoms and further complications.

And as Scott Paul identified there are 4 further barriers which are limiting the progress of research into OI treatments and therapies:
"1) It is difficult to put the proper binding techniques in place (therapists know what each patient is doing)
2) Using a control group may not be good medicine (can we justify NOT providing physical therapy?)
3) There are multiple side effects impacting growth and development
4) There are many variations in administration of treatment."[92]

Each of Paul's points come with equal validity. His first point has greatest validity when it comes to trialling new therapies and treatments on more of an international level as getting that level of coordination between the lead on the trial and the therapist and hospitals the treatment has been devolved to is difficult at this current stage, therefore to reduce this as a barrier communication needs to be strengthened between all parties involved. To his second point, I believe to be the most poignant as to get a fair result you need to have a group which doesn't get the trial treatment/ therapy but in doing this you

[91] Helen Budge, Clinical Associate Professor and Reader in Neonatology, Faculty of Medicine & Health Sciences, University of Nottingham
[92] Scott Paul, MD. (2006). New Research and Clinical Strategies in OI. Available: http://www.oif.org/site/DocServer/2006sciencemeetingsummary.pdf?docID=3441. Last accessed 30/01/2013.

are stopping them from receiving other treatments such as the whole body vibrations, the patients have to stop receiving Pamidronate up to a year before they start the trial. Now this can have detrimental effects to the individual especially if the whole body vibration does not show positive improvements. This third point depends upon if the benefits carried by receiving the treatment have more benefits than the demerits bought on by the side effects. His final point is true with any new treatments, again down to the level of communication. If all these moral questions posed by question 2 and 3 and the communication issues outlined in point 1 and 4 can be effectively managed than there may be a possibility that the speed at which we achieve progress occurs will speed up.

Now, returning back to the initial question that I posed, 'Will there ever be a cure for Osteogenesis Imperfecta?'. I think the evidence I have provided shows good progress being made but in order to put a time frame on this, the best method to do this would be to compare it with another genetic condition and compare the progress in both in order to analyse if the speed at which progress is occurring for OI is on the same level as other genetic conditions or if it is on a slower track to reaching the final goal. Cystic Fibrosis is a "is a life-shortening inherited disease, affecting almost 10,000 people in the UK.[93]" People with CF have their lungs and digestive systems clogged with mucus as the gene which regulates the movement of salt and water in and out of cells is defective which makes it difficult for those with CF to breathe and to digest food[94]. As with OI, a cure for CF has not yet been found and the research and therapies have all been surrounded regarding improving quality of life as well as life expectancy. I believe this to be a good condition to which to compare OI to in order to estimate the timescale for which a cure for OI may be found.

Below you can see a timeline of all the major research breakthroughs in regards to CF, courtesy of timetoast[95]:

Event Date:	Event Title:
1st Jan, 1938	**First Comprehensive Medical report written about CF**
4th Feb, 1955	**CF Research goes National**
16th Mar, 1962	**Predicted survival age is 10 years old**
18th Sep, 1962	**30 CF Care Centres Open**
8th Jun, 1978	**More than 100 CF Care Centres open**
16th Mar, 1980	**Research Program is created**
20th Mar, 1988	**First CF Pharmacy**
10th Nov, 1989	**A defective gene is found.**
25th Oct, 1993	**Gene Therapy trials begin**

[93] CF Trust. (2012). About cystic fibrosis. Available: http://www.cftrust.org.uk/about-cf.aspx. Last accessed 30/03/2013.
[94] CF Trust. (2012). What is cystic fibrosis?. Available: http://www.cftrust.org.uk/about-cf/what-is-cystic-fibrosis.aspx. Last accessed 30/03/2013.
[95] christina1989. (2011). Research Milestones for Cystic Fibrosis. Available: http://www.timetoast.com/timelines/research-milestones-for-cystic-fibrosis. Last accessed 30/03/2013.

