Universidade do Minho
Escola de Engenharia

Ana Filipa Amorim Arieira

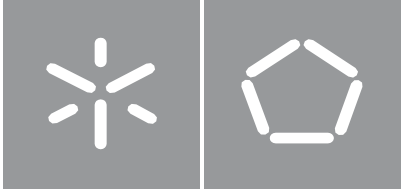
Design and development of an internal bone distractor activated by a shape memory material

March 2021

Design and development of an internal bone distractor activated by a shape memory material

Ana Filipa Amorim Arieira

UMinho | 2021



Universidade do Minho
Escola de Engenharia

Ana Filipa Amorim Arieira

Design and development of an internal bone distractor activated by a shape memory material

M. Sc. Dissertation
Integrated Master in Biomedical Engineering
Biomaterials, Rehabilitation and Biomechanics

Dissertation realized under the supervision of
Professor Doutor Óscar Samuel Novais de Carvalho
and **Doutora Ana Isabel Neto Cardoso Leal**

March 2021

ACKNOWLEDGEMENTS

It would not have been possible to write this dissertation without the guidance, help, cooperation, and encouragement of all the kind people around me. This dissertation represents not only the end of my master's degree but also the closure of one of the most thrilling journeys of my life.

First of all, I would like to thank my supervisor, Professor Óscar Carvalho, for all the support, availability, dedication, commitment, encouragement, and all the laughs and funny moments, and for having shared with me excellent teachings and advice.

To my co-supervisor Ana Leal, I would like to thank all the help, encouragement, and guidance throughout this work, through orientations, corrections, and suggestions that were always very relevant. This work would have been impossible without all the soothing and uplifting words.

To Professor Filipe Silva, who gave me the opportunity to be able to carry out this project and accompanied me throughout its entire course, sharing his knowledge and experience and always encouraging me to take it a step further.

To Doctor Alberto Pereira, I would like to thank for all the insights in the medical field of this work, for all de help in developing the systematic review integrated into this dissertation, and for all the time available and the meetings held, even in times of a pandemic.

I would like to thank PhD student Mafalda Costa for all the time spent with me and on our adventures with liquid nitrogen and for all the help in the lab.

I would like to thank the most incredible friends in the world. To my childhood friends: Tânia, Lenha, Maria, Inês and Cláudia who accompanied me through this long journey and encouraged me to never give up. To my university friends “Metade d’As Otcho”: Rita, Rute and Helena for always being there for me when I needed it, and for the amazing friendship that I intend to take for life.

To my best friend and boyfriend João, for always showing to the whole world how proud he is of me and for cheering all my accomplishments as if they were his. For always being there for me and never failing to motivate me into achieving my best. Above all, I would like to thank for all the patient and for restoring my mental health when I needed it.

Finally, and above all, a very special word of thanks goes to my parents, grandparents, brother, and sister (in-law), who have been my greatest support encouraging me to never give up, without ever raising an eyebrow when I claimed my thesis would be finished ‘in the next weeks’ for nearly half a year. I would like to thank them for the endless love, for the unceasing support, for all the motivation and patience, not only along this year but throughout my entire life.

STATEMENT OF INTEGRITY

I hereby declare having conducted this academic work with integrity. I confirm that I have not used plagiarism or any form of undue use of information or falsification of results along the process leading to its elaboration.

I further declare that I have fully acknowledged the Code of Ethical Conduct of the University of Minho.

SUMÁRIO

A mandíbula, também conhecida como maxilar inferior, é o maior e mais forte osso do crânio humano. As anomalias maxilares e mandibulares constituem uma percentagem significativa das anomalias craniofaciais. A deficiência mandibular pode ser de desenvolvimento, como no caso de microssomia hemifacial (1 em 3500) e síndromes como a síndrome de Treacher Collins (1 em 25000), ou adquirida devido à perda precoce da dentição, fraturas, cancro e anquilose da articulação temporomandibular.

A correção das deformidades maxilofaciais pode ser realizada por meio de cirurgias ortognáticas convencionais, algumas vezes necessitando enxertos ósseos ou, mais recentemente, por distração osteogénica (DO). A técnica de DO é baseada no princípio de "tension-stress" e é definida como um processo biológico de neoformação óssea entre duas superfícies de segmentos ósseos que se vão separando gradualmente devido a uma força de tração induzida por um dispositivo de distração. Embora a DO seja um processo vantajoso, os distratores ósseos atualmente disponíveis originam algumas complicações (p. ex., infeção, lesão do nevo e dente, cicatrizes, mordida aberta, recidiva, falha do dispositivo e 'desapertar/soltar' dos pinos/parafuso) e possuem limitações associadas (p. ex., questões estéticas e a incapacidade dos dispositivos internos de alterar a direção do vetor de distração). Tendo tudo isso em consideração, a possibilidade de aprimoramento dos dispositivos de DO mandibular é notória.

O desenvolvimento do presente projeto está dividido em várias etapas, desde a identificação das áreas de melhoria, a criação de um conjunto de conceitos e a seleção dos conceitos finais. Com a colaboração do Dr. Alberto Pereira, que exerce funções como Chefe da Unidade de Cirurgia Reconstrutiva Facial do Hospital Luz Lisboa e Presidente do Grupo de Trabalho de Distração da Fundação AOCMF, foram identificadas áreas de melhoria e foram definidos os requisitos e objetivos que o novo dispositivo deveria cumprir. Os conceitos foram modulados com um programa CAD para permitir uma compreensão clara dos elementos, mecanismos e do respetivo funcionamento.

Os conceitos selecionados visam superar grande parte das complicações observadas e permitem ajustes do vetor de distração durante a fase de ativação, de forma a obter os melhores resultados possíveis em termos de simetria facial. Além disso, ambos os conceitos possuem um inovador mecanismo de ativação composto por materiais com memória de forma. O mecanismo de ativação difere ligeiramente entre os dois conceitos, porém o princípio de funcionamento é o mesmo. O presente dispositivo médico visa ter a capacidade de melhorar a qualidade do tratamento e eliminar totalmente os problemas estéticos, sendo um dispositivo totalmente interno e praticamente impercetível.

KEYWORDS: DISTRAÇÃO OSTEOGÉNICA; DISTRATOR; PROJETO DE DESIGN; MANDIBULA; MEMÓRIA DE FORMA.

ABSTRACT

The mandible, also known as the lower jaw, is the largest and strongest bone in the human skull. Maxillary and mandibular anomalies constitute a significant portion of craniofacial anomalies. Mandibular deficiency may be developmental, as in the case of hemifacial microsomia (1 in 3500 live births) and syndromes like Goldenhar syndrome or Treacher Collins syndrome (1 in every 25,000 births), or acquired due to early loss of dentition, trauma (e.g., fractures), cancer and temporomandibular joint ankylosis.

The correction of maxillofacial deformities can be performed through conventional orthognathic surgeries, sometimes requiring bone grafts or, more recently, through distraction osteogenesis (DO). The DO technique is based on the principle of "tension-stress" and is defined as a biological process of new bone formation between two surfaces of bone segments that are gradually separated due to traction force induced by a distraction device. Although DO is an advantageous process, bone distractors currently available have some associated complications (e.g., infection, nerve and tooth injury, scarring, open bite, relapse, device failure and pin/screw loosening) and limitations (e.g., aesthetically unappealing and the inability of internal devices to alter the direction of the distraction vector). Taking all this into account, the possibility of improving the mandibular osteogenic distraction devices is noteworthy.

The development of the present project is divided into several stages, from the identification of areas for improvement and the creation of a set of concepts to the selection of the final concepts. With the input of Doctor Alberto Pereira, who holds positions such as Head of Facial Reconstructive Surgery unit at Luz Lisbon Hospital and Chair of the AOCMF Foundation distraction taskforce, were identified areas for improvement and the requirements and objectives that the new concept should accomplish were defined. The concepts of the medical device were modulated with a CAD program to allow a clear comprehension of the respective functionality.

The final selected concepts aim to overcome most of the complications currently observed and they allow for distraction vector adjustments during the activation phase in order to obtain the best possible results in terms of facial symmetry. Additionally, both concepts have an innovative activation mechanism composed of shape memory materials. The activation mechanism of the two concepts is slightly different, however, the principle of operation is the same. In this sense, the present medical device aims to have the ability to improve the quality of medical treatment and to eliminate the aesthetic issues with the device being completely internal and practically imperceptible.

KEYWORDS: DESIGN PROJECT; DISTRACTION OSTEOGENESIS; DISTRACTOR; MANDIBLE; SHAPE MEMORY.

INDEX

LIST OF IMAGES

LIST OF TABLES

LIST OF ABBREVIATIONS AND ACRONYMS

TMJ	*Temporomandibular Joint*
DO	*Distraction Osteogenesis*
MDO	*Mandibular Distraction Osteogenesis*
IAN	*Inferior Alveolar Nerve*
IAA	*Inferior Alveolar Artery*
HFM	*Hemifacial Microsomia*
CFM	*Craniofacial Microsomia*
PRS	*Pierre Robin Sequence*
GS	*Goldenhar Syndrome*
TCS	*Treacher Collins Syndrome*
OSA	*Obstructive Sleep Apnoea*
MSC	*Mesenchymal Stem Cell*
ECM	*Extracellular Matrix*
OMSDs	*Oral and Maxillofacial Skeleton Deformities*
BSSO	*Bilateral Sagittal Split Osteotomy*
BSSRO	*Bilateral Sagittal Split Ramus Osteotomy*
IVRO	*Intraoral Vertical Ramus Osteotomy*
CT	*Computed Tomography*
MRI	*Magnetic Resonance Imaging*
TDO	*Transport Distraction Osteogenesis*
SMA	*Shape Memory Alloy*
SM	*Shape Memory*
SME	*Shape Memory Effect*
SE	*Superelastic Effect*
OWSM	*One-way Shape Memory*
OWSME	*One-way Shape Memory Effect*
TWSM	*Two-way Shape Memory*
TWSME	*Two-way Shape Memory Effect*
A	*Austenite*
M	*Martensite*

As	*Austenite start temperature*
Af	*Austenite finish temperature*
Ms	*Martensite start temperature*
Mf	*Martensite finish temperature*
Md	*Martensite deformation temperature*
PE	*Pseudoelastic*
DSC	*Differential scanning calorimetry*
BMP-2	*Bone Morphogenetic Protein 2*
IGF-1	*Insulin-like Growth Factor 1*
FGF-2	*Fibroblast Growth Factor 2*

1. INTRODUCTION

1.1 Motivation

The development of the human skull and face is an extremely complex and coordinated three-dimensional process and craniofacial malformations that occur because of abnormal development are among the most common birth defects (Evans, Hing, & Cunningham, 2018). Maxillary and mandibular anomalies constitute a significant portion of craniofacial anomalies. Mandibular deficiency may be developmental, as in the case of hemifacial microsomia (HFM) and syndromes like Goldenhar syndrome (GS) or Treacher Collins syndrome (TCS), or acquired due to early loss of dentition, trauma (e.g., fractures), cancer and temporomandibular joint (TMJ) ankylosis (N. K. Sahoo, Issar, & Thakral, 2019). Besides the obvious aesthetic limitations, these anomalies are commonly associated with difficulties in feeding, swallowing, and breathing that can lead to lifelong treatments or, in some cases, death.

The correction of maxillofacial deformities can be performed through conventional orthognathic surgeries, sometimes requiring bone grafts or, more recently, through distraction osteogenesis (DO). The distraction osteogenesis technique, first introduced in the field of orthopaedics in the treatment of discrepancies in the dimension between the lower limbs, has overcome the main disadvantages and limitations associated with orthognathic surgery. These include limitations in the distraction range, the complication rates of the osteotomies used and the fact that the conventional orthognathic method cannot be undertaken while the patient's growth is incomplete. The DO technique is based on the principle of “tension-stress” (Guerrero, Rivera, Mujica, Henriquez, & Gonzalez, 2012) and is defined as a biological process of new bone formation between two surfaces of bone segments that are gradually separated due to the application of an incremental and controlled traction force (George & Hegde, 2012). This traction force, and therefore separation of bone segments, is achieved by means of a distraction device.

Although DO is an advantageous and simpler process, bone distractors currently available for the treatment of cranial and maxillofacial deformities are highly invasive since part of the mechanisms are inside the body and part outside (e.g., internal devices), making it propitious to bacterial infections. In addition, these types of distractors are extremely uncomfortable and

aesthetically unappealing, interfering with the patient's normal daily life. Furthermore, DO is still associated with several complications and limitations. Besides infections, other complications include nerve or tooth injury, scarring, open bite, relapse, device failure and pin/screw loosening. Additionally, other major limitations of today's distractors are related to the inability to change the distraction vector in the case of internal distractors.

Taking all this into account, the possibility of improving the mandibular distraction osteogenesis devices is noteworthy. The present devices and concepts developed in this thesis, in addition to being customizable and multifunctional, combine a new activation technique (using shape memory materials) with the ability to vary the distraction vector to allow for corrections of the movement, and the ability to overcome several of the complications observed in the devices currently used such as scarring, open bite, infections and relapse.

1.2 Objectives

The main objective of this work is to design and develop a new medical device for distraction osteogenesis, in particular the mandibular distraction, capable of overcoming the obstacles currently observed with the current devices. To fulfil this purpose, a set of specific objectives were outlined:

- Survey mandibular anomalies as well as their main causes and treatments;
- Analyse the biomechanics, process, and protocol of distraction osteogenesis as well as the factors that can influence the final outcome;
- Review of the complications currently observed, their causes and actual corrective measures;
- Analyse the currently used medical devices to identify their limitations and, therefore, improve the performance of the purposed medical device;
- Design ideas for fully internal devices with external activation;
- Verify and validate the alloy's (nitinol) one-way shape memory and two-way shape memory effect;
- Writing of a patent on the developed concepts and respective innovative activation methods.

1.3 Structure of the Dissertation

This works aims to develop a new medical device for distraction osteogenesis. Bearing that in mind, the most relevant issues about the mandible abnormalities, diagnostic methods, mandibular distraction osteogenesis protocol and influencing factors must be addressed. For that purpose, this dissertation was divided into eight chapters, as follows:

In Chapter 1, an overview of the dissertation is provided, focusing on the motivation for the development of this subject as well as the outlined objectives for this project.

In Chapter 2, the anatomical and functional description of the mandible is presented. The chapter includes a description of the musculoskeletal system of the mandible as well as a brief reference to the articular system of the temporomandibular joint. This chapter also includes a brief description of the nervous system and blood supply of the mandible.

Chapter 3 focuses on the pathologies that cause mandibular defects and the existing techniques of diagnostic and treatment. Purposely, the chapter addresses the most common pathologies such as hemifacial microsomia, Pierre Robin sequence and Treacher Collins Syndrome and their severe functional and aesthetic limitations in terms of feeding, swallowing, breathing, voice function, and overall development. In addition, other causes of mandibular abnormalities such as trauma, cancer and temporomandibular joint ankylosis are also mentioned.

Chapter 4 covers a detailed literature review of the distraction osteogenesis process. It focuses on the biological process of the mandibular distraction osteogenesis (MDO), the differences between DO and the standard orthognathic surgeries, and the types of mandibular distractors devices commercialized. This chapter provides all the information regarding the factors that directly or indirectly affect the process of DO. Information about the biomechanics of MDO and the influence of the surrounding tissues, masticatory forces, and impact on the temporomandibular joint is also provided.

In Chapter 5 is presented a systematic review of the complications observed in mandibular distraction osteogenesis in the treatment of mandibular hypoplasia. This chapter concisely describes all the problems observed with the protocols and devices currently used in MDO, thus making it easier to identify the areas susceptible to improvement.

In Chapter 6, and taking into consideration all the obtained information in the previous literature review, the concept development of the new medical device and device activation is generated. The requirements and objectives of the new device are addressed, as well as the generated and selected concepts. It should be noted that this chapter does not present in detail

the device developed, its components or materials since there is a patent in the process of submission.

Chapter 7 provides the laboratory data acquired related to the validation process of the one-way and two-way shape memory effect of the shape memory alloy (nitinol).

Chapter 8 summarizes the main conclusions of the present work as well as some perspectives for future work.

Appendix A presents the O.M.E.N.S (+) Classification of hemifacial microsomia.

In Appendix B there is a summary table of the information of the analysed patents.

Appendix C presents schematic representations of the main anatomical planes of the head in order to better contextualize the mandibular movements during the distraction process.

Appendix D presents the anthropometric measures of the mandible used in the development of the new concepts.

In Appendix E there is a brief state of the art on shape memory materials, focused on nitinol, essential to better understand its functioning and use in the medical field.

2. Anatomy And Function Of The Mandible

2.1 Skeletal system

The mandible, Figure 2-1, also known as the lower jaw, is the largest and strongest bone in the human skull acting as a receptacle for the lower teeth (Breeland, Aktar, & Patel, 2020). It is located inferiorly in the facial skeleton and, along with the maxilla (upper jaw), forms the mouth structure.

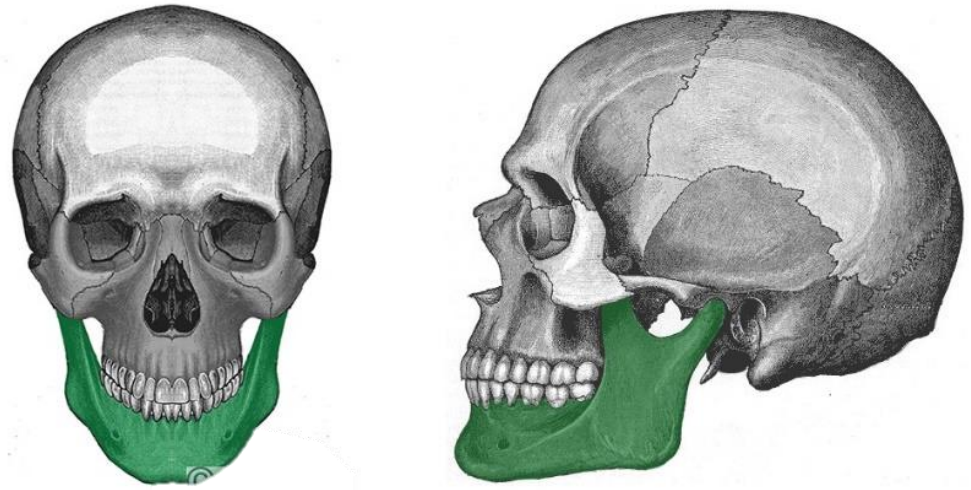


Figure 2-1: Mandibular bone.
(Sieroslawska, 2021)

The mandible is a singular bone that is symmetrical on both sides and consists of two main portions: the body, which is the anterior portion of the mandible, represented in Figure 2-2 a), and the ramus (branch), Figure 2-2 b), which extends superiorly from the body towards the temporal bone (VanPutte, 2004). Both portions connect at the angle of the mandible, also known as the gonial angle, Figure 2-2 c). The gonial angle is approximately 160 degrees at birth. However, by adulthood, the gonial angle is decreased roughly to 120 degrees because of complete teeth formation. Usually, males tend to have a decreased gonial angle (90 degrees) compared to females, resulting in squarer and prominent mandibles (Breeland et al., 2020).

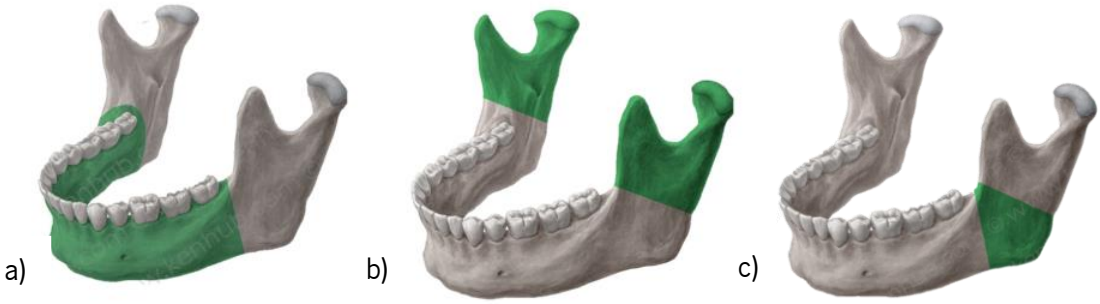


Figure 2-2: a) Body, b) ramus and c) gonial angle of the mandible.
(Sieroslawska, 2021)

The body is bound by two borders: the alveolar process which is the superior border and contains the hollow cavities in which the lower sixteen teeth reside (Figure 2-3), and the inferior border that creates the lower jawline. This portion of the mandible is marked in the midline by the mandibular symphysis which is a small ridge of bone that represents the fusion of right and left mandibular processes during the embryologic development of the mandible (Breeland et al., 2020). Like other symphyses in the body, this is a midline articulation where the bones are joined by fibrocartilage (Fehrenbach & Herring, 2015).

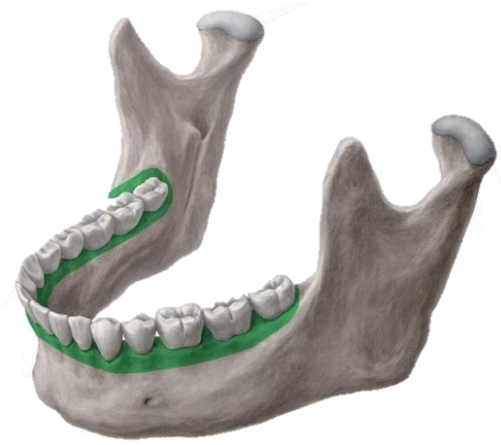


Figure 2-3: Alveolar process of the mandible.
(Sieroslawska, 2021)

The ramus extends from the angle upwards, in the temporal direction. The most superior point of the ramus divides into two processes: anteriorly, sits the coronoid process (Figure 2-4 a)), in which the *temporalis* muscle is inserted, and posteriorly, the condylar process (Figure 2-4 b)), which articulates with the glenoid cavity of the temporal bone.

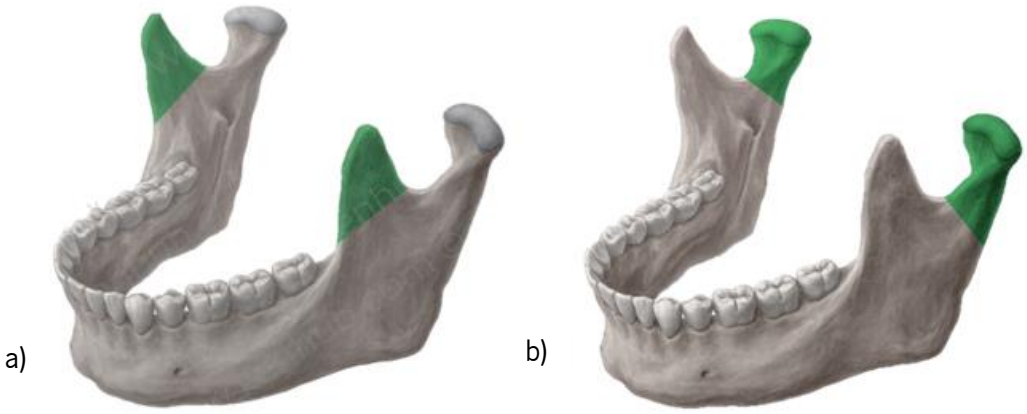


Figure 2-4: a) Coronoid process and b) condylar process of the ramus.
(Sieroslawska, 2021)

The internal surface of the ramus contains the mandibular foramen (Figure 2-5 a)), which serves as a conduit for the inferior alveolar nerve (IAN) and inferior alveolar artery (IAA). They travel through the mandibular foramen, into the mandibular canal, and exit at the mental foramen (Figure 2-5 b)) situated in the external surface of the mandibular body, below the second premolar tooth.

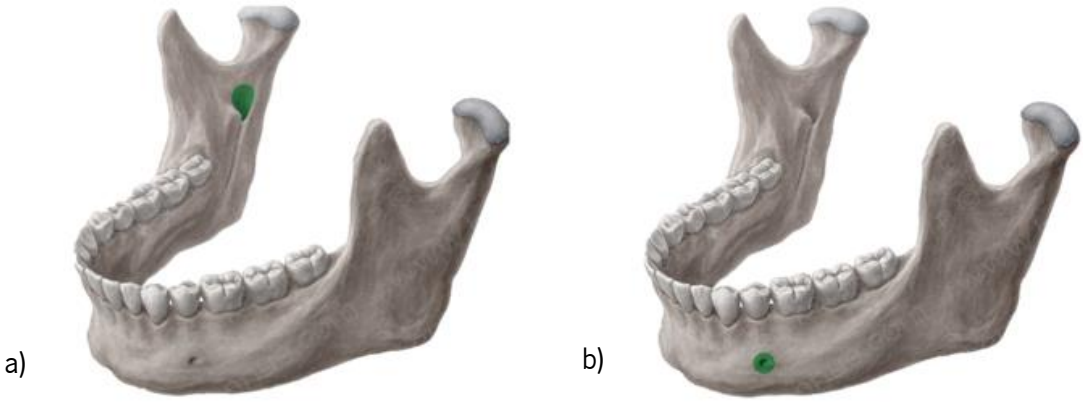


Figure 2-5: a) Mandibular foramen and b) mental foramen.
(Sieroslawska, 2021)

2.2 Articular system

The superior aspect of each ramus has a mandibular condyle which is the point of articulation between the mandible and the rest of the skull, and the coronoid process to which the powerful *temporalis* muscle, one of the masticatory muscles, attaches (Figure 2-6), thus creating the temporomandibular joint (TMJ) which permits mobility. The mandible and the temporal bone are separated by a fibrocartilage articular disk. The joint is surrounded by a fibrous capsule to which

the edge of the meniscus is attached and is reinforced by the external and internal lateral ligaments (Fehrenbach & Herring, 2015; VanPutte, 2004).

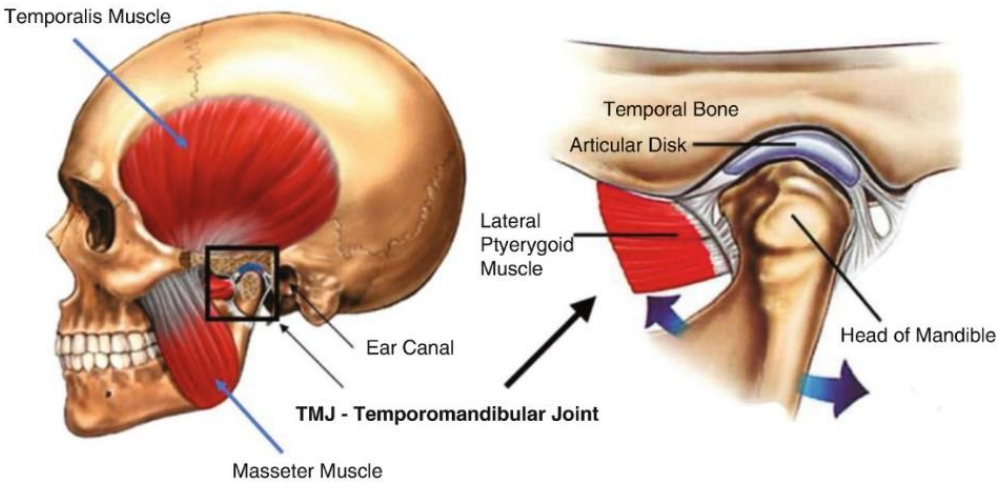


Figure 2-6: Temporomandibular joint and associated muscles.
(VanPutte, 2004)

The TMJ is an important joint, essential in daily tasks such as talking, eating, and even sleeping. In technical terms, this joint is classified as ellipsoid with multi-axial movements. All mandibular motion is either translational (gliding or sliding movements) or rotational (or hinge movements). The translational movement allows the mandible to move forward or backwards. Bringing the mandible forward results in protraction of the lower jaw, on the other hand, moving the mandible backwards involves retraction of the lower jaw (Figure 2-7 a)). Rotational movements of the TMJ are characterized by the head of the condyle rotating around an approximately transverse axis and the movements accomplished are depression and elevation of the mandible (Figure 2-7 b)) (VanPutte, 2004).

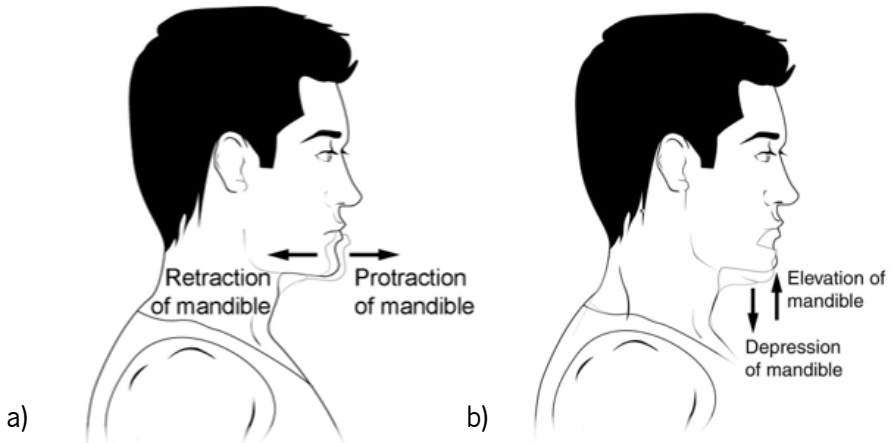


Figure 2-7: Representation of a) protraction and retraction and b) elevation and depression of the mandible.
(*Adapted from* Carter & Rutherford, 2020)

With the combination of translation and rotation movements, it is possible to perform all the movements of the lower jaw, including opening and closing the mandible and shifting the lower jaw to one side (Fehrenbach & Herring, 2015). The opening and closing movements of the mouth presuppose anterior and posterior sliding movements of the meniscus and condyle, respectively, in relation to the temporal bone, which are practically the same movements that occurred in protraction and retraction. The lateral excursion represented in Figure 2-8 refers to moving the mandible to either the right or left of the midline during activities such as grinding the teeth or chewing (VanPutte, 2004).

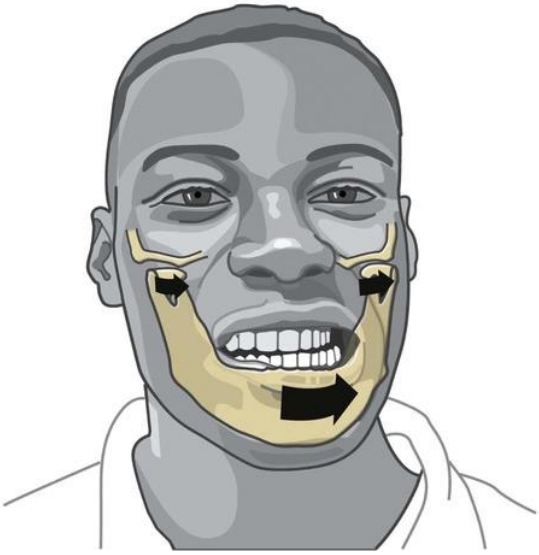


Figure 2-8: Lateral excursion of the mandible.
(Neumann, 2010)

2.3 Muscular system

The jaw is suspended bilaterally by a system of muscles, tendons, and ligaments that allow its movements. As represented in Figure 2-9, the muscles attached to the mandibular body, on the external surface are the *mentalis, buccinator, platysma, depressor labii inferioris, depressor angulioris*; and the internal surface is covered by the *genioglossus, geniohyoid, mylohyoid* and *digastric* muscles. When it comes to the mandibular ramus, the muscles attached are the *masseter, temporalis, medial pterygoid,* and *lateral pterygoid*.

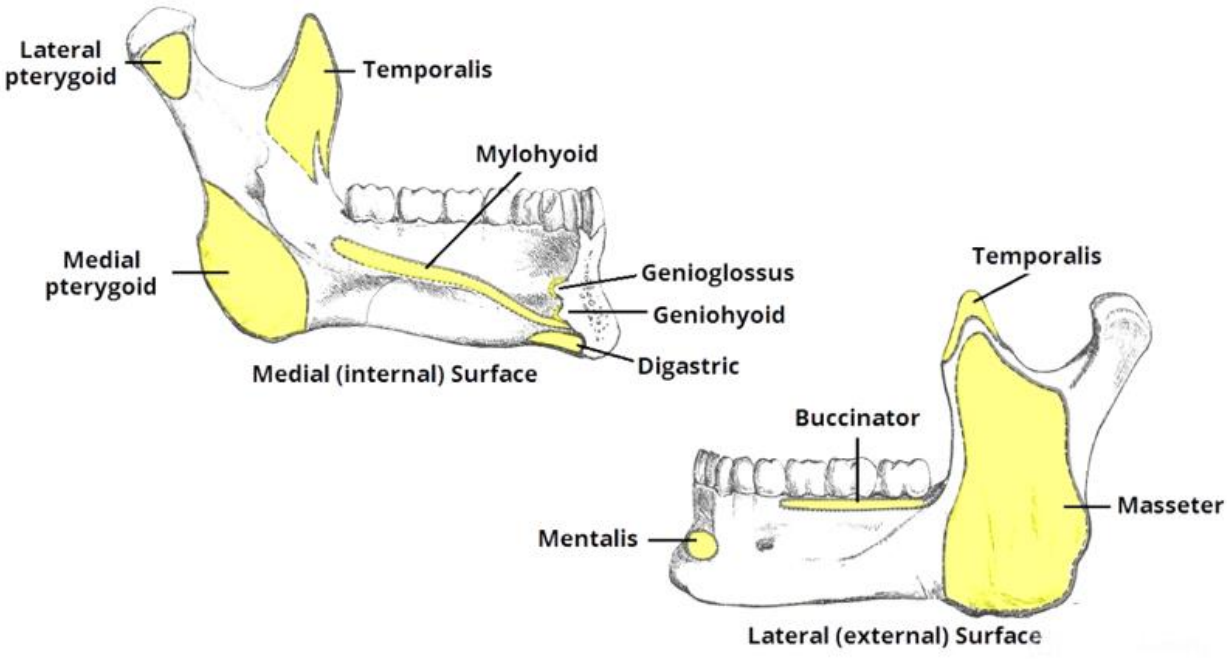


Figure 2-9: Mandible main muscles.
(Emin, 2019)

The muscles responsible for mandibular movement are those of the masticatory process and the hyoid muscles. The latter are located in the neck area. As for the muscles involved in mastication, they provide a set of coordinated movements that facilitate the process of grinding food. They are composed of four paired muscles that are located deeper within the face than the muscles of facial expression. These muscles are: the *masseter, temporalis, medial pterygoid,* and *lateral pterygoid* muscles. Table 2-1 summarizes the muscles of mastication and associated mandibular movements.

Table 2-1: Muscles involved in the mastication process and their associated mandibular movements.
(Adapted from VanPutte, 2004)

Muscles	Associated Mandibular Movements
Masseter	Bilateral contraction: elevation of the mandible during the closing of jaws
Temporalis	Bilateral contraction of entire muscle: elevation of the mandible during the closing of jaws Bilateral contraction of only posterior part: retraction of mandible
Medial pterygoid	Bilateral contraction: elevation of the mandible during the closing of jaws
Lateral pterygoid	Unilateral contraction: lateral deviation of the mandible, shift mandible to the contralateral side Bilateral contraction: mainly protrusion of mandible, slight depression of mandible during the opening of jaws

2.4 Nervous system and blood supply

The inferior alveolar nerve (IAN) is the main nerve associated with the mandible. It enters the mandibular foramen and courses anteriorly in the mandibular canal where it branches to the lower teeth and ends in the mental foramen. In the mental foramen the IAN branches into the incisive and mental nerve providing innervation to the mandibular premolar, canine, and lateral and central incisors and sensation to the lower lip, accordingly (Breeland et al., 2020). The location of the mandibular nerves can be seen in Figure 2-10.

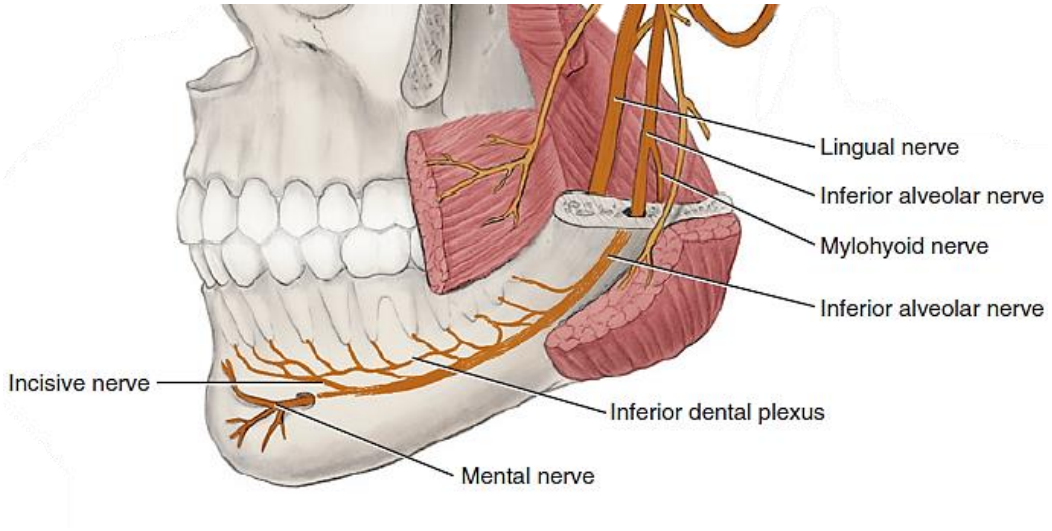


Figure 2-10: Location of mandibular nerves.
(Sieroslawska, 2021)

Blood supply to the mandible is via small periosteal and endosteal vessels. The periosteum is a double-layer connective tissue membrane that covers the outer surface of a bone (Figure 2-11) except where cartilage exists. The inner layer is composed of a single layer of bone cells including osteoblasts, osteoclasts, and osteochondral progenitor cells. The outer fibrous layer is a dense and irregular collagenous connective tissue that contains blood vessels and nerves (VanPutte, 2004). The ramus of the mandible is supplied by the periosteal vessels that arise mainly from the inferior alveolar nerve. On the other hand, the blood of the body of the mandible is provided by endosteal vessels. The periosteum provides osteoprogenitor cells necessary for bone formation and deposition and has an important role in supplying many of the osteochondroprogenitors that participate in the healing of fractures as distraction osteogenesis (Shrivats, Alvarez, Schutte, & Hollinger, 2014).

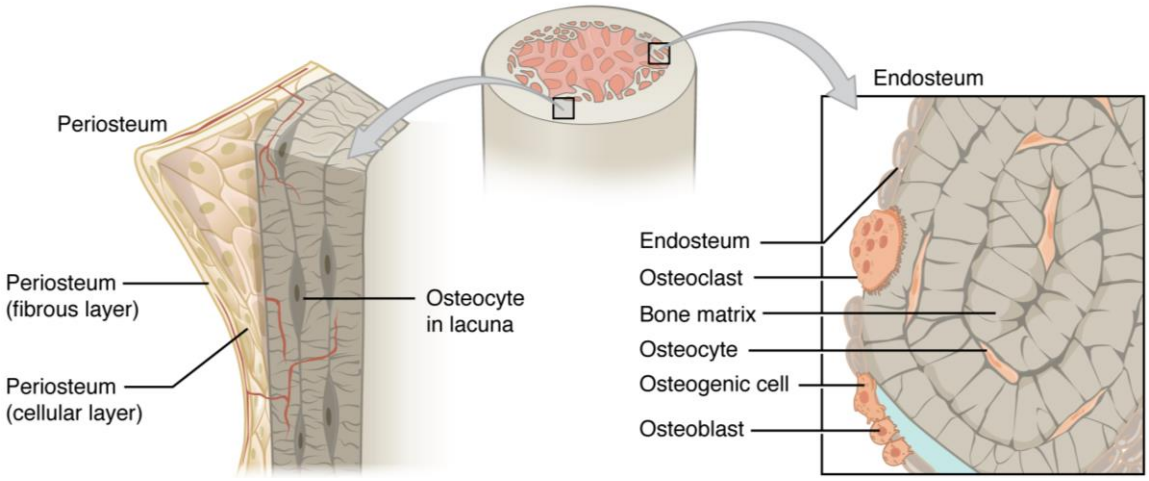


Figure 2-11: Periosteum and endosteum: The periosteum forms the outer surface of the bone, and the endosteum lines the medullary cavity.
(Biga et al., n.d.)

3. MANDIBLE PATHOLOGIES AND DIAGNOSIS

The development of the human skull is an extremely complex and coordinated three-dimensional morphogenic process. Craniofacial malformations that occur because of abnormal development are among the most common birth defects (Evans et al., 2018). These anomalies are associated with increased mortality and, in many cases, the need for lifelong treatment.

Maxillary and mandibular anomalies constitute a significant portion of craniofacial anomalies. As previously stated, mandibular deficiency may be developmental, as in the case of hemifacial microsomia and syndromes like Goldenhar syndrome or Treacher Collins syndrome, or acquired due to early loss of dentition, trauma (e.g., fractures), cancer and TMJ ankylosis (N. K. Sahoo et al., 2019). Mandibular defects can lead to severe functional and aesthetic limitations in terms of feeding, swallowing, breathing, voice function, and overall development. Having a basic understanding of these issues will result in better-targeted evaluations and therapies for each patient (Goodwin, Kim, Bush, & Klein, 2015). Over the past few decades, remarkable advances in the surgical and medical field have led to improvements in patient outcomes.

3.1 Micrognathia

Micrognathia, also known as mandibular hypoplasia or micrognathism, is a category of craniofacial anomalies characterized by hypoplasia or atrophy of a portion of the craniofacial soft tissue and skeleton. Pierre Robin sequence (PRS), hemifacial microsomia (HFM), including Goldenhar syndrome (GS), Treacher Collins syndrome (TCS), and Romberg's disease are examples of these anomalies (Cladis, Grunwaldt, & Losee, 2011). Table 3-1 resumes the most common causes of micrognathia.

Table 3-1: Most common causes of micrognathia.
(*Adapted from* Sankaran & Kyle, 2015)

Most common causes of Micrognathia	
Idiopathic	Mild form
Chromosomal disease	Trisomy 18
Skeletal dysplasias	Campomelic dysplasia Achondrogenesis Osteochondrodysplasia
Genetic syndromes	Treacher Collins syndrome Hemifacial Microsomia Goldenhar syndrome Pierre Robin syndrome Roberts syndrome Miller syndrome

In the late 1960s, Pruzansky published an article presenting the classification of mandibular anomalies according to three degrees (Type I through Type III) in conformity with the extent of hypoplasia of the mandibular condyle and ramus. However, the Pruzansky classification was refined by Kaban to further clarify the degree of glenoid fossa–condyle–ascending ramus malformation observed in patients with HFM. The Pruzansky-Kaban classification, presented in Table 3-2, provides an excellent starting point for defining the most appropriate therapy for each patient (Sankaran & Kyle, 2015).

Table 3-2: Pruzansky-Kaban classification of mandibular hypoplasia.
(Adapted from Posnick, 2013; Yates & Sinn, 2017)

Pruzansky-Kaban classification of mandibular hypoplasia	
Type I	• Minimal degree of hypoplasia; • Mild retrognathia and apertognathia; • All of the skeletal and masticatory muscles components are present and function is within normal limits.

Table 3-2: (Continued).

Pruzansky-Kaban classification of mandibular hypoplasia	
Type IIa	• Mild to moderate hypoplasia; • The masticatory muscles have a variable degree of hypoplasia; • Mild to moderate retrognathia and apertognathia; • Anterior open bite is frequently seen.
Type IIb	• Severe hypoplasia of condyle and ramus; • More than one muscle is hypoplastic; • Marked retrognathia and apertognathia; • TMJ abnormally placed inferiorly, medially, and anteriorly.
Type III	• Severe hypoplasia — no discernible fossa; • Absent condyle and ramus; • Severe hypoplasia of multiple muscles of mastication; • Absent disk and TMJ capsule severely deformed or not present; • Severe loss of posterior facial height; • Apertognathia and retrognathia.

The following sub-chapters present the main medical conditions and syndromes that cause mandibular micrognathia, their influence on the patient's life and their treatments.

3.1.1 Hemifacial Microsomia

Hemifacial microsomia or craniofacial microsomia (CFM) is the second most common craniofacial anomaly after cleft lip and palate with a reported incidence ranging from 1 in 3500 to 1 in 26,500 live births (Resnick, Kaban, & Padwa, 2017). Historically, many names have been used to describe this syndrome, including hemignathia and microtia syndrome, lateral facial dysplasia, otomandibular dysostosis, facio-auriculo-vertebral spectrum, auriculo-branchiogenic dysplasia, intrauterine facial necrosis, necrotic facial dysplasia, oto-mandibular-facial dysmorphogenesis, mandibular laterognathism, first and second branchial arch syndrome, oculoauriculovertebral spectrum, and facio-auriculo-vertebral malformation complex (Yates & Sinn, 2017).

This craniofacial malformation is characterized by structural abnormalities of the orbit, maxilla, mandible, external and middle ear, cranial nerves, and facial soft tissues. Skeletal abnormalities can be observed in Figure 3-1. Males and females are affected similarly, with no difference in the predominant side (left versus right) and in some cases, both sides of the face are affected (5% to 30% of the cases) (Yates & Sinn, 2017). The most distinctive feature of HFM, whether unilateral or bilateral, is asymmetry (Cladis et al., 2011; Resnick et al., 2017). On the affected side, tooth development can be observed, and it is proportionate to the degree of mandibular deformity. Disrupted tooth development can cause serious malocclusions, worsening functional problems.

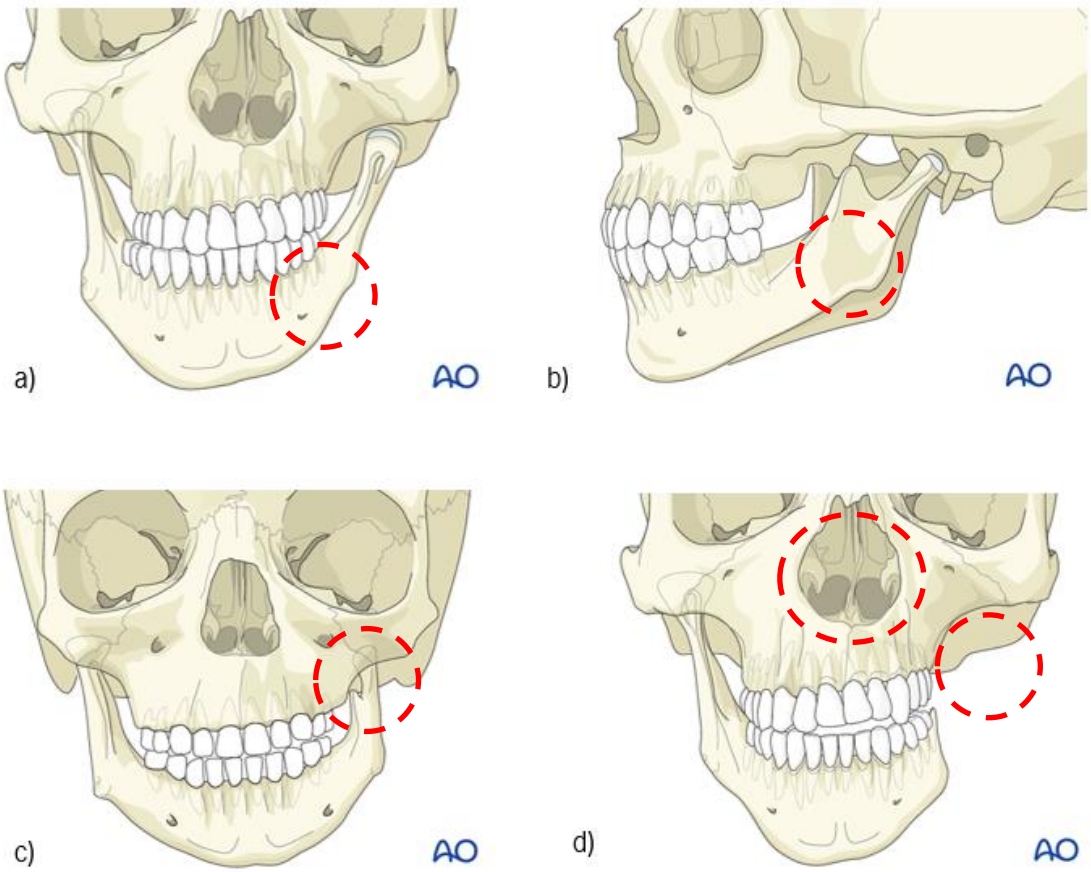


Figure 3-1: Degrees of hemifacial microsomia according to the Pruzansky-Kaban classification: a) type I (minimal degree of hypoplasia), b) type IIa (mild to moderate hypoplasia), c) type IIb (TMJ abnormally placed inferiorly, medially, and anteriorly) and d) type III (severe hypoplasia – no discernible fossa and absent condyle and ramus).
(*Adapted from* Bartlett, Ehrenfeld, Mast, & Sugar, 2012)

Other associated anomalies of hemifacial microsomia include cardiac, renal, and neurologic defects. Most patients with hemifacial microsomia are nonsyndromic but a small percentage have Goldenhar syndrome (Cladis et al., 2011). Goldenhar syndrome is considered a

variant of HFM, it is present in about 10% of HFM patients and is characterized by additional anomalies of the ribs and vertebrae and the presence of epibulbar dermoids (Posnick, 2013; Resnick et al., 2017). As the head grows, the affected side becomes worst compared to the normal side, which grows at a standard rate. Therefore, HFM can be considered a progressive deformity. Patients with hemifacial microsomia can have significant upper airway obstruction and obstructive sleep apnoea (OSA).

