Role of mesenchyme stem cells in the chondro-osseous graft reconstruction of temporomandibular joint for continuous growth of the mandible and midface

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Abstract

Introduction

This study included 37 children who were treated by reconstruction of the temporomandibular joint (TMJ) by chondro-osseous graft from the iliac crest. The role of granular mesenchyme stem cells of the graft is to simulate normal condyle for continuous growth; it is also involved in repair and remodelling of the condyle, as shown by experimental studies conducted on rabbits and by clinical application. This technique has been used in treatment of ankylosis of the TMJ, hemifacial microsomia and traumatic hypoplasia of the condyle. The total number of cases was 37 children: 26 cases with ankylosis of the TMJ (10 girls and 16 boys), 10 children with hemifacial microsomia or first arch dysplasia syndrome (4 girls and 6 boys) and 1 girl with traumatic hypoplasia of the condyle. Their age was between 4 and 13 years (mean, 8.5 years). Follow-up period was between 3 and 10 years; all cases were treated in the Maxillofacial Unit, Surgical Specialty Hospital, Medical City, Baghdad, Iraq. The aim of this research is to discuss the role of mesenchyme stem cells of the chondro-osseous graft reconstruction of the TMJ for continuous growth of the mandible and midface.

Materials and methods

Animal experiments were performed on six rabbits (age, 3 months);

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TMJ reconstruction was done after excision of the condyle. Three months later, the animals were killed and post-mortem studies macroscopically showed that the chondro-osseous graft was united, remodelled and healed with the ramus; the head shape was similar to that of the control.

Results

The graft was fixed by a stainless steel wire of 0.5 mm and did not show any corrosive property, infection or resorption of the bone surrounding the wire or changes in the colour of the wire. Microscopically, there were four distinct zones or layers; the first layer, consisting of fibrocartilage layer, was thick due to functional demand of hard masticatory processes; the second proliferative layer showed several layers of active round granular mesenchyme stem cells; the third layer showed hypertrophic chondrocyte conversion into osteocyte and the cartilage arranged in a multidirectional fashion due to environmental changes in masticatory function requirements instead of vertical columnar growth pattern as in iliac crest as a weight bearing bone; and the fourth layer was an os-teoid layer with bone marrow spaces in between.

Conclusion

This valuable research shows the ability of the chondro-osseous graft to be a good substitute of the condyle with regard to both growth and function in children.

Introduction

Surgery of the temporomandibular joint (TMJ) is usually difficult in the management of diseases such as ankylosis, mild hemifacial microsomia or hypoplasia of the condyle. It has always been a challenge to maxillofacial surgeons, particularly in the West for the last four decades, as they do not encounter many such cases.

Many attempts have been made in the past for biological reconstruction of the TMJ by autogenous tissue-like metatarsal phalangeal bone graft, sterno-clavicular head, bone graft from iliac crest or rib graft for the reconstruction of the condyle. All these attempts have failed to show a continuous growth in the condyle.

The application of the costo-chondral graft by Sir Harold Gilles, introduced in early last century, on patients by Kennet (1973) and the experimental studies of costo-chondral graft on iris monkeys by Possillo (1974) made great advances in the usage of this graft for TMJ reconstruction. Over the last 4 decades, it has become the only popular technique to be practiced.

The TMJ is unique as it is the only joint with two compartments with an inter-articular disc in between; it has no role in the growth of the condyle, but it acts as a protector to the head of the condyle. It also plays a role in the sliding movement, for maintaining lubrication of the condyle and for the protection of the head of the condyle during masticatory function. It helps in advancing the condyle during mouth opening with the lateral pterygoid muscle.

TMJ development begins later during the embryonic stage, after development of other joints has been completed. In the lower compartment, the head of the condyle grows in an upward direction to establish...
contact with the base of the skull. Continuous growth toward the base of the skull and downward growth toward the body is important in the growth of the mandible and midface.