22nd Jan, 1994	**FDA approves Pulmozyme**
16th Mar, 1997	**First Therapeutic Program**
13th Jun, 1997	**First antibiotic created.**
16th Mar, 2000	**Various drug discoveries.**
25th Sep, 2000	**Genetic structure created**
8th Jul, 2004	**Supported studies in Austria**
22nd May, 2006	**X-770 enters clinical trial**
22nd Dec, 2006	**Survival age increases to 37.**
16th Mar, 2007	**FDA approves antibiotic**
3rd Aug, 2007	**Second potential drug created.**
3rd Sep, 2008	**Proof of achievement**
20th Nov, 2009	**All new borns scanned for CF**
16th Oct, 2010	**New drug shows results.**

In order to allow a comparison to be made, I have also assembled a rough timeline of some of the key points in OI history:

Date	**Event**
1788	Earliest study of OI by Olof Jakob Ekman.
1833	Lobstein named OI as Lobstein syndrome and deals with patients with that condition.
1895	Lobstein Syndrome becomes known as Osteogenesis Imperfecta.
1979	Sillence founded the four initial types of OI. Type 1 – 4 and categorised them by symptoms.
1984	Rodding used to treat individuals with OI.
2000	Use of Pamidronate to treat individuals with OI
2001	First finding of gene therapy published by Horwitz, bone marrow transplantation in severe cases of OI
2006	Recessive genes causing OI found
2007	First whole body vibration pilot in Cologne, Germany
2012	Ali and Hasan prompt the use of Phlorotannin Incorporated Mesenchymal Stem Cells as a way of treating OI. [96]

While the history of OI predates that of CF, most of the developments in OI treatment have roughly occurred in the same period as that of CF. In both conditions we can see in the past thirty year there have been major strides in research and both conditions

[96] Amanda. (2011). History of Osteogenesis Imperfecta. Available: http://unbreakablejourney.com/2011/01/historyofoi/. Last accessed 30/03/2013.

researching into gene therapy. I believe that if research continues at the same rate, if not quicker with developing technologies and increasing knowledge we should see a cure in possibly the next 20 years for both conditions.

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Appendix

Appendix 1 – Interview with Dr Högler

E-mail interview conducted with Dr Wolfgang Högler, MD DSc FRCPCH, (Clinical Lead, Dept of Endocrinology & Diabetes, Consultant Paediatric Endocrinologist, Birmingham Children's Hospital, Honorary Senior Lecturer, University of Birmingham) discussing his trial of Whole Body Vibrations at Birmingham Children Hospital

1) Having read the short proposal on the Brittle Bone Society website it mentioned that participants of this study would have had to been off bisphosphonates for more than 6 months or more than 2 years, and I was just curious as to the reasons behind that? Is there a medical reason behind this or is it just to see the impacts of the study without any other medication having an influence on it?

XXXX During the first 2 years of bisphosphonate therapy, there is usually a significant improvement in bone density and mobility. This would introduce bias into our analysis.

2) Also I was wondering if I could get a hold of a more detailed course of procedure for the whole body vibration as the description of the study was quite brief in the article on the website.

XXXXX I am attaching an information sheet for teenagers.

3) Obviously I am aware that I don't know the full extent of the study but I was wondering if there are any side effects or implications in getting involved with the study for the participants?

XXXX No. The forces exerted by the vibration plate are less than during normal walking. One of the inclusion criteria is the minimal ability to rise from a chair.

4) I was also wondering what the intended outcomes of this study are from a medical viewpoints? What are you hoping to see at the end of the study in the participants?

XXXX Improved mobility, measure by force plate (chair rising test, balance) and 6-minute walk test. Improved bone structure/mass/density.

5) In preparation for these test cases, what prior preparations have been done in order to make sure the most effective data is collected from the participants of the study?

XXXX I do not quite understand this question. Preparations: In-depth literature review, correspondence with and input from other leading OI centres (esp Cologne), the biomechanical experts of the company producing the vibration plates, statistical advice, peer reviewed funding application, and “user” input by one of our OI families. Last but not least, protocol approval by scientific advisory committee, ethics committee and R&D office.