Besides the Pruzansky-Kaban classification, another common classification scheme used for this disorder is the **OMENS (+)** system, Appendix A, which scores the most common deformities seen on a 0 to 3 scale of severity: **O**rbital asymmetry, **M**andibular hypoplasia, **E**ar deformity, **N**erve dysfunction, **S**oft-tissue deficiency, and **(+)** extracranial manifestations (Yates & Sinn, 2017).

The treatment approach varies according to the patient and is dictated by the type (I, IIa, IIb, III) of the mandibular deformity, by the midface deformity, age, and psychosocial adjustment of the child. The ultimate goal of the selected treatment in childhood is to achieve improved function and optimal facial symmetry and aesthetics when craniofacial growth is complete (Posnick, 2013; Resnick et al., 2017).

3.1.2 Pierre Robin sequence

Pierre Robin sequence previously referred to as Pierre Robin syndrome is a heterogeneous birth defect that has a prevalence of approximately 1 per 8500 to 14000 live births. ("Isolated Pierre Robin sequence: MedlinePlus Genetics," n.d.). PRS is not a syndrome, but rather a sequence of disorders, with one abnormality resulting in the next (Hsieh & Woo, 2019). This sequence is characterized by a succession of interrelated abnormalities affecting the face and neck, comprising of a small mandible (micrognathia) which translates into an abnormal posterior placement of the tongue (glossoptosis) culminating in airway obstruction, as illustrated in Figure 3-2. In addition to the specified malformations, most people who suffer from PRS are also born with an opening in the roof of the mouth, a cleft palate. In about 91,7% of cases, micrognathia is reported and it is characterized by a small mandibular body and retraction of the inferior dental arch 10-12 mm behind the superior arch (Hsieh & Woo, 2019). In some cases, the growth of the mandible catches up by age 5-6 years and as adults, these individuals have normal-sized chins.

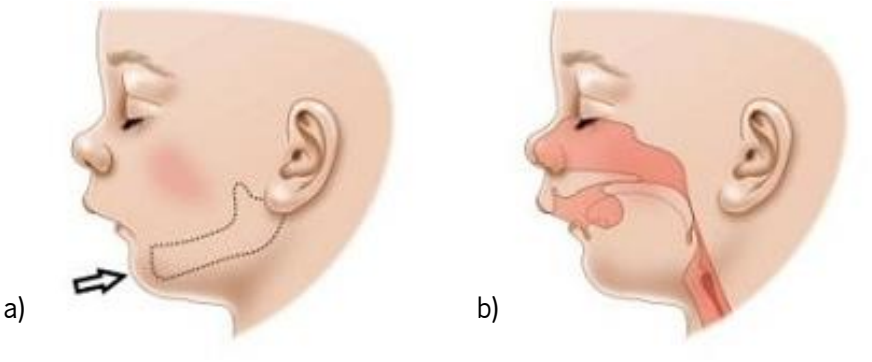


Figure 3-2: a) Micrognathia and b) a small airway channel and tongue causing airway obstruction.
("Kids Health Information : Pierre Robin sequence (PRS)," 2020)

The combination of all these aspects that characterize PRS can lead to extremely serious clinical problems such as difficulty in breathing and feeding. As a result, a great percentage of affected babies are unable to develop normally due to their inability to grow and gain weight at the expected rate. ("Pierre Robin Syndrome: Background, Etiology and Pathogenesis, Otolaryngologic Manifestations," n.d.; Hsieh & Woo, 2019).

Infants with PRS should undergo a thorough clinical evaluation to assess the anatomic findings and address the feeding and breathing issues caused by the airway obstruction. For this task, a multidisciplinary approach is ideally appropriate, consisting of specialists from plastic and reconstructive surgery, paediatric otolaryngology, paediatric pulmonology, speech pathology, nursing, paediatric anaesthesia, and neonatology. In the majority of cases, the breathing and feeding problems are overcome through the placement of nasopharyngeal and nasogastric tubes, accordingly. However, many studies show that there is a subset of PRS infants that do not respond to these conservative measures and require further intervention. The most commonly used methods for surgical management of airway obstruction include tongue-lip adhesion, tracheostomy and most recently distraction osteogenesis.

3.1.3 Treacher Collins Syndrome

Treacher Collins Syndrome, also known as Franceschetti-Zwahlen-Klein syndrome, is the most common mandibulofacial dysostosis affecting about 1 in every 25,000 to 50,000 births. TCS is always a genetic syndrome but is not usually inherited. This condition is caused by an abnormal gene that regulates the development of bones and other tissues of the face.

The range of presentation of this syndrome is extensive, varying from mild cases with minimal deformity and no functional deficit, to severe cases resulting in airway compromise leading

to death in the perinatal period (Koppel, 2017). Babies who bear this disease are differentiated by having hypoplasia of facial bones, particularly the mandible and zygoma (78 % of the cases have mandibular hypoplasia), external ear anomalies or microtia, lower eyelid colobomas, external auditory canal atresia, bilateral conductive hearing loss and lateral downward sloping palpebral fissures. Figure 3-3 portrays a case of TCS. Such conditions cause simple and basic tasks such as breathing, sleeping, eating, and hearing to be a challenge for infants. From birth, the efficacy of the airway is of primary concern. The degree of airway obstruction is strongly related to the degree of maxillary and mandibular hypoplasia and glossoptosis (Cladis et al., 2011; Yates & Sinn, 2017). Treacher Collins syndrome may be mistaken for bilateral craniofacial microsomia however, TCS is symmetrical and has a well-defined inheritance pattern. Diagnosis of TCS is usually made clinically and can be confirmed with genetic testing (Evans et al., 2018).

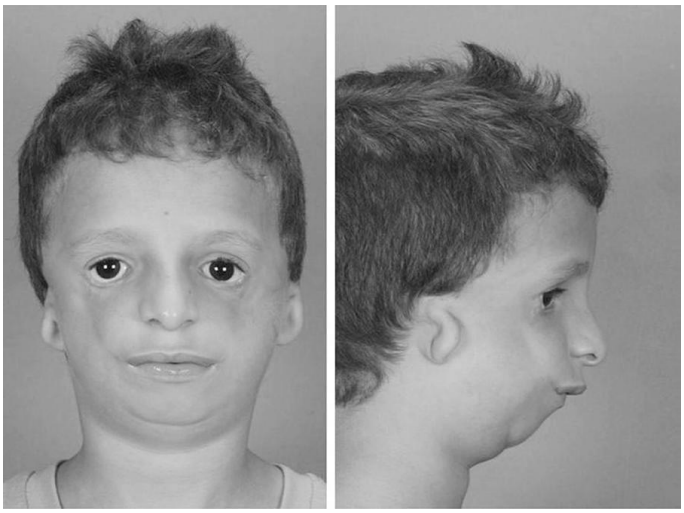


Figure 3-3: Treacher Collins Syndrome case.
(Lodovichi et al., 2018)

Table 3-3 describes the timing of treatment interventions for most cases of Treacher Collins Syndrome cases.

Table 3-3: Treatment interventions for TCS.
(*Adapted from* Koppel, 2017; Yates & Sinn, 2017)

Timeline	Treatment description
Perinatal period	• Airway support if necessary, including tracheostomy; • Feeding support; • Introduction to the craniofacial team Introduction to a support group.

Table 3-3: (Continued).

Timeline	Treatment description
Infancy	• Hearing aid; • Growth and development monitoring; • Airway and feeding support if necessary; • Early distraction in cases of extreme retrognathia with airway problems; • Cleft palate repair at 6 months unless contraindicated by airway problems.
Childhood	• Early orthognathic/mandibular procedures. Ramus reconstruction by rib graft or distraction. Mandibular lengthening by DO can be considered; • Eyelid surgery, orthodontics, and ear reconstruction.
Adolescence and maturity	• Reconstruction of the mature facial skeleton: orthognathic surgery, mandibular and/or facial procedures (usually BSSO and Le Fort I); • Rhinoplasty; • Soft tissue refinements: midface lift.

In the majority of the less complicated cases of TCS, lengthening of the mandible must be delayed until the jawbone growth has been completed. The younger the mandible, the riskier and technically demanding is the procedure. Therefore, early DO (age 12 or younger) should be reserved for patients that exhibit severe airway compromise (Koppel, 2017).

4. DISTRACTION OSTEOGENESIS

Distraction osteogenesis (DO), also known as callus distraction, callotasis and osteo-distraction, is a relatively new surgical technique and involves a slow and continuous application of a constant and controlled force to a created osteotomy gap, resulting in the formation of new bone and soft tissues between the two surfaces of bone segment (George & Hegde, 2012). This bone elongation method is based on an essential law developed by Ilizarov – "Law of Tension Stress", which claims that gradual tension on living tissues creates stress that can stimulate and maintain regeneration and active growth of involved tissues (Guerrero et al., 2012; M. Singh, Vashistha, Chaudhary, & Kaur, 2016). This traction force and therefore separation of bone segments is achieved by means of a distraction device.

In 1905, Allessandro Codivilla performed the first attempt at lengthening a femoral fracture in Bologna, Italy. Abbot, in 1927, published a similar report, however, the technique was fraught with complications related to the insufficient study of the biological principles and poorly designed devices, culminating in not so favourable results. It was the orthopaedic surgeon Gavril Ilizarov from Kurgan, Russia, that in the 1950s pioneered the biological principles of bone and soft tissue regeneration and popularized the technique of distraction osteogenesis without bone grafts by using an external device to apply slow and gradual traction to a fractured and shortened leg (Hamdy, Rendon, & Tabrizim, 2012). DO procedures gained popularity in the '70s and '80s. Since then, the application of these principles has extended to all forms of orthopaedic correction, including craniofacial surgery (George & Hegde, 2012; Guerrero et al., 2012).

4.1 Mandibular distraction osteogenesis (MDO)

Snyder et al. introduced mandibular distraction in membranous bones of canine models in 1973 (Snyder, Levine, Swasson, & Browne, 1973). However, it was only in 1992 when the first successful distraction of the human jaw was reported by McCarthy. Commonly treated conditions include craniofacial deficiencies, syndromic craniosynostosis, PRS, HFM, posttraumatic deformities, and sleep-related breathing disorders (Hamdy et al., 2012).

Typically, the distraction process implies a previous surgical procedure, an osteotomy or corticotomy, which consists of cutting the bone on a specific place in order to separate segments

of bone. This procedure must ensure total nerve and blood supply preservation (Drahansky et al., 2016). Although cases where bone lengthening is achieved without the need of an osteotomy can be observed, these are very uncommon and are only seen in infants, since the bone is not fully formed and mineralized, thus allowing it to be more easily shaped. A case study conducted by Graewe et al. demonstrated positive results in the distraction of the middle face in babies (midface hypoplasia) with only 3 months of age, without resorting to bone-cutting (Graewe, Morkel, Hartzenberg, Ross, & Zuehlke, 2008). Several other studies have been done on animals, and the conclusion reached was common to all of them: the bone distraction process without recourse to osteotomy is closely related to the subject's age. The older you are, the less effective the process is, with no changes in bone (Graewe et al., 2008; Tung h., Thomas, Robertson, Bradley R., D.D.S., Jonathan M. Winograd, Tarun Mullick, & N. Manson, Paul, 1999). Although bone lengthening proved to be possible without osteotomy, this method is not standard in DO due to its susceptibility and variability among patients.

The distraction process usually consists of 4 phases (Figure 4-1): the latency period, the distraction or activation phase, the consolidation phase, and the remodelling period. The first phase is the latency period, and it occurs just after the performance of the osteotomy/corticotomy and application of the distraction device. This phase involves the early stages of bone healing at the osteotomy bony interface and can last from 1 to 7 days depending on the age of the patient and the site of distraction. In some patients, especially in the youngest, as in the case of babies with only a few days or months, this phase can be suppressed and the activation phase occurs right after the osteotomy. Following the latency period, gradual distraction forces are applied during the distraction phase to separate the edges of the bone segments and induce bone formation. At the end of activation, the distracted bone is maintained in fixation to allow for consolidation of the newly formed bone — the consolidation phase, which typically lasts between 8 and 12 weeks. In this phase takes place the mineralization of the regenerated bone. Then the appliance is removed followed by remodelling which is the period from the application of normal functional loads to the complete maturation of the bone (George & Hegde, 2012).

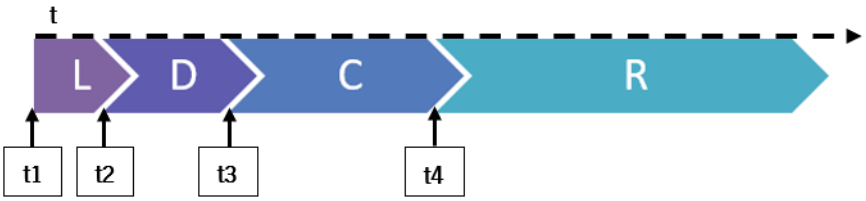


Figure 4-1: Phases of distraction osteogenesis. L – Latency period (0 – 7 days); D – distraction phase; C – consolidation phase; R – Remodelling period; t – timeline; t1 – osteotomy and device placement; t2 – end of latency period and start of activation; t3 – end of activation and start of consolidation period; t4 – end of consolidation period and device removal.

4.1.1 Biological processes of Distraction osteogenesis

Understanding the physiological aspect of bone and the features that allow it to operate in response to mechanical loading is essential to comprehend the effects of the induced stress during MDO. Similarly, comprehension of the biomechanical aspects of the bone healing process is crucial in creating the optimal healing environment.

Bone is a complex and extremely specialized supporting structure of the body and it is characterized by its stiffness, rigidity and power of repair and regeneration (M. Singh et al., 2016). For practical purposes, bone is characterized as a composite material having an organic and inorganic phase. About 20% of bone is water and the dry weight consists of 30%-35% organic and 65%-70% inorganic substances. While organic material (collagen and concolagenic proteins), gives bone its resilience and tensile strength, the mineralized matrix (crystalline mineral salts and calcium in the form of hydroxyapatite) gives bone its resistance to compression (Natu et al., 2014). The cellular components of bone include osteoblasts, osteocytes, osteoclasts, and osteogenic precursor cells (mesenchymal osteoprogenitor cells). Osteoblasts and osteocytes differ from the mesenchymal stem cells (MSC) considering that osteocytes are mature osteoblasts trapped in the lacunae and osteoblasts produce collagen. Besides their primary function (synthesis, regulation, deposition, and mineralization of the extracellular matrix - ECM) these cells play a part in blood-calcium homeostasis and act as a mechanosensor for bones. (Oryan, Monazzah, & Bigham-Sadegh, 2015)

Overall, bones are classified according to their shape, which in turn is related to the function they perform in the body. There are five major bone types: flat bones such as the skull and thoracic cage which protect internal organs; long bones (e.g., femur, tibia, humerus, phalanges, etc.) which support weight and facilitate movement; short bones located in the wrist and ankle joints and provide stability and some movement; sesamoid bones which are bone

embedded in tendons (e.g., patella) to protect them from stress and wear; and irregular bones (e.g., vertebrae, sacrum, coccyx, maxilla or mandible) which, due to their peculiar form, cannot be grouped in any category mentioned above. The purpose of irregular bones includes the protection of the nervous tissue, affording multiple anchor points for skeletal muscle attachment and maintaining the support of the pharynx, trachea, and tongue. Irregular bones, such as the mandible, consist of cancellous tissue (spongy/trabecular bone) enclosed within a thin layer of compact (cortical) bone (Figure 4-2) ("Types of Bones | Learn Skeleton Anatomy," n.d.; "Bone Classification and Structure | Anatomy and Physiology," n.d.). The thickness of the cortical layer varies from 0.5 mm to 2.5 mm throughout the mandibular bone.

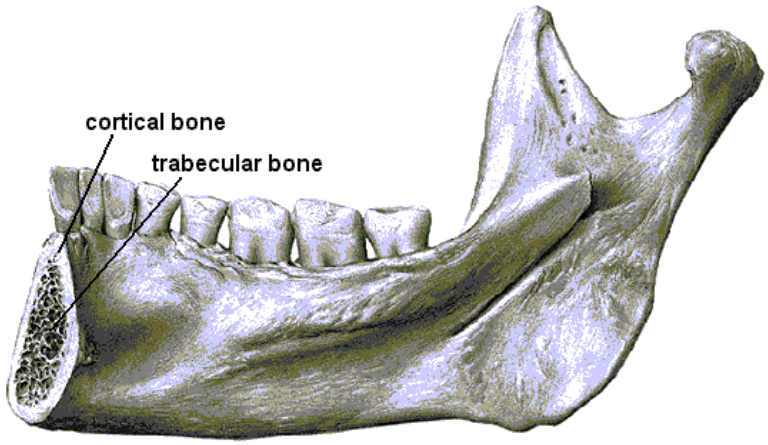


Figure 4-2: Mandible composition: the outer layer of the cortical (compact) bone surrounding the inner layer of trabecular bone. (Kober, Erdmann, Lang, & Deuflhard, 2001)

Both cortical and trabecular bone tissue are similar in cell type and matrix however, cortical bone is highly calcified (80-90% of the volume) providing its high density. Cortical bone is stiffer and brittle and has a slower turnover rate than the trabecular bone. The Young's modulus is high, and failure occurs at 2% strain. On the other hand, trabecular bone has more vascular and bone marrow intrabecular spacing conferring its porosity. Because it is more elastic than compact bone, trabecular bone has the ability to store significantly more energy before failure. Young's modulus is low, and the failure normally occurs at 75% strain. Trabecular bone plays an important role in sustaining weight-bearing tensions and supporting joint cartilage (Shrivats et al., 2014).

Synthesizing of bone can be made according to three mechanisms: endochondral ossification, intermembrane ossification or a combination of both. Figure 4-3 represents the synthesizing mechanism of the different bones of the head. Endochondral bone formation includes recruitment, proliferation, and differentiation of the undifferentiated mesenchymal cells into cartilage, which is followed by calcification and replacement with bone. This mechanism is

responsible for the formation of the entire appendicular (limbs and pelvis) and much of the axial skeleton, including the ribs, scapulae, and skull base (Ghiasi, Chen, Vaziri, Rodriguez, & Nazarian, 2017; Runyan & Gabrick, 2017). On the other hand, intramembranous bone formation is achieved by direct transformation of mesenchymal cells into osteoblasts, without the mediation of a cartilage phase intermediate. It is the process responsible for the formation of the flats bones of the cranial vault, including the mandible (Ghiasi et al., 2017; Karaplis, 2008).

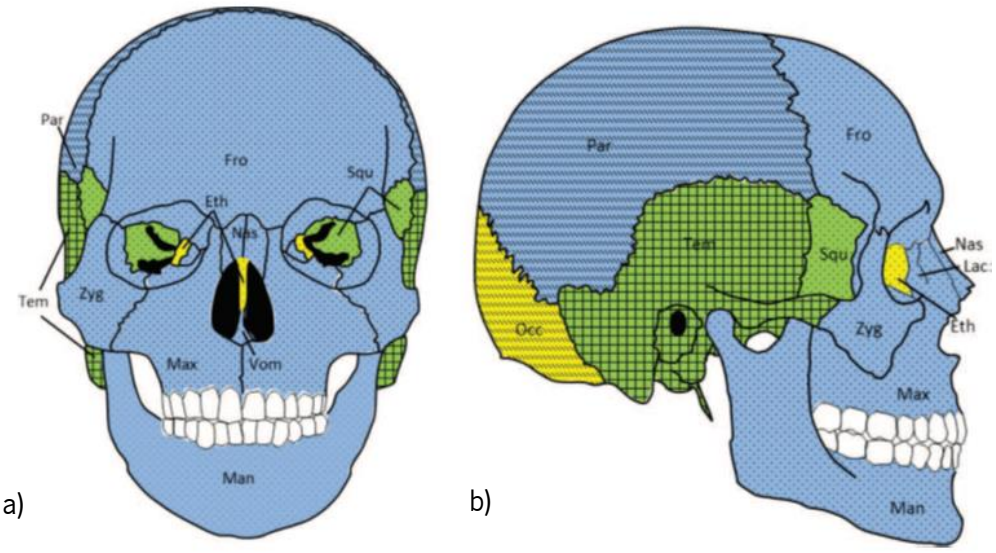


Figure 4-3: Synthesizing mechanism of the different bones of the head. Two different views of the human craniofacial skeleton including a) frontal, b) lateral. Blue - intramembranous ossification. Yellow - endochondral ossification. Green - both intramembranous and endochondral ossification.
(Runyan & Gabrick, 2017)

According to Karp et al., at the histologic level, the healing process in a fracture differs from that of healing in DO in two fundamental aspects (Karp, McCarthy, Schreiber, Sissons, & Thorne, 1992):

- In DO controlled micro-trauma is present in between distraction gap.
- In DO, instead of endochondral ossification, membranous ossification occurs.

This process is of extreme complexity and cellular dynamics involving the migration, differentiation, and proliferation of various cells, and can overall be organized into three phases:

I. Hematoma phase
II. Mechanical strain
III. Consolidation period and remodelling phase

When performing the osteotomy and consequent separation of bone fragments, the cortex ruptures, resulting in haemorrhage and, subsequently, the formation of a fibrin clot and fracture

hematoma between and around the sectioned segments. The initial hematoma becomes a blood clot, and a process of necrosis begins on the margins of bone fragments caused by the local hypoxia. According to McCarthy this hypoxic zone of injury stimulates an angiogenic response and initiates the migration of primitive mesenchymal cells (primarily derived from the periosteum) and the synthesis of collagen Type I, replacing the blood cloth with granulation tissue and then fibrous tissue leading to the formation of the initial soft callus around (periosteal callus) and between (endosteal callus) the osteotomized bone segments. This callus tissue contains inflammatory cells, fibroblasts, a rich fibrin matrix, collagen, invading capillaries and cells with osteogenic potential (Karp et al., 1992). This callus will act as the body for the distraction.

Tensile strains are the main stimuli for bone regeneration. Throughout the activation period, the bone segments are gradually separated, causing the callus to stretch and immature woven bone, whose fibres are parallel to distraction force, to form. Several osteogenesis phenomena are then observed: proliferation of progenitor MSCs, increased blood flow, vascular proliferation and local increase of growth factors and matrix proteins necessary for bone formation. Consequently, the mesenchymal progenitor cells begin to undergo differentiation into angioblasts, fibroblasts, and osteoblasts. Osteoblasts release an uncalcified bone matrix also known as osteoid. With the addition of calcium salts and the enzyme Alkaline Phosphatase acting as a catalyst, the osteoid is then calcified and the osteoblasts can be further differentiated into osteocytes which house themselves in the lacunae (Figure 4-4). This is the start of the primary trabeculation (Natu et al., 2014; Oryan et al., 2015; M. Singh et al., 2016).

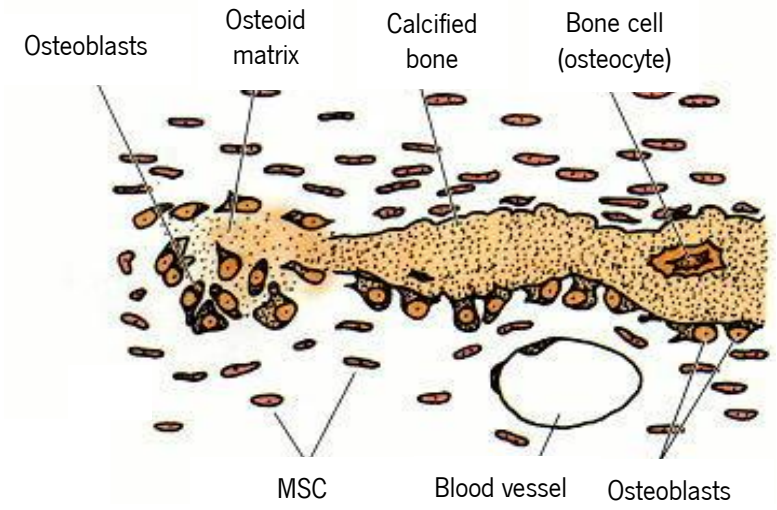


Figure 4-4: Process of intramembranous ossification.
(Gilbert, 2009)

It is commonly suggested that distraction forces leading to cellular deformation are signalled to the cellular genome through mechanotransduction. Active distraction creates pressure, fluid

flow, tensile strain, and tissue dilatation (local deformation occurring equally in all directions) within and around the distraction area. Fluid movement causes shear stress and drag forces that act on osteocytes within the bone. Studies indicate that these shear stresses will activate osteocytes and signal osteoblasts to initiate new bone formation (Natu et al., 2014). This process is denominated mechanotransduction (Amir, Everts, & Bronckers, 2009). The mechanism o mechanotransduction is essential for bone adaptation to mechanical loading and is based on the principle that bone cells can detect and transform physical force signals into biochemical signals. These biochemical signals will result in cellular responses of osteoblasts and osteoclasts which will lead to appropriate changes in the architecture of bone (Natu et al., 2014).

In the consolidation period, the separation of the bone segments ends and the ossification process continues forming the hard callus. This period ends with the removal of the device. Patients are encouraged to perform active physical therapy causing the newly formed regenerate to undergo a functional remodelling process to form a regenerate which resembles native bone in shape, size, and biomechanical competency (Oryan et al., 2015; M. Singh et al., 2016).

A concise schematic of the biological phases of MDO can be seen in Table 4-1.

Table 4-1: Schematic representation of the cellular stages of osteogenic distraction.

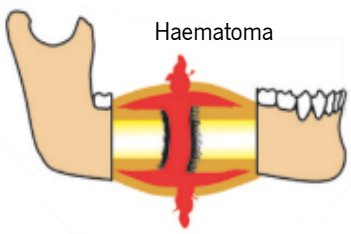
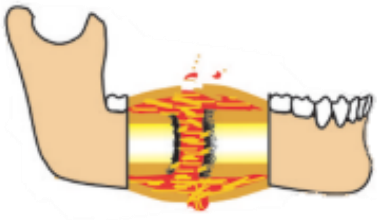
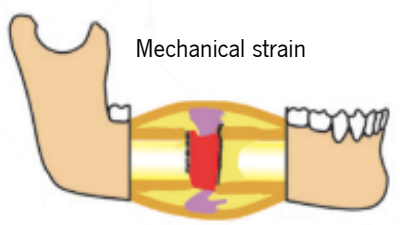
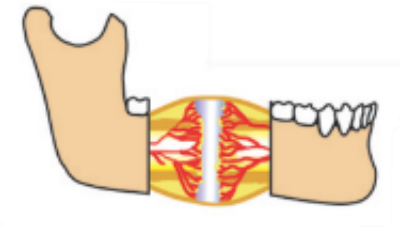
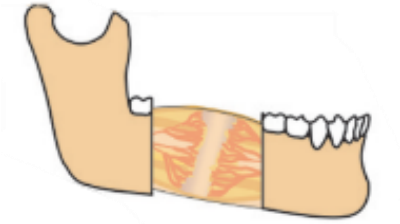
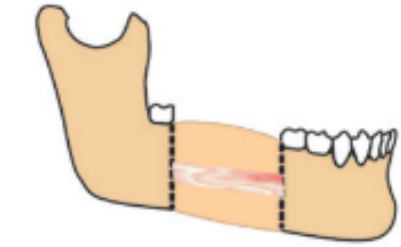
DISTRACTION PHASES	BIOLOGICAL BEHAVIOUR
Osteotomy	
	• Formation of haematoma in the gap; • The haematoma is converted to a blood clot and bone necrosis occurs at the ends of the fracture segments.
Latency Period	
	• Stage of inflammation; • Ingrowth of vasoformative elements and capillaries (angiogenesis) for the restoration of blood supply; • Cellular proliferation; • The clot is replaced with granulation tissue; • The granulation tissue is converted to fibrous tissue by fibroblasts leading to the formation of soft callus.

Table 4-1: (Continued).

DISTRACTION PHASES	BIOLOGICAL BEHAVIOUR
Distraction Period	
	• MSCs begin to undergo differentiation into angioblasts, fibroblasts, and osteoblasts; • Start of the primary trabeculation.
Consolidation Period (no distraction)	
	• Formation of the hard callus.
Distractor removal	
	• Gradual corticalization of the regenerate.
Remodelling process	
	• Formation of the medullary canal.

In summary, a microscopic examination of the distraction gap revealed that there are three distinct histologic zones of the development of the bony regenerate as observed in Figure 4-5 (Guerrero & Bell, 1999):

A. Two zones of osteotomized bone margin composed by mature bone.

B. Two zones of bone formation, where the columns of newly formed bone tissue (yellow) gradually extend from the osteotomized bone margin towards the central fibrous zone. In orange, the newly formed bone tissue is going through the remodelling process where bone spicules are lined by osteoblasts and osteoclasts;

C. A central zone of fibrous tissue with active mesenchymal proliferation and consisting of highly organized, longitudinally oriented parallel strands of collagen with spindle-shaped fibroblasts and undifferentiated mesenchymal precursor cells throughout the matrix. The fibrous zone functions as true growth zones preventing the union of the bone segments. This growth dynamic ceases when the device stops being activated and the fibrous zone disappears, allowing the complete union of the bone segments. There are more blood vessels (V) in this area.

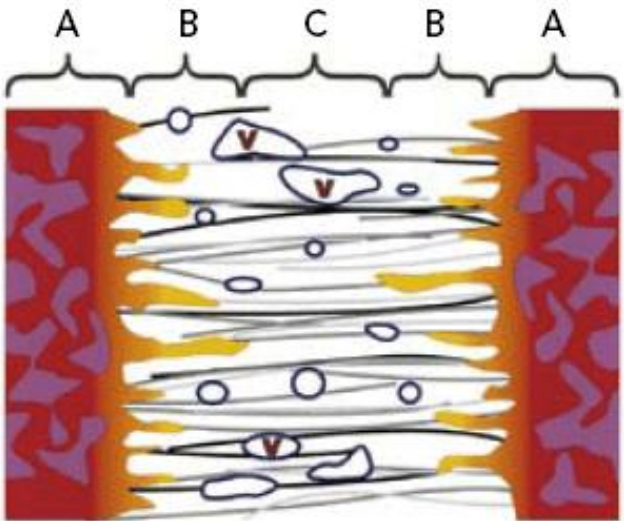


Figure 4-5: Schematic representation of the microanatomy of the regeneration region during the distraction period. A – zones of mature bone, B – zones of bone formation, C – zones of fibrous tissue with active mesenchymal proliferation; V – blood vessels. (*Adapted from* Mathes, 2007)

In distraction, as the segments are separated under the influence of tensional stresses, the overlying soft tissues envelop is also stretched, initiating a sequence of adaptive changes named distraction histogenesis. Active histogenesis occurs in different tissues: skin, fascia, blood vessels, nerves, muscle, ligament, cartilage, and periosteum. Histological evidence showed that all these soft tissues also grow in de direction of the applied stress (Ilizarov, 1989). These adaptive changes in the soft tissues may allow larger skeletal movements while minimizing the potential relapse seen in acute orthopaedic corrections (J. B. Cope, Samchukov, & Cherkashin, 1999). Simpson et al. confirmed that a slower rate of distraction provides better muscle adaptation whereas rapid rates of distraction are associated with necrosis, disorganization of muscle structure

(Simpson, Williams, Kyberd, Goldspink, & Kenwright, 1995). A similar response is observed in the other soft tissues. More factors and their influence on the DO process are presented in the sub-Chapter 4.2.

4.1.2 Orthognathic surgery and distraction osteogenesis in maxillofacial surgery

Correction of developmental or acquired oral and maxillofacial skeleton deformities (OMSDs) can be performed through orthognathic surgery with or whithout bone grafts, and flap surgeries. Orthognathic surgery is closely connected with orthodontics; therefore, the correction of maxillofacial deformities implies cooperation between the orthodontist and the maxillofacial surgeon. Orthognathic surgery consists of adjunctive procedures to improve hard and soft tissue contours. During the last decades, orthognathic surgery has undergone considerable advances in surgical osteotomy techniques and instrumentation. However, the basic surgical principles remained more or less identical (Kashani & Rasmusson, 2016). Some of the surgical techniques used for the correction of maxillofacial deformities are Le Fort (I, II and III), bilateral sagittal split osteotomy (BSSO) of the mandible, vertical ramus osteotomy, inverted L ramus osteotomy, anterior subapical osteotomy, and genioplasty. Table 4-2 presents a brief overview and representation of the most common orthognathic surgeries.

Table 4-2: Brief overview and representation of some of the orthognathic surgeries.
(*Illustrations adapted from* Kashani & Rasmusson, 2016b)

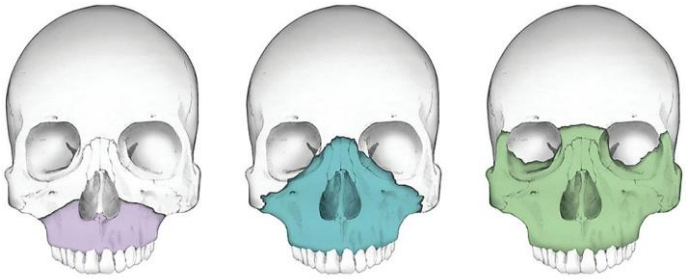
Orthognathic surgery	Brief overview
Le Fort (I, II and III)	 The Le Fort I Osteotomy procedure is chosen most commonly when only the upper jaw needs to be moved forward. The Le Fort II Osteotomy is rare and involves the movement of the nose and upper jaw together. The Le Fort III Osteotomy is designed to move the entire face forward, including portions of the eye sockets and is typically used in the treatment of midface deficiencies ("Le Fort Osteotomy: Procedures 1, 2 & 3," n.d.).

Table 4-2: (Continued).

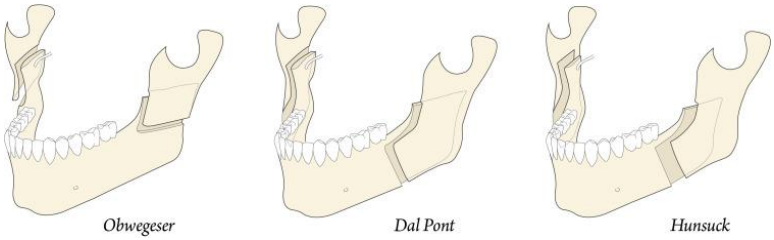
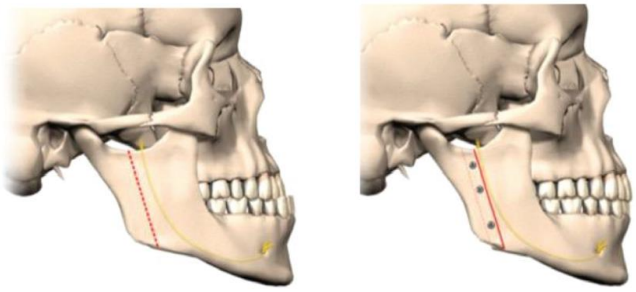
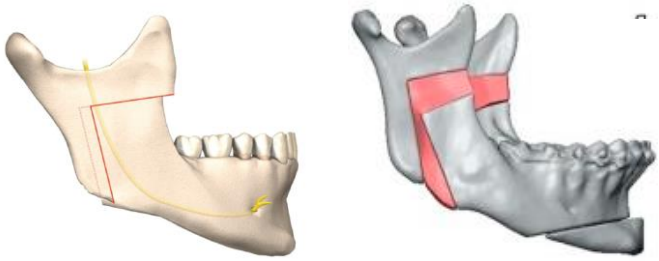
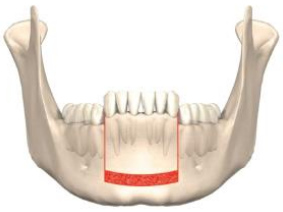
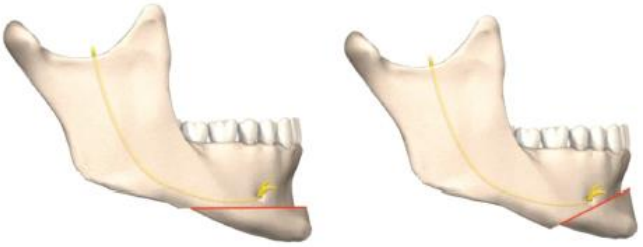
Orthognathic surgery	Brief overview
Bilateral Sagittal Split Osteotomy (BSSO)	 It is generally the procedure of choice for mandibular advancement in the treatment of micrognathia. It is used in cases where the ramus has insufficient bone volume making it difficult to proximally fix the intraoral device. This osteotomy provides more contact surface for callus formation (Kashani & Rasmusson, 2016).
Intraoral Vertical Ramus Osteotomy (IVRO)	 Indicated for the management of horizontal mandibular excess and asymmetry. Up to 10 mm of mandibular setback is possible with IVRO. Additionally, small segment advancement (less than 2 mm) can be achieved (McKenna & King, 2016).
Inverted L Ramus Osteotomy	 Frequently applied to class II skeletal deformities that possess a short vertical ramus height and concomitant high mandibular plane angle. The skeletal correction often requires significant counterclockwise movement to improve the projection of the lower face (Franco & Farrell, 2016).

Table 4-2: (Continued).

Orthognathic surgery	Brief overview
Anterior subapical osteotomy	 This procedure allows teeth and supporting alveolar bone to be repositioned into a proper relationship with the remaining occlusion and creates adequate space for aesthetic and functional restorations (Schmitt, Cronin, & Berg, 1992).
Genioplasty	 Genioplasty procedures can alter the position of the chin in all three planes of space. Chin position is most commonly changed by a sliding osteotomy (Wolford & Goncalves, 2017).

The advantages of conventional orthognathic surgeries are numerous. These procedures are single-stage and allow for immediate results. There is less need for patient compliance, segmental discrepancies can be addressed, and fewer post-surgical orthodontic adjustments are required. The scars are minimal and imperceptible since the majority of orthognathic surgeries are performed within the mouth. On the other hand, pre-surgical orthodontics is always required and the main drawback of orthognathic surgery is that it cannot be undertaken while the patient's growth is incomplete, and during this period, the patient has to bear a lot of psychological trauma. In addition, in orthognathic surgery advancements of more than 7 mm are not advisable and those of more than 10 mm are considered to be of elevated risk of relapse. In advancements of more than 7 mm, bone grafts are desirable to stabilize the osteotomized segments (Ramanathan et al., 2020).

Another more recent method of treating craniofacial malformations is distraction osteogenesis. This method possesses significant vantages such as reduced operating time, no need for bone grafts, greater stability, a greater probability of maintaining vascularity and neurosensory integrity, and the ability to produce greater skeletal movements compared to orthognathic surgery. Additionally, this procedure is versatile and can be performed at any age (Ramanathan et al., 2020). At the same time, DO requires precise placement of the device to minimise unwanted results such as open bites and asymmetries, the cost of the surgery is higher, the procedure demands for patient compliance and frequent appointments, and mild overcorrection of the segments is advised to reduce later discrepancies that may occur during growth. The main advantages and disadvantages of these two procedures are shown in Table 4-3.

Table 4-3: Advantages and disadvantages of conventional orthognathic surgery and distraction osteogenesis.

Conventional Orthognathic Surgery		Distraction Osteogenesis	
Vantages	Disadvantages	Vantages	Disadvantages
Single-stage and allows for immediate results	Smaller skeletal movements	Ability to produce larger skeletal movements	Two procedures: placement and removal of the distractors.
More precise skeletal movements with a low mean error	Higher risk of relapse	Better long-term stability	Need for device's precise positioning to produce the desired bone movement
Scars are minimal and imperceptible	BSSO has larger incidences of inferior alveolar nerve disturbances	Decreased neuro-sensory loss	Increased cost
Minimal infection rates	Occasional need for bone grafts	Elimination of the need for bone grafts	Higher risk of infection due to distraction rods penetrating the oral mucosa
Less need for patient compliance	Cannot be undertaken while the patient's growth is incomplete	Can be performed at any age, from neonates to adults	Need for patient compliance and frequent appointments
Less post-surgical orthodontic adjustments required		Less trauma to TMJ	

Taking into consideration the various advantages, the distraction osteogenesis method has been favoured by many surgical units. It is necessary to bear in mind that it is not accurate to directly compare osteogenic distraction with orthognathic surgery. DO is a reconstructive procedure that is utilised for larger skeletal movements that are not obtainable with conventional orthognathic surgery.

4.1.3 Types of mandibular distraction devices

There is a wide variety of distractors, which can be classified according to the following criteria (Figure 4-6):

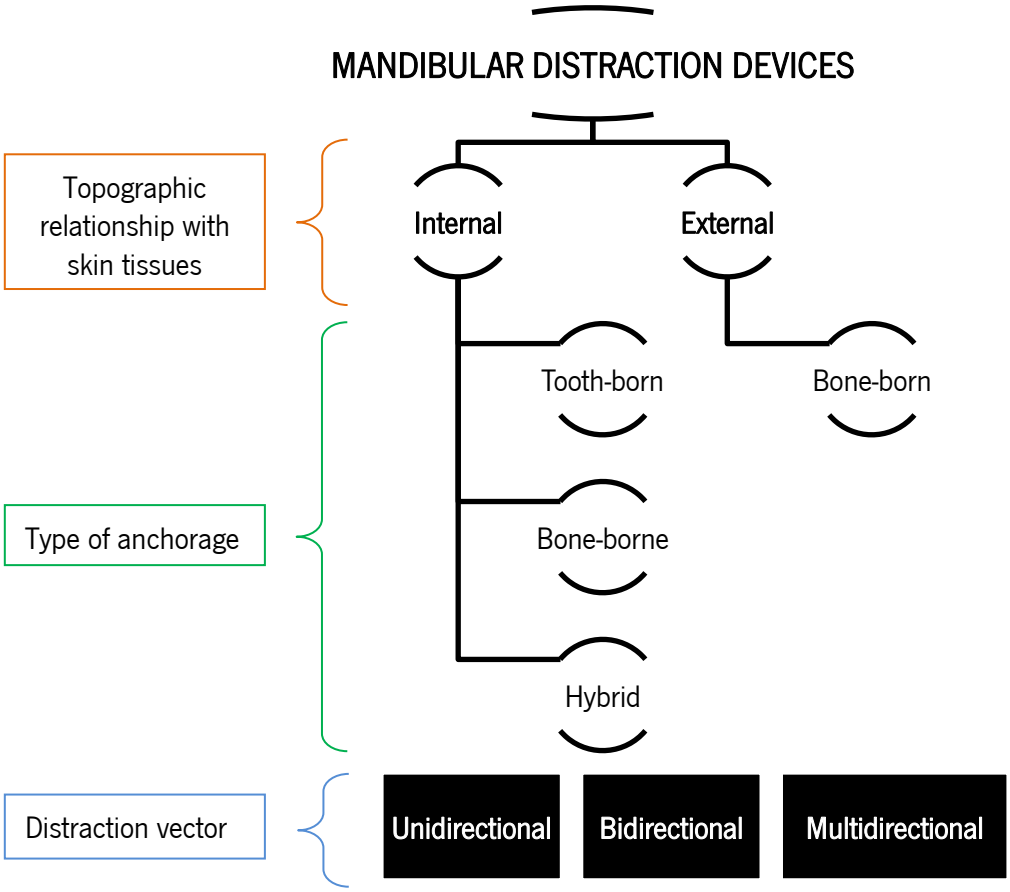


Figure 4-6: Classification of bone distractors.

a. Topographic relationship with skin tissues

The devices can be external or internal. Internal distractors (Figure 4-7 a)) are placed inside the oral cavity and are, therefore, also called intraoral. Due to the limited available intraoral space, especially in new-borns and infants, these devices must have reduced dimensions which can

compromise their desirable rigidity and stability during distraction. The difficult access to the oral cavity also limits its location and consequently its field of action.

External or extra-oral devices (Figure 4-7 b)) are entirely placed outside the organism and are attached to the bone by percutaneous pins (Drahansky et al., 2016). They were the first to be developed and are currently used for larger bone advancements and in cases where there is not sufficient intraoral space or bone to fixate internal devices.

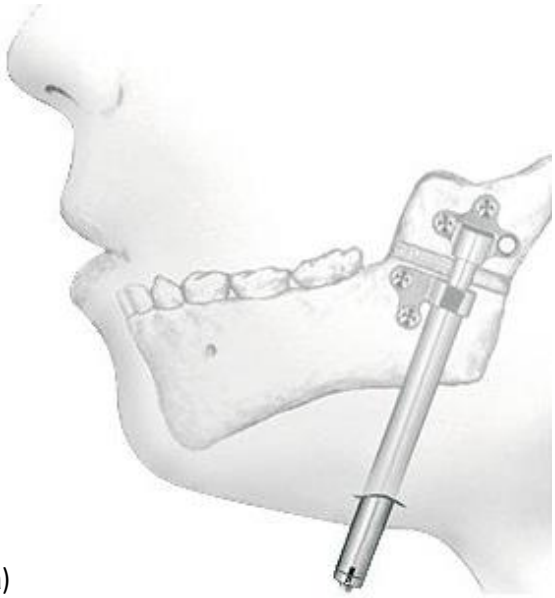
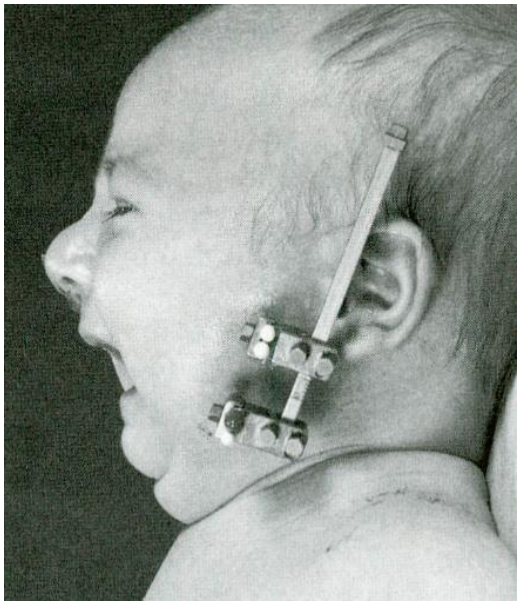
a)  b) 

Figure 4-7: Examples of a) internal and b) external devices.
(Denny, 2002)

Both internal and external distractors have their advantages and disadvantages. The choice between the two for clinical application should be well studied and based on the different variables that affect each DO case. Some of these variables are the patient's age, the area where the distraction will be planted, the type and size of the bone, the existence of other pathologies, among others.

The most favourable vantages of internal distractors are the improved psycho-social comfort of the patient, the elimination of skin scarring caused by translation of transcutaneous fixation pins, improved stability of the attachment of the device to the bone, better patient compliance during the consolidation phase and lower risk of infection. However, there are major drawbacks, such as the need for precise positioning of the device, the inability to alter the distraction vector during the distraction process and the need for a second operation for the distractor removal (Meling, Høgevold, Due-Tønnessen, & Skjelbred, 2011). In the case of external

distractors, their most valuable benefits are the ability to alter the distraction vector during the process, and the avoidance of major surgery for device removal after the consolidation phase. Despite these advantages, external devices are prone to major skin scarring and infection around the pins, pin loosening, pin migration (mainly on cranial distractions), increased risk of injury to dental organs and nervous structures and the need for patient compliance (Drahansky et al., 2016). Table 4-4 resumes the advantages and disadvantages of internal and external devices.

