Pathogenesis of traumatic temporomandibular joint ankylosis: a narrative review

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Abstract
Objective: To comprehensively review the literature and summarize the results from human and animal studies related to the possible causes and pathogenesis of traumatic temporomandibular joint ankylosis (TMJA).
Materials and Methods: The Google Scholar, Embase, and Web of Science databases were used to search for articles related to traumatic TMJA from 2011 to 2020. All articles were screened according to the inclusion and exclusion criteria, collected, and analyzed.
Results: Nineteen relevant articles were collected. These articles were classified into three groups: predisposing and etiological factors, cellular studies, and molecular studies.
Conclusion: The pathological mechanisms are similar between TMJA and nonunion hypertrophy. Aberrant structural and etiological factors as well as disordered cellular and molecular mechanisms might contribute to TMJA formation. Although preclinical and clinical data have provided new evidence on the pathogenesis of traumatic TMJA, the molecular mechanisms and biological events require further exploration.

Keywords
Traumatic temporomandibular joint ankylosis, fracture healing, bone mass, bone remodeling, pathogenesis, review

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Introduction

Traumatic temporomandibular joint (TMJ) ankylosis (TMJA) refers to trauma-induced fibrous or bony fusion between the condyle and TMJ fossa. This condition may lead to chronic, persistent, and progressive inability to open the jaw, facial deformity, and obstructive sleep apnea–hypopnea syndrome. At present, osteotomy of the bone mass with gap arthroplasty is the only effective treatment approach to release the fused TMJ and relieve the clinical symptoms of TMJA. However, this surgery is challenging and technically demanding because of the proximity among the nerves, vessels, and skull base in this region. In addition, the exact molecular mechanisms of TMJA remain unclear.

In the present study, we examined and summarized the pathological characteristics and mechanisms of TMJA.

Materials and methods

Two investigators searched the Google Scholar, Embase, and Web of Science databases for English-language literature published from 2011 to 2020 using the following keywords: “temporomandibular joint ankyloses,” “TMJ ankylosed bone mass,” or “ankylosed TMJ.” The survey included only pathological studies of TMJA. The selection process involved an evaluation of the abstracts and main content of the articles based on the following predetermined inclusion criteria: English-language articles published in a peer-reviewed journal; histopathologic, animal model, cellular, and molecular biological studies and hypotheses of TMJA development; and full-text articles. The exclusion criteria were articles that included any form of clinical treatment or management of TMJA.

Results and discussion

Nineteen articles that investigated the pathology of traumatic TMJA were finally included. These articles were classified into three groups: predisposing factors and etiological factors, cellular studies, and molecular studies (Table 1).

Predisposing and etiological factors

TMJA structure and composition. Traumatic TMJA can be classified into fibrous, fibro-osseous, and bony ankylosis. According to clinical data, TMJ disc displacement (which often results from trauma or infection but may also be congenital) is believed to be the leading cause of TMJA. Moreover, according to animal models, the characteristic pathological feature of TMJA is abundant fibrous connective tissue occupying the joint space with or without cartilage on the traumatic articular surfaces. However, the type of articular surface damage that leads to TMJA, especially bony ankylosis, remains unclear. To further explore this phenomenon, we performed two surgical methods based on previous sagittal condyle fracture and disc dissection in TMJA models. In one group, we carved deep grooves into the fibrocartilage of the glenoid fossa until the callous bone was exposed to induce more severe glenoid bone injury. In the other group, we only removed the fibrocartilage of the glenoid fossa without deeply carving into the callous bone. The results showed that cartilage injury of the glenoid fossa might lead to fibrous ankylosis whereas bone injury of the glenoid fossa might lead to bony ankylosis under conditions of disc displacement. These data further suggest that the severity of glenoid fossa injury might be the essential factor in promoting TMJ bony ankylosis. However, what components of the articular surfaces may induce ankylosis remains unclear.
| First author, year | Research object | Results and conclusion | Reference No. |
|-------------------|-----------------|------------------------|---------------|
| Yan et al., 2013  | Animal model    | Mild injury of glenoid fossa leads to fibrotic ankylosis whereas severe injury of glenoid fossa leads to bony TMJA | 4 |
| Deng et al., 2016 | Animal model    | The lateral pterygoid simulates the effects of distraction osteogenesis and contributes to TMJA | 21 |
| Meng et al., 2009 | Hypothesis      | Distraction osteogenesis of the lateral pterygoid muscle plays an important role in TMJA formation | 20 |
| Liu et al., 2012  | Animal model    | Lateral pterygoid muscle reconstructs the condyle fracture healing shape, which causes TMJA | 22 |
| Yang et al., 2020 | Animal model    | Condylar fibrous layer removal (instead of glenoid fibrous layer removal) combined with discectomy leads to traumatic TMJA | 15 |
| Wang et al., 2019 | Animal model    | Articular fibrous layer removal combined with discectomy leads to traumatic TMJA | 14 |
| Zhao et al., 2020 | Animal model    | Macrophage depletion reduces chondrogenesis and prevents TMJA bone formation | 13 |
| Liang et al., 2019 | Animal model    | Higher expression of angiogenic factors (Hif-1α, VEGF, Ang1, vWF) in bony TMJA than fibrotic TMJA and increased angiogenesis might contribute to TMJA | 17 |
| Bhatt et al., 2013 | Hypothesis      | Hypercoagulability/reduced fibrinolytic activity secondary to protein C deficiency might play a role in TMJA | 18 |
| Yan et al., 2012  | Hypothesis      | The development of TMJA is similar to the course of hypertrophic nonunion from medical history, etiology, imaging features, histology, and disease turnover | 5 |
| Li et al., 2014   | Human radiologic and histology samples | Bony traumatic TMJA forms by osteophyte proliferation and endochondral ossification | 12 |
| Porto et al., 2011 | Animal model    | MSC application induces more bone formation in the TMJ damage area and more severe ankylosis symptoms than bone graft application | 8 |
| Xiao et al., 2013 | Human samples   | BMSCs derived from radiolucent zone of TMJA exhibit lower osteogenic potential, and radiolucent zone might be an important pool of BMSCs for bone formation | 7 |
| He et al., 2015   | Human samples   | Bone remodeling suppression caused by osteoclast deficiency contributes to bone mass formation of TMJA | 6 |
| Yan et al., 2014a | Animal model    | Wnt signaling is involved in bone formation of TMJA | 10 |
| Yan et al., 2014b | Animal model    | | 9 |