The hypothesis of the condylar cartilage as a growth centre was not accepted in the past by many researchers worldwide, including Poswillo (1974). He stated that the condyle has no active role in the growth of the mandible and midface. This statement was based on the theory that continuous growth of the condyle leads condylar hypertrophy. Moreover, the growth of the mandible and midface occurs due to the functional demand of the periosteal matrix of the facial skeleton. This theory is no longer accepted by the author, as the only theory to control growth by proving that the condyle is a growth centre was based on his experimental and clinical studies involving excision of the condyle in a new born rabbit (age, 3 months); 3 months later, he noticed a severe deformity of the lower jaw in the affected side. However, we did not exclude Moss’s theory on functional demand of periosteal matrix, and we accept both theories to establish the growth of the mandible and midface.

During TMJ ankylosis as a result of traumatic injury to the condyle and capsule contents with limitation of mouth opening due to intra-articular haemorrhage, pain, oedema and spasm of the TMJ muscles in a child, with formation of callus later between the skull base and the ascending rami of the mandible, ends with damages to the functional periosteal matrix of muscles involved in mastication and ligaments of the TMJ and bone. This severe insult greatly affected the growth of the mandible and midface. Compensatory growth in the muscular attachment of masti catory muscles occurred as a result of TMJ stiffness and elongation of coronoid, short rami, prominent angle and downward inclination of the short body featuring antegonial notch in the lower border of the mandible; this was also considered as an important clinical sign of TMJ ankylosis.

Experimental studies in rabbit TMJ reconstruction by chondro-osseous graft proved the presence of an active layer of mesenchyme stem cells in the graft. These mesenchyme stem cells differentiate to form chondrocyte and osteocyte; the chondrocyte cells converted cartilage cells, by series of differentiations, to hypertrophic chondrocyte to osteoblast. These stem cells are involved in bone formation, maintaining continuous growth of the TMJ and involved in repair and remodelling of the joints.

The aim of this research is to demonstrate the use of the chondro-osseous graft to establish a continuous balanced growth of the mandible and midface without using any distraction or osteotomy for correction of the deformity.

Materials and methods
This work conforms to the values laid down in the Declaration of Helsinki (1964). The protocol of this study has been approved by the relevant ethical committee related to our institution in which it was performed. All subjects gave full informed consent to participate in this study. Animal care was in accordance with the institution guidelines.

Thirty-seven children were treated by reconstruction of the TMJ by chondro-osseous graft in three diseases that required biological reconstruction of the TMJ for restoration of function, growth, remodelling and repair. These diseases were ankylosis, hemifacial microsomia and hypoplasia of the condyle. This graft was tested experimentally for viability in the TMJ, in new environments of articulation with the glenoid fossa and masticatory function to meet the force of mastication and to restore the growth of the condyle, mandible and midface and to continue growth, remodelling and repair.

A total number of 37 cases were included: 26 children including 10 girls and 16 boys with ankylosis of the TMJ, 10 cases including 4 females and 6 males with first arch dysplasia or hemifacial microsomia, and 1 female with traumatic hypoplasia. Their ages ranged between 4 and 13 years (mean 8.5 years), and the follow-up time ranged between 3 and 6 years.

All cases were treated in the Maxillofacial Unit, Surgical Specialty Hospital Medical City, Baghdad, Iraq.

Experimental studies
Experimental studies were conducted on eight young rabbits (age, 3 months; approximately the same weight of 1.5 kg) and two animals were used as a control (1 left and 1 right). In this experiment, the rabbits were divided into two groups; each group had four rabbits. The TMJ rabbits were subjected to meniscectomy and codylectomy. Surgery was performed via a curve incision, extending from the outer canthus of the eye to the pre-auricular region, and the zygoma was palpated as a landmark for localization of the TMJ. A piece of full thickness bicortical bone segment of the iliac crest graft, measuring 1.8 cm, with a cartilage cap was fixed to the outer surface of the ascending ramus, and before that, de-cortication of the ramus and graft was done before fixation of the graft by a soft stainless steel wire of 0.5 mm. The graft was fitted to the glenoid fossa before fixation of the graft (Figure 1A).