Table 4-4: Advantages and disadvantages of internal and external distractors.
(*Adapted from* Drahansky et al., 2016)

	Internal	External
Vantages	• Minimal skin scarring; • Improved device stability; • Improved patient compliance; • Lower infection risk.	• Multidirectional lengthening with angular adjustment possible during DO; • Ability to alter the distraction vector; • Can be removed without the need for a second operative procedure; • Relatively simple to apply intraoperatively; • Easy for patient to activate.
Disadvantages	• Need for precise positioning of the device, which can be challenging in patients with previous operations or cranial deficiencies; • The inability to alter the distraction vector; • The need for a second major operation for distractor removal; • Design limitations due to the limited size of device and restricted access to oral cavity.	• Patient apprehension to wear bulky external devices; • Major skin scarring and infection around the pins; • Pin loosening; • Need for patient compliance during the consolidation phase.

b. Type of anchorage

According to the type of hard tissues to which the device is attached, distractors can be divided into: bone-borne (Figure 4-8 c)) if the device is attached to the bone, tooth-borne (Figure 4-8 a)) if the device is attached to the teeth or hybrid (Figure 4-8 b)) if the anchorage of the device is via both tooth and bone born (Andrade, Gandhewar, & Kalra, 2011). Tooth-anchored distractors are cemented to the teeth and are exclusively intraoral. The bone-anchored distractors can be fixed to the bone by cortical, trans-cortical screws and mini-implants, which allow for greater stability and resistance due to the osteointegration.

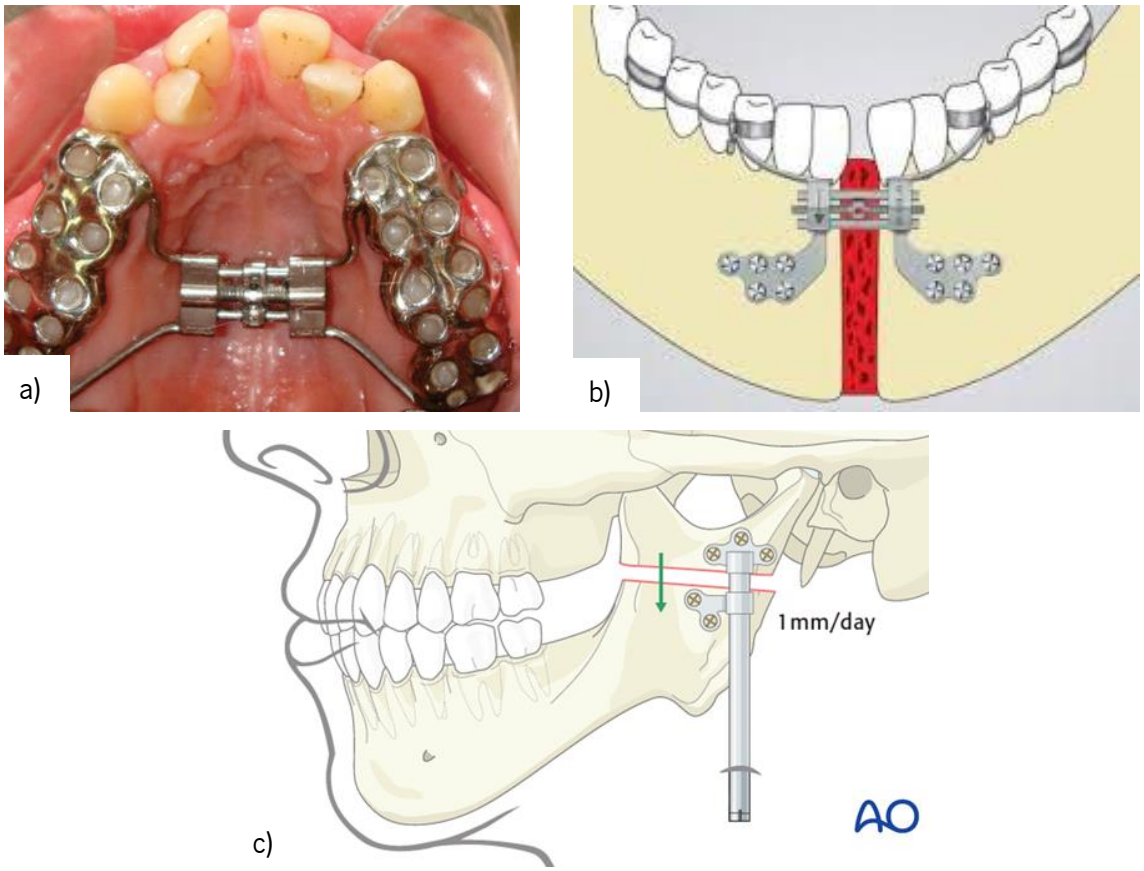


Figure 4-8: Examples of a) tooth-born, b) hybrid and c) bone-born devices.
(AO Fundation, n.d.; KLS Martin Group, 2020; Krüsi, Eliades, & Papageorgiou, 2019)

c. Distraction vector

Depending on the direction of formation of new bone i.e., the distractor vector, devices have been classified as unidirectional, bidirectional, or multidirectional devices.

Unidirectional devices (e.g., Figure 4-8 c)) provide stretching of the callus according to a single vector, in a straight direction. They are the most used in deformities involving only the

mandibular ascending branch or the mandibular body, as they do not allow the treatment of more severe three-dimensional deformities that simultaneously involve the branch, the body, and the angle of the mandible.

The distraction of the mandible often requires the bone to be moved in three directions, as opposed to just one (the longitudinal direction), as in a limb. Because of that bidirectional and multidirectional devices began to be commercialized.

Bidirectional distractors have two distraction vectors that are independently activated. Example of these are most external devices used in MDO and technologically, they are no more than two distractors united, allowing the clinician greater freedom and control in the desired movement and the ability to perform vector rectifications and bone angulations. Examples of these type of devices are presented in Figure 4-9 a) and b). They allow for more complex paths of growth (Andrade et al., 2011; Natu et al., 2014). There are also curvilinear devices (Figure 4-9 c)) whose vector allows distraction to occur both horizontally and vertically simultaneously (Drahansky et al., 2016).

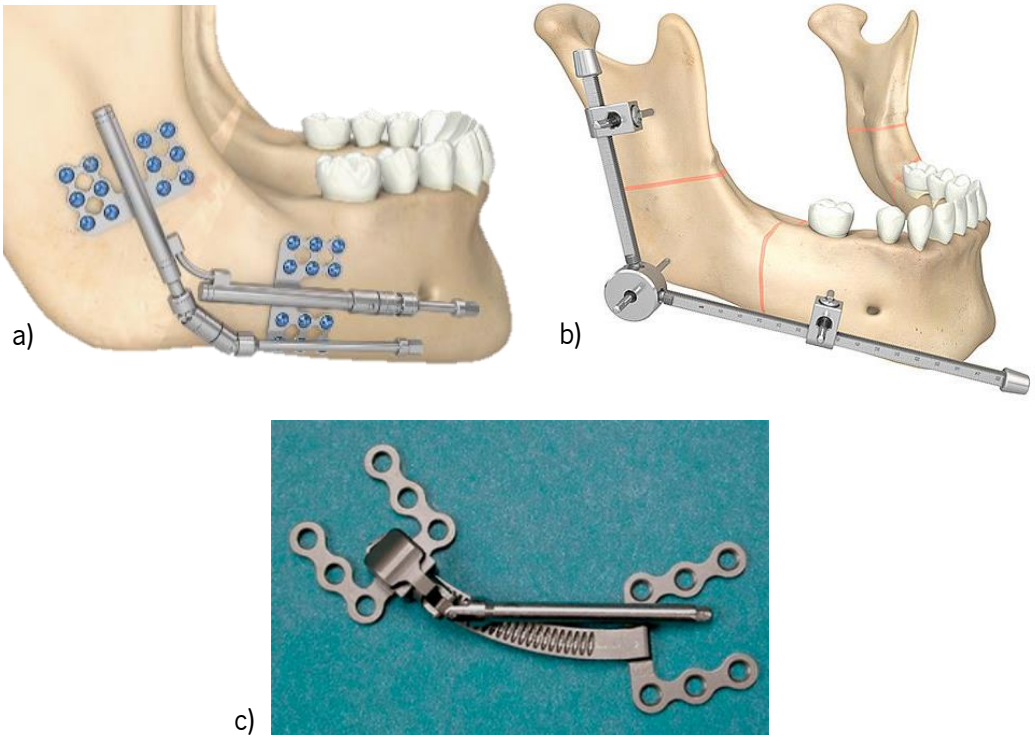


Figure 4-9: Examples of a) internal bidirectional, b) external bidirectional and c) curvilinear devices.
(Kaban et al., 2009; KLS Martin Group, n.d.)

Multidirectional distractors besides linear, allow for a transverse movement (rotation or translation) in a third direction caused by an angular adjustment as seen in Figure 4-10. These distractors allow for multiplanar manipulation of the mandibular segments and fine adjustments of

the maxillomandibular relationship (Mahrous Mohamed, Al Bishri, & Haroun Mohamed, 2011). The handling of these devices is very complex, and the protocols are constantly being changed. Bearing this in mind, the final result of the distraction and the quality of the regenerated bone is highly dependent on the clinician's experience.

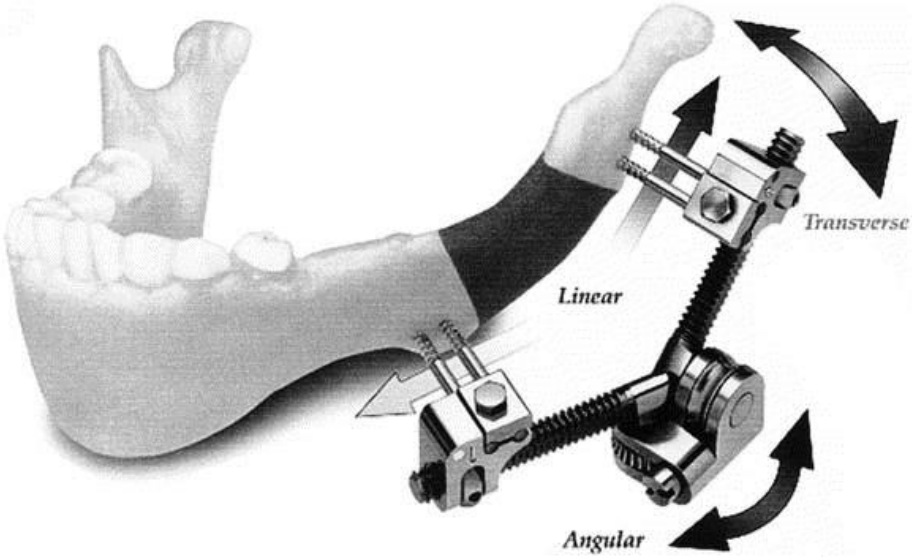


Figure 4-10: Example of multidirectional mandibular distraction device (Howmedica Leibinger, Inc., Rutherford, NJ) developed by McCarthy.
(J. B. Cope et al., 1999)

4.2 Factors affecting the physiologic process of DO

Correction of maxillofacial deformities requires careful analysis of the bone and surrounding soft tissue with clinical examination and supporting photographs, skeletal evaluation with standardized exams such as orthopantomograms, lateral cephalograms and posteroanterior cephalogram, computed tomography (CT) scans, magnetic resonance imaging (MRI), and dental evaluation with study dental casts. CT scans are a fast and efficacious technique for evaluating musculoskeletal disorders and they divulge finer details of the anatomic variations (Berquist, 2009). This proves to be an essential exam to allow proper planning of the vectors, aid in locating the tooth buds, the inferior alveolar nerve, and also in assessing the temporomandibular joint. Close cooperation between surgeons, dentists, orthodontists, and at times the restorative prosthodontists is fundamental for the formulation of the treatment plan. These medical examinations are usually sufficient to decide which distraction protocol to use. Although it is not mandatory, in recent times, virtual pre-operative planning to simulate three-dimensional (3D) movements and the optimum osteotomy site provides more details leading to a decrease in clinical errors. In order to reduce

operative time, distractors can be adapted pre-operatively using stereolithographic (Ramanathan et al., 2020).

The DO process is complex and involves the interdependence of several factors that can affect the final result of the process. It must be adapted and personalized to each specific case according to the patient's pathology and physical characteristics. The factors may derive from the surgical process, the distraction protocol, the patient, or the device itself.

4.2.1 Surgical factors

i. Minimal disturbance of bone and soft tissues

The first studies in long bones determined that the formation of new bone at the osteotomy site is influenced by the amount of damage to the bone, medullary cavity, and periosteum, therefore many advocated that osteotomy should be performed only through a minimal periosteal opening. Researchers have shown that periosteum alone can provide sufficient osteogenic capacity for healthy regeneration (Hamdy et al., 2012). Bone cuts are made under abundant irrigation and every effort is made to prevent bone overheating and damage to soft tissues.

ii. Insertion torque

On another note, excessive pin-insertion or drilling pre-screw insertion torque can result in thermal damage to the bone with secondary necrosis. Thermal and mechanical damage to the bone is one of the main identified causes of pin/screw loosening (Moroni, Vannini, Mosca, & Giannini, 2002).

iii. Rigidity of the device

The rigidity of the device during distraction and consolidation is a critical element in ensuring that bending or cutting forces do not result in microfractures in the new bone. The device must be rigidly fixated to prevent motion at the distraction site to avoid fibrous non-union. A study performed by Ilizarov on the canine tibia revealed that better bone quality and earlier consolidation occurred with more rigid constructs. In the group with the least stability, pseudoarthrosis was developed (Ilizarov, 1989). A stable fixation improves osteogenesis and prevents the formation of fibrous tissue and repetitive mechanisms of capillary rupture with haemorrhage, resulting from microfractures.

iv. Blood supply

An adequate supply of blood to the place of distraction must be ensured. Arterial insufficiency can lead to ischemic fibrogenesis within the regenerate, producing an irregular collagen network instead of the dense and desirable regular pattern of collagen. The surgeon, therefore, must ensure that the soft tissues around the distraction site are well vascularized. In addition, an adequate blood supply to the bone and the surrounding soft tissues allows for improved distraction histogenesis (Natu et al., 2014; M. Singh et al., 2016).

v. Precise preoperative planning

Precise preoperative planning is essential to determine the optimal vector of distraction, the site of osteotomy, and the amount of advancement needed. Only with detailed pre-surgical planning is it possible to ensure an adequate final result, adapted to each patient. Another factor to take into account is when distraction is performed, especially in children, it is essential to plan a degree of overcorrection of the deformity since the hypoplastic bone that is being distracted often will not grow proportionately with the surrounding bones. This way, facial symmetry is guaranteed, even years after the intervention when bone growth ceases (Guerrero et al., 2012).

4.2.2 Distraction protocol factors

i. Latency period

The latency period should be short enough to prevent calcification of the callus which causes the distraction to stop and long enough for proper callus formation. Most maxillofacial surgeons recommend 0-7 days waiting following osteotomy before initiating distraction. In younger children, the rate of bone metabolism is higher, allowing for a shorter latency period. In these cases, waiting too long increases the risk of premature bone union enabling the callus to be stretched (Hamdy et al., 2012; Menon et al., 2005).

ii. Rate of distraction

Experimental studies have shown that bone neoformation is directly related to the tension caused in the distraction space and, thus, directly related to the magnitude of the daily induced stretching (Mehrotra, Chellappa, Gupta, Passi, & Kumar, 2012).

Distraction osteogenesis can occur at rates ranging from 0.5 mm/day to 2 mm/day. The optimum rate of distraction was found by Ilizarov to be 1 mm/day (Hamdy et al., 2012) in order

to allow optimal bone regeneration. If the distraction is performed quickly, the distracted area can culminate in non-union, fibrous union or bone weakening, resulting not only in poor bone formation but also in severe soft tissue contractures and nervous problems. A decrease in the rate has been shown to lead to premature consolidation. Accelerated rates (1.5 to 2 mm) are reserved for neonate or infant patients (Al Ruhaimi, 2001; Kessler, Merten, Neukam, & Wiltfang, 2002).

iii. Rhythm of distraction

Illizarov reports established the optimum rhythm of distraction to be 0.5mm 2 times a day or 0.25mm 4 times a day compared to that performed on a single daily activation of 1 mm. He found that a higher frequency of activation also reduces the damaging effects on the skin, periosteum, muscle, nerves, and blood vessels (Ilizarov, 1989).

In an experimental study carried out by Kessler et al., it was examined the effects of continuous and discontinuous distraction rhythm on the speed of regeneration of the newly formed bone in the distraction space. They concluded that continuous rhythm allowed a higher speed of bone regeneration (Wiltfang, Keßler, Merten, & Neukam, 2001). On the other hand, other studies demonstrated that different distraction rhythms did not produce significant differences on the regenerated bone and it was the rate and not the frequency of application of the mechanical load that influenced cell differentiation during osteogenesis (Meyer et al., 1999).

Taking everything into account, there seems to be little consensus on the ideal rhythm for distraction and even on the true relevance of this parameter between the authors. Additionally, a continuous form of distraction is very impractical resulting in the single daily activation being the one used and recommended by clinicians (Menon et al., 2005; Al Ruhaimi, 2001).

iv. Consolidation period

This period normally varies from 8 to 12 weeks and consists of the time needed for the new bone to mineralize and become homogeneous with the surrounding bone. Consolidation is complete when radiographs show mineralization of the generated bone. Since the consolidation period represents the longest part of the DO procedure, most researchers' efforts at reducing the time required for osteodistraction are focused on it. Physical modifications including ultrasound and electrical stimulation as well as substances with osteogenic activities, including insulin-like growth factor 1 (IGF-1), Vitamin D3 and fibroblast growth factor 2 (FGF-2) seem to have positive influences on reducing the consolidation time (King et al., 2003).

4.2.3 Patient Factors

i. Age

Age is an essential factor in distraction osteogenesis. Bone formation and mineralization are significantly faster in children than those seen in adults. It seems that the rapid bone regeneration in skeletally immature individuals is related to the presence of a large number of undifferentiated mesenchymal cells. Therefore, this becomes a factor to bear in mind when determining distraction rates (Natu et al., 2014).

ii. Bone quality and quantity

Another important factor is bone quality, defined as the union of all of the characteristics of bone (bone turnover, bone mineralisation, matrix and mineral composition, microarchitecture, and vascularity) that influence its resistance to fracture and therefore the strength available to support the fixation device. Numerous conditions such as disorders in bone remodelling, bone vascularization, disorders of mineral homeostasis, collagen disorders, radiation and drugs affect bone quality. Also, the patient's age can affect the bone quality, being good examples of normal bone the new-born "soft" bone and the "brittle" bone of the elderly. Finally, there must be sufficient bone stock to create an osteotomy and to secure the device with pins and screws (Compston, 2006).

4.2.4 Device factors

i. Dimensions

The dimensions of the internal devices must be as small as possible. As previously mentioned in sub-Chapter 4.2.1 the periosteum alone is capable of providing sufficient osteogenic capacity for healthy regeneration. Since the internal devices are placed under the periosteum, a distractor of too large dimensions will act as a barrier between the periosteum and the bone, thus preventing the supplementation of blood and all the resources necessary for healthy bone regeneration.

4.3 Biomechanics of Distraction Osteogenesis

This chapter addresses the influence of the forces and tensions that occur during the process of MDO with an internal distractor. The influence of the surrounding soft tissues, the stimulus produced by the masticatory forces and reactions caused by the distraction process on the TMJ were also analysed.

4.3.1 Distraction and fixation forces

During the distraction phase, the device, when activated, generates a force that will act upon the bone segments causing them to separate at the same time that the bone callus is elongated. The quantification of the forces necessary to distract the active reparative bone callus is made through the determination of the torque-force values for the facial bones. Torque is the force needed to cause a rotational movement and is measured in Newton-meters (N-m) or Newton-centimetres (N-cm). Since most distraction devices use a threaded drive shaft to move the ends apart, clinical measurements of torque are easy to obtain. Even though torque is reflective of the load on the device, it is not a direct measure of the distraction force exerted at the osteotomy site. The diameter of the driveshaft, the pitch angle of the threads in the gears, the coefficient of friction of the materials, the surrounding soft tissue, and the bone callus all influence the measured torque value. Therefore, torque measurements are specific to a particular device, being necessary to establish the relationship between the torque and the load for each individual device design. This linear correlation allows for indirect measurement of the force of distraction at the bone level for a given torque observed during activation (Robinson, O'Neal, & Robinson, 2001).

Robinson et al. carried out a study where five internal craniofacial distraction devices were mounted on an apparatus (Figure 4-11) to test load limits and torque measurements during unidirectional distraction. *In vitro* data revealed that the average force at failure was 235.8 N applied in the direction of the distraction vector. However, this *in vitro* testing neglects to account for lateral forces, such as forces from the *suprahyoid* muscles that are frequently encountered during mandibular lengthening as well as the masticatory loads. Additionally, torque measurements conducted *in vivo,* in unilateral and bilateral cases, showed an average torque of 4.2 N-cm for distracting the human mandible 0.5 mm twice a day, with an equivalent force of 35.6 N. This torque value means that the force necessary to distract the callus 0.5 mm during a regular rate and rhythm of 0.5 mm twice per day is approximately 35.6 ± 13.4 N. This rate and rhythm have permitted the establishment of an average torque that falls within a range of 1.5 to 7.0 N-cm (≈13

to ≈59 N) for a total distraction distance ranging from 4 to 17 mm. Clinical experience has demonstrated that torque-force values that fall within this range appear to be an acceptable measurement during uneventful lengthening of the human mandible. Torque increased with each successive turn. Higher distraction distances at each activation required higher distraction forces (Robinson et al., 2001). It is important to refer that this study was performed in 8 patients (1 male, 7 females), whose ages ranged from 6 to 20 years of age at the time of distraction. Burstein et al., in a study conducted in "Measurement of Torque During Mandibular Distraction", determined that the mean force for distraction was 20 N and that older patients required more torque to achieve the same distraction length as younger patients. They concluded that distraction forces were relatively modest, which allows for greater freedom of distractor design (Burstein, Lukas, & Forsthoffer, 2008).

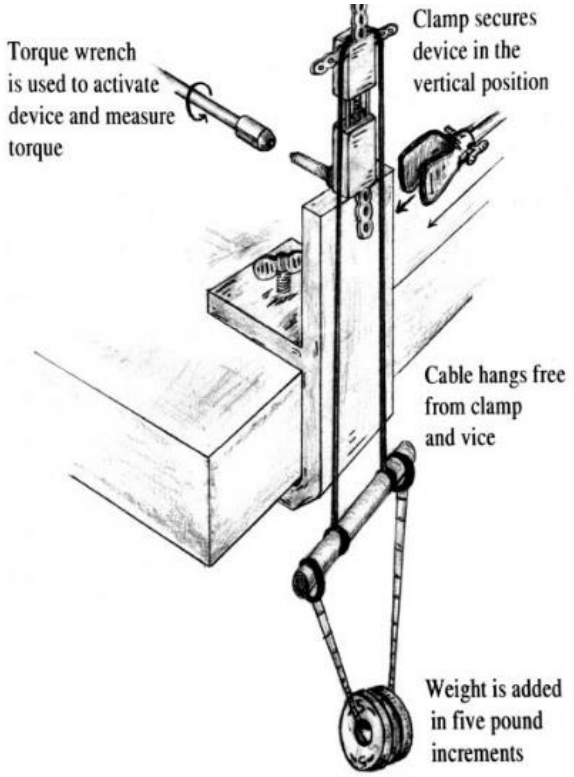


Figure 4-11: Developed apparatus used to test in vitro load limits and torque measurements during unidirectional distraction. (Robinson et al., 2001)

Bonnet et al., in an *in vivo* study of human mandibular distraction osteogenesis, revealed a much lower value of distraction forces (peak of ≈ 5 N) compared to the study carried out by Robinson et al., (35.6 ± 13.4 N). This difference in the values was due to the fact that for all patients treated by Robinson et al., relatively stiff distraction devices were used, so the whole imposed displacement was practically instantaneously applied to the regenerate (callus),

generating a high reaction of the viscous tissues. On the other hand, the device used by Bonnet et al. was an external and custom-made device with low stiffness leading to a much slower callus extension and consequently smaller strains i.e., part of the forces generated by the device were lost due to, for example, the bending of the pins and were not transferred to the callus. Another reason was the fact that the patient's soft tissues in the Bonnet et al. study were greatly destroyed by a bullet and did not participate in resistance to the lengthening (Bonnet, Dubois, Lipinski, & Schouman, 2012).

A study conducted by Bohludi et al. assessing the biomechanical stress tolerance of screws used in 9 different fixation methods after bilateral sagittal split ramus osteotomy (BSSRO) revealed that most fixation methods withstood vertical loads up to 600 N applied on the posterior teeth perpendicularly to the occlusal plane (Bohluli et al., 2010). They used FEM for analysing the stress distribution around the rigid fixation screws and surrounding bone. FEM is used to analyse the stress and strain deformities of structures under force and has been accurately used to describe the biomechanical behaviour of the mandible. As with orthognathic surgery, in bone distraction is also necessary to ensure optimal fixation and rigidity of the device in order to prevent motion at the distraction site thus avoiding fibrous non-union. Additionally, if the device is poorly fixated, bending or cutting forces can result in microfractures in the new bone (Ilizarov, 1989). They should be stable during the healing period and tolerant of masticatory forces after surgery (Bohluli et al., 2010). This study showed that a desirable configuration of rigid fixation methods can be compared to assess and prevent the excessive stress around fixation screws that may cause bone resorption and screw loosening. An inverted backwards L shape configuration (Figure 4-12 a)) had the lowest stress distributed on the screws. In another study, Feng et al. concluded that bone resorption triggered by high radial stress and not axial stress, as seen in Figure 4-12 b), is the initiator of the screw loosening process (Feng et al., 2019).

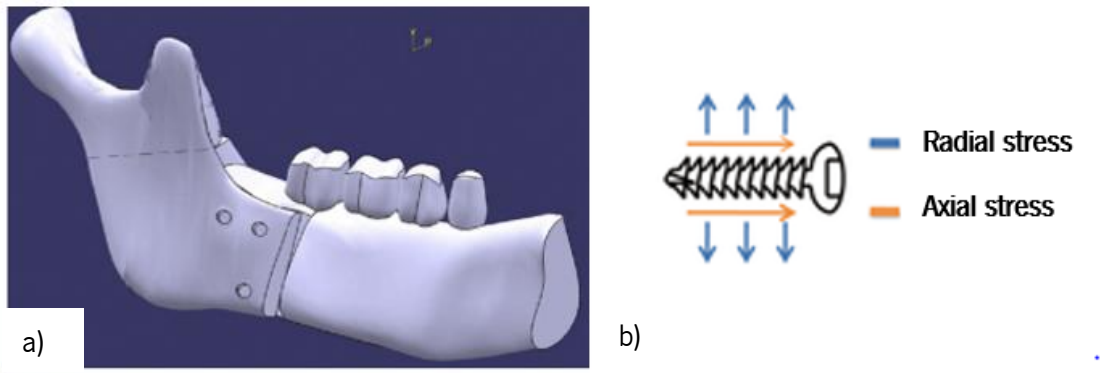


Figure 4-12: a) Inverted backwards L shape configuration and b) types of stress in screws.
(Bohluli et al., 2010)

FEM analysis of mandibular bone distractors revealed that the high-stress zones are located in fixation plates. In cases where these high-stress zones indeed affect the anchorage of the device and therefore the stability of the alveolar bone, increase of the thickness of the base plate and/or increase the length and diameter of the screws and/or the number of screws can easily compensate this stress distribution (Cerrolaza, Carrero, Cedeño, & Valencia, 2015).

It is important to establish that in most models for FEM analysis, the bone and the materials used are usually defined as isotropic and homogeneous. This assumption seems to be acceptable since some studies have reported differences of less than 10% between anisotropic models and isotropic models (Cerrolaza et al., 2015). The mechanical properties of the different elements that influence the distraction process are presented in Table 4-5 below.

Table 4-5: Mechanical properties of the different anatomical elements.

	Young modulus (MPa)	Poisson Ratio (ν)
Trabecular bone	200 – 500[a]	0.3[a]
Cortical bone	6000 – 18000[a]	0.3[a]
Teeth	17600[b]	0.25[b]
Callus tissue	500[c]	0.3[c]
Muscular elements	0.00075[d]	0.3[d]
Skin	0.0015[d]	0.3[d]
Articular TMJ disks	6[d]	0.4[d]
TMJ ligaments	0.27[d]	0.3[d]

a - (Baldini et al., 2008); b - (Reina-Romo et al., 2010); c - (Şensoy, Kaymaz, Ertaş, & Kiki, 2018); d - (Kofod, Cattaneo, Dalstra, & Melsen, 2005)

The ability to anticipate and quantify the force encountered in mandibular distraction enhances the development and design of devices. Torque-force measurements will contribute to manufacturing standards and will help to establish an adequate margin of safety. Additionally, this information can be used to give immediate clinical feedback regarding what may be happening in the distraction site (e.g., premature consolidation, device failure, or incomplete osteotomies) (Robinson et al., 2001).

4.3.2 Influence of surrounding tissues and masticatory forces

The research in the area of mandibular distraction osteogenesis has for the most part been focused on the histological characteristics of the growing callus. The biomechanical effects of the

distractor and the influence of the soft tissues surrounding the mandible have only recently been studied in the process of MDO. Nevertheless, the long-term success of osteogenic distraction is greatly dependant on the ability of adjacent soft tissues to tolerate distraction forces and adapt to the increase in bone length and volume (Ilizarov, 1989).

Soft tissues bear a large part of the lengthening load. In the literature concerning lower limb distraction, 25% of this load is generally attributed to soft tissue resistance (Bonnet et al., 2012). Bearing this in mind, during the FEM analysis soft tissues such as the periosteum, muscles, ligaments, nerves, etc. must be added to the model to obtain more accurate results.

An experiment conducted by Debelmas et al. about the contribution of the periosteum to mandibular distraction revealed that the periosteum is the primary tissue contributing to the load-opposing distraction at the beginning of distraction activation. Eighteen mandibular periosteal samples were harvested in old, partially, or totally edentulous cadavers and uniaxial tensile tests were performed on the specimens, providing a load for each millimeter of distraction (Figure 4-13). They showed that the periosteum is directly stretched by the distraction activation and that the stress-strain relationship of the human mandibular periosteum is nonlinear viscoelastic, typical of biological tissues composed of collagen and elastin. During the distraction process, the forces generated by the periosteum increased from 11.6 to 50.6 N (stretched from 1 mm to 20 mm) (Debelmas, Picard, Kadlub, & Boisson, 2018). These values were of a similar order of magnitude as the mean load measured *in vivo* by Robinson et al. (35.6 N) and Burstein et al. (20 N) (Burstein et al., 2008; Robinson et al., 2001).

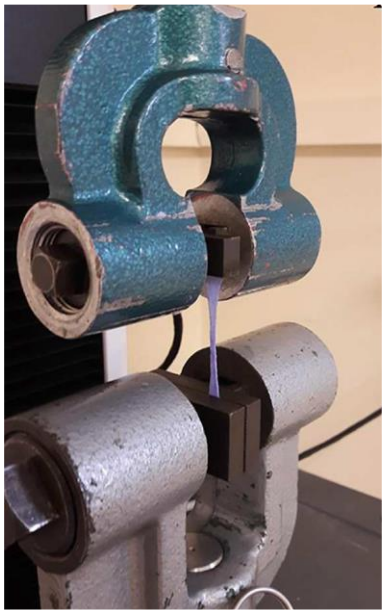


Figure 4-13: Picture of the tensile test apparatus.
(Debelmas et al., 2018)

Mastication

During mastication, the mandible moves in relation to the rest of the skull, registering forces at the attachment sites of the masticatory muscles (*masseter, temporalis, digastric,* and *lateral pterygoid* muscles) and in the occlusal plane in the bite region. In Figure 4-14 is shown the insertion points of the masticatory muscles as well as the direction of the forces caused during the mastication process. The bite force is usually higher in men, and the average values are between 200N and 300N in the region of the incisors, between 300N and 500N in the region of the premolars, and between 500N and 700N in the molar region. However, during normal day-to-day chewing, the values that are found are much lower than these (Rudderman & Mullen, 2012).

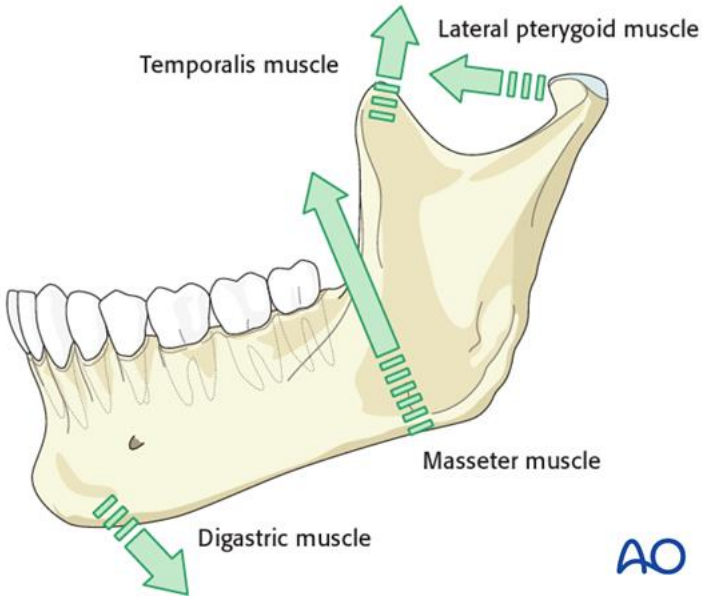


Figure 4-14: Insertion points of the masticatory muscles and the direction of the forces caused during the mastication process. (Homsi, Rodrigues, Aniceto, Hammer, & Bartlett, n.d.)

The masticatory process translates into a combination of sagittal bending, corpus rotation, and transverse bending. The result is a complex pattern of stresses and strains (compressive, tensile, shear, torsional) in the mandible, which varies quickly and according to the loading situation. Figure 4-15, shows the result of the incidence of external forces in a ruptured jaw. The application of external force anteriorly results in tension forces superiorly and compression forces inferiorly within the mandible, contrary to what happens when the load is applied posteriorly. In mandible distraction osteogenesis, during the activation period, the stimulus produced by the masticatory forces are usually neglected and are not considered a problem for the distraction process since it is much smaller than the distraction stimulus (Reina-Romo et al., 2010).

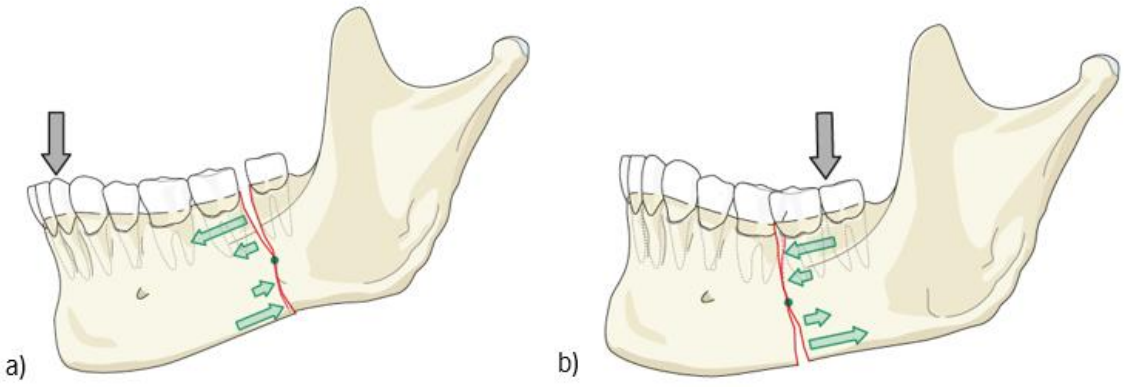


Figure 4-15: Effect of the incidence of forces a) anteriorly and b) posteriorly in a fractured mandible.
(Reina-Romo et al., 2010)

4.3.3 Impact on the TMJ

The TMJ can undergo changes due to osteogenic distraction directly, due to the force produced on the mandible during the active distraction process, and indirectly through changes in occlusal and skeletal relationships (e.g., open bite), induced by mandibular elongation.

Kofod et al. presented a three-dimensional finite element analysis of the mandible and TMJ during left vertical ramus elongation by distraction osteogenesis. In this model, the forces generated by the passive resistance from the muscles and surrounding soft tissue envelope caused by the gradual displacement of the mandibular segments were taken into consideration. By converging the data sets generated from the CT and MRI scans, a more precise description of the bony structures and muscles was achieved. That way, the insertion points of the muscles on the mandible were precisely allocated and then transferred to the FEM model. The activation of the device was made in increments of 0.4 mm (from 0 mm to 16 mm). The study revealed that during the active distraction phase, the resultant reaction forces in the TMJ, as seen in Figure 4-16, are higher on the distraction side (0.2 N at 1.2 mm of distraction and 97 N at 16mm) than those on the non-distracted side (0 N at 1.2 mm and 33 N at 16 mm) (Kofod, Cattaneo, et al., 2005).

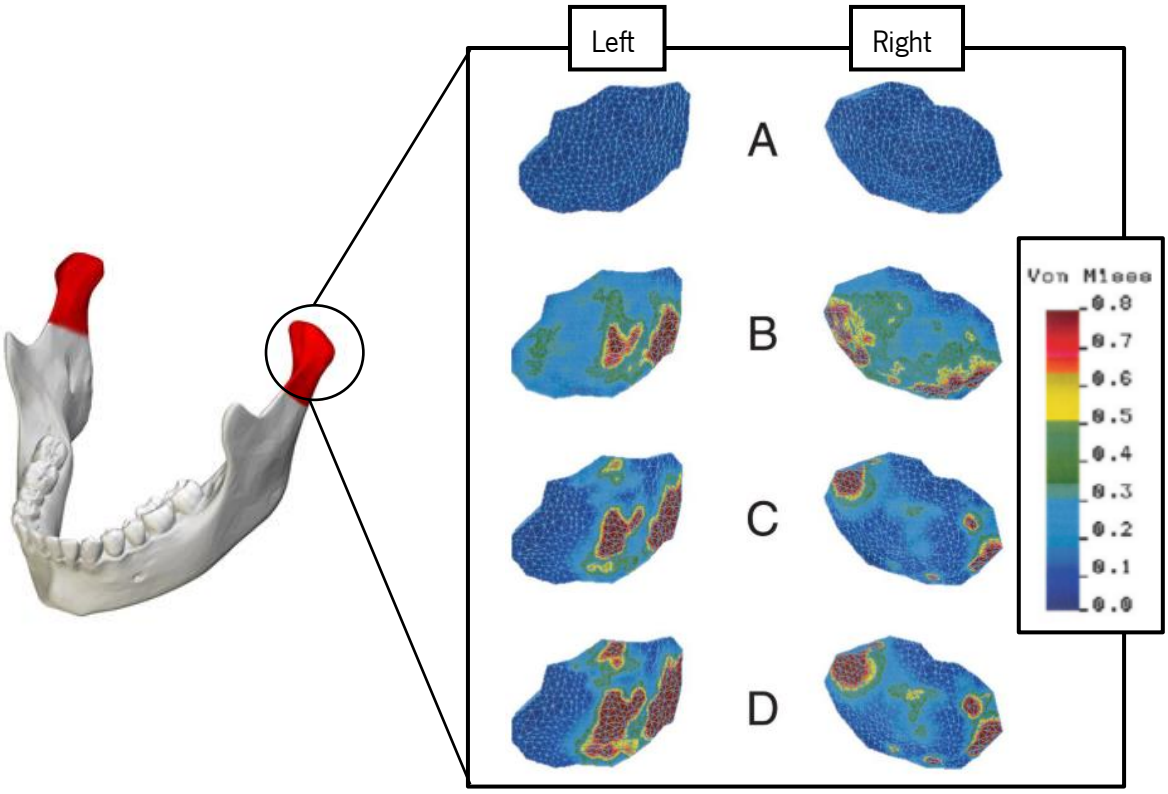


Figure 4-16: Stress distribution on the condyles during the different steps of active distraction: 1.2 mm (A), 5mm (B), 10mm (C), and 16mm (D). The side of the distraction corresponded to the left side.
(Kofod, Cattaneo, et al., 2005)

It was also concluded that the level of stress generated by the passive restraining elements (muscles, ligaments, skin, and remaining soft tissue) opposing elongation of the mandibular ramus is low and the forces transferred to the TMJ during distraction are only one-third to one-fourth of the maximal forces transferred to the TMJ during maximal bite forces (Kofod, Cattaneo, et al., 2005). Korioth et al, found maximal joint forces around 120 N during maximal clenching. It was considered that the forces generated by the distraction process are too low to generate detrimental effects in the TMJs of human beings (Korioth, Romilly, & Hannam, 1992).

Studies by other authors on the effects of osteogenic distraction on TMJ conclude that despite some eventful minor changes, they were fully reversible after the consolidation period. However, condylar rotation secondary to osteodistraction may require moderate to significant adaptation within the tissues of the TMJ. These rotational forces could contribute to degenerative changes in these tissues. It is therefore prudent to assess the functional integrity of the TMJ in patients before initiation of mandibular osteodistraction (Jason B. Cope, Yamashita, Healy, Dechow, & Harper, 2000).

5. Main Complications of Mandibular Distraction Osteogenesis in the Treatment of Mandibular Hypoplasia – a Systematic Review

Ana Arieira[1], Alberto Pereira[2], Óscar Carvalho[1], Filipe Silva[1] and Ana Leal[3]

[1] Center for MicroElectroMechanical Systems (CMEMS-UMinho), University of Minho, Campus de Azurém, 4800-058, Guimarães, Portugal

[2] Head of Facial Reconstructive Unit, Luz Hospital, Av. Lusíada 100, Lisbon, Portugal; Plastic and Reconstructive Surgery Unit, Instituto Português de Oncologia Francisco Gentil, R. Prof. Lima Basto, Lisbon, Portugal;

[3] Center for MicroElectroMechanical Systems (CMEMS-UMinho), University of Minho, Campus de Azurém, 4800-058, Guimaraes, Portugal; Dom Henrique Research Centre (DHRC), Porto, Portugal

ABSTRACT

A systematic review, following the PRISMA statement, was carried out in order to assess the prevalence of complications associated with the mandibular distraction osteogenesis (MDO) process on patients with mandibular hypoplasia as well as the parameters of the distraction protocol. The following Boolean search was used: (distractor) AND (mandibular distraction osteogenesis) AND (mandibular hypoplasia OR mandibular micrognathia OR micrognathism OR retrognathia). A search using SCOPUS, MEDLINE, PubMed, and Web of Science yielded a total of 256 articles published between 2000 and 2019. After screening, 34 articles on MDO were eligible, yielding a total number of 447 patients. The complications reported in the articles included scarring (11.6%), infection (6%), relapse (8.3%), nerve injury (7.1%), tooth injury (8%), pin/screw loosening (13%), device failure (9%), and open bite (9.8%). These complications were further screened in order to exclude common and unavoidable intercurrences that are inherent to osteogenic distraction treatment and that could have been misunderstood as complications. This systematic review revealed an evident lack of coherence and adequate classifications to distinguish the real

complications from transient intercurrences of mandibular distraction osteogenesis. In addition, there was a significant lack of information regarding reported complications, such as their cause and corrective measures.

Keywords: distraction osteogenesis, complication, mandible, mandibular hypoplasia, orthognathic surgery, distractor, systematic review, PRISMA statement

INTRODUCTION

Micrognathia, also known as mandibular hypoplasia or micrognathism, is a category of craniofacial anomalies characterized by hypoplasia or atrophy of the mandible and the surrounding soft tissues and can be classified into three groups: congenital (syndromic or non-syndromic), developmental and acquired (including sequels of oncologic defects, infections, radiotherapy and trauma) (D. J. Singh & Bartlett, 2005). Among the syndromic, hemifacial microsomia, Treacher-Collins and Nager syndromes are the most frequent causing a hypoplastic mandible (Chi, Mirsky, Bello, & Ferson, 2012). The most well-known condition featuring an abnormal mandible is in the Pierre Robin sequence. This condition contributes to breathing and swallowing difficulties caused by tongue posterior displacement and the resulting airway obstruction. The patients require endotracheal intubation or tracheotomy and often gastric tube feeding due to frequent hypoxic episodes and inability to properly feed. Conventional treatment courses include orthognathic surgeries and reconstruction with bone grafts. On the other hand, a more recent and promising approach is the osteogenic distraction of the mandible.

After it had been extensively used by orthopaedists for lengthening of long bones, distraction osteogenesis (DO) has also produced promising outcomes in the treatment of craniofacial deformities. This technique, developed by Ilizarov, is recognized for having a considerably decreased morbidity rate compared to bone grafting and for being less invasive and less time-consuming compared with the traditional methods for craniofacial reconstruction (Rao, Kumar, Kumar, Singh, & Bhatnagar, 2004; Van Strijen, Perdijk, Becking, & Breuning, 2000). Mandibular distraction osteogenesis (MDO) first presented by Rosenthal in 1927, and later by McCarthy, is now the current standard treatment for micrognathia (Rossini, Vinci, Rizzo, Pinho, & Deregibus, 2016; Yuan & Chai, 2019). This process allows for a continuous and controlled distraction of the osteotomized bone along a pre-defined vector, increasing its length and allowing

the formation of new bone between the osteotomized segments without the need for grafts or implants.

The distractors used for this process are mainly categorized into either internal or external distractors. Each type has distinct benefits and drawbacks. External devices allow for distraction vector control after placement of the device facilitating a three-dimensional control of the correction. Disadvantages of these devices include their susceptibility to patient activity and external forces, restricting patients' normal daily activities, the risk of trauma, the risk of pin/screw migration or loosening during distraction and the abnormal scarring caused by the external screws or wires, inducing major psychosocial stress on patients. Opposite to external distractors, internal distractors produce less screw loosening, less if any scars, and soft tissue trauma. They have more stable biomechanics and provide a more efficient application of the distraction force. However, after placement, the vector cannot be altered, and they are technically more challenging to apply having limitations related to the size of the device and the restricted access of the oral cavity. Furthermore, internal devices require a second surgery for removal. Callus moulding by the end of the distraction phase and before finishing the consolidation period and the technique of open callus manipulation allow to control or change the final vector of distraction, obtaining the ideal position of the distracted segments and the ideal final result regarding mandibular conformation and dental occlusion. Open callus manipulation has the additional advantage of reducing the total treatment time since the consolidation phase with devices in place is spared (Kunz, Hammer, & Prein, 2000; Pereira & Pereira, 2019).

Although DO is now the primary method for mandibular elongation in severe micrognathia, there are several complications associated with the distraction process that deserve our attention. The purpose of this review is to assess all the variables involved in MDO as well as the prevalence of the main complications, their causes, and possible solutions.

MATERIALS AND METHODS

A systematic review was carried out in order to assess all the variables involved in mandibular distraction in cases of micrognathia as well as the prevalence of the main complications associated with the process. The electronic databases selected to find all relevant studies for the matter object of analysis were the databases SCOPUS, MEDLINE, PubMed, and Web of Science and the review was performed in accordance with the PRISMA statement (Liberati et al., 2009). The following Boolean search was used: (distractor) AND (mandibular distraction osteogenesis)

AND (mandibular hypoplasia OR mandibular micrognathia OR micrognathism OR retrognathia). The search was conducted in October 2020 and the terms used in the search were adapted according to the database in question. Although osteogenic distraction is not the primary treatment for retrognathic cases considering that most patients require small mandibular advancements obtained with orthognathic surgery, the keyword retrognathia was also added to the search in order to not miss information since there are cases where DO is performed. The final search translated into a total number of 256 studies subject to analysis. All duplicates were excluded, returning 112 studies eligible for title and abstract review. Criteria for eligibility and exclusion were decided beforehand. Non-human (n=3) and non-English (n=18) studies, as well as reports regarding transport distraction osteogenesis (n=2) and bone grafting, were excluded. The abstract review allowed to exclude 5 review articles, 19 articles not related to MDO and 20 articles that did not demonstrate relevance to the subject under analysis. After a full-text review, 11 articles were excluded due to not being relevant to the subject or having no qualitative or quantitative information. At the end of studies screening and eligibility, 34 articles were qualified for analysis. A flowchart of the literature search and selection process through the different steps of the systematic review (PRISMA) is given in Figure 5-1.