Appendix 2 – Talk at King's College London

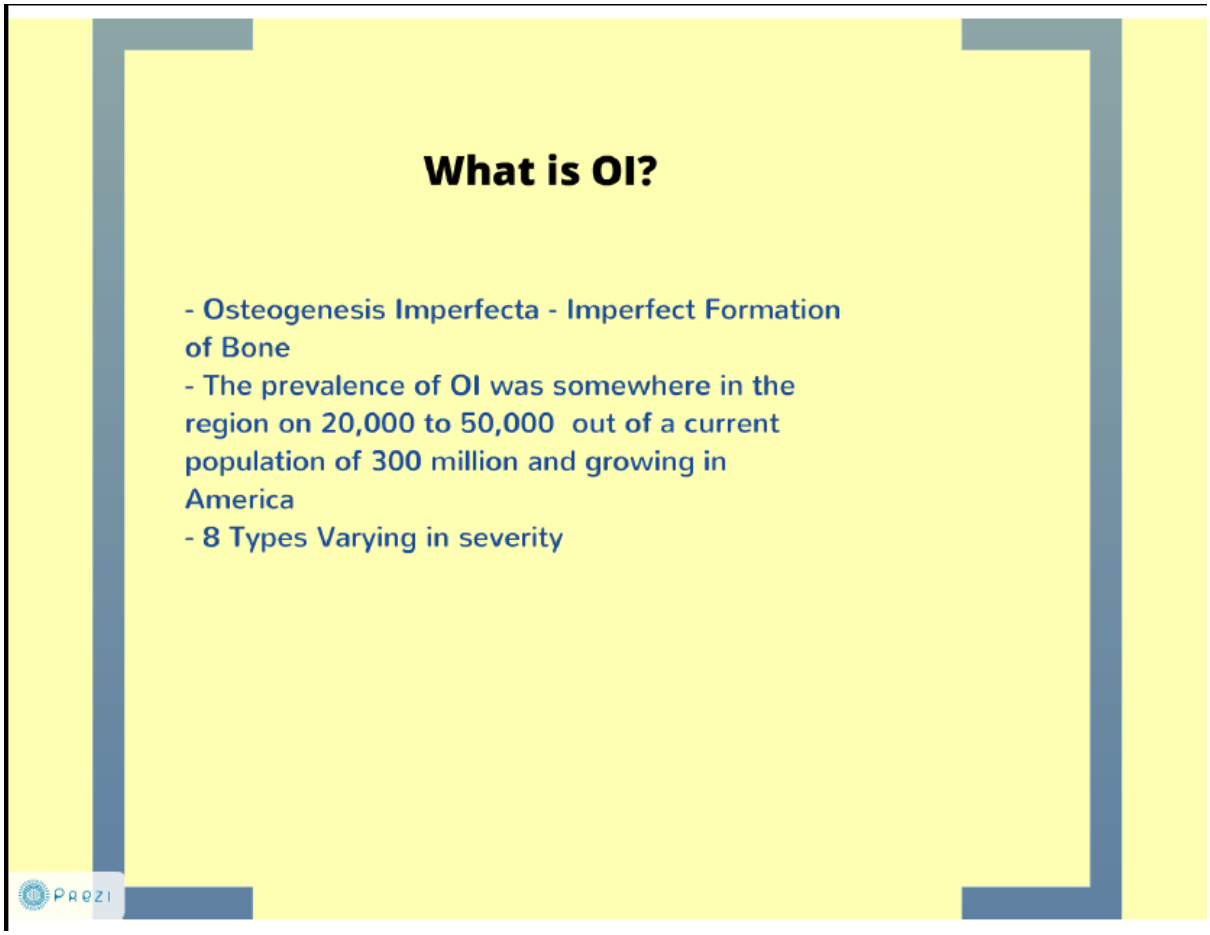
http://youtu.be/o37ioaGJUG0

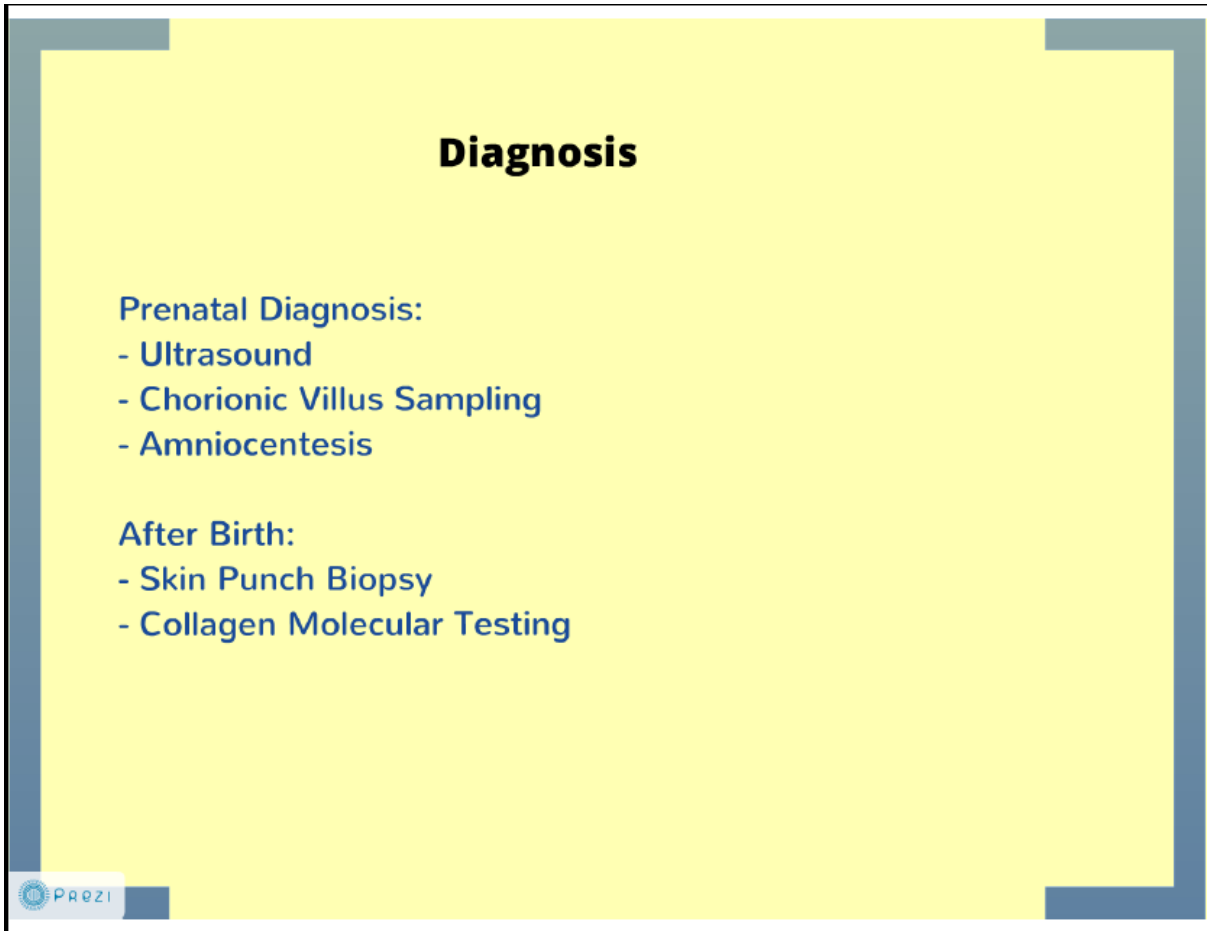
Candidate Name: Thines Ganeshamoorthy
Candidate Number: 5136
Project Title: Will there ever be a cure for Osteogenesis Imperfecta?