Surgical procedure was performed under ketamine hydrochloride sedation (Vetalar Ketamine HCL, Astrapin, Germany) of 50 mg/kg of body weight IM with infiltration of TMJ by a local anaesthetic agent, Lingo spasm (lignocaine hydrochloride 2% with adrenaline 1/80000, St. Maur, France) (Figure 1A).
Results
All animals showed neither restriction of mouth opening nor difficulty in mastication; by the end of the experiment after 3 months, the rabbit gained approximately 0.8 kg of body weight, one animal had an infection in the TMJ, which was controlled by antibiotics, and in one rabbit, the graft got displaced due to a technical error; this had no effect on the masticatory process of the rabbits, occlusion was good and two animals showed a midline shift (Figure 2).

Post-mortem and histological studies of the graft

Macroscopic feature

Surgical reconstruction of the TMJ in rabbits by chondro-osseous graft rapidly adapted to the new function of masticatory process requirements and formed condyle and neck similar to the TMJ of the control animals. On macroscopic examination of the TMJ, we found an excellent union between the chondro-osseous graft and the ramus with no evidence of bony resorption, ossification or chondrofication of the graft. There was no corrosion around the stainless steel wires at the site of graft fixation, and no evidence of infection or changes in the colour of the wire, giving the impression of a biologically inert stainless steel wire. The animals were killed and the graft was dissected and kept in 10% buffered formalin for 10 days, immersed in 4-N formic acid for decalcification and stained by haematoxylin and eosin (H&E) (Figure 3A & B).

Microscopic studies

The histological studies showed that the cellular pattern of the cells resembled the cellular pattern of the histology of the non-operated condyle with four distinct zones as layers of endochondral ossification; the first layer represents the articular layer and consists of a thick fibrocartilage cap layer; the second layer consists of several active mesenchyme stem cells, representing the proliferative layer; and the third layer showed the cells of the iliac crest converted from vertical columnar growth pattern of

Figure 1: (A) Chondro-osseous graft from the iliac of a rabbit showing the cap of the cartilage and the osseous element beneath. (B) Chondro-osseous graft from the iliac of a child showing the cartilage part attached to the bone shaft.

Figure 2: Deformity of the lower jaw of a rabbit due to condyle resection in the affected side.

Figure 3: (A) Resected condyle of a rabbit. (B) Post-mortem specimen of the TMJ showing the chondro-osseous graft united to the ramus after 3 months.
weight bearing in the iliac crest to a multidirectional growth fashion simulating the condyle due to changes in the environment from the iliac crest to masticatory requirement of the graft in the TMJ. In this layer, endochondral ossification occurred; in this zone, the chondrocyte undergoes differentiation through a series of changes to hypertrophic chondrocyte and the endochondral cells converted into osteoid cells. This layer was similar to the third layer in the control group but slightly thicker and more active. The fourth layer represents the osteoid layer with bony trabecular and bone marrow spaces in between and contains living cells arranged in a multidirectional fashion and distributed according to the direction of the masticatory forces (Figures 4A, 4B, 5A and 5B).

Clinical application
The clinical cases were divided into the following:

- **Cases with ankylosis of the TMJ**
- **Cases with mild first arch dysplasia syndrome**
- **Cases with hypoplasia of the condyle due to trauma or infection**

There were two diseases showing hypoplasia of the condyle. The first one due to embryonic defects as a result of early occlusion of the artery, the main nutrient vessel of the first arch, and the second one due to trauma affecting only the condyle, while in other diseases of ankylosis, the traumatic episode not only affects the condyle but also the content of the TMJ capsule with fragmentation of the meniscus and may even extend to the base of the skull.

The pathogenesis of these diseases differs, but basically, the treatment of these cases remains the same. All cases required early reconstruction by the chondro-osseous graft for restoration of growth and function.

All cases of TMJ ankylosis in children were treated by excision of the ankylosed joint, with hyperplastic coronoid (coronoidectomy) to prevent any obstacle for full movements of the joint after reconstruction by chondro-osseous graft. The operation was performed using full thickness of fascio-cutaneous of the auricular-temporal flap with further extension of the flap posteriorly for better and easy access to the TMJ and to avoid vital structures of the area.