Specific variables were extracted which included: age, gender, and diagnosis. Further data regarding the type of device used, average distraction range and rate, latency, and consolidation periods, as well as final outcomes and identified complications, were also extracted. The information obtained from the literature review was logged into an electronic spreadsheet (Microsoft Excel, Microsoft Office, Redmond, Washington).

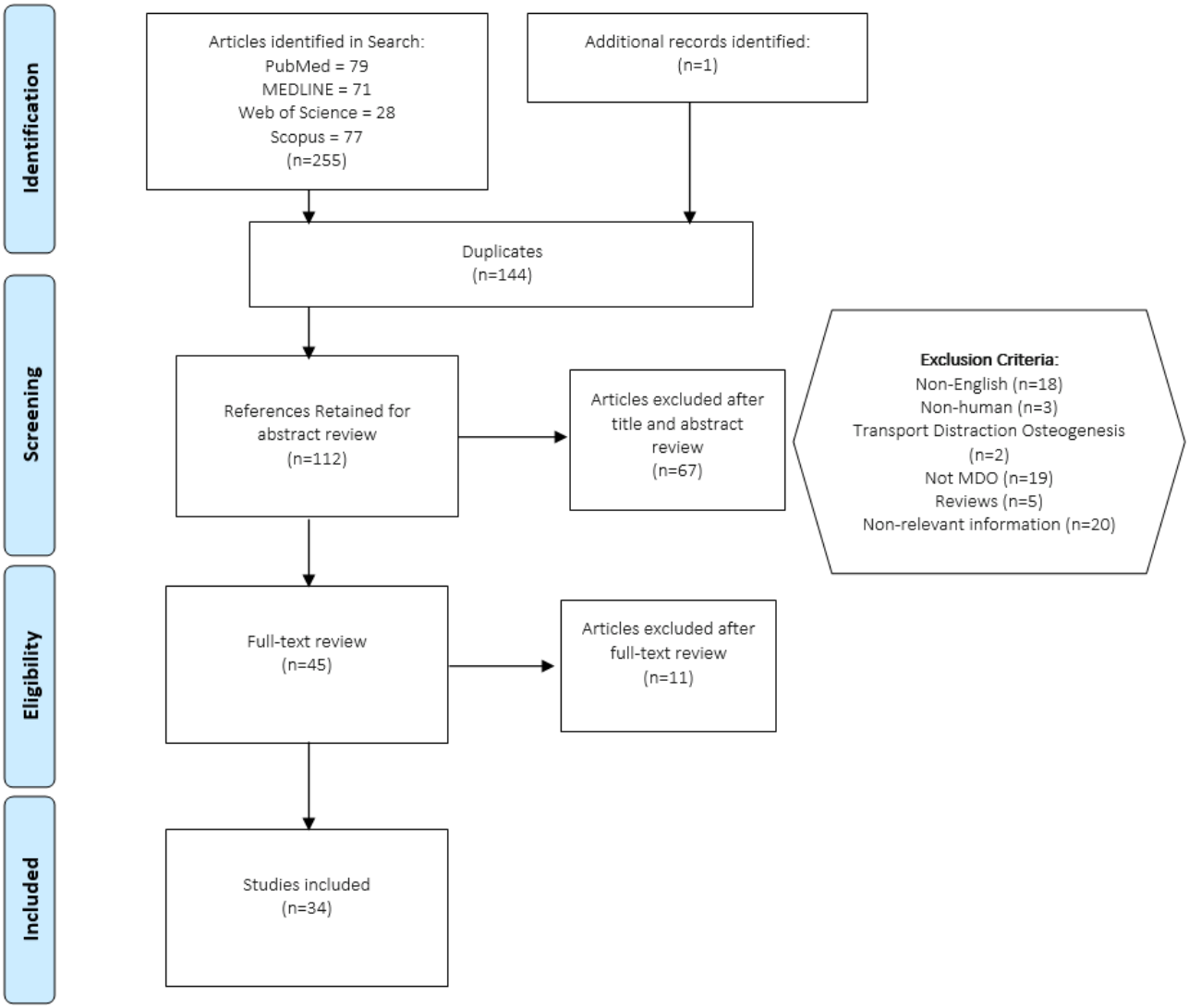


Figure 5-1: Flow diagram showing criteria and strategy for studies screening and eligibility.

Methodological quality appraisal

To analyse previous research focused on employing distraction osteogenesis to correct mandibular anomalies, nine research questions were defined and applied to the selected studies for coherent data extraction. The questions concern three main topics of interest: the targeted patients' characteristics, the distractor and distraction protocol, and the reported complications and their corrective measures. Each question of the checklist was scored individually in a range from 0 to 2, where 0 means the study does not provide any information, 1 the study provides limited information, and 2 means the study provides satisfying information. The quality checklist comprises 9 items which are: Q1: Are the research objectives clearly stated?, Q2: Is the scientific context clearly explained?, Q3: Are the population characteristics clearly defined?, Q4: Is the surgical technique clearly described?, Q5: Is the distraction protocol clearly described? (range, rate and periods of latency and consolidation), Q6: Is the type of distractor used clearly stated?

(internal/external, unidirectional/bidirectional), Q7: Are the complications and their causes clearly reported?, Q8: Are the corrections or treatments of the complications clearly described?, Q9: Are conclusions drawn from the study clearly stated?. The majority of the selected studies were of high quality with a mean score of 85.3% (Table 5-1). However, some questions, those who had a lower score, were only partially answered. The questions that had a lower score were related to the surgical procedure (1.5%), reported complications and its causes (1.5%) and their respective corrective measures (1.4%). In opposition, the highest scores were observed in the questions related to the device type (1.9%) and distraction protocol (1.8%). All studies clearly stated the research objectives (2.0%)

Table 5-1: Methodological quality appraisal.

Study, year	Questions									Score (%)
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	
(Giraddi, Arora, & Sai Anusha, 2016)	2	2	2	2	1	2	1	0	2	**77,8**
(Rao et al., 2004)	2	2	1	2	2	2	1	2	2	**88,9**
(Margulis, Patel, Daw, & Bauer, 2003)	2	2	1	2	2	2	2	2	2	**94,4**
(Kaban et al., 2009)	2	1	2	2	2	2	2	2	1	**88,9**
(Van Strijen et al., 2000)	2	2	2	1	2	2	2	1	1	**83,3**
(Miller, Kahn, Lorenz, & Schendel, 2007)	2	2	1	2	2	2	1	0	2	**77,8**
(Schendel & Linck, 2004)	2	1	2	2	1	2	2	2	1	**83,3**
(Burstein, 2008)	2	2	2	1	2	1	2	1	2	**83,3**
(Abdelfattah A Sadakah, Elshall, & Farhat, 2009)	2	2	2	1	2	2	2	1	2	**88,9**
(A. A. Sadakah, Elgazzar, & Abdelhady, 2006)	2	2	2	2	2	2	2	2	2	**100,0**
(Yu, Shen, Zhang, & Wang, 2009)	2	2	2	1	2	2	1	2	1	**83,3**
(Trahar, Sheffield, Kawamoto, Lee, & Ting, 2003)	2	2	2	2	2	1	2	0	2	**83,3**
(Mahrous Mohamed et al., 2011)	2	2	2	1	2	2	1	2	2	**88,9**
(Iatrou, Theologie-Lygidakis, & Schoinohoriti, 2010)	2	2	2	1	2	2	2	2	2	**94,4**
(Shi et al., 2015)	2	1	2	2	2	2	2	2	1	**88,9**

Table 5-1: (Continued).

Study, year	Questions									Score (%)
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	
(Kofod, Nørholt, Pedersen, & Jensen, 2005)	2	2	2	2	2	2	1	2	1	**88,9**
(Al-Mahdi & Al-Jumaily, 2013)	2	2	2	2	2	2	2	1	2	**94,4**
(Fariña, Castellón, Nagelash, & Valladares, 2011)	2	2	1	2	2	2	1	0	2	**77,8**
(Cascone et al., 2015)	2	2	1	2	2	2	1	2	1	**83,3**
(Yin, Tang, Shi, Yin, & Zhang, 2014)	2	2	1	1	2	2	1	1	2	**77,8**
(N. Sahoo, Roy, Dalal, & Bhandari, 2016)	2	2	2	1	2	2	2	2	1	**88,9**
(Schoemann, Burstein, Bakthavachalam, & Williams, 2012)	2	2	2	2	2	2	1	0	2	**83,3**
(Badiali, Cutolo, Roncari, Marchetti, & Bianchi, 2017)	2	2	2	1	0	2	0	0	1	**55,6**
(Menon et al., 2005)	2	1	2	0	2	2	1	2	2	**77,8**
(Watanabe, Sasaki, Matsuno, & Akizuki, 2019)	2	2	2	2	2	2	2	2	2	**100,0**
(Keçik, Aydoğdu, Ateş, & Uçkan, 2010)	2	2	2	1	2	2	1	1	2	**83,3**
(Hassan & Mohamed, 2019)	2	2	1	2	2	2	1	2	2	**88,9**
(Denny, 2002)	2	2	1	0	1	2	1	2	2	**72,2**
(Shen, Jie, Chen, Zou, & Ji, 2009)	2	1	1	2	1	2	2	2	1	**77,8**
(Baas, Van Gemert, Bierenbroodspot, Milstein, & De Lange, 2015)	2	2	2	2	2	2	2	2	1	**94,4**
(Zenha et al., 2012)	2	2	1	2	2	2	2	2	2	**94,4**
(Dolanmaz et al., 2009)	2	2	2	1	2	2	1	1	2	**83,3**
(Mehrotra, Dhasmanaa, & Kumar, 2009)	2	2	2	0	2	2	1	1	1	**72,2**
(Bukhari et al., 2012)	2	2	2	2	2	2	2	2	2	**100,0**
Average	**2.0**	**1.9**	**1.7**	**1.5**	**1.8**	**1.9**	**1.5**	**1.4**	**1.6**	**85,3**

Q1: Are the research objectives clearly stated?, Q2: Is the scientific context clearly explained?, Q3: Are the population characteristics clearly defined?, Q4: Is the surgical technique clearly described?, Q5: Is the distraction protocol clearly described? (range, rate and periods of latency and consolidation), Q6: Is the type of distractor used clearly stated? (internal/external, unidirectional/bidirectional), Q7: Are the complications and their causes clearly reported?, Q8: Are the corrections or treatments of the complications clearly described?, Q9: Were conclusions drawn from the study clearly stated?.

RESULTS

The 34 included studies were published between 2000 and 2019 and yielded a total of 447 patients who underwent MDO for analysis. Patient demographic information, including gender, age, primary diagnosis, distractor type and distraction protocol, are summarized in Table 5-2. Data regarding the diagnosis is present in Table 5-3 in a more concise way.

Table 5-2: Profiles of included articles, patient demographics, and distraction protocol.

							Distraction protocol			
Serial no.	Author, year	No. of patients	Gender	Mean/ range age (yr.)	Primary diagnosis	Distractor type	Latency phase (days)	Mean distraction range (mm)	Distraction rate (mm/day)	Consolidation phase (wk.)
1	(Giraddi et al., 2016)	9	4M + 5F	14.88	TMJ ankylosis (n=9)	Internal / Bilateral / Unidirectional	5	-	-	12
2	(Rao et al., 2004)	6	-	8.5	TMJ ankylosis (n=6)	External / Unilateral / Unidirectional **(Adler Ltd.., India)**	5	12.75	1mm/d (0.5mm twice a day)	6 - 8
3	(Margulis et al., 2003)	7	-	(3.2 – 7)	HFM (n=6), NS (n=1)	Internal / Unilateral (6), Bilateral (1) / Unidirectional **(Resorbable device)**	1	20	1mm/d	6
4	(Kaban et al., 2009)	13	5M + 8F	11.9	TCS (n=3), NS (n=3), HFM (n=2), TMJ Ankylosis (n=1)	Internal / Bilateral / Multidirectional (Curvilinear) **(Synthes CMF, Pennsylvania)**	2 - 4	-	1mm/d	-
5	(Van Strijen et al., 2000)	14	7M + 7F	14.1	-	Internal / Bilateral **(Stryker-Leibinger, Howmedica, Germany)**	6	7.6	1mm/d (0.5mm twice a day)	6
6	(Miller et al., 2007)	12	-	0.29	PRS (n=7), HFM (n=2), syndromic (n=3)	Internal / Multidirectional (Curvilinear) **(Osteomed Corporation, Texas)**	1	-	2mm (1mm twice a day)	2 - 3
7	(Schendel & Linck, 2004)	1	F	22	HFM (n=1)	Internal / Unilateral / Multidirectional (Curvilinear) **(Osteomed Logic 52mm)**	7	43	1mm/d	-
8	(Burstein, 2008)	100	51M + 49F	4.24	PRS (n=43), HFM (n=37), TCS (n=8), NS (n=4)	Internal / Unilateral (32), Bilateral (68) **(Resorbable device)**	2	25.4	2mm/d	4 - 6
9	(Abdelfattah A Sadakah et al., 2009)	7	3M + 4F	2.8	-	Internal / Unilateral / Unidirectional **(KLS Martin Group, Germany)**	3	20.4	1mm/d (0.5mm twice a day)	4
10	(A. A. Sadakah et al., 2006)	9	5M + 4F	19	TMJ Ankylosis (n=9)	Internal / Unilateral (7), Bilateral (2) / Unidirectional	5 - 7	20.7	1mm/d (0.5mm twice a day)	8 - 12

Table 5-3: (Continued).

Serial no.	Author, year	No. of patients	Gender	Mean/ range age (yr.)	Primary diagnosis	Distractor type	Distraction protocol			
							Latency phase (days)	Mean distraction range (mm)	Distraction rate (mm/day)	Consolidation phase (wk.)
11	(Yu et al., 2009)	11	5M + 6F	10.3	TMJ Ankylosis (n=11)	Internal / Unilateral / Unidirectional	5	12.4	1mm/d (0.5mm twice a day)	12
12	(Trahar et al., 2003)	6	3M + 3F	10.4	HFM (n=6)	Internal / Unilateral	5 - 7	-	1mm/d	9.3
13	(Mahrous Mohamed et al., 2011)	11	5M + 6F	0.38	PRS (n=11)	Internal / Bilateral / Unidirectional **(KLS Martin Group, Germany)**	1	18	1mm/d (0.5mm twice a day)	10
14	(Iatrou et al., 2010)	1	1M	0.75	PRS (1)	External / Bilateral / Unidirectional	4	20	1mm/d	4 - 8.7
15	(Shi et al., 2015)	6	4M + 2F	8.3	HFM (n=6)	Internal / Unilateral / Unidirectional	7	21.7	1mm/d	26 - 43.5 (30.4)
16	(Kofod, Nørholt, et al., 2005)	27	13M + 14F	14.7	Trauma (n=12), juvenile idiopathic arthritis (n=10), arthrosis (n=2), infection (n=1), torticollis (n=1), HFM (n=1)	Internal / Unilateral /Unidirectional **(Medicon)**	4	17	0.8mm – 1.2 mm (0.4 mm 2 or 3 times a day)	6 - 12 (9)
17	(Al-Mahdi & Al-Jumaily, 2013)	9	3M + 6F	11.7	HFM (n=6), trauma (n=2) infection (n=1)	External / Unilateral (2), Bilateral (7) / Multidirectional **(Stryker-Leibinger, Howmedica, Germany)**	5	-	1mm/d (0.5mm twice a day)	8.7
18	(Fariña et al., 2011)	3	-	0.14	PRS (n=3)	External / Bilateral / Unidirectional	3	22.7	1mm/day (0.5mm twice a day)	4
19	(Cascone et al., 2015)	5	2M + 3F	(9 – 16)	PRS (n=4), Larsen Syndrome (n=1)	External / Bilateral / Unidirectional **(KLS Martin Group, Germany)**	2	18	2mm/d (1mm twice a day)	4

Table 5-3: (Continued).

Serial no.	Author, year	No. of patients	Gender	Mean/ range age (yr.)	Primary diagnosis	Distractor type	Distraction protocol			
							Latency phase (days)	Mean distraction range (mm)	Distraction rate (mm/day)	Consolidation phase (wk.)
20	(Yin et al., 2014)	36	-	20.3	TCS (n=3), auriculocondylar syndrome (n=1), Parry-Romberg syndrome (n=2), HFM (n=20), severe mandibular deviation (n=2)	Internal / Unilateral (24), Bilateral (12) / Unidirectional	7	26.2	1mm/d	26 - 34.8
21	(N. Sahoo et al., 2016)	1	1F	0.7	PRS (n=1)	Internal / Bilateral / Unidirectional **(KLS Martin Group, Germany)**	2	12	1mm/d (0.5mm twice a day)	10
22	(Schoemann et al., 2012)	22	15M + 7F	1.8	PRS (n=18), TCS (n=2), HFM (n=2)	Internal / Bilateral / Unidirectional **(Biomet Inc, Indianapolis) (Resorbable device)**	1	24	2mm/d	4
23	(Badiali et al., 2017)	7	3M + 4F	6.1	HFM (n=2), NS (n=2), Trauma (n=1), TCS (n=1)	Internal / Unilateral (3), Bilateral (4) / Unidirectional **(KLS Martin Group, Germany)**	-	25	-	-
24	(Menon et al., 2005)	9	3M + 6F	17.5	TMJ Ankylosis (n=6), facial cleft (n=1), condylar agenesis (n=1)	Internal / Unilateral (2), Bilateral (7) / Unidirectional	4 - 7	12.3	0.8mm/d (0.4mm twice a day)	8
25	(Watanabe et al., 2019)	5	1M + 4F	21.2	HFM (n=5)	Internal / Unidirectional **(NAVID System, Medical U&A, Japan)**	7	16	0.5 to 1 mm/d	26
26	(Keçik et al., 2010)	1	1M	13	PRS (n=1)	Internal / Bilateral / Multidirectional (Curvilinear)	7	-	1 mm/d	17.4
27	(Hassan & Mohamed, 2019)	20	6M + 14F	20.5	TMJ ankylosis (n=20)	External / Unilateral (12), Bilateral (8) / Multidirectional **(Stryker-Leibinger, Howmedica Germany)**	5	-	1mm/d	12

Table 5-3: (Continued).

Serial no.	Author, year	No. of patients	Gender	Mean/ range age (yr.)	Primary diagnosis	Distractor type	Distraction protocol			
							Latency phase (days)	Mean distraction range (mm)	Distraction rate (mm/day)	Consolidation phase (wk.)
28	(Denny, 2002)	5	-	14.5	PRS (n=5)	External/ Bilateral **(Stryker Howmedica Osteonics, New Jersey)**	-	12.4	1 to 2 mm/d	4
29	(Shen et al., 2009)	6	-	13.14	PRS (n=6)	Internal / Unidirectional **(Cibei Inc)**	-	-	1 to 1.2mm/d	4
30	(Baas et al., 2015)	34	16M + 18F	21.3	-	Internal / Unidirectional / Bilateral **(Zurich Distractor, KLS Martin Group, Germany)**	5 - 7	7.3	1mm/day (0.5mm twice a day)	9
31	(Zenha et al., 2012)	2		0.03	PRS (n=2)	Internal / Unidirectional / Bilateral **(Synthes, Switzerland)**	0	21.23	1mm/d to 2 mm/d	9
32	(Dolanmaz et al., 2009)	5	3M + 2F	18.4	Infection (n=1), trauma (n=1) sagittal mandibular deficiency (n=3)	Internal (4), External (1) / Unidirectional (4), Multidirectional (1) / Unilateral (2), Bilateral (3) **(Vasquez- Diner intra-oral, Leibinger, Germany)** **(Medartis, Modus MDO 2.0, Switzerland)** **(Molina bi-directional extraoral, KLS Martin, USA)**	7	14.5	1mm/day (0.5mm twice a day))	12
33	(Mehrotra et al., 2009)	30	17M + 13F	12	TMJ ankylosis (n=13)	Internal (5), External (25) / Unilateral (21), Bilateral (9)	5	27.17	1mm/day (0.5mm twice a day)	13
34	(Bukhari et al., 2012)	7	3M + 4F	12.57	TMJ ankylosis (n=5), micrognathia (n=1), skeletal class III deformity (n=1)	Internal / Unilateral (1), Bilateral (6) **(Tri-Med, Turkey)**	7	15.04	1mm/day (0.5mm twice a day)	8.7
		Total: 447	**Total: 179M + 191F**	**Mean: 10.98**			**Mean: 4**	**Mean: 20.3**	**Mean: 1 mm/d**	**Mean: 10**

M – Males; F – Females; HFM – Hemifacial Microsomia; TCS – Treacher Collins Syndrome; PRS – Pierre Robin sequence; NG – Nager Syndrome; TMJ – Temporomandibular Joint

Demographics

From the 447 patients who underwent MDO, 174 (40%) were males, 191 (42.7%) were females, and the remaining cases did not state the gender. The age at the start of treatment in the evaluated samples ranged from 3 days to 39 years the mean age being 10.98 years. The most frequently mentioned diagnosis were Pierre Robin sequence (22.8%), hemifacial microsomia (21.5%) and TMJ Ankylosis/trauma/infection (22.1%).

Table 5-3: *Most common primary diagnosis of patients having undergone MDO.*

Primary Diagnosis	No. of Cases (%)
Pierre Robin sequence	102 (22.8)
Hemifacial microsomia	96 (21.5)
TMJ Ankylosis/Trauma/Infection	99 (22.1)
Treacher Collins syndrome	17 (3.8)
Nager syndrome	10 (2.2)
Other/Unknown	123 (27.5)

Distraction device and distraction protocol

Internal distractors are considerably more implemented, with 372 cases (83.2%), than external distractors, with 75 cases (16.8%). The difference in the percentage of unilateral (39.4%) and bilateral (64.4%) distractors used is significant, with a higher number of reported cases of bilateral mandibular distraction. Further information regarding the distractor type can be seen in Table 5-4.

Table 5-4: *Types of distractors applied in MDO as well as the total number of unilateral and bilateral reported cases.*

Distractor type	Number of cases where distractor type was specified (%)	Unilateral cases (%)	Bilateral cases (%)
Internal	372 (83.2)		
External	75 (16.8)		
Unidirectional	229 (51.2)	176	248
Multidirectional	56 (12.5)	(39.4)	(64.4)
Resorbable	129 (28.9)		
Non-resorbable	318 (71.1)		

The most applied distraction rate was 1mm/day, with activation two times a day. When it comes to latency and consolidation period the mean period was 4 days (n=429) and 10 weeks (n=426), respectively. The average total distance distracted was 20.3 mm. Mean consolidation periods were slightly longer when internal distractors were applied (internal device, 10 weeks; external device, 8.8 weeks). Distraction range was slightly higher in cases were external distractors were used (external device, 22 mm; internal device, 20.1 mm). Further information comparing the distraction protocol of internal and external devices is shown in Table 5-5. It is essential to take into consideration that the number of cases where internal distractors were applied is considerably higher than the cases of external distraction. This fact can be crucial for the analysis of the obtained data.

Table 5-5: *Distraction protocol for MDO. Comparison between internal and external devices.*

	No. of cases	Mean			Range
		Total	Internal	External	
Latency period (days)	429	4	3.9	4.7	1 – 7
Consolidation Period (wk.)	426	10	10	8.8	4 – 27
Distraction Range (mm)	371	20.3	20.1	22	7.6 – 43

Complications

The most reported complications included the development of open bite after distraction (9.8%), scarring (11.6%), any type of nerve injury or weakness and paraesthesia (7.1%) and infection (6%). There were 8 device failures during the activation period and a total of 37 relapses after device removal, constituting a percentage of 1.8% and 8.3% accordingly. More detailed information about the reported complications, as well as causes and solutions, when mentioned in the studies, is listed in Table 5-6. Most articles do not discuss the factors that cause the complications, especially regarding open bite and relapse.

After assessing all the complications reported by the authors, these complications were screened in order to exclude common and unavoidable intercurrences that are inherent to osteogenic distraction treatment and that could have been misunderstood as complications. Example of these is the suppuration around pins or activation ports without inflammatory signs not requiring any surgical drainage or any antibiotic treatment that is sometimes reported as an infectious complication. Transient nerve dysfunction resultant from neuropraxia was included as complications in some studies, but since they have a difficult evaluation and are self-limited not

requiring additional treatment they were excluded from complications. Also, open bite at the final of distraction phase that is reported as solved utilizing callus moulding or callus manipulation was discarded as complication since these are nowadays procedures considered as part of the technique, not requiring any additional surgery or treatment procedure apart of the routine orthodontic appliances and elastics. Therefore, only an unexpected event that jeopardizes the patient's health or the final result of the treatment and that requires additional therapeutic measure was considered as a complication. Table 5-7 shows the complications after this screening.

Table 5-6: Reported complications and their causes associated with MDO technique.

Serial no.	Nerve Injury/ Weakness	Open Bite	Infection	Relapse	Scarring	Tooth Injury	Device Failure	Pin/Screw loosening
1	n=0	NR	**n=1**	n=0	NR	**n=2 -** During osteotomy	n=0	NR
2	NR	**n=2 -** Solved by using acrylic occlusal splints	**n=1 -** Significant pin site infection., Completely resolved after distractor removal.	n=0	**n=6 -** (external distractors)	**n=1**	n=0	NR
3	n=0	n=0	n=0	n=0	n=0	n=0	**n=1 -** Activation rod was broken when it was caught in a seat belt. Additional surgery needed to replace the rod.	n=0
4	NR	n=0	n=0	**n=1 -** Device turned back on itself. Correct jaw positioning was achieved after reactivation	n=0	n=0	**n=1** Malfunction of the stop that prevents spontaneous reversal of the device. This caused relapse which was corrected by device re-activation	n=0
5	**n=4 -** transient paraesthesia of the inferior alveolar nerve. Normal sensation at the end	**n=8 -** Closed within a week using elastic band traction	**n=1 -** Minor local infection. Required prolonged antimicrobial medication and oral hygiene instruction	**n=6 -** Can be explained by condylar resorption	n=0	n=0	**n=3 -** Broken distraction rods. One during surgery, two due to high distraction forces caused by little mobilization of the corticotomy site. Required replacement.	**n=7 -** Result of micromovements due to loading or caused by distraction itself
6	**n=1** Healed in 2 months	n=0	n=0	NR	NR	n=0	n=0	n=0

Table 5-6: *(Continued).*

Serial no.	Nerve Injury/ Weakness	Open Bite	Infection	Relapse	Scarring	Tooth Injury	Device Failure	Pin/Screw loosening
7	n=0	**n=1** Pre-existing open bite. Distraction did not correct. Closed in 9 months using elastics	n=0	NR	n=0	n=0	n=0	n=0
8	n=0	NR	**n=2 -** Granules of the distractor's material extruded from the wound, causing an inflammatory reaction	n=0	NR	n=0	**n=1-** Distal plate became detached from the mandible caused by technical error. Device had to be reapplied.	n=0
9	n=0	**n=2 -** Self-corrected	n=0	**n=1 -** Re-operation upon at the age of 4.5 years with good results	NR	**n=1 -** Near the osteotomy site	n=0	NR
10	n=0	n=0	n=0	**n=8 -** Not found to be clinically significant. Explained by the fact that the patients did not have a normal TMJ	n=0	n=0	n=0	NR
11	n=0	**"Some patients" –** Corrected with postoperative orthodontic treatment	n=0	n=0	NR	n=0	n=0	NR

Table 5-6: *(Continued).*

Serial no.	Nerve Injury/ Weakness	Open Bite	Infection	Relapse	Scarring	Tooth Injury	Device Failure	Pin/Screw loosening
12	n=0	**"some patients" –** self-corrected by the time of device removal	NR	**n=6 –** Relapse was explained by the growth of the patients	NR	n=0	n=0	NR
13	**n=1 –** Improved spontaneously before removal of the distractor	n=0	**n=3 –** Treated with systemic antibiotics and dressings	NR	**n=11**	NR	n=0	NR
14	n=0	n=0	n=0	n=0	n=0	n=0	n=0	n=0
15	n=0	NR	NR	NR	NR	n=0	n=0	NR
16	NR	**n=1 –** Treated with orthodontic procedures	**n=1 –** Resolved after peroral antibiotic therapy	NR	NR	NR	n=0	NR
17	n=0	NI	**n=1 –** Infection due to micromotion caused by pin loosening	**n=1 –** No relation to consolidation period. The suggested reason is the intrinsic growth retardation	**n=9**	n=0	n=0	**n=1 –** Pin loosening caused micromotion which led to infection
18	n=0	n=0	NR	n=0	n=0	n=0	n=0	n=0
19	NR	NR	NR	NR	NR	**n=3 –** Caused by fixating screws and site/shape of osteotomy	**n=1 –** Loss of external pin during the consolidation period. Was immediately repositioned outpatient	NR
20	n=0	**"Some patients" –** Corrected by Le Fort I	**n=1 –** Healed after several dressing changes	**n=12**	n=0	NI	n=0	NR
21	NR	NR	NR	NR	n=0	NR	n=0	NR

Table 5-6: *(Continued).*

Serial no.	Nerve Injury/ Weakness	Open Bite	Infection	Relapse	Scarring	Tooth Injury	Device Failure	Pin/Screw loosening
22	NR	NR	**"Some patients" –** Minor infections at the drive screw cutaneous junction	NR	NR	NR	n=0	NR
23	n=0	NA	NR	NA	NR	NR	NA	NA
24	NR	**n=9 –** Corrected by moulding the callus	NR	NR	NR	NR	NR	NR
25	NR	NR	NR	n=0	NR	NR	n=0	NR
26	NR	**n=1 –** Corrected with light intraoral elastics	NR	**n=1 –** Caused by pterygomasseteric sling	NR	NR	n=0	NR
27	**n=20 –** Resolved by the follow-up at the end of the first year	**n=8 –** Corrected using elastics	n=0	n=0 Overcorrection was made.	n=0	**n=1**	n=0	n=0
28	n=0	NR	n=0	n=0 Overcorrection was made	NR	NR	**n=1 –** Device replaced 72 hours postoperatively	n=0
29	n=0	n=0	n=0	n=0	n=0	n=0	n=0	n=0
30	n=0	NA	**n=12** Treated with antibiotics and drainage of the abscess under local anaesthesia	NA	NR	NA	NA	NA
31	n=0	n=0	n=0	n=0	n=0	n=0	n=0	n=0
32	**n=5** – Disappeared in the long term	**n=3** - Result of misplacement of the distractor and reduced vector control	NR	**n=1** – Long term relapse.	**n=1**	NR	**n=1** – Rod broke at the end of the distraction. Distractor was removed and replaced after 3 months of consolidation	n=0

Table 5-6: *(Continued).*

Serial no.	Nerve Injury/ Weakness	Open Bite	Infection	Relapse	Scarring	Tooth Injury	Device Failure	Pin/Screw loosening
33	n=0	**n=9 -** Corrected by callus moulding post distraction.	**n=4** – Caused by the loosening of the pins/screws	NR	**n=25** – Faded with time (external distractors)	NR	n=0	**n=4**
34	**n=1**	NR	NR	n=0 Overcorrection was made	NR		n=0	**n=1** – Caused by technical error. Required second surgery
Total	**n=32 (7.1%)**	**n=44 (9.8%)**	**n=27 (6%)**	**n=37 (8.3%)**	**n=52 (11.6%)**	**n=8 (1.8%)**	**n=9 (2%)**	**n=13 (2.9%)**

NR – non-reported, NA – non-applicable

Table 5-7: Final complications after screening.

Serial no.	Nerve Injury/Weakness	Open Bite	Infection	Relapse	Scarring	Tooth Injury	Device Failure	Pin/Screw loosening
1						**n=2 -** During osteotomy		
2					**n=6 –** (external distractors)	**n=1**		
3							**n=1 -** Activation rod was broken when it was caught in a seat belt. Additional surgery needed.	
4							**n=1 -** Malfunction of the stop that prevents spontaneous reversal of the device. This caused relapse which was corrected by device re-activation	

Table 5-7: *(Continued)*

Serial no.	Nerve Injury/Weakness	Open Bite	Infection	Relapse	Scarring	Tooth Injury	Device Failure	Pin/Screw loosening
5				**n=6 -** Can be explained by condylar resorption			**n=3 -** Broken distraction rods: 1 during surgery, 2 due to high distraction forces caused by little mobilization of the corticotomy site	**n=7 -** Result of micromovements due to loading or caused by distraction
8			**n=2 -** Granules of the distractor's material extruded from the wound				**n=1 -** Distal plate became detached from the mandible. Device hat to be reapplied	
9						**n=1 -** Near the osteotomy site		
13			**n=3** Treated with systemic antibiotics and dressings		**n=11**			
16			**n=1** - Resolved after peroral antibiotic therapy					
17					**n=9**			**n=1 –** Pin loosening caused micromotion which led to infection
19						**n=3 -** Fixating screws and site/shape of osteotomy	**n=1 –** Loss of external pin during the consolidation period. Was immediately repositioned outpatient	
20				**n=12**				
27						**n=1**		
28							**n=1 –** Device replaced 72 hours postoperatively	

Table 5-7: *(Continued)*

Serial no.	Nerve Injury/Weakness	Open Bite	Infection	Relapse	Scarring	Tooth Injury	Device Failure	Pin/Screw loosening
30			**n=12** Treated with antibiotics and drainage of the abscess under local anaesthesia					
32		**n=3** - Misplacement of the distractor and reduced vector control			**n=1**		**n=1** – Rod broke at the end of the distraction. Distractor was removed and replaced after 3 months of consolidation	
33			**n=4** – Caused by the loosening of the pins/screws		**n=25** – Faded with time (external distractors)			**n=4**
34	**n=1**							**n=1** - Caused by technical error. Required second surgery
Total	n=1 (0.2)	n=3 (0.7%)	n=22 (5.9%)	n=18 (4%)	n=52 (11.6)	n=8 (1.8%)	n=9 (2%)	n=13 (2.9%)

Episodes of open bite (7.6%), infection (5.4%), relapse (7.8%), device failure (1.6%) and pin/screw loosening (2.7%) were more frequent in cases of internal distraction. On the other hand, with the use of external distractors, complications such as nerve injury (4.5%) and tooth injury (1.1%) were more regular. Scarring is also more common in external distraction (9.2%), which conforms with the literature since the fixation of this type of distraction requires the use of transcutaneous pins. More complete and comparative information can be found in Table 5-8. As mentioned before, the number of cases where internal distractors were applied is considerably higher than the cases of external distraction which can affect the statistics when analysing the data.

Table 5-8: Comparison of complications between internal and external distractors.

Complications	Internal Distraction Devices (%)	External distraction Devices (%)
Nerve Injury	12 (2.7)	20 (4.5)
Open Bite	34 (7.6)	10 (2.2)
Infection	24 (5.4)	2 (0.4)
Relapse	35 (7.8)	1 (0.2)
Scarring	11 (2.4)	41 (9.2)
Tooth Injury	1 (0.2)	5 (1.1)
Device Failure	7 (1.6)	2 (0.4)
Pin/Screw Loosening	12 (2.7)	1 (0.2)

DISCUSSION

The present systematic review represents an overview of the literature on studies of MDO in cases of micrognathia and retrognathia. All variables involved in the process were assessed as well as the prevalence of the main complications associated with the process. Using the inclusion and exclusion criteria, 34 relevant papers were found. Overall, MDO is a powerful tool for the treatment of hypoplastic mandibles, allowing great mandibular advancements with great impacts on minimizing airway obstruction. However, MDO can be technically challenging and is associated with some degree of complications.

After analysing the papers, it was possible to verify that MDO is a process used in a wide range of ages such as new-borns, children and adults, and the decision to apply this method is strongly dependent on the severity of the deformity and the functional problems associated with it. The most common diagnoses were hemifacial microsomia (n=96) and Pierre Robin sequence (n=102) and there was significantly greater use of internal distractors (n=372) compared to external distractors (n=75). The choice between internal and external devices for mandibular advancement seems to be related to the age of the patient, the practices and training of individual craniofacial surgeons. The final analysis supports

the general opinion that the efficacy in achieving mandibular advancement can be similar in both internal and external distractor devices. However, distraction range was slightly greater when external devices were used (internal device, 20.1mm; external device, 22mm), and the mean consolidation period was slightly shorter with external devices (internal device, 10 weeks; external device, 8.8 weeks). The last one is consistent with protocols in the literature involving earlier removal of external devices because of their higher dislodgment risks and impact on patient's daily life.

Taking into consideration the various advantages, the distraction osteogenesis method has been favoured by many surgical units to prevent donor site morbidities, prolonged anaesthetic time as well as to minimize the common grafts complications associated with the conventional orthognathic surgeries (Agarwal, 2013; Hopper et al., 2020). It is necessary to bear in mind that it is not precise to directly compare osteogenic distraction with orthognathic surgery. DO is a reconstructive procedure that is utilised for larger mandibular elongations that are not obtainable with conventional orthognathic surgery. Despite the significant improvements brought by DO to mandibular advancement, complications associated with this method are numerous (Hopper et al., 2020). Of all the articles analysed, only a small number clearly and directly addressed the type of complications found and their possible causes and treatment. This fact makes the analysis process difficult and inconsistent. Therefore, a screening of the reported complications was made, in order to exclude the complications not clearly described and those minor transient intercurrences that did not require any additional treatment. Thereby, expected episodes of an osteogenic distraction process that were wrongly reported as complications, as occurred in most cases of transient sensory loss, open bite orthodontically corrected, and suppurations not requiring any treatment, were excluded. In a significant number of articles, these expected intercurrences of DO considered as complications increase statistically its impact and negatively contribute to the invalidation of the technique or device under study.

The complications that arise with MDO can generally be divided into three groups - complications related to the surgical technique, those related to the device and others due to inadequate patient care. Complications caused by the technique and surgical procedure are the most common, as it is the case of nerve and tooth injuries, relapse, open bite or inadequate positioning of the bone segments and fixation problems (pin/screw loosening and plate detachment). The frequency of this type of complications may vary based on surgeon experience (Master, Hanson, & Gosain, 2010). On the other hand, complications caused by the device itself comprise device failure and device malfunction (the device stops activating or moves backwards). Finally, related to the patient, we have complications such as infections due to poor hygiene and failure of the device due to the lack of care from the patient. In addition to the complications

mentioned above, infection and scarring can also occur. The main experienced issues that most affect the outcomes of the distraction process were device-related such as loosening of pins/screws and hardware failure. Issues related to the planning or execution of the surgical technique such as distractors improper vector control or planning is thought to be the cause of misalignments and open bite observed in some of the outcomes (Hassan & Mohamed, 2019). Only seven clinical studies, a total of 35 patients, reported relapse as one of the complications found.

Scarring was reported in 52 of the 447 patients. One study reported 25 cases of scarring due to external devices (Mehrotra et al., 2009). Although scarring is inevitable from any surgical process especially in cases of external distraction, in this study the final condition of the scar was not specified, it was only reported that the scars "faded with time". Therefore, these 25 patients were included in this review. Scarring can be caused either due to the external approach to perform the osteotomy and/or device fixation, the transcutaneous pins of the external distractors or the skin activation ports in internal distractors. The intraoral approach, whenever possible, allows reducing the amount of scars except the ones related to the pins-tracks unavoidable with the utilization of external devices. Also, the intraoral approach and intraoral placement of the activation ports and activation rods avoids additional external scars of the internal devices, reducing them virtually to zero (Agarwal, 2013; Master et al., 2010).

In the case of infections, it was essential to distinguish real complications from the minor inflammations that follow the normal inflammatory process of an osteogenic distraction intervention. That being said, only infections that required additional treatment, such as antibiotics and abscess drainage, were considered complications in Table 5-7. All others that were reported but resolved spontaneously or with local disinfection were excluded. Twenty-two out of the twenty-seven cases of infection reported on the articles were considered real complications after the screening. Two patients showed an inflammatory response due to loose particles of the distractor material and five were due to micro-movements caused by the loosening of the pins/screws. Generation of debris was only reported in one study where a bioresorbable distractor was implanted (Burstein, 2008) and it occurred during the breakdown of the device. These debris induce an extensive biological cascade of adverse cellular responses, culminating in an inflammatory process. During the design of resorbable distractors, parameters such as the materials used and types of treatments applied as well as reabsorption rates must be extensively investigated to prove their biocompatibility and avoid the production of toxic debris (Jin, Zheng, Li, & Zhou, 2016). In the end, all the infections were successfully treated and did not require removal of the device.

Tooth injury and nerve injury comprised, respectively, 8 and 32 of the complication cases reported in the studies. Typically, injury to the tooth or the dental bud and the mandibular nerves occur

at the time of osteotomy and/or pin/screws fixation. The osteotomy and distractor pins/screws should be placed far enough from tooth buds so as not to interfere with subsequent tooth development. This can be avoided with the acquisition of preoperative imaging to determine the precise locations of molar teeth and buds thus allowing accurate positioning of the selected pins/screws utilizing intraoperative patient-specific guides (Jin et al., 2016). Considering that all the reported nervous injuries and weakness were minor, transient, and subsided spontaneously, these were excluded from complications. The exclusion was applied since they were expected episodes of the process, did not compromise the final result and did not require any additional therapy (Agarwal, 2013). In order to minimize these cases, it is essential to determine the optimum osteotomy line as well as the fixation pins/screws position, specific for each patient (Şensoy et al., 2018). On the other hand, and although the process of gradual expansion of the soft tissues is a benefit that distinguishes osteogenic distraction from other methods, it is necessary to take into account that oral tissues, composed of bone, nerves, blood vessels, and other tissues have different regenerations rates and often are not synchronized with that of jawbones. An inadequate tension applied to the forming regenerating tissues can generate forces of distraction that lead to soft tissue overstretching (Agarwal, 2013; Master et al., 2010). The occurrence and severity of potential injuries to nervous structures appear to be dependent on the amount of stretching produced by the distraction (Ippolito et al., 1994).

According to the articles reviewed, relapse was reported in 37 cases however, only 18 were classified as real complications despite not having a specific reason except for 6 cases where the relapse was caused by condylar resorption (Van Strijen et al., 2000). Relapses whose cause has been identified as intrinsic growth retardation were removed from the complications since this is a deficit in the growth potential of the mandible and not a problem of the distraction process itself. Some studies state that there is no correlation between the age and sex of patients and the possibility of relapse (Hassan & Mohamed, 2019). Some relapse cases may not be considered clinically significant and facial asymmetry is not noticeable, thus not requiring any extra treatment and not being considered as a complication. However, in certain cases, reoperation (in case of device failure/malfunction) or reactivation of the distractor is necessary. To achieve the planned outcome, some authors (Table 5-6) suggest overcorrection of the necessary distraction distance to ensure that the outcome is as symmetrical as possible (Hassan & Mohamed, 2019). However, overcorrections and in DO have to be addressed based on a specific case-by-case basis. Since early device removal is pointed out by the authors as one of the most frequent causes of relapse, a possible solution could be not removing the device at the end of the consolidation phase in cases of internal distraction. This way, the distractor would always exert a certain tension, offering more

stability to the callus during remineralization and preventing any possible relapse. It is important to emphasize that the application of this concept could only be possible in adult patients since the presence of the hardware could jeopardize the growth of the facial skeleton of paediatric patients. This possibility would also avoid the need for a second surgical intervention to remove the device.

Device failure, reported in 9 cases, is another major distraction problem that can occur during surgery or the activation or consolidation period. Device failures can be due to occasional iatrogenic errors made by the treating surgeon during surgery such as incomplete osteotomies with poor mobilization of the segments causing hardware failure due to excessive distraction forces (Van Strijen et al., 2000). The diagnosis of incomplete osteotomy must be made intraoperatively. It is part of the surgical technique to check if after the fracture the segments are mobile and if the device is able to move the segments when activated. On the other hand, they can also be due to incidental trauma (e.g., the rod broke because it was caught in a seat belt (Margulis et al., 2003)). In one case, malfunction of the stop that prevents the spontaneous reversal of the device was reported. This caused the device to reverse, which resulted in the relapse of the patients' mandible (Van Strijen et al., 2000).

Pin/screw loosening was observed in 13 patients, 7 of them caused by micromovements due to daily life loading motion or caused by distraction itself (Van Strijen et al., 2000). The fixing power of a pin/screw and its ability to support loads are dependent on intrinsic factors such as the outer diameter and the configuration and length of the thread, and extrinsic factors such as bone quality and quantity, bone type, insertion orientation of the screws and the tightening torque (Kummer, 2012). On another note, additional research on the matter revealed that thermal and mechanical damage of the bone during pin/screw insertion and formation of fibrous tissue at the bone-pin/screw interface have been identified as causes of pin/screw loosening (Moroni et al., 2002). Pin/screw loosening can be precisely evaluated by measuring the extraction torque (torque wrench) and compare it to the initial insertion torque. If lower than the insertion torque, it is an indication of deterioration of the bone-pin interface strength. Excessive pin-insertion or drilling pre-screw insertion torque can result in thermal damage to the bone with secondary necrosis. Another important factor is bone quality, defined as the union of all of the characteristics of bone (bone turnover, bone mineralisation, matrix and mineral composition, microarchitecture and vascularity) that influence its resistance to fracture and therefore the strength available to support the fixation device (Aydin, Bulut, & Bulut, 2017; Kummer, 2012). Numerous conditions such as disorders in bone remodelling, bone vascularization, disorders of mineral homeostasis, collagen disorders, radiation and drugs affect bone quality. Also, the age of the patient affects the bone quality, being good examples of normal bone the new-born "soft" bone and the "brittle" bone of the

elderly. That being so, a patient's mandibular bone evaluation before surgery is an essential step in preventing future fixation problems. Other factors to consider during the customization of the fixating pins/screws are those related to the pin/screw design and the insertion protocol. Pin/screw tip design, for example, was seen to influence heat generation and insertion torque (Wikenheiser, Markel, Lewallen, & Chao, 1995) at the same time, titanium pins were found to have higher osteointegration compared to similar pins made of stainless steel (Moroni et al., 2002).

Many authors reported the presence of open bite following MDO, however, as mentioned before, the majority of the analysed studies fail to explain the specific causes behind those complications. Overall, 44 cases of open bite were reported, 3 of which whose cause was the misplacement of the distractor and reduced vector control. Further research on this issue revealed that poor knowledge of the technique and, therefore, inadequate planning of the distraction vector can lead to inaccurate skeletal movements that often result in poor occlusal, such as open bites and midline shift (Balaji, 2017). On the other hand, incorrect distractor placement and angular deviations from the optimum osteotomy line might result in deep-bite or open-bite, affecting callus stability (Conley & Legan, 2014; Robinson et al., 2001). Forty-one of the forty-four cases of open bite were excluded from the complications since they either self-corrected or were treated through the callus moulding or open callus manipulation. These methods cannot be considered as a complication associated with the distraction process, but rather as technical options implemented throughout the treatment.

Distraction vector plays an important role in achieving functional and occlusal goals. A thoroughly clinical examination of the patients' mandibular deformity provides the necessary information to determine the optimal distraction vector. Diagnostic aids in selecting the distraction vector include clinical evaluation; panoramic, lateral, and posteroanterior cephalometric radiographs; and CT scan with three-dimensional reconstruction and virtual surgical planning. In other to ensure that the distracted bone is moving along the predetermined path, it is essential to carefully evaluate the distraction vector during the activation period. Most common complications observed during DO are due to axial deviation of the distracted segment in any of the three axes. This axial deviation may occur due to strategic errors including the use of inappropriate size and strength of the device, inadequate osteotomy level or inadequate device orientation. On the other hand, incorrect alignment of the distractor device, insufficient anchorage of the distractor, overcorrection of the deformity and an incorrect rate of distraction constitute the technical and tactical errors that lead to axial deviation (Agarwal, 2013). More recently, software development has contributed to making vector determination more practical and accurate. That way, determination of movement of the osteotomised bone segment and precise pin/screw location can be

planned preoperatively. Vector errors can be greatly minimised in this approach. However, it is necessary to keep in mind that distraction is a dynamic process that involves an interaction of mechanical and biologic factors that influence each other. The applied distraction forces, the loading created by the surrounding muscles, the rigidity of fixation, the properties of the soft tissues, including the tissue formed at the distraction site and the movements of the temporomandibular joint, all together influence the ideally planned vector and can change its direction (Guerrero & Bell, 1999). Being a dynamic process, it is necessary to make corrections to the vector as the device is activated. Examples of this are the external devices that allow the vector to be changed, callus moulding using elastics or the method of acute open callus manipulation and fixation.