(continued)
The fibrocartilaginous tissue layers covering the condyle contain a fibrous layer, a proliferating zone, a hypertrophy zone, and a calcification zone. Wang et al. found that removing the fibrous layer of the articular surface with partial disc resection could induce traumatic TMJA. In addition, Yang et al. demonstrated that condyle fibrous layer removal is more critical for traumatic TMJA than glenoid fossa fibrous layer removal, although the bony ankylosis seemed typical and not severe.

During the fracture healing process, hematomas are organized by fibrous granulation tissues, after which soft and hard calluses are formed and remodeled. Based on Sawhney’s classification, we found that fibrous and cartilaginous tissues were arranged in layers and that numerous capillaries were present in the fibrous area. However, few capillaries were present in the cartilaginous area in type I ankylosis; abundant fibrocartilaginous tissues and capillaries were found in the junction between the cartilaginous ankylosis and the bony surface and in the osteophyte centers in type II ankylosis. Moreover, we also discovered that fibrocartilaginous and cartilaginous tissues were positive for immunohistochemical staining of type II collagen in the radiolucent zone, and the ossifying bone tissues adjacent to the radiolucent zone were positive for immunohistochemical staining of type I collagen.

Table 1. Continued.

| First author, year | Research object | Results and conclusion | Reference No. |
|--------------------|-----------------|------------------------|---------------|
| Pilmane and Skagers, 2011 | Human samples | Osteogenic mRNA expression of bony TMJA was higher than that of fibrotic TMJA but lower than that of condyle fracture healing, suggesting that the course of TMJA is similar to that of hypertrophic nonunion | 11 |
| Duan et al., 2015 | Human samples | High TGF-β1 expression and persistent Msx2 expression lead to persistent bone formation and limited programmed cell death in TMJA | 16 |
| Corso et al., 2019 | Human samples | Fibrocartilage and chondro-osseous structures exist in the TMJA joint space, suggesting the main pattern of TMJA bone formation | 19 |

TMJA, temporomandibular joint ankylosis; Hif-1α, hypoxia-inducible factor 1-alpha; VEGF, vascular endothelial growth factor; Ang1, angiopoietin 1; vWF, von Willebrand factor; MSCs, mesenchymal stem cells; BMSCs, bone marrow-derived mesenchymal stem cells; TGF-β1, transforming growth factor-beta 1; Msx2, msh homeobox 2; OPG, osteoprotegerin.
Some researchers have argued that specific characteristics might contribute to ankylosis. Bhatt et al.\textsuperscript{18} reviewed four cases of bilateral TMJA. They hypothesized that the hypercoagulable state and reduced fibrinolytic activity might promote hematoma formation and neo-angiogenesis, contributing to the formation of TMJA. This hypothesis might explain the low incidence of traumatic TMJA to some extent. However, not all patients with TMJA develop a hypercoagulable state. Additionally, whether this hypercoagulable state is directly associated with the severity of TMJ trauma requires further exploration.

**Osteoprotegerin (OPG) gene polymorphism.** Previous studies have shown that gene mutations or changes in gene expression play essential roles in many bone-related diseases. Thus, some researchers believe that genetic factors might have an essential role in TMJA. For example, the polymorphism rs2073618 of the OPG gene has been suggested as a possible marker associated with the risk of TMJA manifestation.\textsuperscript{19} OPG is an essential cytokine that inhibits osteoclast function. Abnormal expression of OPG might be involved in TMJA. However, the underlying mechanism of OPG gene polymorphism in TMJA is not clear.