The dissection of the flap was started from the temporal region; reflection of the flap was done by Haworth elevator inserted down to the temporal process of the zygomatic arch and capsule of the TMJ incised through L-shaped incision for exposing the ankylosis. Haworth perioisteal elevator was inserted behind the posterior border of the neck of the condyle as a quid for insertion of special condylar retractor as designed by the author to protect the underlying soft tissue structures and maxillary artery. Another incision was done in the submandibular area for reattachment of the masseter and medial pterygoid muscles and also used an access for insertion and fixation of the graft. When the graft advanced upwards to the glenoid fossa, the graft was fixed to the ascending ramus by stainless steel wires of 0.5 mm; these cases showed an excellent result to mouth opening or growth of mandible and midface\(^3,4\).

This procedure was only applied on ankylosed joint. All cases showed good results, except two cases; in one case, all procedures and steps for reconstruction of the condyle by chondro-osseous graft was done, but the coronoid process left without resection. After few years, we noticed that mouth opening was reasonable but not maximum and the growth of the face was unsatisfactory. We thus decided to intraorally resect the coronoid to establish a fully functional movement and to enhance growth (Figures 6A, 6B, 7A–E and 1B).

The fault in the second case is that the operation was performed without resection of the coronoid due to technical errors; this fault ends with...
Discussion

Autologous bony structures for reconstruction of the TMJ have been greater challenges to maxillofacial surgeons for the past four decades. Two biological techniques have successfully been used: the costo-chondral graft and the chondro-osseous graft for reconstruction of the TMJ, and both techniques were experimentally tested for assessment of these grafts for viabilities for growth potential and masticatory force processes. Kennett\textsuperscript{8} tested the costo-chondral graft clinically, and Poswillo\textsuperscript{9} studied the graft experimentally on iris monkeys. In his experiments, he used the costo-chondral graft for reconstruction of the TMJ condyle on monkeys and he also did a vertical sub-sigmoid osteotomy on the posterior border of the ascending ramus for sliding the posterior segment upwards to fill the glenoid fossa and to simulate the condyle after resection and to work as a stump. He found that the costo-chondral graft successfully replaced the condyle as a good substitute for restoration of growth and function of the condyle, but in the sliding graft, he found that it replaced the condyle for functional movements, without any evidence for growth potential.

The author did an experimental study using rabbits by reconstruction of the condyle by chondro-osseous graft harvested from the iliac crest of rabbits. After 3 months, the animals were sacrificed for post-mortem studies of the TMJ specimen. We found excellent healing and union between the chondro-osseous

Figure 7: (A) Deformity of a face of a 4-year-old child due to TMJ ankylosis of the left side of the face. (B) CT scan of the left TMJ showing deformity of the joint. (C) Post-operative photograph showing remarkable growth of the face after 3 months. (D) Mouth opening after operation. (E) Lateral oblique of the left side of lower jaw showing reconstruction of the left TMJ by chondro-osseous graft after 3 months.
In this study, they also found that a G-protein coupled receptor (CXCR4) is predominantly expressed in hypertrophic chondrocyte, while its ligand chemokine stromal cell-derived factor (SDF-1) is expressed in the bone marrow adjacent to hypertrophic chondrocyte.10,12.

The objection about chondro-osseous graft once harvested from the iliac crest may affect the growth of the iliac bone in children. During follow-up, we did not observe any deformity of the iliac crest. During follow-up, none of the patients complained about it; the second objection is the use of stainless wire which may cause infection; the author has been practising wire fixation for the last four decades successfully for the fixation of fragments of bones in maxillofacial surgery including bone grafting, injuries or fixation of fragments after osteotomy in facial deformity or in controlling bone fragments in cases with blast war injuries.10,11.

The chondro-osseous graft been used successfully by the author for the last four decades for the reconstruction of TMJ ankylosis in children and also for the reconstruction of TMJ with hemifacial microsomia, first arch dysplasia syndrome and in cases with traumatic hypoplasia of the condyle.10 The result was very optimistic in all cases for restoration of growth, function and aesthetic features of the face, and the graft did not show resorbtion or substitution by ossification or chondrofaciation. Further, the condyle and TMJ were able to fulfil the functional demands of growth, remodelling and repair of the condyle due to the presence of mesenchym stem cells.3.

Conclusion
Damages of the TMJ as result of congenital or acquired traumatic diseases in children require an urgent reconstruction of the joint by chondro-osseous graft. This graft has an ability to withstand the force of mastication and to continually grow, repair and remodel due to the presence of mesenchyme stem cells.

References