In conclusion, after screening, the systematic review shows that scarring, infection, relapse, pin/screw loosening and device failure represent the highest incidence of complications with 11.7, 5.9, 4, 2.9 and 2 percent accordingly. During this systematic review, it was evident the lack of coherence and adequate classifications to distinguish the real complications from transient intercurrences of mandibular distraction osteogenesis. In addition, there was a significant lack of information regarding reported complications, such as their cause and corrective measures. This fact made it difficult to analyse the data. As a consequence, a screening of the initial data was carried out where all the minor transient intercurrences of MDO that did not require any additional treatment were excluded. Therefore, only an unexpected event that jeopardizes the patient's health or the final result of the treatment and that requires additional therapeutic measure was considered as a complication.

Taking this into account, there is a need for authors to be more rigorous in their definition of complication and this definition should be made explicit in future articles in other to prevent misinterpretations and inconsistencies. A suggestion would be, in addition to greater objectivity, the use of appropriate scales for the classification of complications whenever they are available. For example, scales of classification of scars such as Manchester Scar Scale and Patient and Observer Scar Assessment Scale already exist and can be used to more objectively classify the scarring reported (Fearmonti, Bond, Erdmann, & Levinson, 2010). In relapse cases, it is important to have more consistency and to differentiate real relapse from intrinsic growth retardation, since many authors have wrongly pointed out these situations as relapse.

DECLARATIONS

Funding

None

Competing Interests

None declared

Ethical Approval

Not required

Patient Consent

Not required

6. DESIGN AND DEVELOPMENT OF THE NEW MEDICAL DEVICE

This chapter presents the development of the new medical device and focuses on fundamental steps, such as market research, concept development and material selection. It should be noted that the project did not strictly follow any specific methodology and that the present device developed is in the process of patent submission. Taking this into account, and due to legal and copyright issues, only a general description of the adopted solution is made, focusing on the requirements and objectives imposed both at the structural and functional level.

6.1 Design Methodology

The development of a device always has as its precursor the need for a new product or process or the existence of a problem that should be overcome, and that current devices are unable to do so. In this context, it is important to distinguish between *direct engineering* that is carried out whenever it is intended to develop a new solution and *reverse engineering*, which is used when it is intended to optimize something that already exists, but which has become inadequate in view of current needs.

The definition of maps or models for the development of the design process by authors in the area of design methodology made it simpler to realize that the systematization of procedures has a great advantage by simplifying the development of highly complex projects through teamwork with the guarantee of more effective solutions.

Nowadays, design methodology includes a set of techniques or methods applied in each of the phases until the final solution is reached. It incorporates strategies, rules, and principles to achieve general and specific goals as well as methods to solve individual design problems (Chakrabarti, 1995; Pahl, Beitz, Feldhusen, & Grote, 2006).

The process of developing a new device can be guided by several methodologies. In the literature, there are many different methodologies covering various stages, from the formulation of an idea to its development, which could be adopted for the development of this specific device.

In the present work, the medical device development process did not strictly follow any specific methodology, however, the basic principles were maintained. Market research was carried out, the requirements and objectives of the device were established based on that research and based on the

state of the art presented in the previous chapters. As a final result, new concepts were developed capable of covering all requirements.

This project arose from the necessity of making the distraction osteogenesis process more intuitive and lessen the impact of the treatment on patients' lives. It aims to overcome the limitations observed in the devices currently marketed (such as the fact that there is no vector control in internal devices) as well as the complications inherent to the distraction process (such as infections caused by the perforation of the skin by the activation screws or the pins). In this specific case, the project's main focus was mandibular distraction.

The approach was made in a direct way, in which the main requirements and the intended global objectives were fully defined. As previously stated, a patent for the innovative devices and activation concept was written. Therefore, steps such as the design of different solutions, the CAD drawings, and and the functioning of the various mechanisms constituting the final solution cannot be described in detail in the following sub-chapters.

6.2 Ideation

This stage, also entitled “idea creation”, “opportunity detection” or “planning”, constitutes the start point of the project. In this phase, a generalized market research of the existing devices was carried out in order to evaluate the ways of functioning, the characteristics of the device, and the areas susceptible to improvement, thus assessing the market opportunity for the proposed project.

6.2.1 Market research

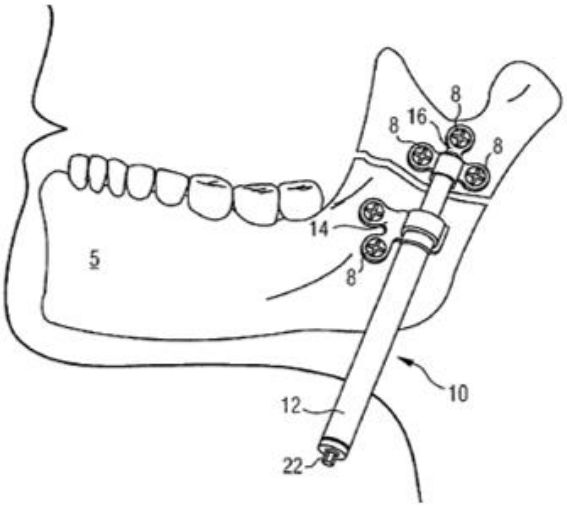
Market research is one of the most important stages for the realization of any project, as it is in this that the existing products and patents are explored. As previously stated, one of the initial phases of the device design process is the research and analysis of all patents related to the type of device under study, whether national or international, valid, or expired. This study is essential because it not only allows the investigation of the existence of gaps in the market that can be explored by the new product to be developed, but also allows the understanding of which methodologies are in use to respond to the various necessities, and their advantages and disadvantages.

Given the intention to design a biomedical device for mandibular bone distraction, an extensive search for patents related to the subject was carried out (Appendix B presents a summary table of these patents). Some patents and other already commercialized products were selected to serve as an example of the different types of distractors currently available on the market as well as their main components

and their mode of operation. In addition to a patent search, a search for the most commonly used distractors deducted from the data obtained from the systematic review was also conducted. Companies like KLS Martin, Stryker, DePuy Synthes Johnson – Johnson and, OsteoMed are currently globally recognized in the area of bone distraction.

Patent No. US20020116002A1, 2002 (Figure 6-1 a)) presents an internal linear orthopaedic system in which the part of the device that attaches to the bone is detachable from the rest of the device (Figure 6-1 b)). That being so, the device can be remotely disengaged from the subcutaneous bone anchors (18), leaving only the fixation plates (14/16) implanted in the patient. The system includes a proximal bone anchor (16), a distal bone anchor (14) and their respective fasteners (8). These anchors are placed on either side of the osteotomy and the activation process is accomplished by rotation of the threaded rod (12/22) in a counter-clockwise rotation (Patent No. WO2011038209, 2011).

a)



b)

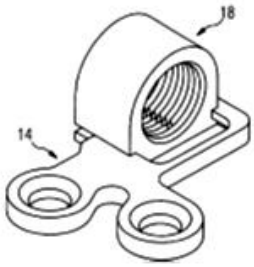


Figure 6-1: a) Internal linear orthopaedic system; b) detaching mechanism.
(Patent No. US20020116002A1, 2002)

Patent No. US20140148812A1 (Figure 6-2), developed by Synthes, relates to a paediatric internal bone distractor whose operation follows the same principle as the previous patent: two fixation plates and a threaded drive rod responsible for the device activation. The only difference is that, in this case, the device itself does not detach from the fixing plates. Both devices only allow for only linear distraction, the distraction vector cannot be changed and the distraction rod penetrates the soft tissues.

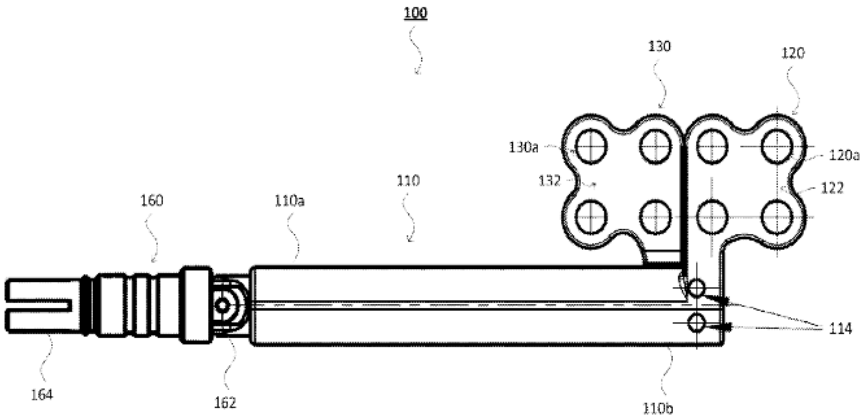


Figure 6-2: Paediatric internal bone distractor.
(Patent No. US20140148812A1, 2014)

Patent No. US6019769A (Figure 6-3), developed by Stryker Leibinger, presents an external bone-altering device that allows for precise, gradual, and easily controlled angular distraction in order to curve or bent a bone segment. The device has two independent arms that allow for linear. The horizontal distractor arm (30) when activated stretches the mandibular body and the vertical arm (20) stretches the mandibular ramus. The arms can be activated independently or simultaneously depending on the deformity allowing the device to perform two-dimensional distraction osteogenesis.

The device is fixated through transcutaneous bone-pins. The device also has a central joint (80) for angularly adjusting the position of the two arms, thus allowing the alteration of the distraction vector, and the distraction to be multidirectional.

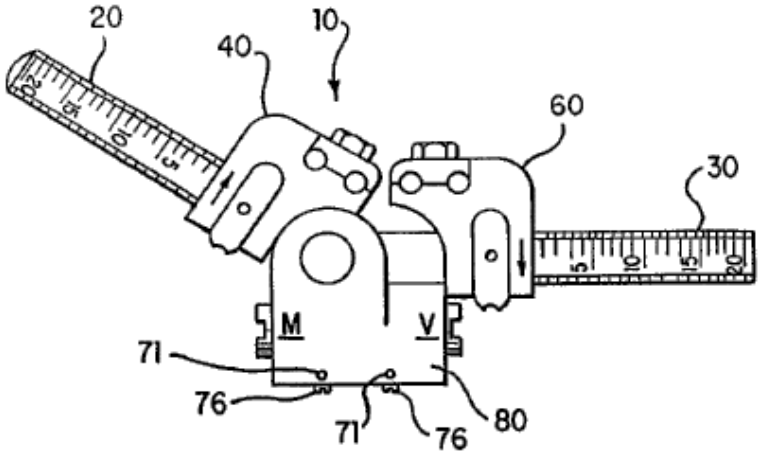


Figure 6-3: External bone-altering device which allows for three-dimensional distraction osteogenesis.
(Patent No. US6019769A, 2000)

Patent No. US2007/0162045, developed by OsteoMed L.P., Figure 6-4, presents an internal bone distractor that allows for linear (Figure 6-4 b)) or curvilinear (Figure 6-4 a)) mandibular distraction osteogenesis. The device is placed intraorally and is composed of a flexible rod with a threaded portion (110), a distraction arm (104) and a mechanism (102) to guide the flexible rod that allows for some degree of adjustment of the orientation of the distraction arm. These adjustments allow for corrections of the distraction vector however, these corrections can only be made during surgery. After device implantation, the vector cannot be altered again. The activation is achieved by turning the "interface 114" clockwise. The activation wire can be cut during the consolidation period reducing the risk of infection while promoting soft tissue healing. This device is capable of distraction lengths of up to 25mm and allows the choice between straight and curved bars with fixed curvilinear trajectories that mimic the natural growth curve of the mandible

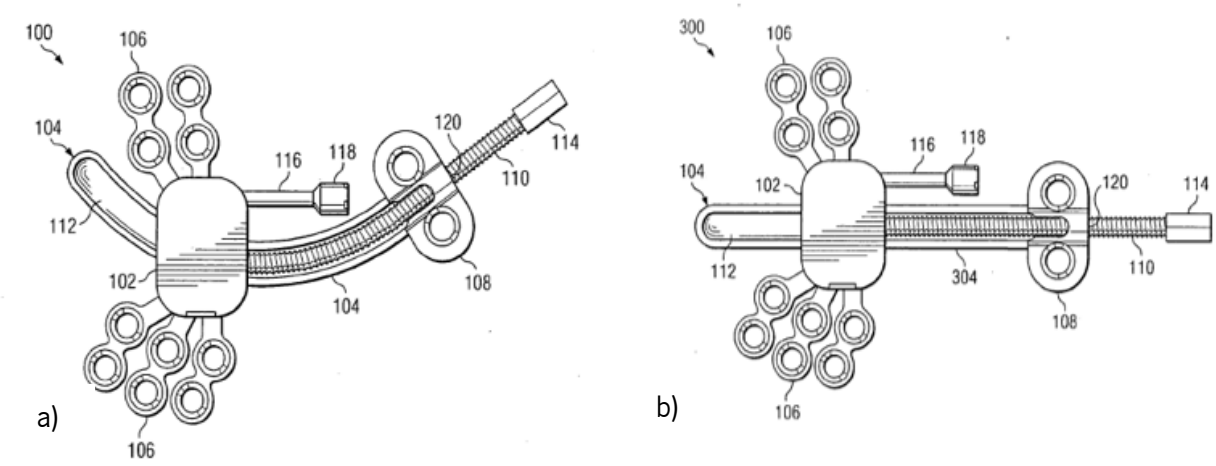


Figure 6-4: Internal mandibular bone distractor that allows for a) curvilinear and b) linear distraction.
(Patent No. US2007/0162045, 2007)

In addition to this patent search, another more selective search was also carried out regarding patents that incorporated shape-memory materials in the device design or were part of the device activation method. The research resulted in a significantly reduced number of patents. The patents in Appendix B give an overall representation of the different types of use of shape memory materials in mandibular bone distraction.

Patent WO2019081909A1 (Figure 6-5) represents a fully implantable distractor that comprises a fixable portion (12), a movable portion and (14) and a single distractor arm (16) which defines the movement path. The movement is accomplished by the activation, through external stimuli, of the shape memory material located between the movable and the fixable portion (18). This device allows only linear distraction.

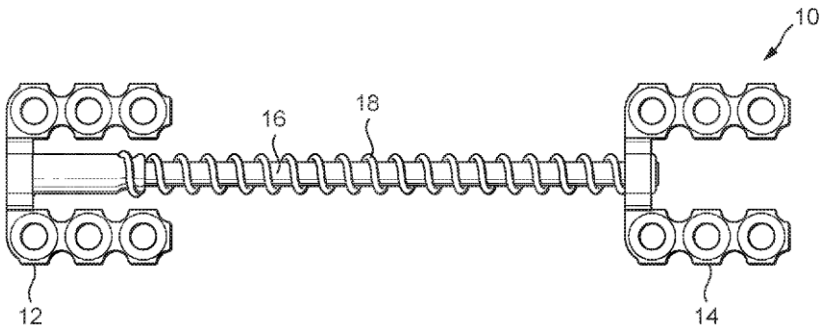


Figure 6-5: Fully implantable linear distractor activated by a shape memory material.
(Patent No. WO2019081909A1, 2018)

The purpose of patent CN100427158C, Figure 6-6, is to propose a new method of bone distraction or transport distraction osteogenesis (TDO) using a comfortable, not easily infected, small, and completely embedded in the body stretcher made of the titanium-nickel shape memory alloy. The said stretcher is composed of two parts: the fixing part and the part that exerts the tension to separate the bone segments (7). The fixing part is located at both ends of the distractor. The activation part can be designed into S-shaped, C-shaped, Z-shaped, or multi-curved Z-shaped according to the different forces required. At the temperature of the human body, the stretcher automatically expands, causing the bone segments to separate, thus allowing new bone formation in the resulting gap. The number of stretchers can be adapted as needed.

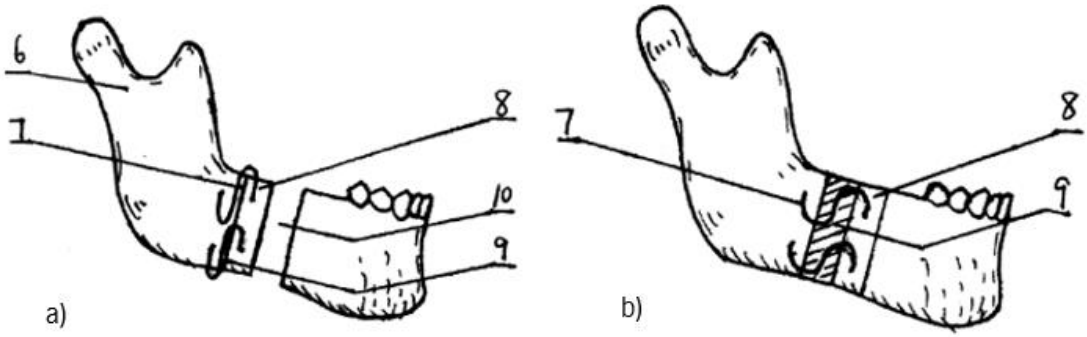


Figure 6-6: New method of bone distraction or TDO using shape-memory materials. a) device before activation; b) device after activation.
(Patent No. CN100427158C, 2008)

Patent WO2016046549A1 introduces a device for modulating biological tissue and/or bone conformation in at least two dimensions simultaneously. The apparatus is comprised of a mesh or plate of a shape memory material (Figure 6-7 a)), preferably nitinol (Ni-Ti), that is moulded to the specific conformations of the areas to be treated (Figure 6-7 b)). At the application of an external stimulus (such as a change in temperature) the mesh acquires its initial pre-programmed shape thus allowing the tissues

and bone to be moulded into the desired morphology (Figure 6-7 c)). The device can be applied either internally or externally.

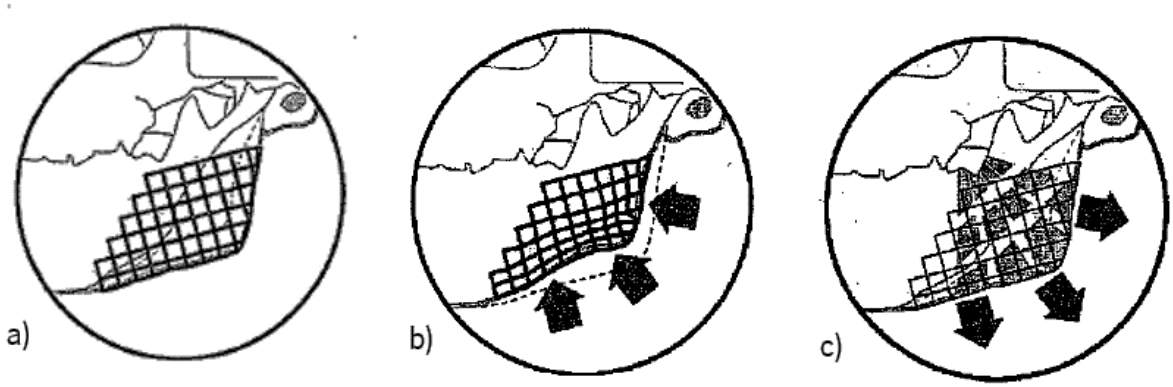


Figure 6-7: Multidimensional bone and soft tissue modulating device composed of a mesh or plate. a) Mesh/plate before moulding and shape memory activation; b) moulding the mesh/plate to the area to be treated; c) activation of the mesh/plate allowing the tissues and bone to be moulded into the desired morphology.
(Patent No. WO2016046549A1, 2016)

6.3 Concept Development

In this stage, alternative concepts to the medical device are generated and evaluated and, as the output of this phase, it is achieved the final concept, which constitutes the final solution to be developed. The concept development concentrates all the information ranging from the characteristics of the product, its composition (materials and components), drawings, the manufacturing process, information relative to the clinical evaluations, testing protocols and results.

6.3.1 Definition of device requirements and new device objectives.

For this stage of concept and device development, it was necessary to rigorously evaluate the complications observed during the mandibular distraction process, presented in the systematic review article in Chapter 5, and determine, through patent analysis, the limitations that the current devices present. On the other hand, it was necessary to seek out health professionals to concretely understand what are the existing needs and the main requirements that the device should fulfil. Therefore, the meetings held with Engineer Ana Leal, Engineer Óscar Carvalho, Professor Filipe Silva, and Doctor Alberto Pereira were fundamental to establish such objectives and requirements. It is worth adding that Doctor Alberto's contribution was of extreme importance since he holds positions such as Head of Facial Reconstructive Surgery unit at Luz Lisbon Hospital and Head of Plastic and Aesthetical Surgery unit at Lisbon Luz Torres Hospital, Senior physician of Plastic and Reconstructive surgery department at

Portuguese Oncological Institute Francisco Gentil, Chair of the AOCMF Foundation distraction taskforce, Member of Craniofacial Expert Group and International CMF Faculty of the AO Foundation, and Member of International Society of Aesthetic Plastic Surgery, which makes him the most suitable person to provide more clinical and technical information regarding maxillofacial reconstruction based on real and specific cases. Additionally, Doctor Alberto Pereira is also one of the co-authors of the review article presented in Chapter 5. Doctor Alberto Pereira, in the development of the concept, also represented the customers' point of view, pointing out areas of interest for improvement.

In addition, the possibility of attending the webinar called "Planning and Performing Maxillo-Mandibular Distraction Osteogenesis" presented by the AO Foundation was a benefit as it allowed to obtain a more medical and practical view of the maxillofacial correction process through osteo-distraction.

Taking everything into account (the systematic review article addressing the complications, the market research and the more concrete and technical input provided by Doctor Alberto Pereira) it was possible to establish the requirements and objectives that the new concept and device should have to differentiate itself from the existing devices and, thus, bring improvements to the MDO process.

In the meetings held, certain requirements were established according to which the development of the device should mandatorily comply. Such requirements are found in Table 6-1.

Table 6-1: Established mandatory requirements for any internal distraction device.

Requirement 1	Device composed of medically commercialized materials
Requirement 2	Insertion cut as small as possible
Requirement 3	Device dimensions as reduced as possible
Requirement 4	Fixation plates placed near the osteotomy cut
Requirement 5	Utilization for right and left mandible
Requirement 6	Utilization of one or more devices simultaneously
Requirement 7	Have an anti-return movement system

Requirement 1 – *Device composed of medically commercialized materials*

This requirement is clear since the device will be placed internally, thus being in direct contact with the internal environment of the human organism. This direct contact with tissues and the human body triggers a biological response. Therefore, the device must be composed of biocompatible and biofunctional materials. Biocompatibility is a property of the material to remain nontoxic through its functional period inside the human body. A biocompatible material cannot produce any allergic reaction

or inflammatory response in the host. The other requirement for the material is its biofunctionality, which is the ability of the material to function desirably for its expected service life in the human body environment. The biocompatibility assessment is standardized in ISO 10993 where the required tests, according to the type of medical device, are outlined.

Requirement 2 - *Insertion cut as small as possible*

The cut for insertion of the device must be as small as possible and, whenever possible, it must be performed intraorally. This factor is extremely important since DO requires minimal disturbance of soft tissues in order to provide sufficient osteogenic capacity for healthy regeneration and a good blood supply to avoid ischemic fibrogenesis within the regenerate. On another note, a smaller incision when made externally translates into a smaller scar.

Requirement 3 – *Device dimensions as reduced as possible*

This requirement is directly related to the previous one (requirement 2). If the insertion cut has to be as small as possible, then, by logic, the device must be of the smallest dimensions possible without, however, jeopardizing its functioning and its ability to withstand the tensions generated in the distraction gap and surrounding tissues. On the other hand, a device of larger dimensions will create a barrier between the periosteum and the bone, which will inhibit the blood supply and therefore influence the efficient operation of the bone regeneration process. In addition, a large device becomes very noticeable when placed under the soft tissues, which causes aesthetic issues that affect the patient's daily life.

Requirement 4 - *Fixation plates placed near the osteotomy cut*

This requirement is common to all internal distraction devices, especially those that concern craniomaxillofacial distraction. The fixation plates placed next to the osteotomy cut allow for a smaller cut of insertion of the device. On the other hand, it is easier to position the device in order to achieve the desired and pre-defined distraction vector when the fixation is close to the bone cut.

Requirement 5 - *Utilization for right and left mandible*

This requirement is clear since the existence of mandibular abnormalities can occur on both the left and right sides of the mandible. In a significant part of the situations and syndromes, the mandibular defect is bilateral, which requires the use of distractors on both sides. Therefore, the device must be versatile in order to be applied on both sides.

Requirement 6 - *Utilization of one or more devices simultaneously*

As mentioned in requirement 5, in a large percentage of mandibular distraction cases the defect is bilateral and requires bilateral distraction. It is, therefore, necessary to be able to simultaneously apply devices on either side of the mandible. In addition, it may also be required to use more than one distractor in a unilateral anomaly, especially if the correction of the anomaly requires a bidirectional distraction vector in order to obtain the best final result of facial symmetry.

Requirement 7 - *Have an anti-return movement system*

Finally, one of the most fundamental requirements of any distraction device is that it must have an anti-return movement mechanism. This system will prevent, during the activation and consolidation period, accidental relapses that jeopardize the entire course of treatment and will offer more security in case of possible device failures.

With this in mind, objectives that the new device should achieve were outlined according to current clinical needs. Table 6-2 presents these objectives.

Table 6-2: Outlined objectives for the new concept and bone distractor device.

Objective 1	Device must be fully internal
Objective 2	Produce minimal to no scarring
Objective 3	Activation is performed through a shape memory material
Objective 4	Modular activation mechanism
Objective 5	Fully external activation of the device
Objective 6	Device can be activated by the patient
Objective 7	Allows for distraction vector control during the activation period
Objective 8	Multifunctional and customizable
Objective 9	Free of internal electrical devices
Objective 10	Avoid the need for a second surgery

Objective 1 - *Device must be fully internal*

In the currently used internal devices, and although the device body is placed internally, the activation rod has to pierce the mandibular soft tissues and frequently the skin in order to allow for device activation. This allows direct contact between the patients' internal environment with the external environment representing a direct means for the spread of bacteria, causing inflammation. On the other

hand, the fact of having part of the distractor penetrating the skin, besides causing some scarring, influences the patient's daily life both at a physical level (since it is necessary to have a lot of care with the device especially in children) and at a psychosocial/aesthetic level. Therefore, one of the main objectives of the new device is that it must be completely internal and practically imperceptible.

Objective 2 - *Produce minimal to no scarring*

Scarring can be caused either due to the external approach to perform the osteotomy and/or device fixation, the transcutaneous pins of the external distractors or the skin activation ports in internal distractors. The intraoral approach and intraoral placement of the activation ports and activation rods avoid additional external scars of the internal devices, reducing them virtually to zero. Since one of the goals of the new device under development is to be fully internal, it is possible to obtain a DO process without any scaring, by deciding on an intraoral approach.

Objective 3 - *Activation is performed through a shape memory material*

One of the main objectives of this device, and what distinguishes it from all existing devices, is related to the activation method. The development of this distractor must be based on the principle that the activation should be performed using shape memory materials. The shape memory material will act as a linear actuator allowing the activation of the device and the bone segments to separate. The device was developed based on this main objective.

Objective 4 – *Modular activation mechanism*

The device must be able to be activated in a modular way, that is, it must be possible to incorporate several activation elements/mechanisms simultaneously into the device. In cases of possible problems with the activation mechanism, the device is prepared for the other elements to be activated in order to guarantee the smooth functioning of the distractor. This factor increases the safety margin of the device's activation mechanism. This is an important objective since, as concluded in the systematic review of Chapter 5, one of the most major complications is the fact that the device activation mechanism (in those cases, the activations rods) breaks, and the distractor can no longer activate. As a rule, these cases require a new surgery to change the device.

Objective 5 - *Fully external activation of the device*

Bearing in mind Objective 1, which states that the device must be fully internal, the activation of the device must then be completely external. For this reason, the activation mechanism that causes the

bone segments to separate must be developed in a way that all its elements are fully internal and the energy to feed the mechanism of actuation is provided by an external source supply.

Objective 6 – *Device can be activated by the patient*

Another objective imposed on the new device is that it must have an intuitive use, allowing the patient to perform the activation of the distractor in the comfort of his home. In addition to reducing the number of necessary consultations, it would give the patient more autonomy and freedom during the course of treatment. Therefore, the activation method must be simple and straightforward so that the patient is able to strictly follow the treatment plan assigned by the doctor.

Objective 7 - *Allows for distraction vector control during the activation period*

The possibility of varying the distraction vector during treatment is only possible with the use of external distractors. However, external distractors, in addition to causing major skin scarring and infection around the fixating pins and create apprehension on the part of the patient in the use of bulky devices and require patient compliance during the consolidation phase. These limitations would be overcome with the development of an internal device with the ability to adjust the distraction vector in the plane as needed. Thus, the new concept should include a system capable of varying the distraction vector allowing for linear and angular corrections in the sagittal plane (more information about the anatomical planes of the head can be consulted in Appendix C) according to the needs during the activation period.

Objective 8 - *Multifunctional and customizable*

One of the main objectives of this new device is that its concept should be applied to more deformities whose treatment is distraction osteogenesis besides mandibular ones. It must be multifunctional and be able to be applied to maxillary, cranium, and even long bone deformities. On the other hand, this device will be fully customizable in terms of dimensions, types of screws and size and shape of the fixing plates, to meet the needs of each specific patient.

Objective 9 – *Free of internal electrical devices*

Despite being a widely explored area in medical devices as in the case of pacemakers, at the mandibular level, the application of devices with electrical elements is not yet completely safe and acceptable. There are some patented devices, however, and according to protocols, commercialized bone distractors only have mechanical components in their constitution. For this reason, the device under development in this thesis should only have simple mechanical elements.

Objective 10 - *Avoid the need for a second surgery*

This objective is the subject of some controversy on the part of clinicians since, as a rule, and whenever possible, all non-essential devices must be removed from the interior of the human body after treatment. However, in the specific case of osteogenic distraction, not removing the distractor can bring several benefits. Since early device removal is pointed out by the authors as one of the most frequent causes of relapse, not removing the device could be a solution. This way, the distractor would always exert a certain tension, offering more stability to the callus during remineralization and preventing any possible relapse. It is important to emphasize that the application of this concept could only be possible in adult patients since the presence of the hardware could jeopardize the growth of the facial skeleton of paediatric patients. This possibility would also avoid the need for a second surgical intervention to remove the device.

In addition to the defined requirements and proposed objectives, it is necessary to take into account the data obtained in the systematic review regarding the distraction protocols. Therefore, the new device should allow an average distraction of 1mm/day and an average distraction range of 20 mm (ranging from 7.6mm to 43mm). It is essential to keep in mind that these values depend entirely on the anomaly to be corrected and that the device must be able to adapt to each specific patient.

6.3.2 Concept generation and selection

With the information collected, the next task at the concept development stage is to generate the concept. This task corresponds to the creation of concepts for the device. The tool chosen for the development of the concepts was brainstorming. This tool proved to be efficient to cross the ideas of all members of the project team and thus generate different concepts. In this way, several initial concepts were created, which underwent necessary gradual changes as they were tested. At the end of this stage, 2 final concepts were selected.

With the generated concepts, a patent is being developed presenting the new innovative and versatile solution for DO. The patent contains, in detail, the description of the device as well as the explanation of its operation system and its constituent elements and mechanism. It includes figures of the various views and positions of the device, of all its elements and sectional views to better explain the operation of the several systems that the device has to offer. Since the patent is in the submission stage and due to copyright, this dissertation only generically presents the concepts developed, without revealing in full detail the design, dimensions and the various systems that allow the device to achieve the proposed objectives.

The 3D modulation of the concepts was performed by the **Computer-Aided Design (CAD)** software, *Solidworks*, to facilitate the understanding of the constituent elements of the model, its general functioning and the functioning of the various mechanisms. The modelling of the concepts was especially important in the analysis of mandibular movements during distraction and to evaluate the distraction vector variation mechanism.

The project for the development of a mandibular distractor always considers three distinct parts:

1. The distractor body, which provides mechanical rigidity, strength, and support for the remaining components;
2. The distraction activation mechanism, which transforms energy into movement to displace the two bone segments;
3. The activation component that transfers the external energy to the activation mechanism.

Both generated concepts are based on the same operating principle - the activation of the device is carried out through a shape memory material. The device is fixated to the bone structure by **two fixation plates** on either side of the osteotomy cut and through bi-cortical screws (the type, size and number of screws is adaptable to each patient) that gives the distractor the necessary rigidity. The activation mechanism(s) is(are) located between the two fixation plates and, when activated, causes them to move apart from each other, thus separating the bone segments and elongating the bone callus. The device configuration can be seen in Figure 6-8. The rigidity of the device during distraction and consolidation is a critical element in ensuring that bending or cutting forces do not result in microfractures in the new bone. The bone distractor must be rigidly fixated to prevent motion at the distraction site to avoid fibrous non-union.

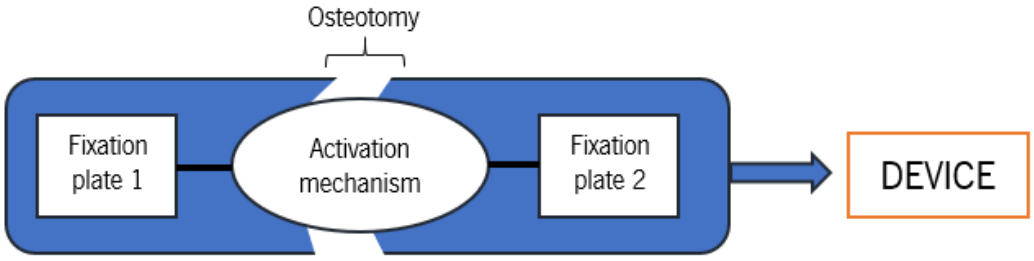


Figure 6-8: Schematic representation of the device.

Its **small dimensions** and the innovative activation method allow the device to be completely internal and all its elements to be placed under the periosteum. Being **fully internal**, the complications related to infection and scarring will theoretically be reduced to zero, since this concept overcomes the limitation of the internal devices with the activation rod penetrating the soft tissues. On the other hand, the fact that it is completely internal increases its susceptibility to the patient's activities and external

forces and impacts, without restricting the patients' normal daily activities. They have less possibility of device failure (broken distraction rods) and by being imperceptible on the external side, there is **no aesthetic problem**.

It should be noted that this device must be modulated and **adapted according to each specific patient**. Therefore, dimensions, shape and size of the fixation plates will be fully dependent on the deformity to be treated and the quality of the patient's bone. For this specific study, and the modulation of the device, a guide found in the literature on the anthropometric dimensions of the male human mandible of a 16-year-old male was followed. Appendix D shows the mandibular growth parameters and landmarks and the average age-related length of Co-Gn, Go-Gn, Co-Go in millimetres.

As previously mentioned, the activation of the device in order to separate the bone segments is done through a **shape memory material**. More information on this concept can be found in Chapter 6.4.1. regarding material selection and in Appendix E regarding the brief state of the art on shape memory materials focused on the nitinol alloy. When properly trained, shape memory alloy (SMA) wires/plates/springs act as linear actuators by contracting/expanding when heated or cooled. The developed linear actuated mechanism has the particularity of being able to control the distraction rate performed, that is, it is possible to activate either 1mm/day in a single daily activation, or to make, for example, two activations of 0.5mm. This allows for greater adaptation in paediatric cases where the distraction rate is usually greater than 1mm, and preferably with several daily activations, since the capacity for bone formation and regeneration in children is much higher than in adults. As a final result, two device concepts were developed, which despite being based on the same principle of operation, one of the concepts was designed to work using the one-way shape memory effect principle and the other concept was designed to work using the two-way shape memory effect principle of the shape memory alloys.

The activation mechanism of both concepts is **modular** to ensure proper device performance in cases of mechanical failure. This avoids having to do second operations to change the device. It should be noted that the mechanisms are interspersed with elements of low conductivity in order to prevent all of them from being activated simultaneously, that is so that the activation of a mechanism does not imply the unwanted activation of the adjacent one.

Like all bone distractors, this new concept also has an **anti-return movement system**, which once the device is activated it prevents the device from acting in the reverse direction. This factor is extremely important in preventing relapses and possible device failures in the bone distraction process.

Since the device is internal and the activation mechanism is composed of a shape memory material, its **actuation must be performed externally with a heat/cold source**. The heat/cold source will transfer external energy to the activation mechanism and this, in turn, transforms energy into movement to displace the two bone segments. In other words, the temperature variation between low and high temperatures, will trigger and control the activation mechanism. The heat source can be specially designed, which allows to precisely control the amount and duration of the heat applied, such **as low-intensity pulsed ultrasound or infrared (IR) devices**, or it can be simpler as the application of something heated (e.g., hot water bag) and ice to promote temperature variations. At the same time, the temperatures to which the patient will be subject will be totally dependent on the activation temperatures of the used memory material. It is necessary to bear in mind specific circumstances like hot water baths, high fevers, and hypothermia in the selection of these temperatures, to prevent unwanted activations of the device. Studies show that low-intensity pulsed ultrasound, in addition to being able to penetrate tissue to a depth of 30 mm, can improve bone regeneration and accelerate bone remodelling in distraction osteogenesis (Jauregui, Ventimiglia, Grieco, Frumberg, & Herzenberg, 2016; Wang et al., 2010). On the other hand, a study carried out on rabbits where IR was applied with wavelengths ranging from 780 nm to 1400 nm revealed that the infrared penetration capacity was still insufficient and that the SMA spring would not be activated if it was under the mastication muscles (Wang et al., 2010). A key factor to keep in mind is the **effect of temperature on soft tissues** in order to not create any adverse reactions or tissues burn. Table 6-3 shows the effects of various temperature ranges on soft tissues and Figure 6-9 shows the effect of temperature as a function of exposure time on coagulation of tissues.

Table 6-3: Thermal, mechanical, and optical effects as a function of temperature.
(Jean & Bende, 2007)

	Effects on tissue		
Temp (°C)	**Thermal**	**Optical**	**Mechanical**
< 37 **40-45**	Reversible damage, only enzyme induction oedema, membrane alteration (cell death);	-	-
60-65	Protein denaturing, whitening;	Whitening, light scattering;	Incipient weakening;
70-85	Collagen denaturing, membrane damage, necrosis;	Opacification;	Waterless tissue desiccation;
90-100	Desiccation;	-	Shrinkage, drying;

Table 6-3: (Continued).

Effects on tissue			
Temp (°C)	Thermal	Optical	Mechanical
>150	Carbonization;	Blackening increased absorption;	Strong mechanical damage;
300 >	Vaporization.	Fumes.	Ablation.

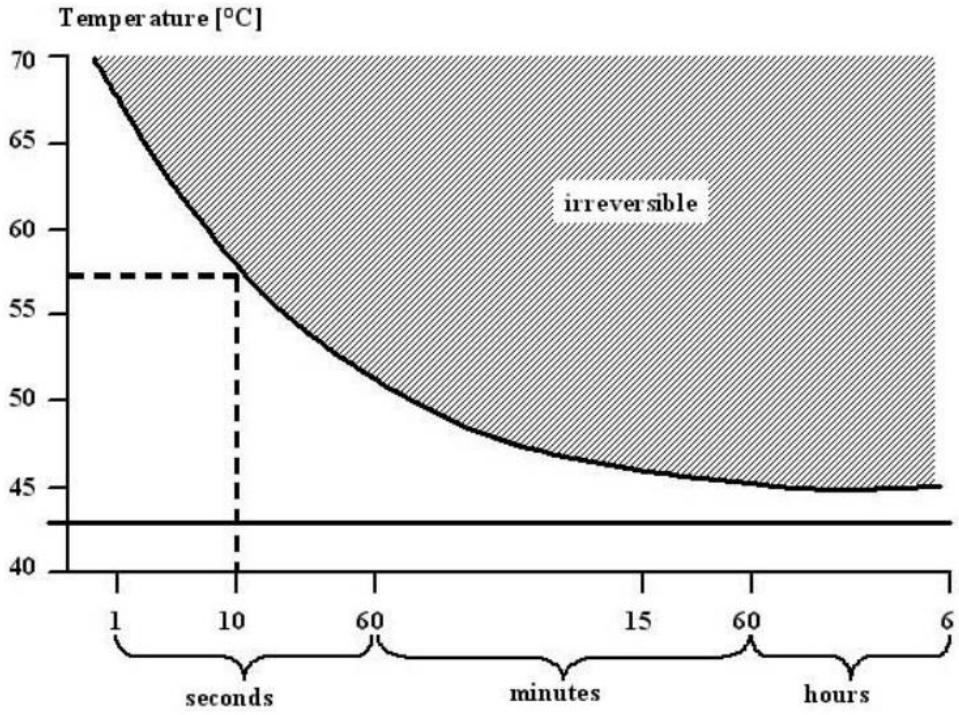
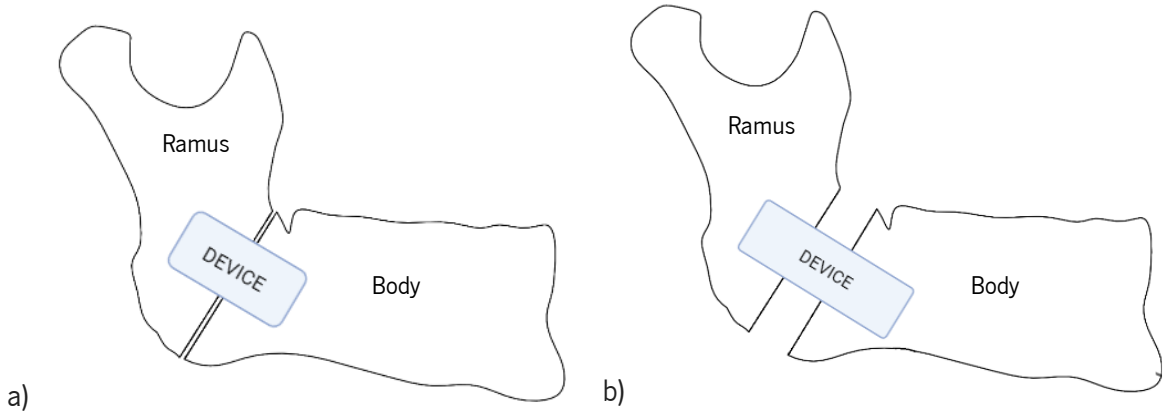


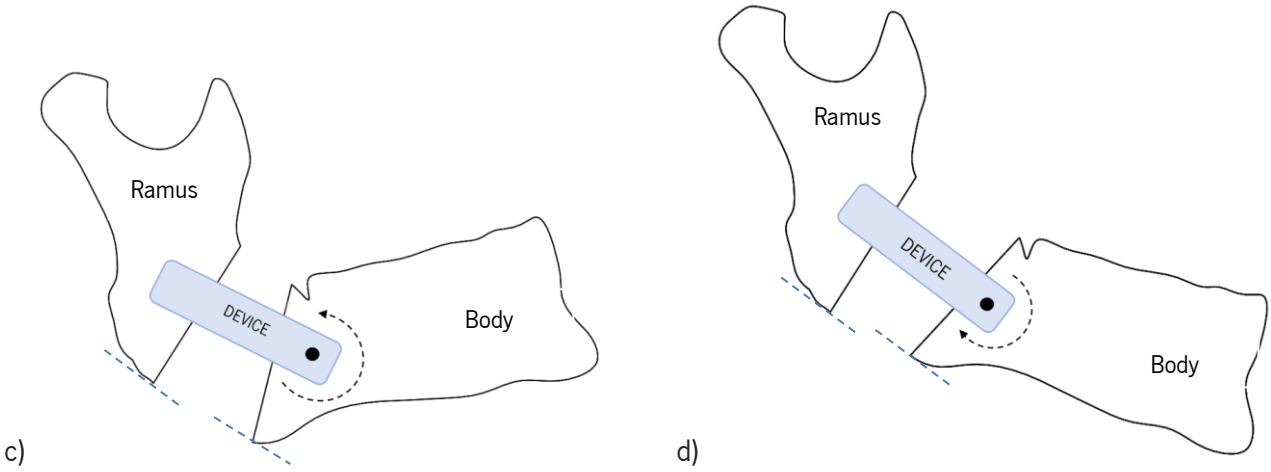
Figure 6-9: Irreversible tissue coagulation as a function of temperature and exposure time.
(Jean & Bende, 2007)

The multidirectional aspect of the device on the sagittal plane is one of the main points of innovation in the area of internal devices. The internal device has a system that allows the **variation of the distraction vector direction** on the sagittal plane whenever it is necessary to correct the trajectory of the mandible during the period of activation. In addition to allowing vector control and variation, the device has another "**movement adaptation**" system, which allows the activation of the device to translate into the most appropriate trajectory for the patient, depending on whether or not there is a need to elevate or lower the mandible. This factor is especially important for the correction of open bites or at least in their minimization. This system is based on the device's fixation points with rotation. This "movement adaptation" system is based on the strategic location of rotation points according to which the device has freedom for some degree of rotation in relation to the mandible. Figure 6-10 shows schematic examples

of this movement adaptation system. In Figure 6-10 a) the system is not activated and in b) the device is activated according to a unidirectional vector. In c) and d), the figures represent the mandibular movements when the device is completely fixed (without rotation movement at that point) to the ramus and the rotation point is in the body of the mandible. This form of fixation, in addition to the forward mandibular growth, allows the free part of the mandible (the body) to rotate at that point, either counterclockwise (c)) or clockwise (d)). On the other hand, if the point of rotation is located in the ramus (with the device fully fixed on the body), in addition to the forward mandibular growth and rotation, there will be elevation (counterclockwise rotation) represented in Figure 6-10 e) or lowering (clockwise rotation) of the whole mandibular body (Figure 6-10 f)). This difference in movement due to the different points of rotation can be more easily interpreted by observing the tangents to the angle of the mandible (represented in the figures in blue interrupted line).



Rotation of the mandible



Elevation of the mandible

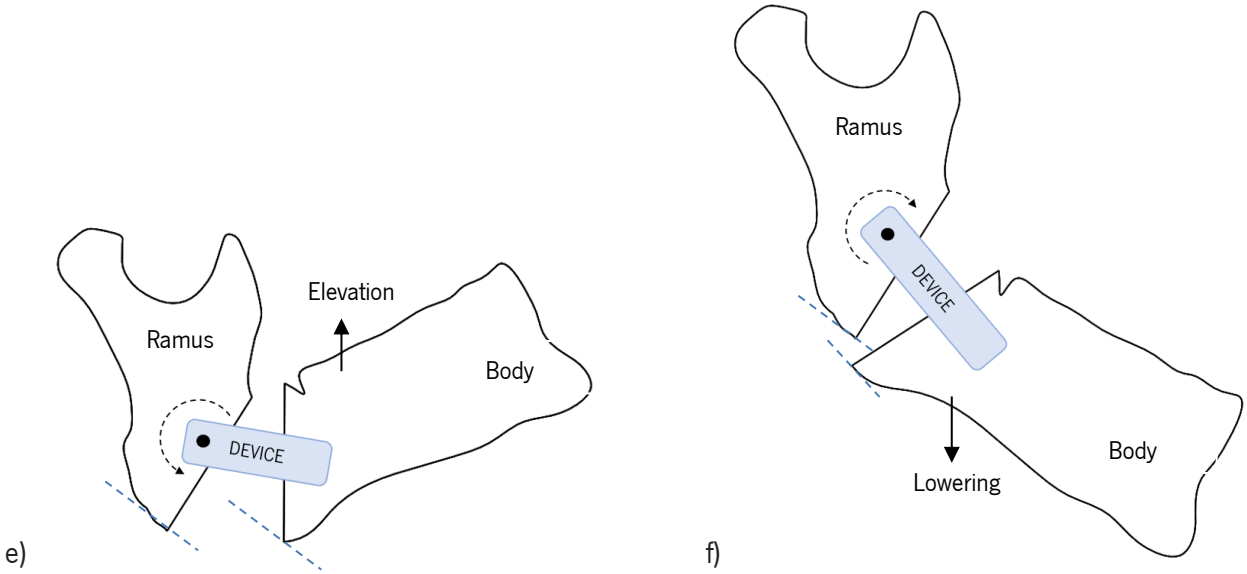


Figure 6-10: Diagram of mandibular movements when the device is activated: a) device not activated; b) device activated without vector variation (unidirectional); c) activated device with rotation over a fixation point to allow the counterclockwise rotation of the mandible; d) activated device with rotation over a fixation point to allow the clockwise rotation of the mandible; e) activated device with rotation over a fixation point to allow the counterclockwise rotation with an elevation of the mandible; f) activated device with rotation over a fixation point to allow the clockwise rotation with an elevation of the mandible.