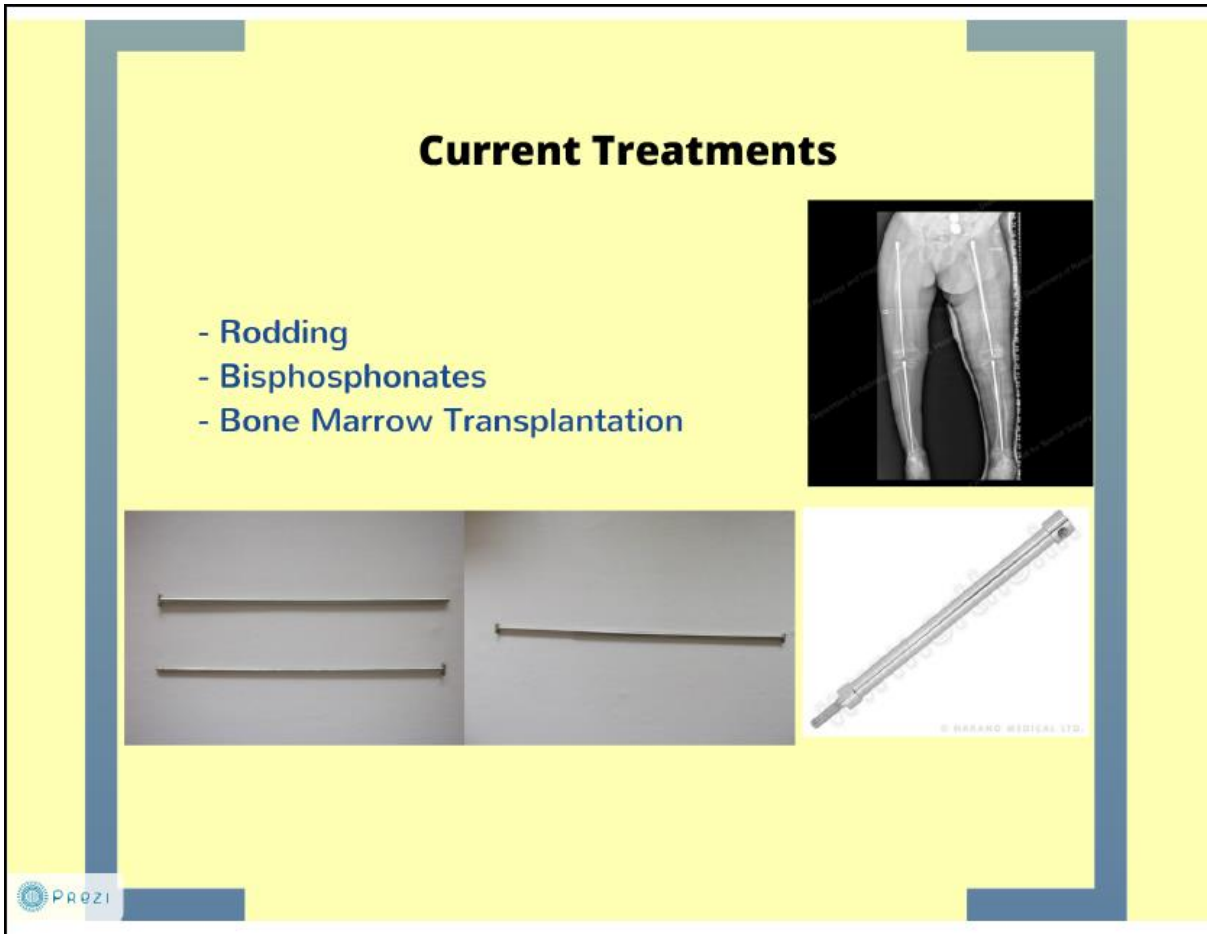
Appendix 3 – Presentation

Can also be found on the Prezi website at the link below:

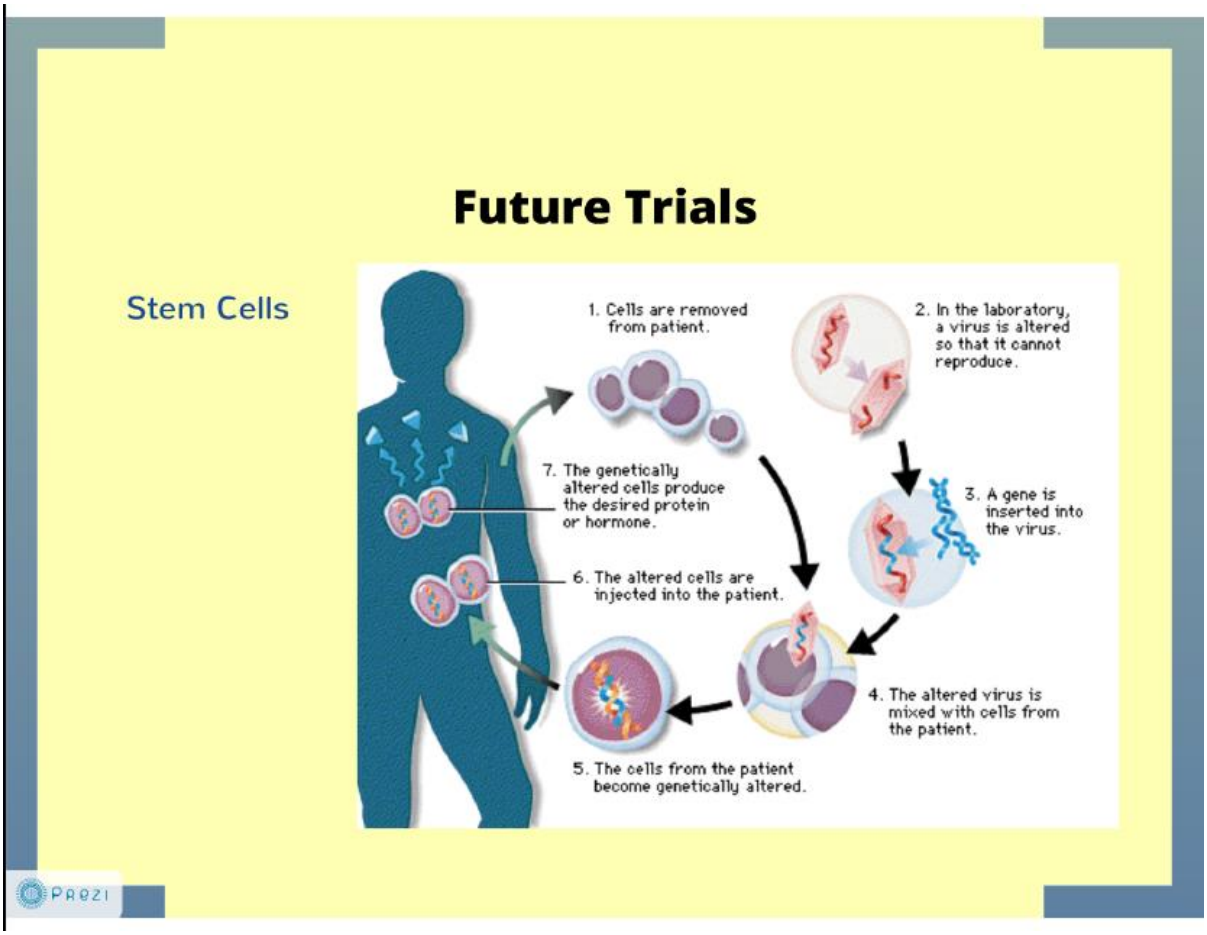
http://prezi.com/8mpoyhwcldqz/will-there-ever-be-a-cure-for-osteogenesis-imperfecta/?kw=view-8mpoyhwcldqz&rc=ref-34234879