It should be noted that all these movements depend on the place of the osteotomy. In the case under study in this thesis, the osteotomy was chosen at the level of the mandible angle, since it is the most common for cases that require bi-directional corrections. If the patient needs to lengthen only the mandibular ramus or just the body of the mandible, the cuts will be perpendicular to these structures.

It is important to note that the mandibular movements shown in Figure 6-10 above are represented exaggeratedly to better explain the difference in the rotational point. The actual movements during MDO are much less pronounced.

Finally, the concept and the developed devices have the ability to be **multifunctional** and to be adapted to other deformities either at the maxillary or cranial level (e.g., deformities caused by the craniosynostosis birth defect). Additionally, this device is designed with the possibility of **not being removed** after the end of the consolidation period in adult patients. As previously stated, this matter is the subject of some controversy on the part of clinicians however the benefits of not removing the device cannot be denied, especially regarding relapse and the need for a second major surgery.

6.4 Material selection

The task of material selection will be discussed in this section.

One of the requirements of the medical device is that it should be associated with imaging exams such as MRI or CT. Metallic implants may create artefacts that significantly degrade the image quality, especially if they contain ferromagnetic impurities. Implants with lower beam attenuation coefficients such as titanium produce fewer artefacts than stainless steel and cobalt-chromium implants (Berquist, 2009). However, this type of examination with MRI and CT scans is only required in the patient's preoperative process. During treatment, the evaluation of the distraction process and the status of the regenerative callus tissue is done through X-rays and by manual clinical examinations during clinical routines. Because of this, the creation of artefacts during MRI or CT scans is not considered a problem. At the same time, the device must be composed of biocompatible and biofunctional materials to avoid triggering unwanted biological responses.

Additionally, the selection of the materials must take into account the tensions caused by mastication and surrounding soft tissues, the force necessary to stretch the bone callus and the tensions generated by the activation of the device. Bearing this in mind, distinct materials were considered suitable for the activation mechanism (shape memory alloy) and the body of the device.

6.4.1 Activation mechanism material – shape memory alloy (Nitinol)

SMAs are called memory materials due to their property of "remembering" thermomechanical treatments (traction, torsion, flexion, etc.) to which they have been subjected and thus their ability to recover their shape (Lexcellent, 2013). There are two main families of SMAs:

- "copper-based" materials: Cu-Al (Zn, Ni, Be, etc.);
- nickel-titanium-X materials (where X is an element present in small proportions): Ni-Ti-(Fe, Cu, Co, etc.).

Besides its use in various fields such as aeronautics, aerospace, nuclear industry and watch-making (Lexcellent, 2013), this type of alloys has been widely applied in medicine with prominence in the cardiovascular, neurovascular, endovascular, orthopaedic, and orthodontic fields (Kumar & Lagoudas, 2006; O'Brien & Bruzzi, 2011).

The SMAs have two key effects associated with the martensitic transformations which are the shape memory effect (SME) and the "superelastic effect" (SE). The SME can either be a one-way shape memory effect (OWSME) or a two-way shape memory effect (TWSME). The devices developed, as previously stated, were developed based on both OWSME and TWSME principles. The TWSME effect

follows the same methodology as the OWSME, however, in TWSME the alloy has de ability to remember a geometrical shape at high temperatures and another shape at low temperatures. This type of behaviour is only achieved after particular training procedures such as overdeformation, shape-memory cycling, pseudoelastic (PE) cycling, Combined SM/PE training, and constrained temperature cycling of deformed martensite (Luo & Abel, 2007; Urbina, 2011; Wada & Liu, 2008). More detailed information on this type of materials, TWSME training methods and the factors that influence the final shape memory ability can be found in Appendix E.

The physical key to shape memory lies in a phase transformation between a parent phase called austenite (A) and a produced phase called martensite (M) (Lexcellent, 2013). The temperatures at which the formation of martensite starts and ends are called Ms and Mf. Austenite formation starts and ends at As and Af, respectively

The choice of nitinol (Ni-Ti) for this device was made based on its varied medical applications. The first use of nitinol in the medical context was in the early 1970s with the application of orthodontic archwires. After that, the use of this alloy became more extensive with applications comprising staples, neurovascular stents, sutures, and heart valve frames (Corporation, 2017). Nitinol is non-ferromagnetic with a lower magnetic susceptibility than stainless steel. Therefore, Nitinol produces few artefacts on MRI and CT scans (Stöckel, 1998).

The nitinol used in the present thesis was a wire (pre-annealed) with 1 mm of diameter marketed by the *SmartsWire* Company, with the Af temperature of 45°C. However, this wire used for the tests carried out in Chapter 7, does not have the appropriate temperatures for the developed distractor. For the distractor, the wires, plates, or springs should have austenite activation temperatures higher than 45°C to avoid unwanted activations due to, for example, high fevers or hot baths.

Properties of Nitinol Alloys are strongly dependent on processing history and ambient temperature. The mechanical and shape memory properties shown in Table 6-4 are typical for standard shape memory Nitinol at room temperature tested in uniaxial tension.

Table 6-4: Mechanical properties of nitinol.
(Matthey, n.d.)

Young's Modulus (GPa)	Tensile strength (MPa)	Poisson's Ratio
28 – 41 (martensite) 83 (austenite)	895 – 1900	0.33

Nitinol is biocompatible. Due to its appropriate surface treatment through electropolishing and passivation, nitinol implants develop a passive titanium oxide layer (TiO_2) which acts as a barrier

preventing corrosion and the release of toxic Ni ions into the bloodstream. The thickness and quality (i.e., homogeneity, defect-free, etc.) of the oxide layer is closely related to the corrosion resistance and biocompatibility of the nitinol (Corporation, 2017; Kapoor, 2017).

Medical devices made from nitinol can be sterilized through most typical sterilization methods including steam (autoclave), ethylene oxide (EtO), or radiation (gamma) without affecting its mechanical and functional properties (Corporation, 2017).

Most nitinol materials have an equiatomic composition of nickel and titanium, i.e., 50 at% of Ni and Ti (about 55 wt.% of Ni). Subtle adjustments in the ratio of the two elements can significantly alter the characteristics of the nitinol, particularly its transformation temperatures. If the composition of Ni increases above 50 at.% the austenite transformation temperature (Af) starts to decrease dramatically and the austenite yield strength increases (Kapoor, 2017; O'Brien & Bruzzi, 2011). Figure 6-11 shows the effect of the increase of nitinol percentage in the transformation temperature. It is worth noting that below 50 at.% nickel, the Af temperature is independent of the composition and remains at its maximum value.

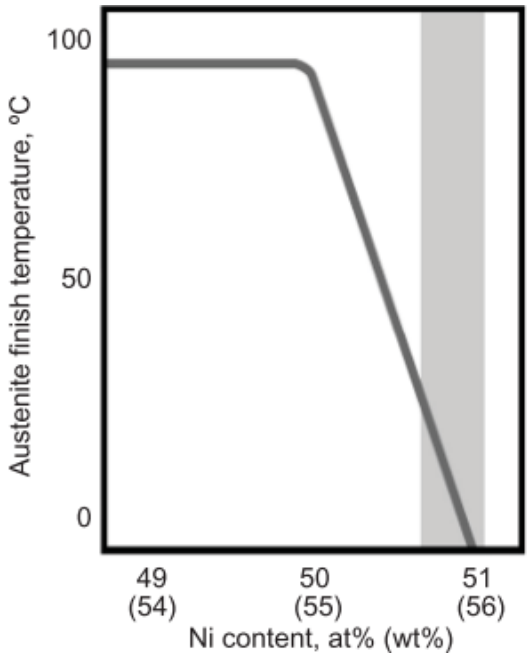


Figure 6-11: Schematic of the effect of the Ni content of Nitinol on the active austenite finish temperature, Af. (Kapoor, 2017)

This sensitivity of the properties to very small increases in the percentage of nickel makes it challenging to manufacture nitinol of uniform and repeatable properties, but at the same time gives manufacturers a powerful method to produce it with the desired transformation temperatures (Kapoor, 2017).

When properly trained, SMA wires act as linear actuators. Therefore, at specific temperatures, these materials, when changing their shape, are capable of generating significant forces. In most nitinol applications the forces generated are normally pulling forces, that is, the force is generated when, for example, the material goes from a straight shape to a bent shape when heated (Figure 6-12 a)). However, the shape memory material can be treated so that, at a proper temperature, it goes from a bent shape to a straight one (Figure 6-12 b)). In this case, we are in the presence of pushing forces.

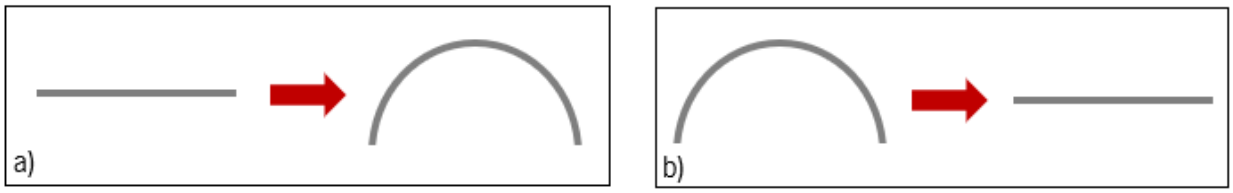


Figure 6-12: Representation of the a) pulling force and b) pushing forces generated by an SMA when altering shape.

Senthilkumar wrote an article analysing the use of nitinol to deflect the plain flap and control the flap angle of an aircraft wing. The relevant information for this dissertation taken from this article was the pulling forces produced by the nitinol wire when heated. It can be inferred that as the wire diameter increases, the pull force also increases, the energy required to heat the material and the time required for cooling also increases considerably (Senthilkumar, 2012). Table 6-5 presents this information.

Table 6-5: Properties of the nitinol wire used in the article.
(Senthilkumar, 2012)

Diameter Size (mm)	Pull Force (N)
0.025	9.07
0.038	20.38
0.050	36.29
0.076	81.75
0.102	145.26
0.127	227.00
0.152	326.81
0.203	581.00
0.254	907.85
0.305	1307.34
0.381	2042.71
0.508	3631.60

There are several studies on the pull forces exerted by nitinol, however, there is little to no data regarding the pushing forces exerted by nitinol elements. A thesis developed by Francisca Dias, in CMEMS–UMinho, entitled "Development of NiTi actuators elements for biomedical applications" presents a test to determine quantitatively the Nitinol's pushing strength when it returns to its original shape after deformation, being the initial shape straight (as in Figure 6-12 b)). In order to achieve the objective, it was necessary to resort to a load cell machine (Dias, 2016). The wire used in this study was a 1mm diameter nitinol wire commercialized by the *SmarsWire* Company, the same wire used in the laboratory tests executed in Chapter 7 of the current thesis. The results of the loads that Nitinol exerts is presented in Figure 6-13.

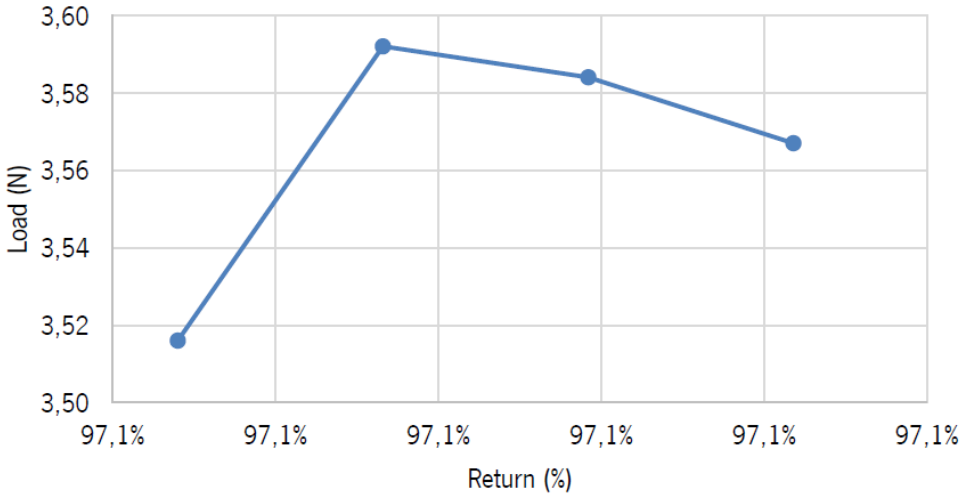


Figure 6-13: Loads achieved by de Ni-Ti wire upon recovering shape after deformation.

The nitinol wire of 1mm of diameter has the ability to produce maximum pushing forces of 3.59N. However, as previously stated, as the wire diameter or area of the material increases, the forces generated also increases. This way, a spring or a plate can produce much larger forces than a 1mm diameter wire. However, these results cannot be considered fully valid since it was also noted that the machine where the test was performed was not deemed ideal for this type of wires with this scale.

6.4.2 Device body material

The body of the device should exhibit enough material stiffness and toughness in order to withstand the loads exerted on them. It must also have an excellent surface finish, must be resistant to the corrosion of the oral environment and has to be biocompatible to avoid any reaction or inflammatory response in the host.

The choice of the materials for the developed distractor body as well as the remaining elements that are not part of the activation mechanism is straightforward. The possible materials were chosen

based on the materials used in the current distraction devices. These materials include **titanium alloy**, **cobalt-chromium alloy,** and **stainless steel** especially 316 and 316L because they have low percentages of impurities and a passivate finish which is very suitable for implantation in the human body. For oral fixation with screws or pins, titanium alloy and stainless steel are used (Cerrolaza et al., 2015).

Pure titanium (Ti–6Al–4V) has been the main biomedical titanium alloy for a long period, however, elements in this alloy can cause problems of toxicity. Because of that, new types of alloys like Ti–6Al–7Nb have been developed. Titanium presents outstanding characteristics such as high strength, high immunity to corrosion, complete inertness to body environment, enhanced biocompatibility, and low young's modulus. Due to its characteristics, whenever titanium is mentioned in the context of medical applications, it is usually assumed that it is a long term implantable devices (Geetha, Singh, Asokamani, & Gogia, 2009; Niinomi, 1998). The mechanical characteristics of the possible materials to be uses in the two developed concepts are shown in Table 6-6.

Table 6-6: Mechanical properties of distractor materials.

Material	Young's Modulus (GPa)	Tensile strength (MPa)	Poisson's Ratio
Ti–6Al–4V	112[a]	895-930[a]	0.32[a]
Ti–6Al–7Nb	110[a]	900-1050[a]	0.32[a]
316 stainless steel	193[b]	758-1689[b]	0.3[b]
316L stainless steel	165[b]	673[b]	0.34[b]
Cobalt-chromium alloy	283[c]	1403[c]	0.3[c]
Zirconia	195 – 210[d]	500 – 650[d]	0.27[d]

a – (Geetha et al., 2009); b – (Mohammad, Zainudin, Sapuan, Zahari, & Ali, 2013); c – (Ahearne, Baron, Keaveney, & Byrne, 2015); d – (Baldini et al., 2008)

Young's modulus describes the relative stiffness of a material, which is measured by the slope of a stress and strain graph. It is calculated by the ratio of stress value to its corresponding strain value. A stiff material will have a higher module of elasticity, while a flexible material will have a lower module of elasticity. The tensile strength of a material is the maximum amount of tensile stress that it can take before failure. Poisson's ratio measures the deformation in the material in a direction perpendicular to the direction of the applied force.

In addition to metallic materials, another option for the body and the components of the bone distractor is zirconia (ZrO_2). The use of zirconia in medicine and dentistry has rapidly expanded over the past decade, driven by its advantageous physical, biological, aesthetic, and corrosion properties. In dentistry, zirconia has been widely adopted for endosseous implants, implant abutments, and all-ceramic

crowns (Chen et al., 2016). Zirconia has been also studied for orthopaedic hip replacements because of its resistance to wear. The mechanical properties of zirconia are presented in Table 6-6. Zirconia has properties similar to titanium and stainless steel, which makes this material suitable for use in bone distractors.

It should be noted that materials and devices must follow specific standards. Some examples are ASTM F2004 – Standard Test Method for Transformation Temperature of Nickel-Titanium Alloys by Thermal Analysis; ASTM F2063 - Standard Specification for Wrought Nickel-Titanium Shape Memory Alloys for Medical Devices and Surgical Implants; ASTM F2005 – Standard Terminology for Nickel-Titanium Shape Memory Alloys; STP1272 - Medical Applications of Titanium and Its Alloys: The Material and Biological Issues and STP1438 - Stainless Steels for Medical and Surgical Applications.

7. OWSME AND TWSME CONCEPT VALIDATION

This chapter presents the tests carried out on a nitinol wire in order to prove the concept of one-way shape memory effect and two-way shape memory effect. The material used was a pre-annealed nitinol wire commercialized by the *SmartWires* Company, with 1mm of diameter. This company no longer markets this product.

7.1 Materials and Methods

7.1.1 Determining the transformation temperatures

In order to validate the one-way and two-way shape memory effects, it was necessary to first determine both austenite and martensite transformation temperatures of the nitinol wire. A differential scanning calorimetry (DSC) was performed to obtain the temperatures of As, Af, Ms and Mf. The DSC is one of the main techniques of thermal analysis which detects endothermic and exothermic transitions. The DSC method produces a curve by measuring the amount of heat given off (i.e., exothermic) or absorbed (i.e., endothermic) by a sample as it is cooled and heated through its phase transformations (Corporation, 2017). The heat flow into or out of a sample is measured as a function of temperature or time, while the sample is exposed to a controlled temperature program. It is a very powerful technique to evaluate material properties such as glass transition temperature, melting, crystallization, specific heat capacity, cure process, purity, oxidation behaviour, and thermal stability. The DSC technique is the standard test method for transformation temperature of nickel-titanium alloys by thermal analysis by ASTM F2004 (Corporation, 2017).

An explanatory example of a DSC, its analysis, and the method of obtaining the transformation temperatures are shown in Figure 7-1. The start and finish transformation temperatures are obtained from the DSC curves by the intersection of a base line and the tangent to a peak slope.

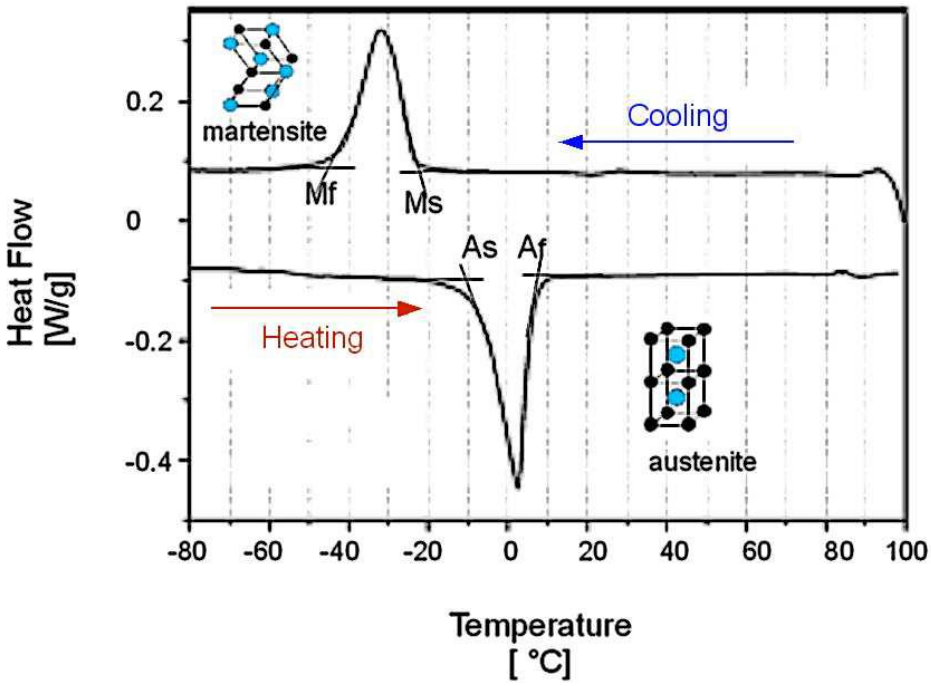


Figure 7-1: DSC example and its analysis.
(Corporation, 2017)

7.1.2 Defining the austenite shape and testing the one-way shape memory effect

Before the TWSME training process, the austenite shape of the wire was modified. The nitinol wire was hand deformed into an "e" shape and then placed in ULTRA-VEST plaster, marketed by Ransom & Randolph in other to immobilize the wire in its deformed shape. The wire was then subjected to a heat treatment of 500°C for 20 minutes so that the material retained that shape as the austenite shape. The heating treatment was carried out using a high-temperature oven available at the CMEMS laboratory. Figure 7-2 represents the desired "e" shape of the Ni-Ti wire before the heat treatment. The shape of the wire was outlined in graph paper in order to observe the possible changes in shape after the heat treatment.

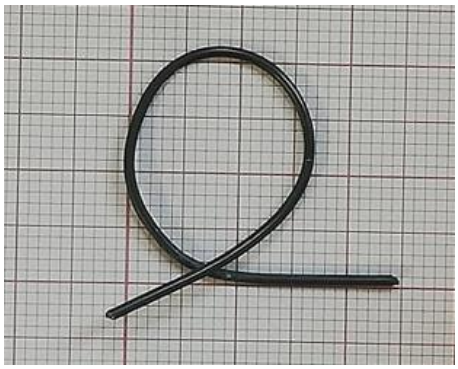


Figure 7-2: Ni-Ti wire hand deformed shape before heat treatment.

The one-way shape memory effect concept test was performed using a hairdryer. The Ni-Ti, after the heat treatment, was deformed until it was in a semi-straight shape and then was heated with a hairdryer (at temperatures above Af) to assess whether the wire returned to the previously defined "e" shape. This process was repeated a few times, going from shape 1 to shape 2, to evaluate if the nitinol would lose its shape memory. A schematic representation of the process is presented in Figure 7-3.

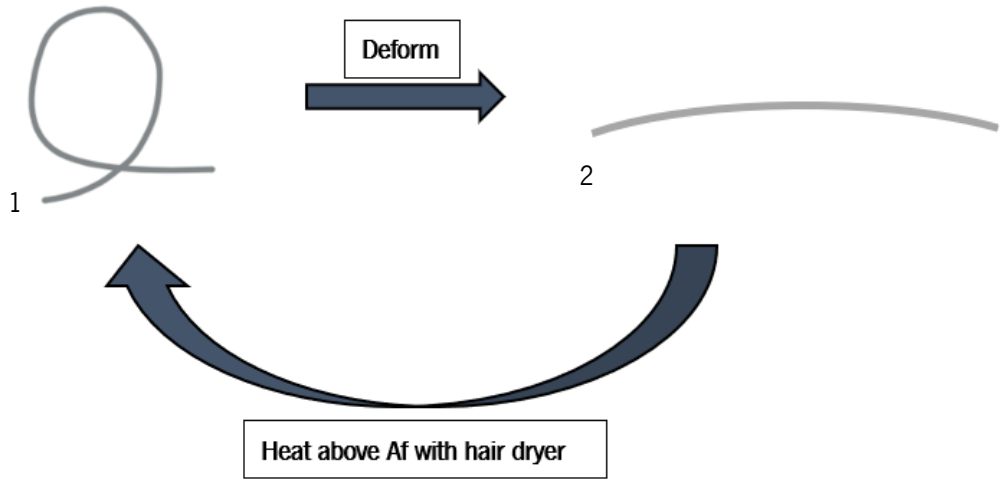


Figure 7-3: Process of evaluating the one-way shape memory effect.

7.1.3 Training the two-way shape memory effect

Thermomechanical cycling treatment is based on the repetition of a cycle that must include the transformation from austenite to preferentially oriented martensite or from deformed martensite to austenite (Luo & Abel, 2007). Training of the TWSME of the piece of nitinol wire was achieved through two distinct methods – shape memory cycling and constrained temperature cycling of deformed martensite. The choice of these methods was based on the fact that they are relatively easy to perform and the literature showed promising results. Another factor took into consideration were the resources available in the CMEMS laboratory.

Method 1: Shape Memory (SM) Cycling

The steps of this training method include: cooling the specimen below Mf, loading it in martensite state to a desired cold shape, unloading it completely and heating it to a temperature above Af. This process is to be repeated for about 5 cycles. The cooling of the specimen below Mf is achieved by placing the nitinol in a freezer for 2 hours in order to reach the minimum capable freezer temperature, around -12.8°C. However, if the Mf temperature is lower than the -12.8°C reached by the freezer, another method of cooling with liquid nitrogen was also used.

The austenite shape is the previously defined “e” and the martensite shape corresponds to the Ni-Ti in a semi-straight. The schematic representation of the process is shown in Figure 7-4.

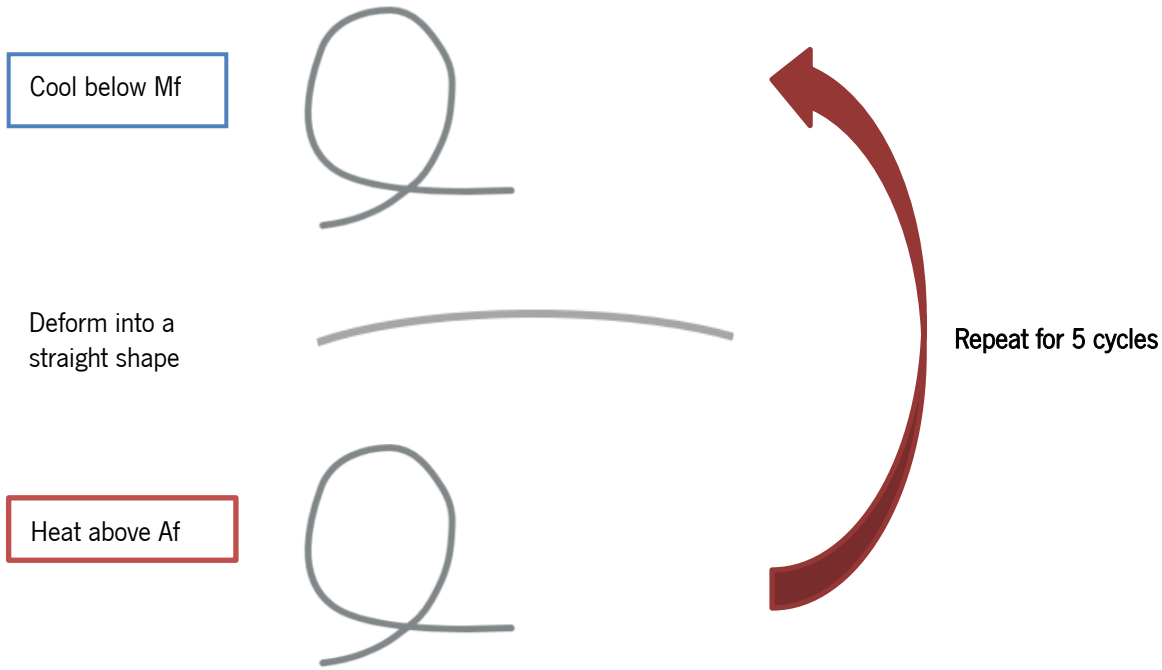


Figure 7-4: Schematic representation of the shape memory cycling process.

The expected final shapes should be semi-straight when the wire is cooled (martensite shape) and the “e” shape when the wire is heated (austenite shape), as seen in Figure 7-5. The TWSM behaviour should happen between those two shapes.

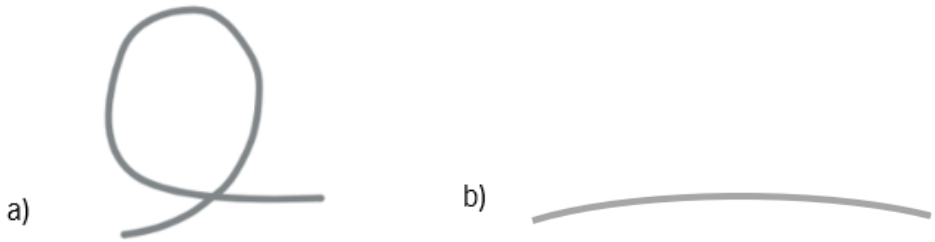


Figure 7-5: Expected final shapes: a) “e” shape in austenite and b) semi-straight shape in martensite.

Method 2: Constrained Temperature Cycling of Deformed Martensite

This training process consists of deforming the specimen below Mf, constraining the deformed condition and then heating up above Af. The sample is typically cycled from below Mf to above Af several times, with the sample constrained in the deformed shape. The training method follows a protocol used

by Zanaboni, 2008, in her thesis entitled "One Way and Two Way–Shape Memory Effect: Thermo–Mechanical Characterization of Ni-Ti wires" (Zanaboni, 2008).

For this training method, only the liquid nitrogen cooling method was applied and a new nitinol wire was used. In this case, no heat treatment was performed to give a specific shape to the nitinol wire. Therefore, in the austenite phase, its shape corresponded to its factory shape – a semi-straight wire, Figure 7-6. As done previously, the shape of the wire was outlined in graph paper to observe the possible differences in shape after each training cycle.

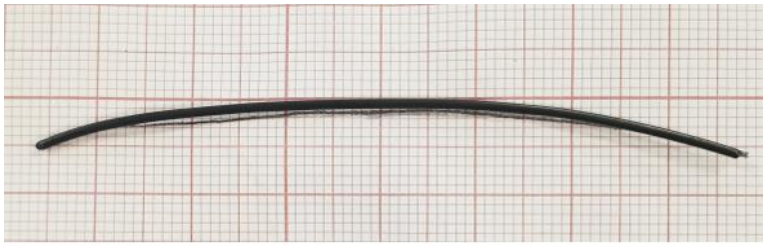


Figure 7-6: Shape of the nitinol wire after heating above Af - austenite shape.

Before starting the training process, a brief test to check if the wire had a previous martensite shape already defined was carried out. In order to do so, the Ni-Ti wire, in its austenite shape, was immersed into the liquid nitrogen, as seen in Figure 7-7.

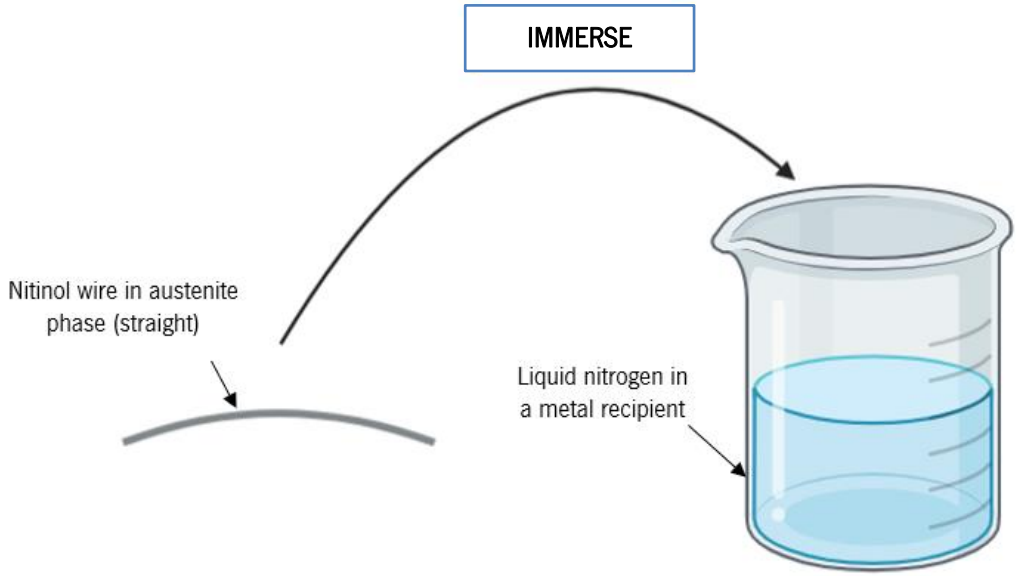


Figure 7-7: Schematic representation of the test carried out to verify if the wire had previous martensite shape already defined.

After that test, the nitinol wire in the austenite shape (semi-straight) was dipped into the liquid nitrogen for 30 seconds, colling the wire below Mf temperature. The wire was then deformed into a curvilinear shape around a cylindrical object and constrained in its desired martensite shape, thus

producing a stress–biased martensitic microstructure. The sample in the constrained condition was heated to above Af using a container with boiling water (water temperature around 95°C). This process is supposed to be repeated about 20 times in order for the specimen to learn the curvilinear shape in the martensite phase. Figure 7-8 shows a schematization of the used procedure.

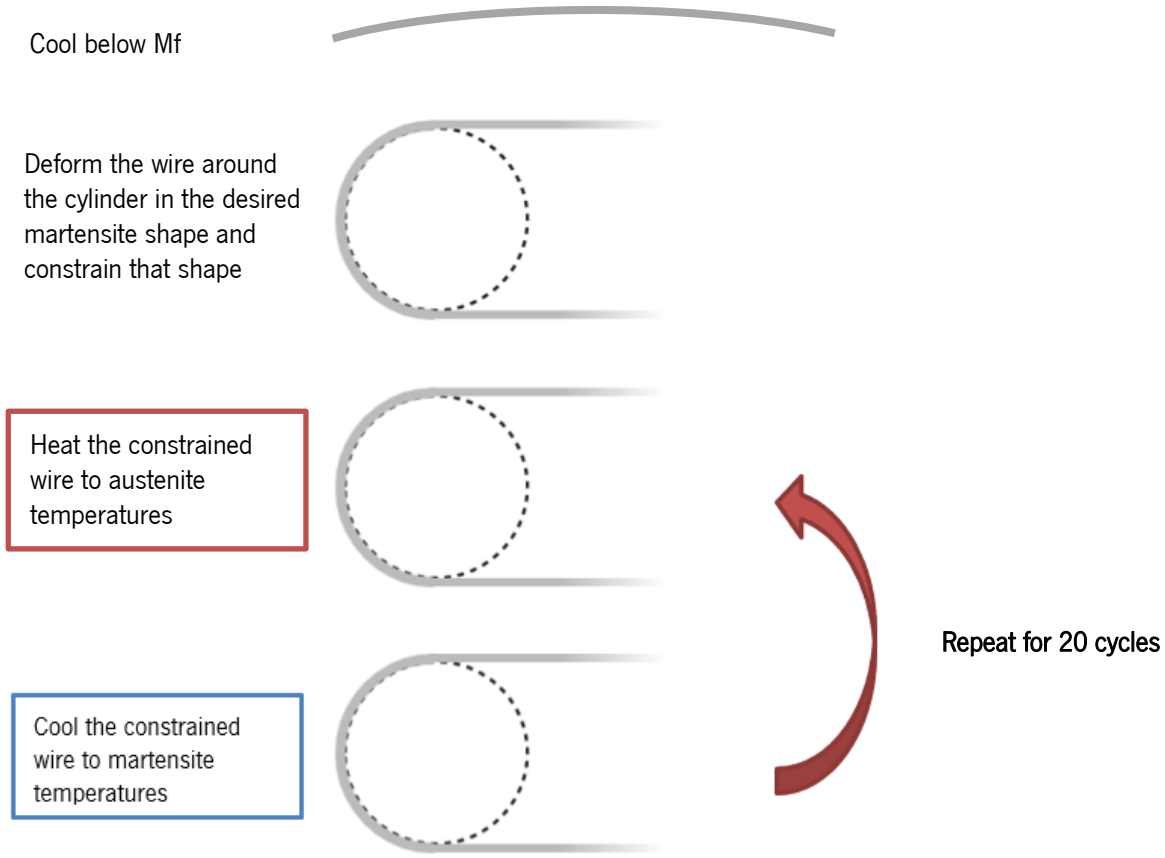


Figure 7-8: Schematic representation of the training method 2.

The expected final shapes should be straight when the wire is heated (austenite shape) and curvilinear when the wire is cooled (martensite phase), as seen in Figure 7-9. The TWSM behaviour should theoretically happen between those two shapes.

Figure 7-9: Representation of the expected final shapes of the nitinol wire in a) austenite phase and b) martensite phase.

7.2 Results and Discussion

7.2.1 Determining the transformation temperatures

The start and finish transformation temperatures were obtained from the DSC curves by the intersection of a base line and the tangent to a peak slope. Taking this into account, the values of As and Af temperatures obtained for the nitinol wire are exhibited in Figure 7-10.

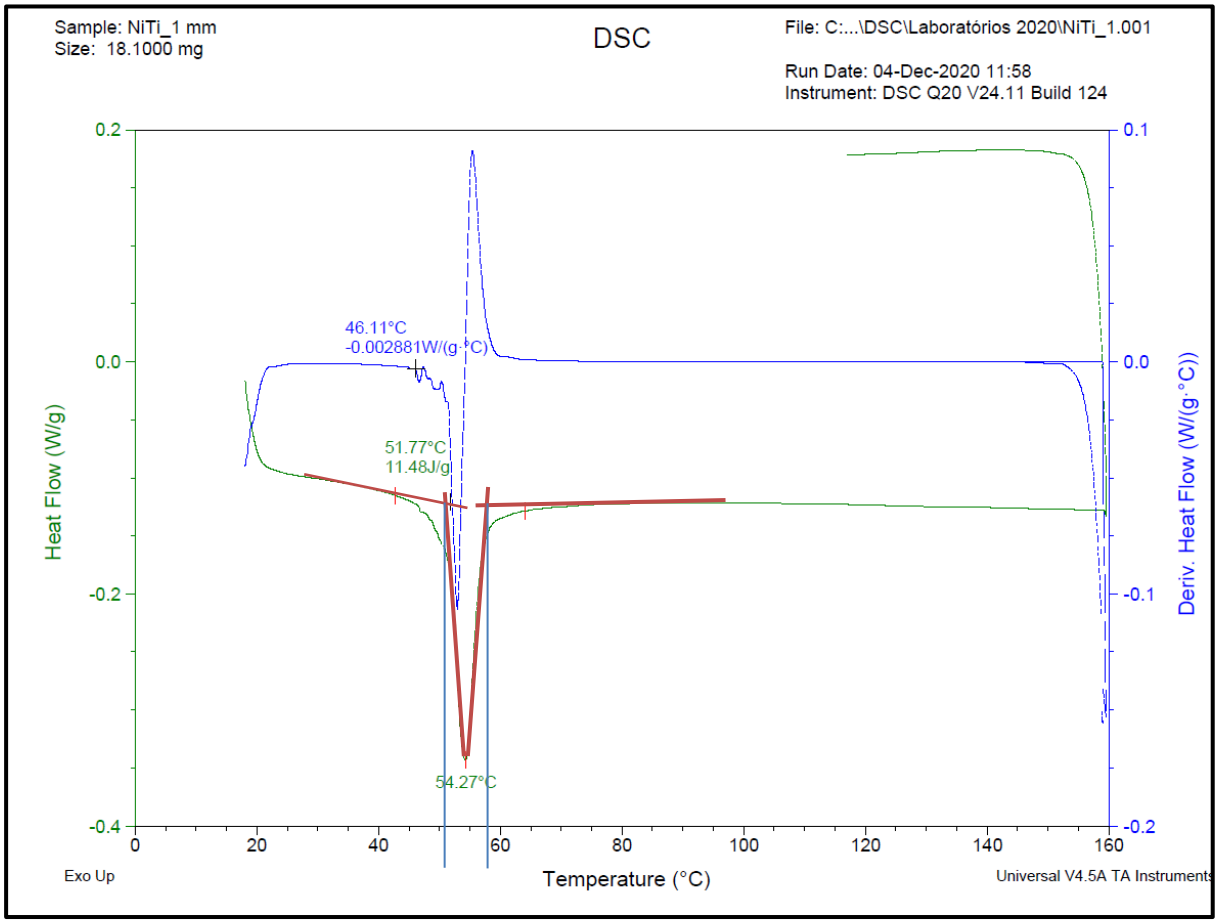


Figure 7-10: DSC results of the 1mm nitinol wire and determination of the transformation temperatures

First of all, through the DSC we were able to verify the martensite to austenite (M→A) phase transition curve upon heating of the specimen. However, the reverse transformation (A→M) was not observed since the DSC equipment available in the laboratory was not prepared to analyse at negative temperatures. Taking this into consideration, it was only possible to determine the austenite start and finish temperatures (As and Af).

Intersecting the base line with the tangent to the heating peak, it was determined that the austenite start temperature was approximately ≈49°C to ≈51°C and the austenite finish temperature

was approximately ≈56°C to ≈58°C. The activation temperature determined by the DSC analysis proved to be higher than the one provided by the company, which states that the activation temperature is 45°C. In conclusion, in this DSC curve, it was possible to observe the austenite transition phase, but not the martensitic phase. This fact led to further obstacles in nitinol two-way shape memory training since martensite transformation temperatures value is essential for the training methods.

7.2.2 Defining the austenite shape and testing the one-way shape memory effect

The austenite shape definition process was successful. The position of the wire after treatment corresponded to the one enforced before the heat treatment. The "e" shape was well defined as the austenite shape without significant differences between the before and after treatment shapes. Figure 7-11 a) represents the shape before treatment and Figure 7-11 b) after treatment.

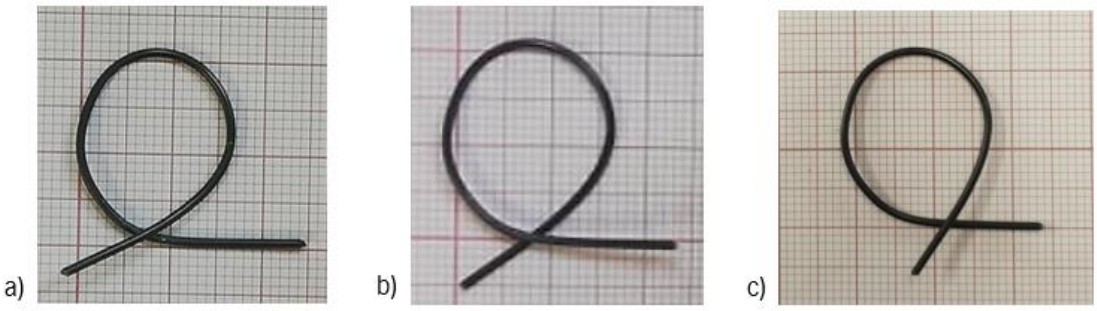


Figure 7-11: Shape of the nitinol wire a) before heat treatment, b) after heat treatment and c) after ten cycles of deforming and heating.

Testing the OWSME by deforming and heating the nitinol repeatedly revealed that its austenite temperature shape remained unchanged. Ten cycles were performed in order to see if there was any memory loss of the austenite shape. Results demonstrated a minimal difference in the shape after the 10 cycles, however, it was considered irrelevant (Figure 7-11 c)).

7.2.3 Training the two-way shape memory effect

Shape Memory (SM) Cycling

The results obtained from TWSME training with SM cycling and assuming that the martensite transformation temperature was above -12.8°C is shown in Figure 7-12 b). Figure 7-12 b) represents the final martensite shape of nitinol after the 5 cycles of training, freezing the wire for two hours. It is clearly observed that the nitinol wire did not retain the desired martensite (semi-straight wire) shape and presents only a slight difference between the austenite shape (Figure 7-12 a)).

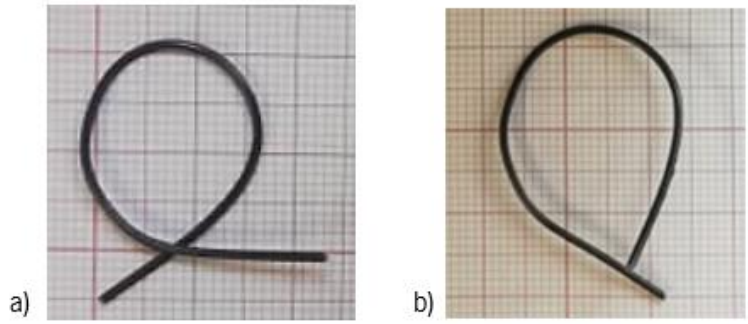


Figure 7-12: Ni-Ti wire in the a) austenite shape and b) martensite shape.

Taking into account the results obtained with the temperature of -12.8°C reached by the freezer, it was decided to carry out the same treatment but with lower temperatures. For this, liquid nitrogen was used, whose temperature reaches -200°C. The results obtained after 5 cycles of training are represented in Figure 7-13 below. As observed, using liquid nitrogen, the final martensite form of nitinol was, once again, not as expected (semi-straight wire). However, the results obtained were slightly better than those obtained using temperatures of -12.8°C.

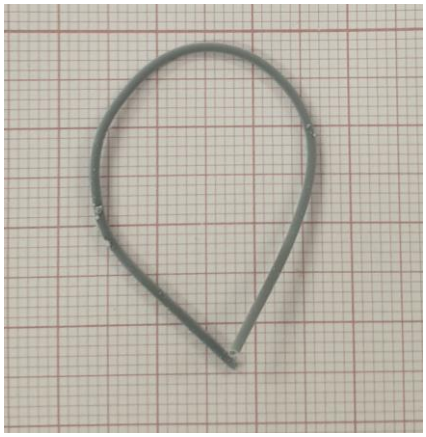


Figure 7-13: Final martensite shape of nitinol using liquid nitrogen in the TWSME training.

With this training method, no favourable results were obtained, which may be related to errors in the process/protocol and to the fact that the same nitinol wire was subjected to two consecutive training sessions at two completely different martensite temperatures.

Constrained Temperature Cycling of Deformed Martensite

Taking into consideration the results of training method 1, it was decided to first evaluate whether the nitinol wire had already some previous two-way shape memory effect. Therefore, by immersing a new nitinol in its austenite form (Figure 7-14 a)) in a container with liquid nitrogen, it was found that the shape of the wire changed significantly, presenting a more arched shape (Figure 7-14 b)). This result shows that

this wire marketed by *SmartsWire* probably already had some previously defined martensite shape. This finding affects the overall data obtained.

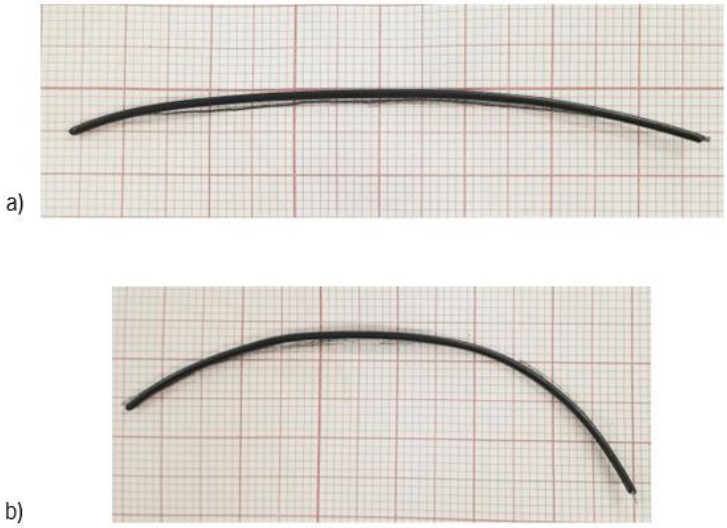


Figure 7-14: Nitinol wire before training a) in austenite shape before liquid nitrogen and b) after immersing in liquid nitrogen.

According to the literature, an average of 20 training cycles were supposed to be performed for the Ni-Ti wire to acquire shape memory in the martensite phase. However, taking into account that the treatment was being carried out at temperatures close to -200 °C and due to the lack of resources in the laboratory to manage components at those temperatures, only one training cycle with the constrained nitinol was possible, making it impossible to perform more training cycles. In the passage from the liquid nitrogen to the boiling water, the wire came loose from the apparatus that was constraining it, due to the high-temperature variation. The apparatus that was constrained the Ni-Ti proved to be unsuitable for the process, enabling further training cycles.

Nevertheless, it was verified whether nitinol had some TWSME or not after just one cycle of training. The test revealed that the wire indeed presented TWSME after only one cycle, as seen in Figure 7-15 b) where it is represented the final martensite shape. This result is not consistent with the literature which states that this training process requires more cycles than the other training methods. However, these results, once again, support the theory that this nitinol wire already had some previous TWSME. Another phenomenon observed was the fact that the initial austenite shape of nitinol (Figure 7-14 a)) suffered significant differences after one training cycle. The shape in the austenite phase became more curved as seen in Figure 7-15 a). Figure 7-15 represents the nitinol wire in the austenite shape (a)) and in the martensite shape (b)) after one cycle.

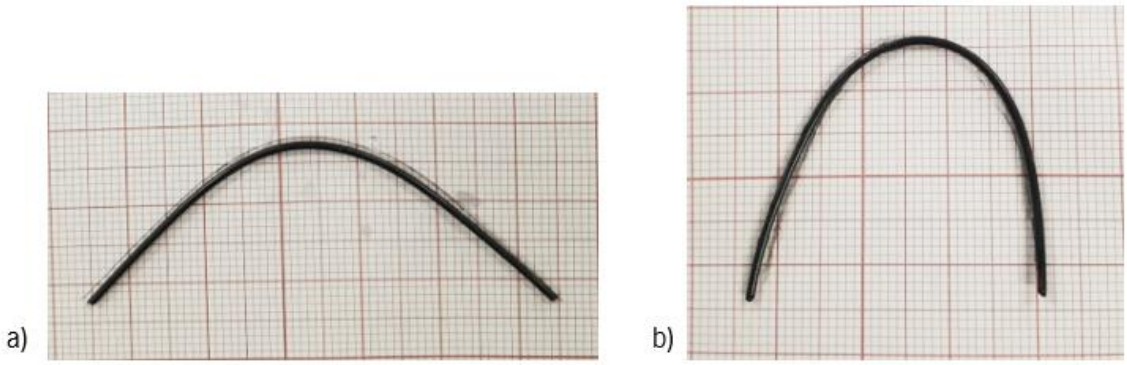


Figure 7-15: Nitinol wire in a) austenite shape and b) martensite shape after one training cycle.

After 8 continuous cycles of passage from the austenite phase to the martensite phase and vice versa, the gradual loss of shape of the martensite form was noticeable, as observed in Figure 7-16. This happened, most likely due to the fact that only one training cycle was done and not the 20 stipulated cycles. Therefore, the TWSME was not fully defined. More training cycles were needed.

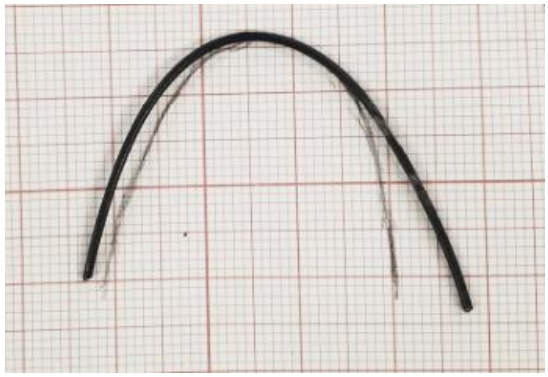


Figure 7-16: Nitinol wire after 8 cycles of passage from A ⟶ M ⟶ A.

7.3 Conclusion

The shape definition of the austenite phase, with the shape being an “e”, was successful. The OWSME concept validation also presented successful outcomes. The Ni-Ti wire demonstrated a good ability to retain the austenite shape when deformed and then heated above As-Af.

Ms and Mf temperatures could not be determined with the material available in the laboratory, thus preventing an accurate Ni-Ti cooling protocol below Mf. Regarding the training methods to induce TWSME, it is quickly concluded that method 1 did not obtain any positive results. Only a minimal deformation of the austenite shape was observed when cooling the Ni-Ti wire with either the freezer or the liquid nitrogen. However, further research in the literature, revealed that this method, despite the amount of final spontaneous shape change on cooling being significantly less than the one induced during the shape memory deformation step, usually achieves more promising results than those obtained in this

experiment (Zanaboni, 2008). This leads to the conclusion that there was an error in the training process implemented in the laboratory (e.g., deformation at inadequate temperatures, overdeformation, etc.) which jeopardized the viability of the results obtained.

Additionally, the fact of applying the liquid nitrogen training method (temperatures of -200°C) on the same Ni-Ti wire that was being trained at temperatures of -12.8°C with the freezer, may have had some influence on the technique failure, since the wire was submitted to two treatments at two very different cold temperatures.

On the other hand, method 2 showed promising results, with the Ni-Ti wire obtaining TWSME. Taking into account the results of method 1, a new nitinol wire was used in this method, in order to obtain more reliable results and without the influence of previous treatments applied to the first wire.

According to the literature, the number of cycles required to induce TWSME in method 1 is relatively smaller than in method 2 (Zanaboni, 2008). However, this was not observed in this study, since with only one cycle in method 2, TWSME was achieved, even if not fully defined. This led to the conclusion, once again, that the Ni-Ti used in this experiment was not the most adequate and could already have some pre-defined martensite shape.

Conclusions about how many times the material exhibited the TWSME cannot be drawn decisively from this experience, since TWSME was not fully achieved. However, research in the literature and other similar tests revealed that the memorized wires with method 2 lose the TWSM behaviour after ≈100 cooling/heating cycles behaving as one-way shape material after (Zanaboni, 2008). These cycles are more than necessary for the device developed.

The creation of an effective two-way shape memory alloy (TWSMA) requires appropriate heat treatment and optimal training conditions. In particular, the training method used plays a key role.

In conclusion, the OWSME and the TWSME properties of nitinol prove to be suitable for its application in the developed device, however further TWSME training tests should be done and preferably, knowing exactly all transformation temperatures.

8. CONCLUDING REMARKS

8.1 Conclusion

The present dissertation presents the development of a new bone distractor with a more focused application at the mandibular level, composed of an innovative activation mechanism using a shape memory alloy. As a final result, two device concepts were developed, which despite being based on the same principle of operation, one of the concepts was designed to work using the OWSME principle and the other concept, whose development was significantly more complex, was designed to work using the TWSME principle of the shape memory alloys.

It should be noted that the project did not strictly follow any specific methodology and that the developed concepts are in the process of patent submission.

All the pre-defined requirements established in the meetings held with Doctor Alberto Pereira were met, as well as the new objectives and functionalities proposed for the new device, differentiating it from the distractors currently commercialized. The device is entirely composed of medically accepted materials and its dimensions are as small as possible in order to make the internal device imperceptible to the patient during treatment and allow the insertion cut (intraoral) to be as small as possible. On the other hand, throughout the development of the device, numerous concepts were idealized, analysed, and adapted to comply with the important requirement that states that fixation plates must be placed near the osteotomy cut. Finally, an anti-return mechanism capable of preventing setbacks/relapses in device activation was developed and applied to the concept.

In the design of the final solution, all new objectives were taken into account, however, some of the characteristics constantly prioritized, besides being activated using a shape memory material, were the fact that the device should be completely internal without elements penetrating the soft tissues, should be free of electrical elements and should have a modular activation mechanism and a mechanism to allow for distraction vector variation and control during the activation phase.

All the above characteristics together resulted in an innovative device with features that do not yet exist in the area of distraction, as seen in the sub-chapter 6.2.1 in which the market research is presented. The combination of all the objectives imposed on the device, in addition to distinguishing it in the target market, makes it possible to overcome complications (such as scarring, open bite, relapse and

aesthetic impact) currently observed during the process of mandibular distraction osteogenesis, as highlighted in Chapter 5.

It is worth mentioning the added value of the developed devices being fully internal with the ability to alter the vector's direction in the sagittal plane throughout the distraction period. This variation will vary from patient to patient and will be totally dependent on the positioning of the distractors and the activation protocol imposed by the doctor

Several studies already conducted on the structural analysis of distractors in the mandibular distraction process can be found in the literature, as seen in sub-chapter 4.3, and all of them conclude that the highest concentration of stresses is found in the fixation plates. Since, overall, the concepts developed in this dissertation have a fixation conformation similar to the devices already structurally analysed in the literature, it was decided not to carry out a structural analysis in this dissertation. As previously mentioned, the high-stress zones found in the fixation plates can be easily compensated by increasing the thickness of the base plate, increasing the length, diameter and number of screws used and avoid sharp edges and 90° angles since they are areas of high concentration of tension. It was then determined that for the context of this dissertation it would be more relevant to analyse and validate the concepts of OWSME and TWSME of shape memory materials in order to corroborate their application in the developed devices. However, a structural analysis of the devices is interesting for future work.

The work carried out in the laboratory proved that the shape memory materials, in this case nitinol, and its OWSME and the TWSME properties are suitable for their application in the developed device. However, further TWSME training tests should be done.

In addition, and unfortunately, the development of the dissertation was largely affected by the current pandemic crisis caused by COVID-19, which prevented a more detailed study and better results in the training of TWSME of the nitinol wire, as well as the development of a prototype and its performance tests, essential to validate the activation concept.

8.2 Future work

The present work presents two different concepts of devices for osteogenic distraction composed by an innovative activation method. Bearing in mind that it is a project never done before and uses unconventional methodologies, there are still a lot of tasks to be carried out until the end of the project.

The last stage of the present work concerned the validation of the one-way and two-way shape memory effect of the nitinol wire through different training methods. Taking this into consideration the data obtained in the practical evaluation reported in Chapter 7, the next stage to consider in this project

development is the creation of prototypes of the activation mechanisms of both concepts in order to evaluate them in terms of functionality and find out which is the best source of energy for the activation. Another important step is to establish the temperatures and the exposure time required for activation.

The next step, before final production, is to make the complete prototype of the device and ascertain at the functional level all the functions and objectives of the device and make improvements to the design through the detection of defects. In this step, materials with similar properties to the bone and soft tissues of animals (for example pig) would be used to simulate the mandible, the skin and facial muscles.

With the necessary alterations achieved, the physical prototype can then be used in pre-clinical studies in cadavers or animals to test the device safety and effectiveness. The next stage to consider after the pre-clinical studies is the clinical studies involving live human testing.

A possible relevant future work, more related to the biological aspect of the distraction osteogenesis, would be to study the factors that may influence the rate of bone regeneration, such as the use of bone morphogenetic protein 2 (BMP-2), insulin-like growth factor 1 (IGF-1), fibroblast growth factor 2 (FGF-2), and vibrational and ultrasound treatments which have demonstrated to potentially induce osteoblast differentiation and improve bone growth and regeneration.

REFERENCES

Agarwal, R. (2013). Unfavourable results with distraction in craniofacial skeleton. *Indian Journal of Plastic Surgery*, *46*(2), 194–203. https://doi.org/10.4103/0970-0358.118594

Ahearne, E., Baron, S., Keaveney, S., & Byrne, G. (Eds.). (2015). An Assessment of Medical Grade Cobalt Chromium Alloy ASTM F1537 as a Difficult-to-Cut (DTC) Material. In *Proceedings of the Machine Tool Technologies Research Foundation 2015*. Retrieved from https://www.researchgate.net/publication/287198713_An_Assessment_of_Medical_Grade_Cobalt_Chromium_Alloy_ASTM_F1537_as_a_Difficult-to-Cut_DTC_Material

Ahmad, S. (2007). *Patent No. US2007/0162045*. US.

Al-Mahdi, A. H., & Al-Jumaily, H. A. H. (2013). Clinical evaluation of distraction osteogenesis in the treatment of mandibular hypoplasia. *Journal of Craniofacial Surgery*, *24*(1), 50–57. https://doi.org/10.1097/SCS.0b013e3182700223

Al Ruhaimi, K. A. (2001). Comparison of different distraction rates in the mandible: An experimental investigation. *International Journal of Oral and Maxillofacial Surgery*, *30*(3), 220–227. https://doi.org/10.1054/ijom.2001.0046

Amir, L. R., Everts, V., & Bronckers, A. L. J. J. (2009). Bone regeneration during distraction osteogenesis. *Odontology*, *97*(2), 63–75. https://doi.org/10.1007/s10266-009-0101-z

Andrade, N., Gandhewar, T., & Kalra, R. (2011). Development and evolution of distraction devices: Use of indigenous appliances for Distraction Osteogenesis-An overview. *Annals of Maxillofacial Surgery*, *1*(1), 58. https://doi.org/10.4103/2231-0746.83159

AO Fundation. (n.d.). Distraction osteogenesis of mandibular ramus. Retrieved March 3, 2021, from https://surgeryreference.aofoundation.org/cmf/congenital-deformities/hemifacial-microsomia/hfm-pruzansky-iii/distraction-osteogenesis-of-mandibular-ramus

Aydin, U., Bulut, A., & Bulut, O. E. (2017). Assessment of maxillary and mandibular bone quality. *European Congress of Radiology*. https://doi.org/10.1594/ecr2017/C-219

Baas, E. M., Van Gemert, B. P. H. M., Bierenbroodspot, F., Milstein, D. M. J., & De Lange, J. (2015). Patient discomfort and other side effects after bilateral sagittal split osteotomy or distraction osteogenesis of the mandible: a randomized clinical trial. *International Journal of Oral and Maxillofacial Surgery*, *44*(9), 1119–1124. https://doi.org/10.1016/j.ijom.2015.05.016

Badiali, G., Cutolo, F., Roncari, A., Marchetti, C., & Bianchi, A. (2017). Simulation-guided navigation for vector control in pediatric mandibular distraction osteogenesis. *Journal of Cranio-Maxillo-Facial Surgery*, *45*(6), 969–980. https://doi.org/https://doi.org/10.1016/j.jcms.2017.02.006

Balaji, S. M. (2017). Identifying Complications in Distraction Osteogenesis. *Annals of Maxillofacial Surgery*, 3–4. https://doi.org/10.4103/ams.ams

Baldini, A., Bruzzesi, G., Zaffe, D., Giacopini, M., Strozzi, A., & De Pol, A. (2008). Biomechanical aspects

in dental replacements. *WIT Transactions on State of the Art in Science and Engineering*, *35*, 197–243. https://doi.org/10.2495/978-1-84564-096-5/09

Bartlett, S., Ehrenfeld, M., Mast, G., & Sugar, A. (2012). AO Surgery Reference. Retrieved January 29, 2021, from Hemifacial Microsomia - Classification website: https://surgeryreference.aofoundation.org/cmf/congenital-deformities/hemifacial-microsomia/further-reading/hemifacial-microsomia-classification?searchurl=%2FSearchResults#pruzansky

Berquist, T. (2009). *Imaging of Orthopaedic Fixation Devices and Prostheses*. Retrieved from http://resourcecenter.ovid.com/site/catalog/Book/5387.pdf

Biga, L. M., Dawson, S., Harwell, A., Hopkins, R., Kaufmann, J., LeMaster, M., … Runyeon, J. (n.d.). Oregon State University - Bone Structure: Anatomy & Physiology. Retrieved December 28, 2020, from https://open.oregonstate.education/aandp/chapter/6-3-bone-structure/

Bohluli, B., Motamedi, M. H. K., Bohluli, P., Sarkarat, F., Moharamnejad, N., & Tabrizi, M. H. S. (2010). Biomechanical stress distribution on fixation screws used in bilateral sagittal split ramus osteotomy: Assessment of 9 methods via finite element method. *Journal of Oral and Maxillofacial Surgery*, *68*(11), 2765–2769. https://doi.org/10.1016/j.joms.2010.03.014

Bone Classification and Structure | Anatomy and Physiology. (n.d.). Retrieved January 5, 2021, from https://courses.lumenlearning.com/nemcc-ap/chapter/bone-classification/

Bonnet, A. S., Dubois, G., Lipinski, P., & Schouman, T. (2012). In vivo study of human mandibular distraction osteogenesis. Part I: Bone transport force determination. *Acta of Bioengineering and Biomechanics*, *14*(4), 3–14. https://doi.org/10.5277/abb120401

Breeland, G., Aktar, A., & Patel, B. C. (2020). *Anatomy , Head and Neck , Tonsils Blood Supply and Lymphatics* (pp. 9–13). pp. 9–13. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK532292/

Bukhari, S. G. A., Ahmed, W., Janjua, O. S., Waheed, A., Junaid, M., & Khan, S. (2012). Distraction osteogenesis for correcting maxillo-mandibular deformities. *Journal of the College of Physicians and Surgeons Pakistan*, *22*(9), 582–585. https://doi.org/09.2012/JCPSP.582585

Burstein, F. D. (2008). Resorbable distraction of the mandible: Technical evolution and clinical experience. *Journal of Craniofacial Surgery*, *19*(3), 637–643. https://doi.org/10.1097/SCS.0b013e31816b6c8f

Burstein, F. D., Lukas, S., & Forsthoffer, D. (2008). Measurement of torque during mandibular distraction. *Journal of Craniofacial Surgery*, *19*(3), 644–647. https://doi.org/10.1097/SCS.0b013e31816ae1a8

Carter, K., & Rutherford, M. (2020). Skeletal System – Building a Medical Terminology Foundation. Retrieved January 4, 2021, from https://ecampusontario.pressbooks.pub/medicalterminology/chapter/musculoskeletal-system/

Cascone, P., Basile, E., Saccucci, M., Di Carlo, G., Angeletti, D., Ramieri, V., & Polimeni, A. (2015). Fast and early mandibular osteodistraction: The long-term follow-up of mandibular distraction

osteogenesis on teeth position. *Journal of Craniofacial Surgery*, *26*(8), 2325–2328. https://doi.org/10.1097/SCS.0000000000001997

Cerrolaza, M., Carrero, W., Cedeño, J., & Valencia, L. (2015). Finite element analysis of a device for alveolar osteogenic distraction in human mandible. *Biomedical Engineering - Applications, Basis and Communications*, *27*(4), 1–11. https://doi.org/10.4015/S1016237215500349

Chakrabarti, A. (1995). Engineering design methods: Strategies for product design. In *Materials & Design* (Vol. 16). https://doi.org/10.1016/0261-3069(95)90023-3

Chen, Y., Moussi, J., Drury, J. L., Wataha, J. C., Moussi, J., Drury, J. L., … Wataha, J. C. (2016). Zirconia in biomedical applications. *Expert Review of Medical Devices*, *4440*(September). https://doi.org/10.1080/17434440.2016.1230017

Chi, T. L., Mirsky, D. M., Bello, J. A., & Ferson, D. Z. (2012). Airway Imaging: Principles and Practical Guide. In C. A. Hagberg (Ed.), *Benumof and Hagberg's Airway Management* (3rd ed.). https://doi.org/10.1016/B978-1-4377-2764-7.00002-6

Cladis, F. P., Grunwaldt, L., & Losee, J. (2011). Anesthesia for Plastic Surgery. In *Smith's Anesthesia for Infants and Children* (Eighth Edi). https://doi.org/10.1016/B978-0-323-06612-9.00025-0

Compston, J. (2006). Bone quality: What is it and how is it measured? *Arquivos Brasileiros de Endocrinologia e Metabologia*, Vol. 50, pp. 579–585. https://doi.org/10.1590/S0004-27302006000400003

Conley, R. S., & Legan, H. L. (2014). Biomechanical Factors in Surgical Orthodontics. In N. Ravindra (Ed.), *Esthetics and Biomechanics in Orthodontics* (2nd ed.). https://doi.org/10.1016/B978-1-4557-5085-6.00023-0

Cope, J. B., Samchukov, M. L., & Cherkashin, A. M. (1999). Mandibular distraction osteogenesis: a historic perspective and future directions. *American Journal of Orthodontics and Dentofacial Orthopedics : Official Publication of the American Association of Orthodontists, Its Constituent Societies, and the American Board of Orthodontics*, *115*(4), 448–460. https://doi.org/10.1016/S0889-5406(99)70266-0

Cope, Jason B., Yamashita, J., Healy, S., Dechow, P. C., & Harper, R. P. (2000). Force level and strain patterns during bilateral mandibular osteodistraction. *Journal of Oral and Maxillofacial Surgery*, *58*(2), 171–178. https://doi.org/10.1016/S0278-2391(00)90333-1

Corporation, M. (2017). Introduction to Nitinol. *Memry Corporation*. Bethel: Memry Corporation.

Debelmas, A., Picard, A., Kadlub, N., & Boisson, J. (2018). Contribution of the periosteum to mandibular distraction. *PLoS ONE*, *13*(6), 1–14. https://doi.org/10.1371/journal.pone.0199116

Denny, A. (2002). Mandibular distraction in neonates: A strategy to avoid tracheostomy. *Plastic and Reconstructive Surgery*, Vol. 109, pp. 905–906. https://doi.org/10.1097/00006534-200203000-00012

Dias, A. F. (2016). *Development of NiTi actuators elements for biomedical applications*. Universidade do Minho.

Dolanmaz, D., Karaman, A. I., Gurel, H. G., Kalayci, A., Kucukkolbasi, H., & Usumez, S. (2009). Correction of Mandibular Retrognathia and Laterognathia by Distraction Osteogenesis: Follow up of 5 cases. *European Journal of Dentistry*, *03*(04), 335–342. https://doi.org/10.1055/s-0039-1697454

Drahansky, M., Paridah, M. ., Moradbak, A., Mohamed, A. ., Owolabi, F. abdulwahab taiwo, Asniza, M., & Abdul Khalid, S. H. . (2016). Distraction Osteogenesis in Oral and Craniomaxillofacial Reconstructive Surgery. *Intech*, *i*(tourism), 13. https://doi.org/http://dx.doi.org/10.5772/57353

Dunaway, D., Borghi, A., Jeelani, O., & Schievano, S. (2016). *Patent No. WO2016046549A1*.

Dunaway, D., Rodgers, W., Borghi, A., Schievano, S., & Jeelani, O. (2018). *Patent No. WO2019081909A1*. GB.

Emin, A. (2019, September 21). The Mandible: structure, attachments, fractures . Retrieved March 25, 2021, from TeachMeAnatomy website: https://teachmeanatomy.info/head/osteology/mandible/

Evans, K. N., Hing, A. V., & Cunningham, M. L. (2018). Craniofacial Malformations. In *Avery's Diseases of the Newborn: Tenth Edition* (Tenth Edit). https://doi.org/10.1016/B978-0-323-40139-5.00100-5

Fariña, R., Castellón, L., Nagelash, E., & Valladares, S. (2011). A new way to anchor the external device in mandibular distraction: Three case reports with a Pierre Robin sequence. *International Journal of Oral and Maxillofacial Surgery*, *40*(5), 471–474. https://doi.org/10.1016/j.ijom.2011.01.003

Fearmonti, R., Bond, J., Erdmann, D., & Levinson, H. (2010). A review of scar scales and scar measuring devices. *Open Access Journal of Plastic Surgery*, *10*, 354–363. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20596233

Fehrenbach, M. J., & Herring, S. W. (2015). Illustrated Anatomy of the Head and Neck. In *SpringerVerlag Berlin Heidelberg* (5th ed., Vol. 16). Retrieved from https://books.google.com/books?id=NCSKCwAAQBAJ&pgis=1

Feng, X., Lin, G., Fang, C. X., Lu, W. W., Chen, B., & Leung, F. K. L. (2019). Bone resorption triggered by high radial stress: The mechanism of screw loosening in plate fixation of long bone fractures. *Journal of Orthopaedic Research*, *37*(7), 1498–1507. https://doi.org/10.1002/jor.24286

Franco, P. B., & Farrell, B. B. (2016). Inverted L osteotomy: A new approach via intraoral access through the advances of virtual surgical planning and custom fixation. *Oral and Maxillofacial Surgery Cases*, *2*(1), 1–9. https://doi.org/10.1016/j.omsc.2016.01.001

Gallardo Fuentes, J. M., Gümpel, P., & Strittmatter, J. (2002). Phase change behavior of nitinol shape memory alloys. *Advanced Engineering Materials*, *4*(7), 437–452. https://doi.org/10.1002/1527-2648(20020717)4:7<437::AID-ADEM437>3.0.CO;2-8

Geetha, M., Singh, A. K., Asokamani, R., & Gogia, A. K. (2009). Ti based biomaterials , the ultimate choice for orthopaedic implants – A review Ti based biomaterials , the ultimate choice for orthopaedic implants – A review. *Progress in Materials Science*, *54*(3), 397–425. https://doi.org/10.1016/j.pmatsci.2008.06.004

George, V. T., & Hegde, V. (2012). Distraction osteogenesis – An overview of principle and its applications. *Indian Journal of Dentistry*, *3*(4), 222–225. https://doi.org/10.1016/j.ijd.2012.08.001

Ghiasi, M. S., Chen, J., Vaziri, A., Rodriguez, E. K., & Nazarian, A. (2017). Bone fracture healing in mechanobiological modeling: A review of principles and methods. *Bone Reports*, *6*, 87–100. https://doi.org/10.1016/j.bonr.2017.03.002

Gilbert, S. F. (2009). *Developmental Biology* (6th editio).

Giraddi, G., Arora, K., & Sai Anusha, A. (2016). Distraction osteogenesis in the treatment of temporomandibular joint ankylosis with mandibular micrognathia. *Annals of Maxillofacial Surgery*, *6*(1), 68. https://doi.org/10.4103/2231-0746.186125

Goodwin, A. F., Kim, R., Bush, J. O., & Klein, O. D. (2015). From Bench to Bedside and Back. Improving Diagnosis and Treatment of Craniofacial Malformations Utilizing Animal Models. In *Current Topics in Developmental Biology* (1st ed., Vol. 115). https://doi.org/10.1016/bs.ctdb.2015.07.003

Graewe, F. R., Morkel, J. A., Hartzenberg, H. B., Ross, R. J., & Zuehlke, A. E. (2008). Midface distraction without osteotomies in an infant with upper respiratory obstruction. *Journal of Craniofacial Surgery*, *19*(6), 1603–1607. https://doi.org/10.1097/SCS.0b013e31818ac242

Guerrero, C. A., & Bell, W. H. (1999). Distraction of the Craniofacial Skeleton. In J. G. McCarthy (Ed.), *Distraction of the Craniofacial Skeleton* (1st ed.). https://doi.org/10.1007/978-1-4612-2140-1

Guerrero, C. A., Rivera, H., Mujica, E. V., Henriquez, M., & Gonzalez, M. (2012). Principles of Distraction Osteogenesis. In *Current Therapy in Oral and Maxillofacial Surgery*. https://doi.org/10.1016/B978-1-4160-2527-6.00011-6

Hamdy, R. C., Rendon, J. S., & Tabrizim, M. (2012). Distraction Osteogenesis and Its Challenges in Bone Regeneration. *Bone Regeneration*, (September 2014). https://doi.org/10.5772/32229

Harris, S. V., Laurens, E. V., & Gorentz, N. (2014). *Patent No. US20140148812A1*.

Hassan, S. A. E.-H., & Mohamed, F. I. (2019). Distraction osteogenesis in the management of mandibular hypoplasia secondary to temporomandibular joint ankylosis. Long term follow up. *Journal of Cranio-Maxillo-Facial Surgery*, *47*(10), 1510–1520. https://doi.org/https://doi.org/10.1016/j.jcms.2019.07.031

Homsi, N., Rodrigues, P., Aniceto, G. S., Hammer, B., & Bartlett, S. (n.d.). AO Surgery Reference - Biomechanics of the mandible. Retrieved March 15, 2021, from https://surgeryreference.aofoundation.org/cmf/trauma/mandible/further-reading/biomechanics-of-the-mandible#muscle-forces

Hopper, R. A., Ettinger, R. E., Purnell, C. A., Dover, M. S., Pereira, A. R., & Tunçbilek, G. (2020). Thirty Years Later: What Has Craniofacial Distraction Osteogenesis Surgery Replaced? *Plastic and Reconstructive Surgery*, 1073E-1088E. https://doi.org/10.1097/PRS.0000000000006821

Hsieh, S. T., & Woo, A. S. (2019). Pierre Robin Sequence. *Clinics in Plastic Surgery*, *46*(2), 249–259. https://doi.org/10.1016/j.cps.2018.11.010

Iatrou, I., Theologie-Lygidakis, N., & Schoinohoriti, O. (2010). Mandibular distraction osteogenesis for severe airway obstruction in Robin Sequence. Case report. *Journal of Cranio-Maxillo-Facial Surgery*, *38*(6), 431–435. https://doi.org/https://doi.org/10.1016/j.jcms.2009.10.019

Ilizarov, G. A. (1989). The Tension-Stress Effect on the Genesis and Growth of Tissues. *Clinical Orthopaedics and Related Research*, (239), 263–285. https://doi.org/10.1097/00003086-198902000-00029

Ippolito, E., Peretti, G., Bellocci, M., Farsetti, P., Tudisco, C., Caterini, R., & De Martino, C. (1994). Histology and ultrastructure of arteries, veins and peripheral nerves during limb lengthening. *Clinical Orthopaedics and Related Research*, (308), 54–62.

Isolated Pierre Robin sequence: MedlinePlus Genetics. (n.d.). Retrieved December 9, 2020, from https://medlineplus.gov/genetics/condition/isolated-pierre-robin-sequence/#diagnosis

Jauregui, J. J., Ventimiglia, A. V., Grieco, P. W., Frumberg, D. B., & Herzenberg, J. E. (2016). Regenerate bone stimulation following limb lengthening: a meta-analysis. *BMC Musculoskeletal Disorders*, *17*(1), 1–8. https://doi.org/10.1186/s12891-016-1259-5

Jean, B., & Bende, T. (2007). Mid-IR Laser Applications in Medicine. *Solid-State Mid-Infrared Laser Sources*, *546*, 530–565. https://doi.org/10.1007/3-540-36491-9_12

Jin, Z. M., Zheng, J., Li, W., & Zhou, Z. R. (2016). Tribology of medical devices. *Biosurface and Biotribology*, *2*(4), 173–192. https://doi.org/10.1016/j.bsbt.2016.12.001

Kaban, L. B., Seldin, E. B., Kikinis, R., Yeshwant, K., Padwa, B. L., & Troulis, M. J. (2009). Clinical Application of Curvilinear Distraction Osteogenesis for Correction of Mandibular Deformities. *Journal of Oral and Maxillofacial Surgery*, *67*(5), 996–1008. https://doi.org/10.1016/j.joms.2009.01.010

Kapoor, D. (2017). Nitinol for Medical Applications: A Brief Introduction to the Properties and Processing of Nickel Titanium Shape Memory Alloys and their Use in Stents. *Johnson Matthey Technology Review*, *61*(1), 66–76. https://doi.org/10.1595/205651317X694524

Karaplis, A. C. (2008). Embryonic Development of Bone and Regulation of Intramembranous and Endochondral Bone Formation. *Principles of Bone Biology, Two-Volume Set*, *1*(C), 53–84. https://doi.org/10.1016/B978-0-12-373884-4.00025-2

Karp, N. S., McCarthy, J. G., Schreiber, J. S., Sissons, H. A., & Thorne, C. H. M. (1992). Membranous bone lengthening: A serial histological study. *Annals of Plastic Surgery*, *29*(1), 2–7. https://doi.org/10.1097/00000637-199207000-00002

Kashani, H., & Rasmusson, L. (2016). Osteotomies in Orthognathic Surgery. *A Textbook of Advanced Oral and Maxillofacial Surgery Volume 3*. https://doi.org/10.5772/63345

Keçik, D., Aydoğdu, E., Ateş, U., & Uçkan, S. (2010). Mandibular hypoplasia with curvilinear distraction. *Journal of Craniofacial Surgery*, *21*(1), 168–173. https://doi.org/10.1097/SCS.0b013e3181c50ff3

Kessler, P. A., Merten, H. A., Neukam, F. W., & Wiltfang, J. (2002). The effects of magnitude and frequency of distraction forces on tissue regeneration in distraction osteogenesis of the mandible.

Plastic and Reconstructive Surgery, *109*(1), 171–180. https://doi.org/10.1097/00006534-200201000-00027

Kids Health Information : Pierre Robin sequence (PRS). (2020, September). Retrieved January 29, 2021, from https://www.rch.org.au/kidsinfo/fact_sheets/Pierre_Robin_sequence_PRS/

King, G. J., Liu, Z. J., Wang, L. L., Chiu, I. Y., Whelan, M. F., & Huang, G. J. (2003). Effect of distraction rate and consolidation period on bone density following mandibular osteodistraction in rats. *Archives of Oral Biology*, *48*(4), 299–308. https://doi.org/10.1016/S0003-9969(03)00004-9

KLS Martin Group. (n.d.). Distractors and fixators for CMF surgery - KLS Martin. Retrieved March 3, 2021, from https://www.klsmartin.com/en/products/implants-cmf/distractors-and-fixators

KLS Martin Group. (2020). Transversal Distraction Overview - Bologna Midline Distractor (BMD). Retrieved March 3, 2021, from www.klsmartin.com

Kober, C., Erdmann, B., Lang, J., & Deuflhard, P. (2001). Linear Elastic Modeling of the Human Mandible. Retrieved January 29, 2021, from http://elib.zib.de/pub/elib/codelib/kardos/projects/mandible.html

Kofod, T., Cattaneo, P. M., Dalstra, M., & Melsen, B. (2005). Three-dimensional finite element analysis of the mandible and temporomandibular joint during vertical ramus elongation by distraction osteogenesis. *Journal of Craniofacial Surgery*, *16*(4), 586–593. https://doi.org/10.1097/01.SCS.0000157305.60505.B5

Kofod, T., Nørholt, S. E., Pedersen, T. K., & Jensen, J. (2005). Unilateral mandibular ramus elongation by intraoral distraction osteogenesis. *Journal of Craniofacial Surgery*, *16*(2), 247–254. https://doi.org/10.1097/00001665-200503000-00010

Koppel, D. A. (2017). 63 - Treacher Collins Syndrome. In *Maxillofacial Surgery* (Third Edit, pp. 894–903). https://doi.org/10.1016/B978-0-7020-6056-4.00017-4

Korioth, T. W. P., Romilly, D. P., & Hannam, A. G. (1992). Three-dimensional finite element stress analysis of the dentate human mandible. *American Journal of Physical Anthropology*, *88*(1), 69–96. https://doi.org/10.1002/ajpa.1330880107

Krüsi, M., Eliades, T., & Papageorgiou, S. N. (2019). Are there benefits from using bone-borne maxillary expansion instead of tooth-borne maxillary expansion? A systematic review with meta-analysis. *Progress in Orthodontics*, *20*(1), 9. https://doi.org/10.1186/s40510-019-0261-5

Kumar, P. K., & Lagoudas, D. C. (2006). Introduction to Shape Memory Alloys. In D. C. Lagoudas (Ed.), *Shape Memory Alloys: Modeling and Engineering Applications* (pp. 1–40). https://doi.org/10.1002/0471732877.emd002

Kummer, F. J. (2012). Biomechanics of Fracture Fixation. In M. Nordin & V. H. Frankel (Eds.), *Basic Biomechanics of the Musculoskeletal System* (4th ed., Vol. 369). https://doi.org/10.1017/CBO9781107415324.004

Kunz, C., Hammer, B., & Prein, J. (2000). Manipulation of callus after linear distraction: A “lifeboat” or an alternative to multivectorial distraction osteogenesis of the mandible? *Plastic and Reconstructive*

Surgery, *105*(2), 674–679. https://doi.org/10.1097/00006534-200002000-00029

Le Fort Osteotomy: Procedures 1, 2 & 3. (n.d.). Retrieved December 22, 2020, from https://deschamps-braly.com/jaw-surgery/le-fort-fracture/

Lexcellent, C. (2013). Shape-memory Alloys Handbook. In *Shape-memory Alloys Handbook* (First). https://doi.org/10.1002/9781118577776

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P. A., … Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *PLoS Medicine*, *6*(7). https://doi.org/10.1371/journal.pmed.1000100

Lodovichi, F. F., Oliveira, J. P., Denadai, R., Raposo-Amaral, C. A., Ghizoni, E., & Raposo-Amaral, C. E. (2018). Does an ear deformity bring an adverse impact on quality of life of treacher collins syndrome individuals? *Ciencia e Saude Coletiva*, *23*(12), 4311–4318. https://doi.org/10.1590/1413-812320182312.21142016

Luo, H. Y., & Abel, E. W. (2007). A comparison of methods for the training of NiTi two-way shape memory alloy. *Smart Materials and Structures*, *16*(6), 2543–2549. https://doi.org/10.1088/0964-1726/16/6/058

Mahrous Mohamed, A., Al Bishri, A., & Haroun Mohamed, A. (2011). Distraction osteogenesis as followed by CT scan in Pierre Robin sequence. *Journal of Cranio-Maxillofacial Surgery*, *39*(6), 412–419. https://doi.org/10.1016/j.jcms.2010.10.016

Margulis, A., Patel, P. K., Daw, J. L., & Bauer, B. S. (2003). Distraction osteogenesis of the mandible with an internal bioresorbable device. *Journal of Craniofacial Surgery*, *14*(5), 32. https://doi.org/10.1097/00001665-200309000-00037

Master, D. L., Hanson, P. R., & Gosain, A. K. (2010). Complications of mandibular distraction osteogenesis. *The Journal of Craniofacial Surgery*, *21*(5), 1565–1570. https://doi.org/10.1097/scs.0b013e3181ecc6e5

Matthey, J. (n.d.). Nitinol technical properties | Johnson Matthey. Retrieved March 15, 2021, from https://matthey.com/en/products-and-services/medical-components/resource-library/nitinol-technical-properties

McCarthy, J. F., & Crombie, J. S. (2000). *Patent No. US6019769A*. USA.

McKenna, S. J., & King, E. E. (2016, March 1). Intraoral Vertical Ramus Osteotomy Procedure and Technique. *Atlas of the Oral and Maxillofacial Surgery Clinics of North America*, Vol. 24, pp. 37–43. https://doi.org/10.1016/j.cxom.2015.10.002

Mehrotra, D., Chellappa, A. A. L., Gupta, C., Passi, D., & Kumar, S. (2012). Reconstruction of ramus-condyle unit with transport distraction osteogenesis: Report of eight cases and review of literature. *Journal of Oral Biology and Craniofacial Research*, *2*(3), 144–148. https://doi.org/10.1016/j.jobcr.2012.10.007

Mehrotra, D., Dhasmanaa, S., & Kumar, S. (2009). Management of temporomandibular ankylosis with

temporal fascia inter-positional arthroplasty and distraction osteogenesis: Report of 30 cases. *Journal of Long-Term Effects of Medical Implants*, *19*(2), 139–148. https://doi.org/10.1615/JLongTermEffMedImplants.v19.i2.50

Meling, T. R., Høgevold, H. E., Due-Tønnessen, B. J., & Skjelbred, P. (2011). Midface distraction osteogenesis: Internal vs. external devices. *International Journal of Oral and Maxillofacial Surgery*, *40*(2), 139–145. https://doi.org/10.1016/j.ijom.2010.10.009

Menon, S., Manerikar, R., Chowdhury, S. K. R., Mohan, S. M., Chowdhury, R., & Mohan, S. M. (2005). Distraction osteogenesis in management of mandibular deformities. *Medical Journal Armed Forces India*, *61*(4), 345–347. https://doi.org/10.1016/S0377-1237(05)80061-9

Meyer, U., Meyer, T., Wiesmann, H. P., Stratmann, U., Kruse-Lösler, B., Maas, H., & Joos, U. (1999). The effect of magnitude and frequency of interfragmentary strain on the tissue response to distraction osteogenesis. *Journal of Oral and Maxillofacial Surgery*, *57*(11), 1331–1339. https://doi.org/10.1016/S0278-2391(99)90872-8

Miller, J. J., Kahn, D., Lorenz, H. P., & Schendel, S. A. (2007). Infant mandibular distraction with an internal curvilinear device. *Journal of Craniofacial Surgery*, *18*(6), 1403–1407. https://doi.org/10.1097/scs.0b013e31814fb6fe

Mitchell, C. D. M. P. S. (2007). Plastic Surgery, 2nd ed. In *Annals of Surgery* (2nd ed., Vol. 246). https://doi.org/10.1097/sla.0b013e318070c62b

Mohammad, K. A., Zainudin, E. S., Sapuan, S., Zahari, N. I., & Ali, A. (2013). Fatigue life for type 316L stainless steel under cyclic loading. *Advanced Materials Research*, *701*, 77–81. https://doi.org/10.4028/www.scientific.net/AMR.701.77

Moroni, A., Vannini, F., Mosca, M., & Giannini, S. (2002). State of the art review: techniques to avoid pin loosening and infection in external fixation. *Journal of Orthopaedic Trauma*, *16*(3), 189–195. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11880783

Mrzezo. (2015, January 8). Anatomy and Physiology - Chapter 4. Retrieved March 25, 2021, from Pocket Dentistry website: https://pocketdentistry.com/4-anatomy-and-physiology/

Natu, S. S., Ali, I., Alam, S., Giri, K. Y., Agarwal, A., & Kulkarni, V. A. (2014). The biology of distraction osteogenesis for correction of mandibular and craniomaxillofacial defects: A review. *Dental Research Journal*, *11*(1), 16–26. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24688555%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3955310

Neumann, D. A. (2010). *Kinesiology of the musculoskeletal system: Foundations for physical rehabilitation* (2nd ed.; Donald A. Neumann, Ed.). St. Louis, Mo: Mosby/Elsevier.

Niinomi, M. (1998). Mechanical properties of biomedical titanium alloys. *Materials Science & Engineering A*, *243*, 231–236. https://doi.org/https://doi.org/10.1016/S0921-5093(97)00806-X

Noon, John, M., Sellman, R., Sellers, Timothy, M., & Shanaman, M. (2011). *Patent No. WO2011038209*.

O'Brien, B., & Bruzzi, M. (2011). Shape memory alloys for use in medicine. In *Comprehensive*

Biomaterials (Vol. 1). https://doi.org/10.1016/b978-0-08-055294-1.00014-3

Oryan, A., Monazzah, S., & Bigham-Sadegh, A. (2015). Bone injury and fracture healing biology. *Biomedical and Environmental Sciences*, *28*(1), 57–71. https://doi.org/10.3967/bes2015.006

Pahl, G., Beitz, W., Feldhusen, J., & Grote, K.-H. (2006). Constructing the future: nD modelling. In K. Wallace & L. Blessing (Eds.), *Engineering Design - A systematic Approach* (Third, pp. 125–141). https://doi.org/10.4324/9780203967461

Pereira, A. R., & Pereira, A. P. (2019). Acute open callus manipulation: Clinical experience with a new surgical technique for solving old problems in distraction osteogenesis. *Journal of Cranio-Maxillofacial Surgery*, *47*(2), 219–227. https://doi.org/10.1016/j.jcms.2018.11.022

Perinetti, G., Contardo, L., Castaldo, A., McNamara, J. A., & Franchi, L. (2016). Diagnostic reliability of the cervical vertebral maturation method and standing height in the identification of the mandibular growth spurt. *The Angle Orthodontist*, *86*(4), 599–609. https://doi.org/10.2319/072415-499.1

Pierre Robin Syndrome: Background, Etiology and Pathogenesis, Otolaryngologic Manifestations. (n.d.). Retrieved December 9, 2020, from https://emedicine.medscape.com/article/844143-overview#a1

Posnick, J. C. (2013). Hemifacial Microsomia: Evaluation and Treatment. In *Orthognathic Surgery: Principles and Practice*. https://doi.org/10.1016/B978-1-4557-2698-1.00028-9

Ramanathan, M., Kiruba, G. A., Christabel, A., Parameswaran, A., Kapoor, S., & Sailer, H. F. (2020). Distraction Osteogenesis Versus Orthognathic Surgery: Demystifying Differences in Concepts, Techniques and Outcomes. *Journal of Maxillofacial and Oral Surgery*, *19*(4), 477–489. https://doi.org/10.1007/s12663-020-01414-y

Rao, K., Kumar, S., Kumar, V., Singh, A. K., & Bhatnagar, S. K. (2004). The role of simultaneous gap arthroplasty and distraction osteogenesis in the management of temporo-mandibular joint ankylosis with mandibular deformity in children. *Journal of Cranio-Maxillofacial Surgery*, *32*(1), 38–42. https://doi.org/https://doi.org/10.1016/j.jcms.2003.07.003

Reina-Romo, E., Sampietro-Fuentes, A., Gómez-Benito, M. J., Domínguez, J., Doblaré, M., & García-Aznar, J. M. (2010). Biomechanical response of a mandible in a patient affected with hemifacial microsomia before and after distraction osteogenesis. *Medical Engineering and Physics*, *32*(8), 860–866. https://doi.org/10.1016/j.medengphy.2010.05.012

Resnick, C. M., Kaban, L. B., & Padwa, B. L. (2017). Hemifacial Microsomia: The Disorder and Its Surgical Management. In *Maxillofacial Surgery* (Third Edit). https://doi.org/10.1016/B978-0-7020-6056-4.00063-0

Robinson, R. C., O'Neal, P. J., & Robinson, G. H. (2001). Mandibular distraction force: Laboratory data and clinical correlation. *Journal of Oral and Maxillofacial Surgery*, *59*(5), 539–544. https://doi.org/10.1053/joms.2001.22688

Rossini, G., Vinci, B., Rizzo, R., Pinho, T. M. D. C., & Deregibus, A. (2016). Mandibular distraction osteogenesis: a systematic review of stability and the effects on hard and soft tissues. *International Journal of Oral and Maxillofacial Surgery*, *45*(11), 1438–1444.

https://doi.org/10.1016/j.ijom.2016.08.012

Rudderman, R., & Mullen, R. (2012). Biomechanics of the craniomaxillofacial skeleton. In M. Ehrenfeld, P. N. Manson, & J. Prein (Eds.), *AOCMF: Principles of Internal Fixation of the Craniomaxillofacial Skeleton Trauma and Orthognathic Surgery* (pp. 21–26). Zürique: Thieme.

Runyan, C. M., & Gabrick, K. S. (2017). Biology of bone formation, fracture healing, and distraction osteogenesis. *Journal of Craniofacial Surgery*, *28*(5), 1380–1389. https://doi.org/10.1097/SCS.0000000000003625

Sadakah, A. A., Elgazzar, R. F., & Abdelhady, A. I. (2006). Intraoral distraction osteogenesis for the correction of facial deformities following temporomandibular joint ankylosis: a modified technique. *International Journal of Oral and Maxillofacial Surgery*, *35*(5), 399–406. https://doi.org/10.1016/j.ijom.2006.01.013

Sadakah, Abdelfattah A, Elshall, M. A., & Farhat, A. A. (2009). Bilateral intra-oral distraction osteogenesis for the management of severe congenital mandibular hypoplasia in early childhood. *Journal of Cranio-Maxillofacial Surgery*, *37*(4), 216–224. https://doi.org/https://doi.org/10.1016/j.jcms.2008.10.014

Sahoo, N. K., Issar, Y., & Thakral, A. (2019). Mandibular Distraction Osteogenesis. *The Journal of Craniofacial Surgery*, *30*(8), e743–e746. https://doi.org/10.1097/SCS.0000000000005753

Sahoo, N., Roy, I., Dalal, S., & Bhandari, A. (2016). Distraction Osteogenesis for Management of Severe OSA in Pierre Robin Sequence: An Approach to Elude Tracheostomy in Infants. *Journal of Maxillofacial and Oral Surgery*, *15*(4), 501–505. https://doi.org/10.1007/s12663-016-0888-4

Sankaran, S., & Kyle, P. (2015). Abnormalities of the Face and Neck. In *Twining's Textbook of Fetal Abnormalities* (Third Edit). https://doi.org/10.1016/b978-0-7020-4591-2.00013-9

Schendel, S. A., & Linck, D. W. (2004). Mandibular Distraction Osteogenesis by Sagittal Split Osteotomy and Intraoral Curvilinear Distraction. *Journal of Craniofacial Surgery*, *15*(4), 631–635. https://doi.org/10.1097/00001665-200407000-00019

Schmitt, S. M., Cronin, R. J., & Berg, S. (1992). Anterior mandibular subapical osteotomy: A useful treatment for patients with severely worn mandibular anterior teeth. *The Journal of Prosthetic Dentistry*, *67*(4), 468–471. https://doi.org/10.1016/0022-3913(92)90074-K

Schoemann, M. B., Burstein, F. D., Bakthavachalam, S., & Williams, J. K. (2012). Immediate mandibular distraction in mandibular hypoplasia and upper airway obstruction. *Journal of Craniofacial Surgery*, *23*(7 SUPPL.1), 1981–1984. https://doi.org/10.1097/SCS.0b013e31825a64d9

Sellers, T. (2002). *Patent No. US2002011600 2A1*. USA.