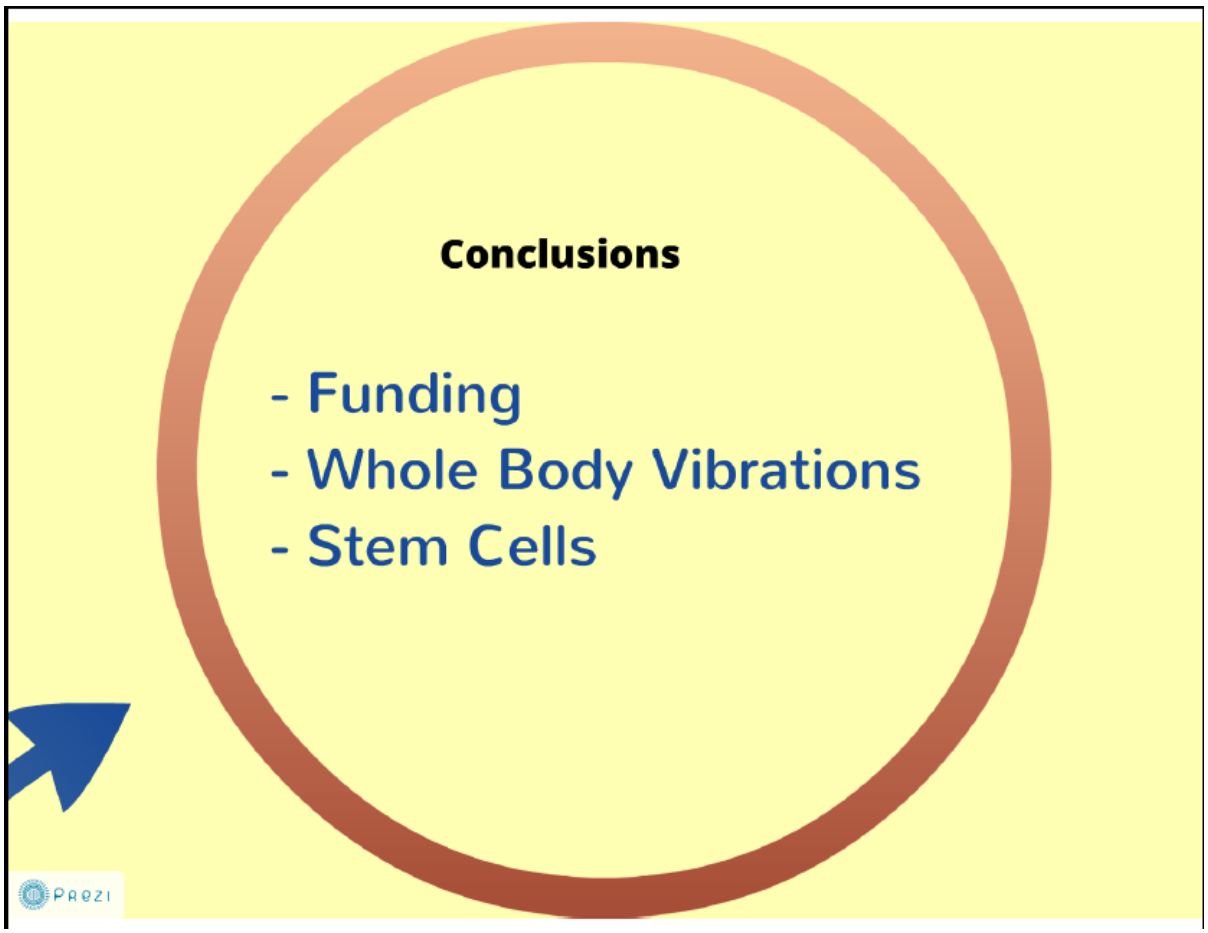

What is OI?
- Osteogenesis Imperfecta - Imperfect Formation of Bone
- The prevalence of OI was somewhere in the region on 20,000 to 50,000 out of a current population of 300 million and growing in America
- 8 Types Varying in severity
Prezi


Diagnosis
Prenatal Diagnosis:
- Ultrasound
- Chorionic Villus Sampling
- Amniocentesis
After Birth:
- Skin Punch Biopsy
- Collagen Molecular Testing
PREZI


Current Treatments
- Rodding
- Bisphosphonates
- Bone Marrow Transplantation
Prezi


Current Research Trials
Whole Body Vibrations
CE
PREZI


Future Trials
Stem Cells
1. Cells are removed from patient.
2. In the laboratory, a virus is altered so that it cannot reproduce.
3. A gene is inserted into the virus.
4. The altered virus is mixed with cells from the patient.
5. The cells from the patient become genetically altered.
6. The altered cells are injected into the patient.
7. The genetically altered cells produce the desired protein or hormone.
Prezi


Conclusions
- Funding
- Whole Body Vibrations
- Stem Cells
Prezi