Şensoy, A. T., Kaymaz, I., Ertaş, Ü., & Kiki, A. (2018). Determining the Patient-Specific Optimum Osteotomy Line for Severe Mandibular Retrognathia Patients. *Journal of Craniofacial Surgery*, *29*(5), e449–e454. https://doi.org/10.1097/SCS.0000000000004470

Senthilkumar, M. (2012). Analysis of SMA Actuated Plain Flap Wing. *Journal of Engineering Science and Technology Review*, *5*(1), 39–43. https://doi.org/10.25103/jestr.051.08

Shen, W., Jie, C., Chen, J., Zou, J., & Ji, Y. (2009). Mandibular distraction osteogenesis to relieve Pierre Robin severe airway obstruction in neonates: Indication and operation. *Journal of Craniofacial Surgery*, *20*(8 SUPPL. 2), 1812–1816. https://doi.org/10.1097/SCS.0b013e3181b6c388

Shi, L., Liu, W., Yin, L., Feng, S., Xu, S., & Zhang, Z. Y. (2015). Surgical guide assistant mandibular distraction osteogenesis and sagittal split osteotomy in the treatment of hemifacial microsomia. *Journal of Craniofacial Surgery*, *26*(2), 498–500. https://doi.org/10.1097/SCS.0000000000001529

Shrivats, a R., Alvarez, P., Schutte, L., & Hollinger, J. O. (2014). Chapter 24: Bone Regeneration. In *Principles of Tissue Engineering*. https://doi.org/10.1016/B978-0-12-410396-2.00041-4

Sieroslawska, A. (2021, February 23). The mandible: Anatomy, structures, fractures. Retrieved March 25, 2021, from Kenhub website: https://www.kenhub.com/en/library/anatomy/the-mandible

Simpson, A. H. R. W., Williams, P. E., Kyberd, P., Goldspink, G., & Kenwright, J. (1995). The response of muscle to leg lengthening. *Journal of Bone and Joint Surgery - Series B*, *77*(4), 630–636. https://doi.org/10.1302/0301-620x.77b4.7615611

Singh, D. J., & Bartlett, S. P. (2005). Congenital mandibular hypoplasia: Analysis and classification. *Journal of Craniofacial Surgery*, *16*(2), 291–300. https://doi.org/10.1097/00001665-200503000-00017

Singh, M., Vashistha, A., Chaudhary, M., & Kaur, G. (2016). Biological basis of distraction osteogenesis - A review. *Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology*, *28*(1), 1–7. https://doi.org/10.1016/j.ajoms.2015.05.006

Snyder, C. C., Levine, G. A., Swasson, H. M., & Browne, E. Z. (1973). Mandibular lengthening by gradual distraction: Preliminary report. *Plastic and Reconstructive Surgery*, *51*(5), 506–508. https://doi.org/10.1097/00006534-197305000-00003

Song, C. (2014). *History and Current Situation of Shape Memory Alloys Devices for Minimally Invasive Surgery*. (December). https://doi.org/10.2174/1875181401002020024

Standerwick, R. G. (2014). Analysis of Average Horizontal and Vertical Mandibular Growth Components Relative to the Horizontal Plane as Determined from Cross-sectional Cephalometric Normal Standards. *J Dent App*, *1*(4), 55–60.

Stöckel, D. (1998). Nitinol - Material with Unusual Properties. *Cordis - NDC, A Johnson & Johnson Company*, pp. 1–5. REMEDICA CO.

Trahar, M., Sheffield, R., Kawamoto, H., Lee, H.-F., & Ting, K. (2003). Cephalometric evaluation of the craniofacial complex in patients treated with an intraoral distraction osteogenesis device: a preliminary report. *American Journal of Orthodontics and Dentofacial Orthopedics*, *124*(6), 639–650. https://doi.org/https://doi.org/10.1016/j.ajodo.2003.04.002

Tung h., Thomas, M. D., Robertson, Bradley R., D.D.S., M. D., Jonathan M. Winograd, M. D., Tarun Mullick, M. D., & N. Manson, Paul, M. D. (1999). *Successful Distraction Osteogenesis across a Growing Cranial Suture without an Osteotomy*.

Types of Bones | Learn Skeleton Anatomy. (n.d.). Retrieved December 16, 2020, from https://www.visiblebody.com/learn/skeleton/types-of-bones

Urbina, C. (2011). *Improvement of the one-way and two-way shape memory effects in Ti-Ni shape memory alloys by thermomechanical treatments*. Universitat Rovira I Virgili.

Van Strijen, P. J., Perdijk, F. B. T. T., Becking, A. G., & Breuning, K. H. (2000). Distraction osteogenesis for mandibular advancement. *International Journal of Oral and Maxillofacial Surgery*, *29*(2), 81–85. https://doi.org/10.1016/S0901-5027(00)80001-6

VanPutte, C. L. (2004). *Seeley's anatomy & physiology* (6th ed.). New York: The McGraw-Hill Companies.

Wada, K., & Liu, Y. (2008). On the two-way shape memory behavior in NiTi alloy-An experimental analysis. *Acta Materialia*, *56*(13), 3266–3277. https://doi.org/10.1016/j.actamat.2008.03.005

Wang, C., Zeng, R. S., Wang, J. N., Huang, H. Z., Sun, J., & Luo, Z. Bin. (2010). The study of distraction osteogenesis with nitinol shape memory alloy spring controlled by infrared light. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology*, *110*(2), 157–166. https://doi.org/10.1016/j.tripleo.2009.12.029

Watanabe, Y., Sasaki, R., Matsuno, I., & Akizuki, T. (2019). Surgery-first orthognathic surgery for severe facial asymmetry combined with mandibular distraction osteogenesis using a three-dimensional internal distractor. *Journal of Craniofacial Surgery*, *30*(1), 39–46. https://doi.org/10.1097/SCS.0000000000004929

Wikenheiser, M. A., Markel, M. D., Lewallen, D. G., & Chao, E. Y. S. (1995). Thermal response and torque resistance of five cortical half-pins under simulated insertion technique. *Journal of Orthopaedic Research*, *13*(4), 615–619. https://doi.org/10.1002/jor.1100130418

Wiltfang, J., Keßler, P., Merten, H. A., & Neukam, F. W. (2001). Continuous and intermittent bone distraction using a microhydraulic cylinder: An experimental study in minipigs. *British Journal of Oral and Maxillofacial Surgery*, *39*(1), 2–7. https://doi.org/10.1054/bjom.2000.0564

Wolford, L. M., & Goncalves, J. R. (2017). Surgical Planning in Orthognathic Surgery and Outcome Stability. In *Maxillofacial Surgery* (pp. 1048–1126). https://doi.org/10.1016/b978-0-7020-6056-4.00074-5

Yates, D. M., & Sinn, D. P. (2017). Classification, Diagnosis, and Etiology of Craniofacial Deformities. In *Maxillofacial Surgery* (Third Edit). https://doi.org/10.1016/b978-0-7020-6056-4.00059-9

Yin, L., Tang, X., Shi, L., Yin, H., & Zhang, Z. (2014). Mandibular distraction combined with orthognathic techniques for the correction of severe adult mandibular hypoplasia. *Journal of Craniofacial Surgery*, *25*(6), 1947–1952. https://doi.org/10.1097/SCS.0000000000000973

Yu, H., Shen, G., Zhang, S., & Wang, X. (2009). Gap arthroplasty combined with distraction osteogenesis in the treatment of unilateral ankylosis of the temporomandibular joint and micrognathia. *British Journal of Oral and Maxillofacial Surgery*, *47*(3), 200–204. https://doi.org/10.1016/j.bjoms.2008.08.003

Yuan, Y., & Chai, Y. (2019). Regulatory mechanisms of jaw bone and tooth development. In B. R. Olsen

(Ed.), *Current Topics in Developmental Biology* (1st ed., Vol. 133). https://doi.org/10.1016/bs.ctdb.2018.12.013

Zanaboni, E. (2008). *One Way and Two Way - Shape Memory Effect : Thermo-Mechanical Characterization of Ni-Ti wires*. Università degli Studi di Pavia.

Zenha, H., Azevedo, L., Rios, L., Pereira, A., Pinto, A., Barroso, M. L., & Costa, H. (2012). Bilateral Mandibular Distraction Osteogenesis in the Neonate with Pierre Robin Sequence and Airway Obstruction: A Primary Option. *Craniomaxillofacial Trauma & Reconstruction*, *5*(1), 25–30. https://doi.org/10.1055/s-0031-1300960

胡敏;, 谢旻;, 姚军;, 周宏志;, 马良;, & 肖红喜. (2008). *Patent No. CN100427158C*.

APPENDIX A – O.M.E.N.S (+) CLASSIFICATION OF HEMIFACIAL MICROSOMIA

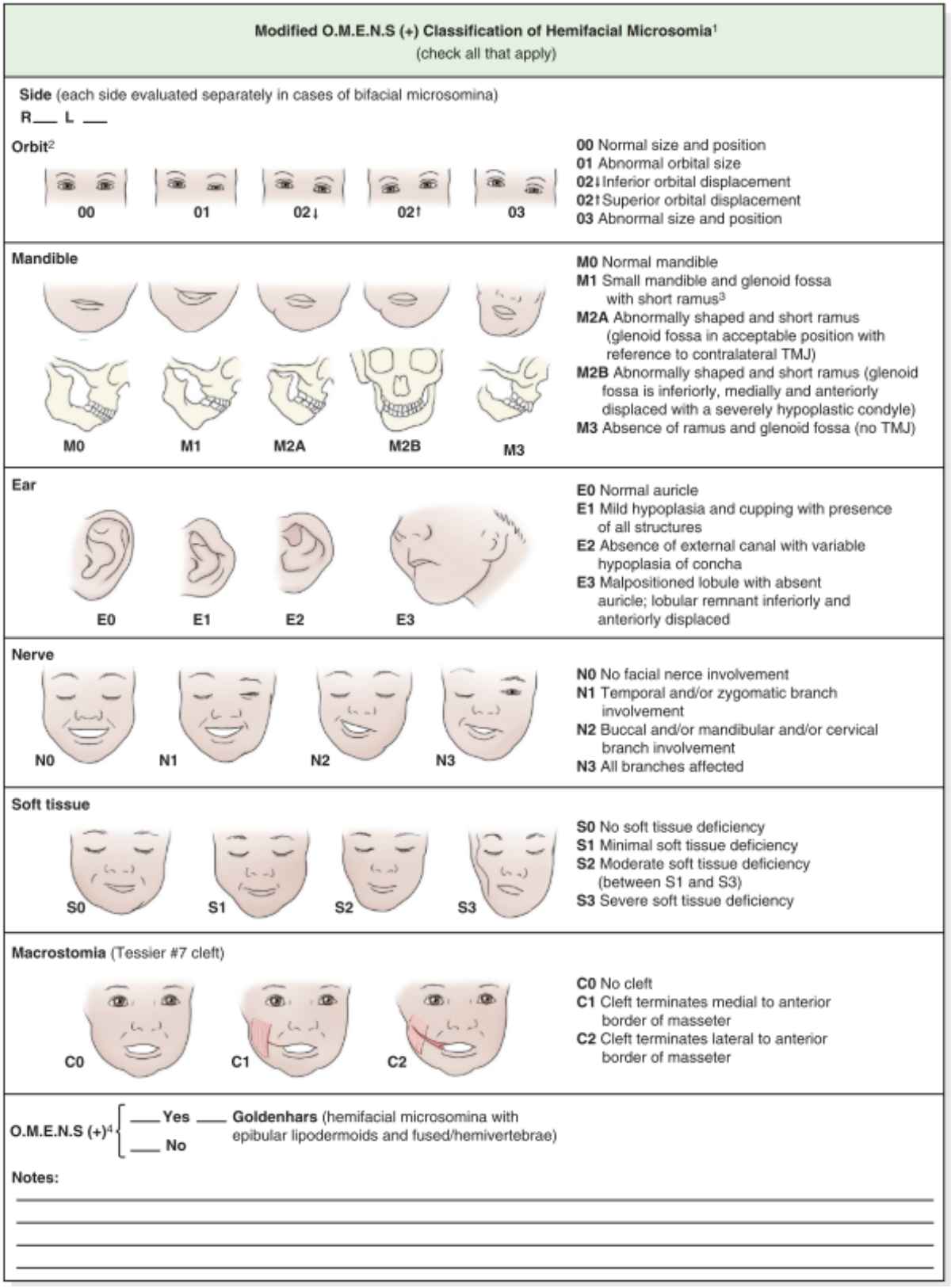
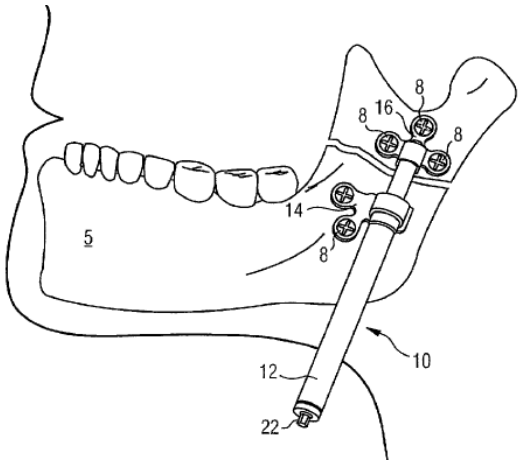
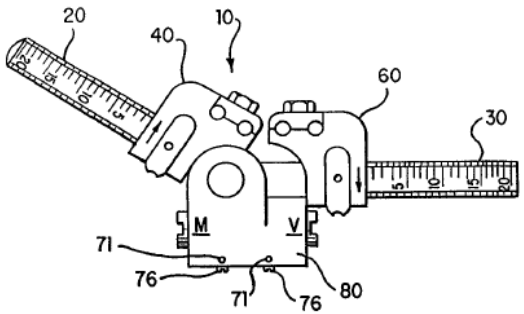
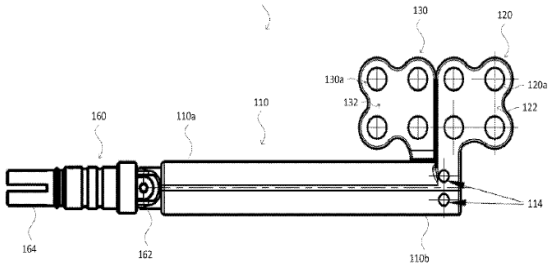
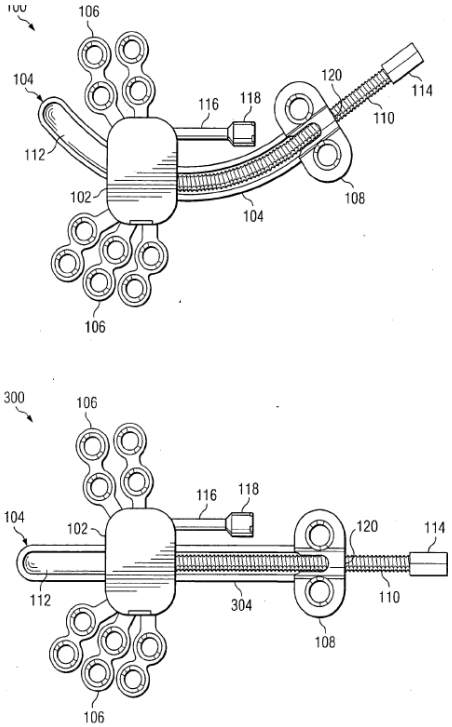


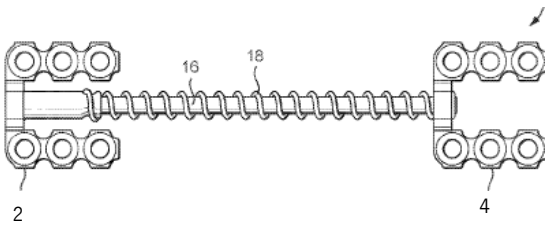
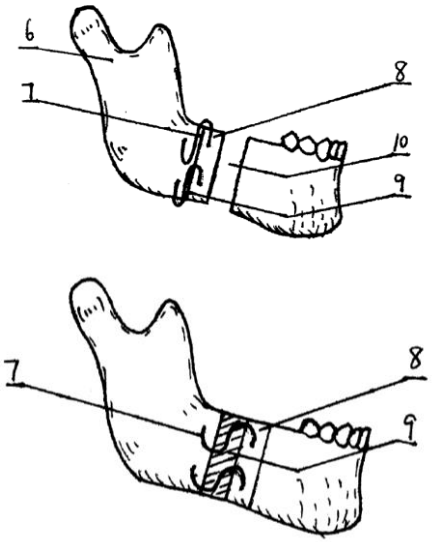
Figure A-1: OMENS (+) classification chart.
(Yates & Sinn, 2017)

APPENDIX B – SUMMARY TABLE OF THE ANALYSED PATENTS

Table B–1: Summary compilation of some of the patented devices for mandibular distraction osteogenesis

Reference	Patent	Title	Date	Figure	Characteristics
1	US20020116002A1 **Assignee:** Synthes (USA)	Orthopaedic system having detachable bone anchors	2002.08.22		**Composition:** two footplates (14/16), one distraction rod (12). The guide screw (22) of the distraction rod (12) is rotated counter-clockwise activating the device and separating the bone segments. The device itself (the part that executes the distraction) can be detached from the fixing elements and be removed.
2	US006019769A **Assignee:** New York University and Howmedica	Bone-adjusting device	2000.02.01		**Composition:** two independent arms (20/30), a central joint for angular regulation (80), transcutaneous bone-pins for fixation. The combination of two linear distraction arms allows for the bone segment to be distracted in two different directions. The central joint allows for angular corrections.

Reference	Patent	Title	Date	Figure	Characteristics
3	US20140148812A1 **Assignee:** Stryker Leibinger GmbH & CO. KG	Paediatric internal mandibular distractor	2014.05.29		**Composition:** two footplates (132/122), one distraction rod (164). The guide screw of the distraction rod is rotated counter-clockwise activating the device and separating the bone segments.
4	US2007/0162045 **Assignee:** OsteoMed L.P.	Curve Linear and Straight Mandibular Distractor with Occlusion Correction Feature	2007.07.12		**Composition:** a flexible rod with a threaded portion (114), a distraction arm (104), a mechanism to guide the flexible rod that allows vector correction (102), to fixation plates (106/108). This is an internal bone distractor that allows for linear or curvilinear MDO, capable of distraction lengths of up to 25mm. The flexible rod is rotated counter-clockwise activating the device and separating the bone segments.

Reference	Patent	Title	Date	Figure	Characteristics
5	WO2019081909A1	Device	2019.05.02		**Composition:** two fixation plates (2/4), a a guiding shaft (16) surrounded by a SM material (18). The arm which defines the movement path and the activation is made through external stimuli on a SM material. This device is unidirectional.
6	CN100427158C	Titanium-nickel memory alloy pull-stretch device and the producing method thereof	2008.10.22		**Composition:** stretcher made of the titanium-nickel shape memory alloy (7). The activation part can be designed into S-shaped, C-shaped, Z-shaped, or multi-curved Z-shaped according to different forces required. At the temperature of the human body, the stretcher automatically expands, causing the bone segments to separate.

Reference	Patent	Title	Date	Figure	Characteristics
7	WO2016046549A1	Device and method of its fabrication	2016.31.03		**Composition:** mesh or plate composed by a shape memory material, preferably nitinol (NiTi). The mesh of shape memory material is moulded to the specific conformation to be treated and through external stimuli the material returns to its original shape and at the same time “pulls” the soft tissues and bone with it.

APPENDIX C – ANATOMICAL PLANES OF THE HEAD

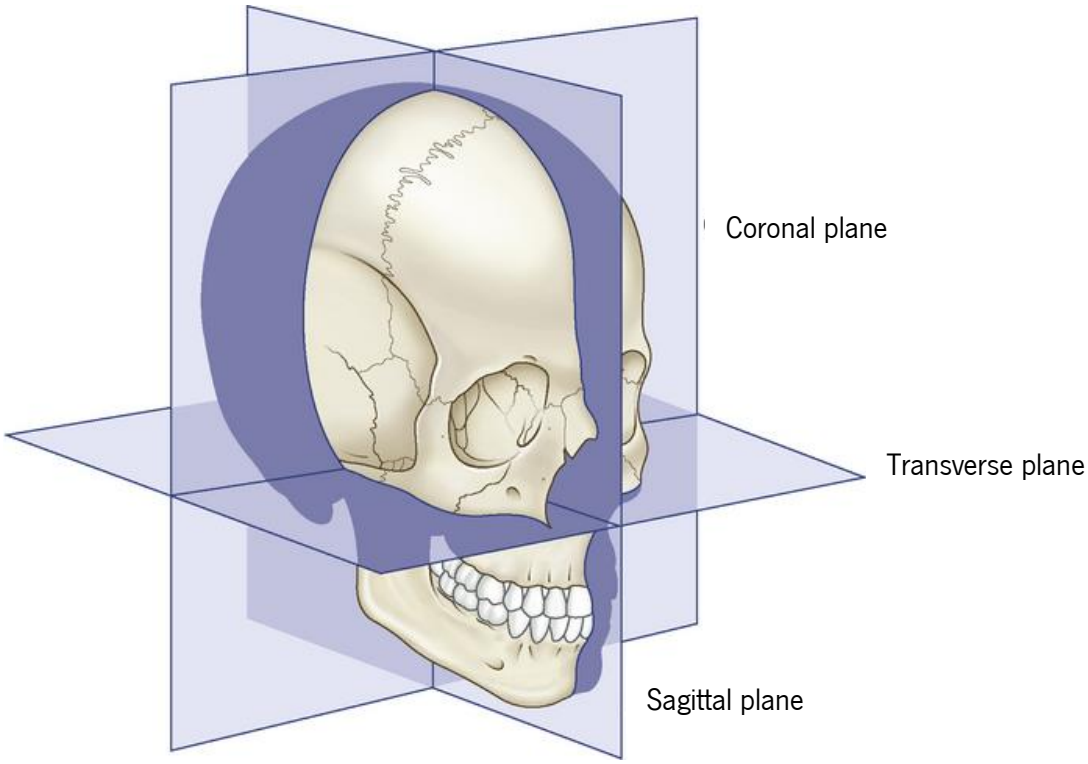


Figure C-1: Sagittal, transverse, and coronal planes of the head.
(Mrzezo, 2015)

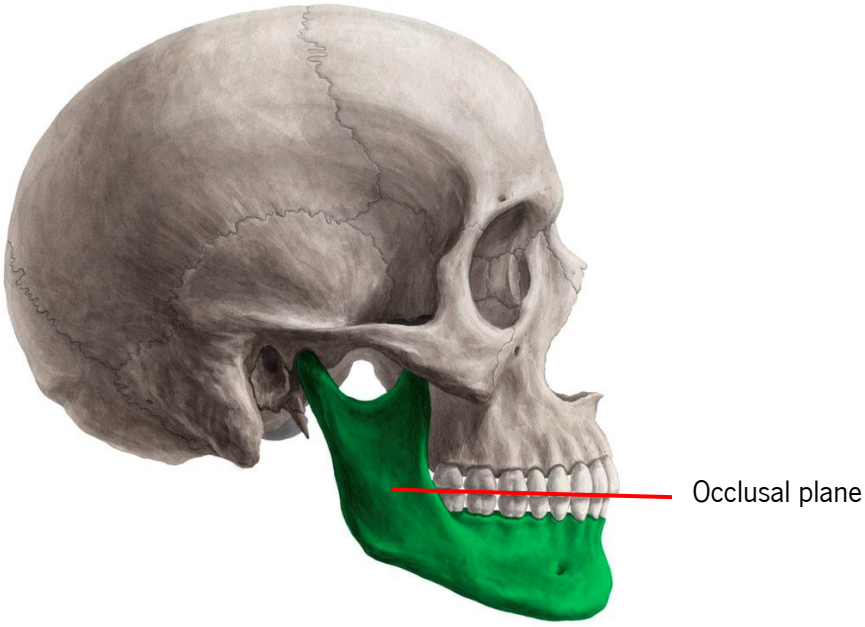


Figure C-2: Representation of the occlusal plane.
(Sieroslawska, 2021)

APPENDIX D – ANTHROPOMETRIC MEASURES OF THE MANDIBLE

Table D–1: Average age-related length of Co-Gn, Go-Gn, Co-Go in millimetres (Co – condylion; Gn – gnathion; Go – gonion). (Standerwick, 2014)

A Average Age related length of Co-Gn (mm)			Average Age related length of Go-Gn (mm)			Average Age related length of Co-Go (mm)		
Co-Gn	Sex		Go-Gn	Sex		Co-Go	Sex	
AGE	M	F	AGE	M	F	AGE	M	F
6	103.0	100.5	6	65.4	65.6	6	48.7	46.5
7	105.3	103.3	7	68.2	67.3	7	49.1	47.7
8	109.2	106.3	8	70.5	69.8	8	51.3	49.1
9	111.7	108.3	9	72.4	70.9	9	52.8	50.8
10	114.5	111.3	10	74.4	73.4	10	54.0	51.5
11	117.6	113.4	11	76.6	75.1	11	55.8	52.4
12	119.7	115.7	12	77.9	75.9	12	57.2	54.6
13	123.1	117.8	13	79.9	77.8	13	59.4	55.1
14	126.5	119.9	14	82.4	78.9	14	61.6	56.8
15	128.7	122.0	15	84.0	80.0	15	62.7	58.9
16	133.6	123.6	16	86.3	81.0	16	66.1	60.5

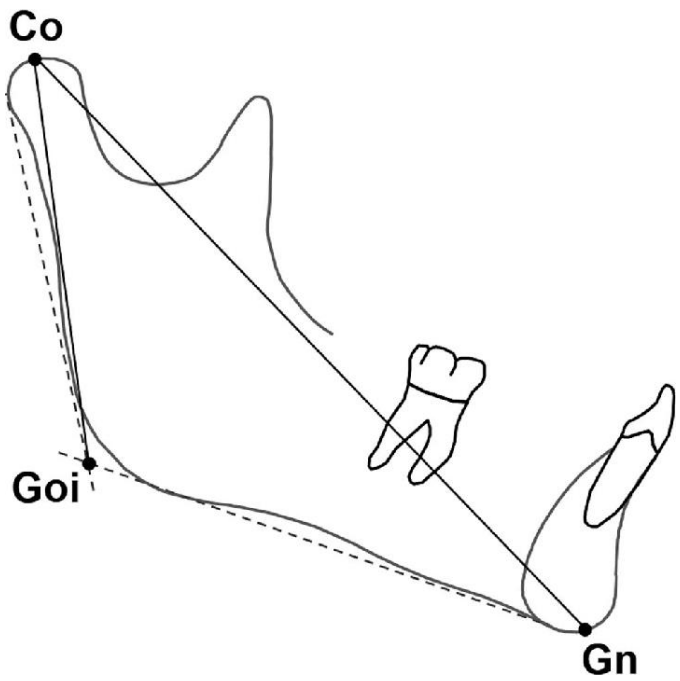


Figure D-1: Mandibular growth parameters. Identified landmarks: Co - Condylion; Goi - Gonion Intersection; and Gn - Gnathion. Goi is defined as the point of intersection between the mandibular and ramus planes.
(Perinetti, Contardo, Castaldo, McNamara, & Franchi, 2016)

APPENDIX E – SHAPE MEMORY ALLOYS (NITINOL): BRIEF STATE OF THE ART

The extraordinary properties of the shape memory alloys (SMA) have been known since the 1930s when Arne Ölander first observed the shape and recovery ability of a gold-cadmium alloy (Au-Cd) (Song, 2014). SMAs are called memory materials due to their property of "remembering" thermomechanical treatments (traction, torsion, flexion, etc.) to which they have been subjected and thus their ability to recover their shape (Lexcellent, 2013). There are two main families of SMAs:

- "copper-based" materials: Cu-Al (Zn, Ni, Be, etc.);
- nickel-titanium-X materials (where X is an element present in small proportions) – Ni-Ti (Fe, Cu, Co, etc.).

These remarkable materials have been at the forefront of research for the last decades. They have been used for a wide variety of applications in various fields such as aeronautics, aerospace, nuclear industry and watch-making (Lexcellent, 2013). In addition to these, this type of alloys has been widely applied in medicine with prominence in the cardiovascular, neurovascular, endovascular, orthopaedic, and orthodontic fields (Kumar & Lagoudas, 2006; O'Brien & Bruzzi, 2011).

The nitinol alloy was discovered by William J. Buehler in 1959 at Naval Ordnance Laboratory in U.S. (Song, 2014). The first use of nitinol in the medical context was in the early 1970s with the application of orthodontic archwires. After that, the use of this alloy became more extensive with applications comprising staples, neurovascular stents, sutures, and heart valve frames (Corporation, 2017). Nitinol is non-ferromagnetic with a lower magnetic susceptibility than stainless steel. Therefore, Nitinol produces few artefacts on MRI and CT scans (Stöckel, 1998).

The behaviour of the SMAs is more intricate than that of common materials, however, this complexity is the basis of their use in many applications. These materials have two key effects associated with the martensitic transformations which are the shape memory effect (SME) and "superelastic effect" (SE) or more accurately called pseudoelasticity. This effect can either be a one-way shape memory effect (OWSME) or two-way shape memory effect (TWSME).

The physical key to shape memory lies in a phase transformation between a parent phase called austenite (A) and a produced phase called martensite (M) (Lexcellent, 2013). This behaviour is known as the martensitic transformation. For SMAs, this phase transformation is described as thermoelastic and it involves a change in the crystalline structure of the material when subjected to a specific variation in temperature (Corporation, 2017). As represented in Figure E-1, in Ni-Ti, the austenite, the high-temperature phase, is usually cubic, and the martensite, the low-temperature phase, has a more complex

twinned monoclinic structure with excellent energy adsorption characteristics (Kumar & Lagoudas, 2006). In addition, the martensite phase is characterized by its remarkable fatigue resistance and easy deformation. Table E-1 summarizes the characteristics of both nitinol crystalline phases.

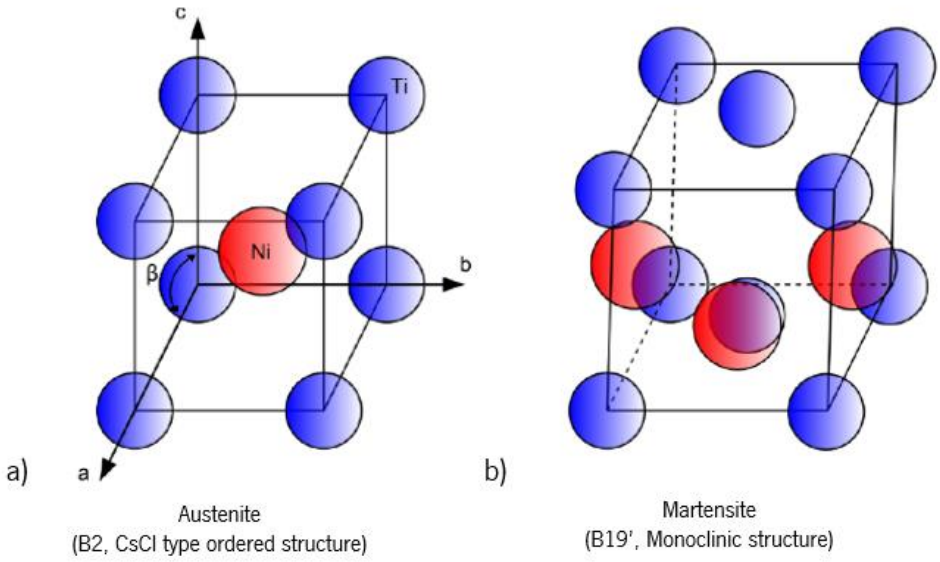


Figure E-1: Geometric appearance of the a) austenite phase and b) martensite phase of nitinol. Distribution of titanium (blue) and nickel (red) atoms.
(Corporation, 2017)

Table E-1: Main characteristics of austenite and martensite phases of nitinol

Austenite phase	Martensite phase
High-temperature phase	Low-temperature phase
High strength	Flexibility and easy deformation
Cubic structure (B2)	Twinned monoclinic structure (B19')

The temperatures at which the formation of martensite starts and ends are called Ms and Mf. Austenite formation starts and ends at As and Af, respectively. Figure E-2 represents the stress-strain-temperature diagram of the crystallographic changes in the SME. To exhibit shape memory behaviour the nitinol alloy must first be cooled below Mf. Starting from the parent phase (point A), the stress-free cooling of austenite below the martensite transformation temperatures (Ms and Mf) results in the formation of twinned martensite (point B). The martensitic variants of the twinned martensite, upon applying mechanical loading (point B to point C), are forced to reorientate into a detwinned martensite phase. The material is then elastically unloaded from C to D and the detwinned martensitic state is retained. When heating, in the absence of stress, reaching the As temperature (point E) initiates the reverse transformation and the detwinned martensite begins to transform into austenite. This process is complete

when the material reaches the Af temperature (point F), above which only the parent austenitic phase exists (point A). This process can be repeated creating the whole cycle of the one-way shape memory effect (Corporation, 2017; Kapoor, 2017; Kumar & Lagoudas, 2006; Lexcellent, 2013).

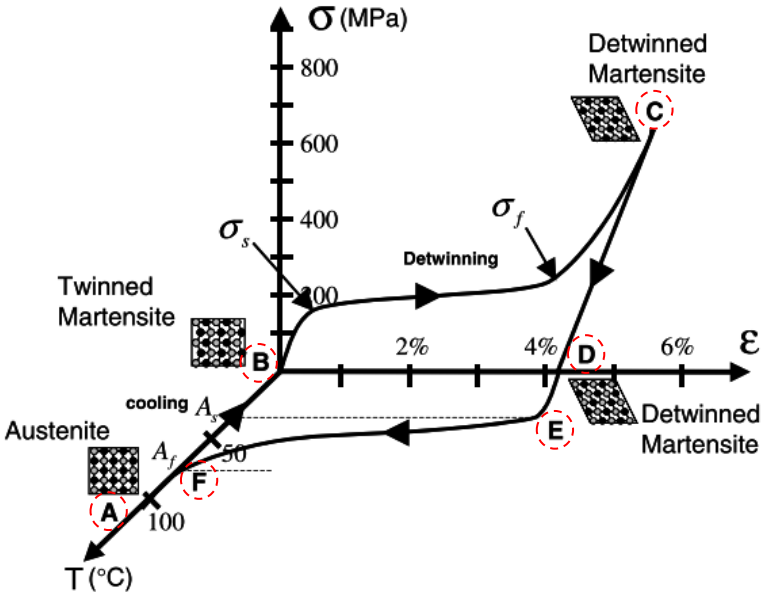


Figure E-2: Schematic critical stress-strain-temperature diagram of the crystallographic changes in the shape memory effect.
(Kumar & Lagoudas, 2006)

Simplifying, during the cooling process, the parent phase transforms to twinned martensite (A → B), then the material is deformed causing stress-induced detwinning (B → C). Upon unloading and heating above Af the material returns to its parent phase (C → A). Figure E-3 represents a simplified version of the shape memory process.

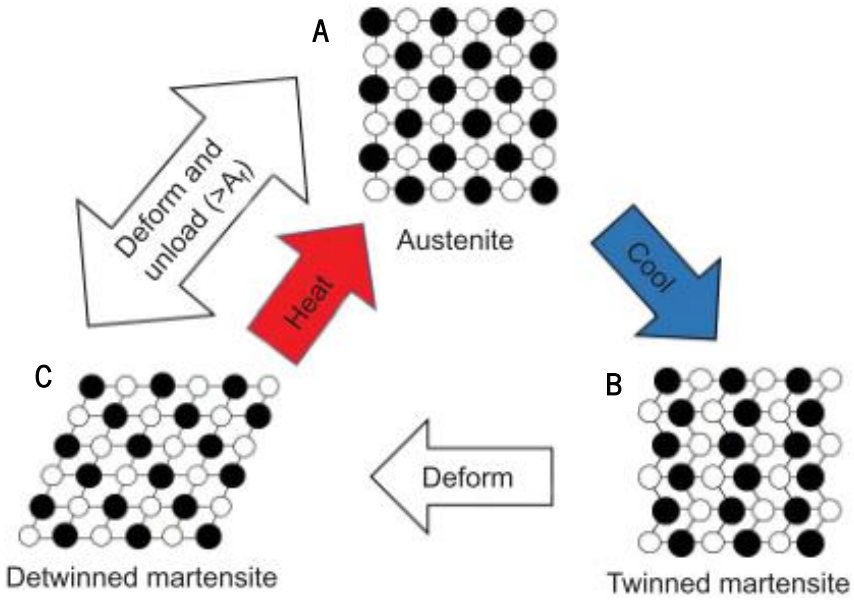


Figure E-3: Schematic illustration of shape memory effect.
(Kapoor, 2017)

Two-way SME

The two-way shape memory effect follows the same methodology as the one-way, however, in the two-way SME the transformation strains are generated during both heating and cooling of the material. Therefore, an alloy with TWSME has de ability to remember a geometrical shape at high temperature, above austenite finish temperature (Af) and another shape at low temperature, below martensite finish temperature (Mf). The difference between both effects is represented in Figure E-4. This type of behaviour is only achieved after particular training procedures that usually involve thermomechanical cycling treatments.

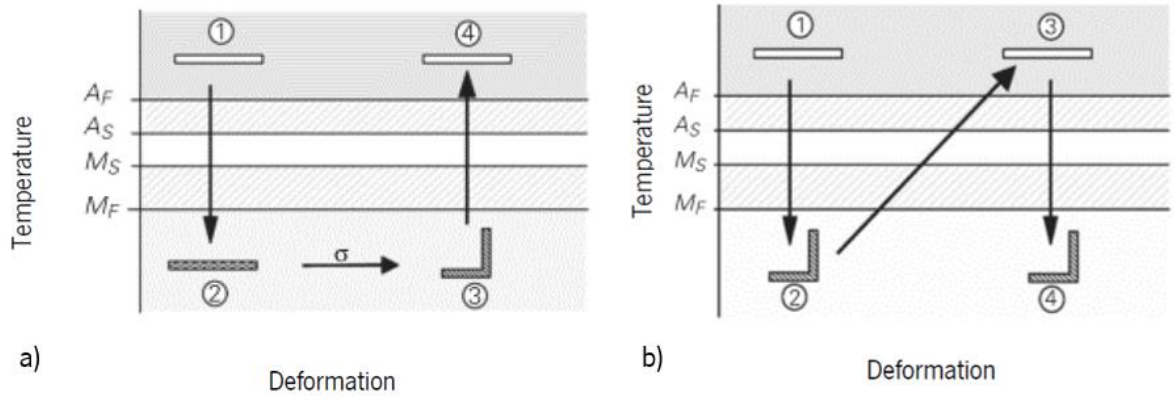


Figure E-4: The effect of a) one-way shape memory and b) two-way shape memory. a) Stage 1 presents the parent phase which is cooled down below Mf and is then deformed (stage 3). When heated, the material recovers its initial form (stage 4); b) Stage 1 presents the parent phase which when cooled down below Mf transforms in a second form (stage 2). After heating the material recovers the first form (stage 3) and if it cooled again the material will have the second form as shown in stage 4.
(Wada & Liu, 2008)

The mechanism of thermomechanical cycling treatment to obtain TWSMA consists of developing some "reminders" of the desired cold shape (known as dislocation arrangements) in the austenite phase of OWSM alloy by repeating the transformation cycle between the martensite phase and the austenite phase. These dislocation arrangements create an anisotropic stress field in the matrix of austenite, which guides the growth of the martensite variants towards the preferred orientations. As a result, a spontaneous shape change towards the trained shape upon cooling will occur (Wada & Liu, 2008).

An insufficient number of training cycles produces a non-stabilized two-way memory effect and over-training generates unwanted effects that reduce the efficiency of training, because of that it is important to define optimal conditions of training. The optimum training procedure has to result in optimum TWSM behaviour - maximum magnitude, reproducibility and stability of the TWSME and a minimum change of the transformation temperatures (Urbina, 2011; Wada & Liu, 2008).

The main training procedures are listed below and include overdeformation, shape-memory cycling, pseudoelastic (PE) cycling, Combined SM/PE training, and constrained temperature cycling of deformed martensite. Other variants or combinations of the above five methods are also documented as other thermomechanical cycling training methods, however, they have shown little performance improvement, so they are not described here (Luo & Abel, 2007).

1. Overdeformation

While in the martensitic condition, the alloy is cooled below Mf and then is severely bent, to well beyond the usual strain limit for completely recoverable shape memory. When reheated to the parent phase (austenite phase), due to excessive deformation of the martensite, the alloy will not completely recover the original shape (Figure E-5). A partial loss of shape memory occurs, however, if cooled again to the martensite range, the alloy will spontaneously revert towards the overdeformed shape. This process is repeated until the martensitic shape is well defined (Gallardo Fuentes, Gümpel, & Strittmatter, 2002; Zanaboni, 2008).

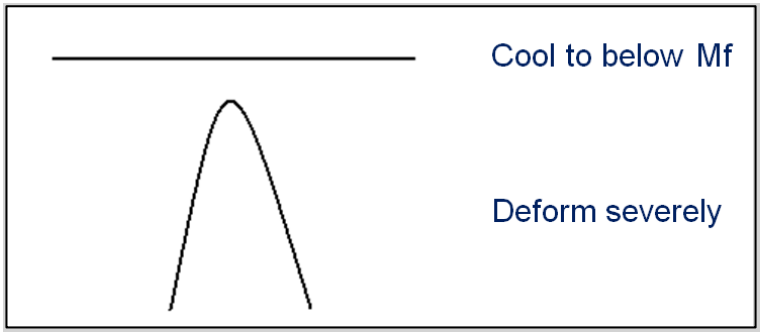


Figure E-5: TWSME training by overdeformation.
(Zanaboni, 2008)

2. Shape Memory (SM) Cycling

This procedure consists of repeatedly carrying out shape memory cycles until the two-way behaviour begins to be demonstrated. The steps of shape memory cycle include: cooling the specimen below Mf, loading it in martensite state to a desired cold shape, unloading it completely and heating it to a temperature above Af (Figure E-6). After a number of cycles (5 to 10) the component will begin to spontaneously change shape upon cooling, moving in the direction in which it has been consistently deformed during the training cycles. The amount of spontaneous shape change on cooling will be significantly less than that which was being induced in the shape memory deformation step. Typically, the spontaneous shape change will perhaps be 1/5 to 1/4 of the training strain; for example, if the strain-

induced during training was 6%, the spontaneous TWME strain is likely to be no more than 1 or 2 % (Gallardo Fuentes et al., 2002; Luo & Abel, 2007; Zanaboni, 2008).

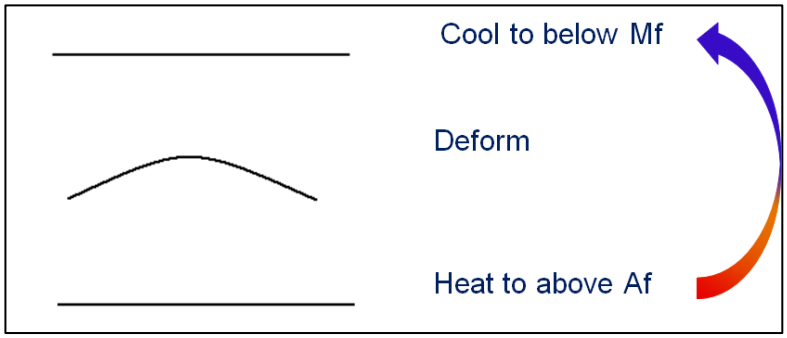


Figure E-6: TWSME training by shape memory cycling.
(Zanaboni, 2008)

3. Pseudoelastic (PE) Cycling

This method consists of repeatedly stress-inducing martensite by loading and unloading the parent phase above the Af temperature, but below the martensite deformation temperature (Md) where pseudoelastic (or superelastic) behaviour is expected (Figure E-7). Martensite deformation temperature represents the highest temperature at which martensite will form from the austenite phase in response to applied stress. At temperatures above Md the Nitinol shape memory alloy will not exhibit superelasticity and will rather exhibit a typical elastic-plastic behaviour when loaded (Corporation, 2017).

The steps of pseudoelastic cycling include: heating the specimen above Af and below Md where pseudoelastic behaviour is expected, loading it in austenite state to a desired cold shape and then unloading it completely. The number of training cycles required is typically on the order of 5 to 10 (Gallardo Fuentes et al., 2002; Luo & Abel, 2007; Zanaboni, 2008).

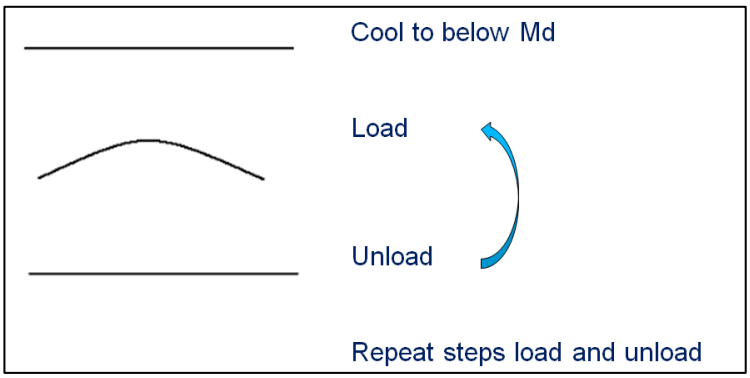


Figure E-7: TWSME training by pseudoelastic cycling.
(Zanaboni, 2008)

4. Combined SM/PE Training

This process of training starts by heating the specimen above Af and then cooled below Md where pseudoelastic behaviour is expected. Then the specimen is loaded in austenite state to a desired cold shape, cooled in the loaded condition below Mf and is finally unloaded completely and heated up to recover the original undeformed shape (Figure E-8). When this routine is repeated a number of times, TWSM behaviour will be obtained on subsequent heating and cooling (Gallardo Fuentes et al., 2002; Luo & Abel, 2007; Zanaboni, 2008).

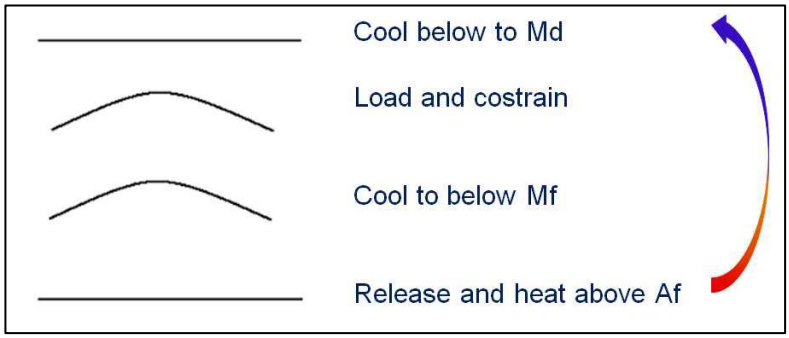


Figure E-8: TWSME training by combined SM/PE training.
(Zanaboni, 2008)

5. Constrained Temperature Cycling of Deformed Martensite

This training process is probably the most commonly used since it is simpler to carry out in terms of temperature control. This method consists of deforming the specimen below Mf (thus producing a stress-biased martensitic microstructure), constraining the deformed condition and then heating up above Af (Figure E-9). The sample is typically cycled from below Mf to above Af a number of times, with the sample constrained in the original deformed shape, to complete the training routine. This training method proves to be particularly effective and is relatively straightforward to carry out (Gallardo Fuentes et al., 2002; Zanaboni, 2008).

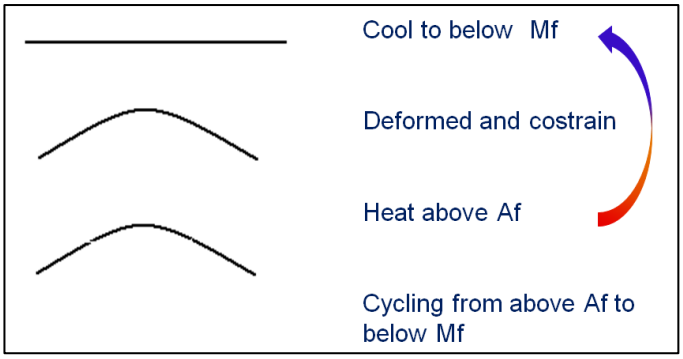


Figure E-9: TWSME training by Constrained Temperature Cycling of Deformed Martensite.
(Zanaboni, 2008)