**Lateral pterygoid muscle.** Anatomically, the lateral pterygoid muscle is attached to the medial side of the condyle. Meng et al.\textsuperscript{20} hypothesized that the stretching action of the lateral pterygoid muscle on the fractured condyle during distraction osteogenesis might be an important factor at the beginning of traumatic TMJA. A sagittal or comminuted fracture of the condyle may result in medial and downward displacement of the cracked condyle due to stretching of the lateral pterygoid muscle. Furthermore, Deng et al.\textsuperscript{21} and Liu et al.\textsuperscript{22} found that the size of the ankylosed bone mass was reduced after blocking the lateral pterygoid muscles during ankylosis model surgery. However, the lateral pterygoid muscles’ distraction osteogenesis, which might be related to horizontal osteogenesis, does not seem to be associated with vertical bone formation of the condyle and thickening of the temporal bone.

**Cellular studies of TMJA**

**Mesenchymal stem cells (MSCs) and bone formation.** Increasing numbers of studies are suggesting that the formation of TMJA follows a process similar to that of hypertrophic nonunion. Nevertheless, in TMJA, the fusion occurs in the TMJ fossa and condyle rather than in the same bone.\textsuperscript{4,5,25} MSCs are essential in bone formation and fracture healing.\textsuperscript{26} During fracture healing, these cells are recruited to injury sites from adjacent bone, bone marrow, or other tissues by cytokines and chemokines such as bone morphogenetic proteins (BMPs), transforming growth factor-beta, and stromal cell-derived factor 1 (SDF1).\textsuperscript{27,28} Kitaori et al.\textsuperscript{29} and Shinohara et al.\textsuperscript{30} found that SDF1 inhibition might decrease the migration capacity of MSCs and impair the fracture healing process. In contrast, SDF1 overexpression can enhance the migration and homing capacities of MSCs and accelerate fracture healing.\textsuperscript{29} These recruited MSCs differentiate into osteoprogenitors and subsequent osteoblasts to form new bone. In TMJA, the fractured condyle, severely injured TMJ fossa, and absence of the disc because of anterior displacement cause the injured condyle to more closely contact the fossa, eventually resulting in fusion.\textsuperscript{4,5} During this process, MSCs are recruited into the TMJ space from the bone marrow, periosteum, vessels, and muscles, after which they differentiate into osteoblasts to form the TMJ bone mass.\textsuperscript{31,32} Iwakura et al.\textsuperscript{33} and Hofmann et al.\textsuperscript{34} found that the tissues
involved in hypertrophic fracture nonunion contain MSCs that can differentiate into osteoblasts, which further suggests that these tissues might represent a potent pool of MSCs for bone formation. Similarly, in our previous work, we isolated MSCs from the radiolucent zone of TMJA and from the bone marrow of the ankylosed bone mass. This suggests that the radiolucent zone and bone marrow might be important sources of MSCs for continuous bone formation of the TMJA bone mass. Nevertheless, the MSCs derived from the radiolucent zone and bone marrow exhibited decreased proliferative and osteogenic behavior, further explaining the long course of TMJA formation. Interestingly, while establishing an animal model of TMJA, Porto et al. reported that application of MSCs induced more bone formation in the damaged area of the TMJ and more severe ankylosis symptoms than application of bone grafts. However, no bone bridge was seen between the condyle and TMJ fossa. In summary, these studies suggest that MSCs might play an essential role in TMJA bone mass formation.

**Osteoclasts and macrophages.** Osteoclasts are critical cells for bone resorption and bone remodeling during fracture healing. Once osteoclast differentiation is inhibited and the resorption capacities become deficient, the bone resorption process is impaired; this eventually leads to a progressive increase in bone density in patients with osteopetrosis or bone nonunion. Gerstenfeld et al. found that treatment with bisphosphonates or receptor activator of nuclear factor-κ B ligand (RANKL) inhibitors may suppress osteoclast differentiation and resorption capacities during fracture healing, potentially leading to hypertrophy and high-density callus formation. Melatonin consistently impairs fracture healing by inhibiting RANKL signaling. Cathepsin K is a key factor secreted by osteoclasts. Its inhibition during fracture healing suppresses osteoclast resorption ability and leads to hypertrophy and high-density callus formation. In one study, OPG-knockout mice showed accelerated fracture healing and formation of small calluses. Moreover, our previous study suggested that a deficiency of transient receptor potential vanilloid type 1, a calcium channel receptor, results in larger calluses and impaired endochondral ossification through inhibition of osteoclast differentiation and resorption abilities. The results of the above studies suggest that osteoclast deficiency might be an essential factor for hypertrophy and high-density callus formation.

Interestingly, hypertrophy and high-density bone mass are the typical radiographic and histologic characteristics of TMJA. Our study showed that the number of osteoclasts decreased, especially in the late stage of TMJA bone mass formation, and that the osteoclast differentiation ability was diminished; this suggests that osteoclast deficiency might contribute to bone mass formation in patients with TMJA. However, the detailed mechanisms of how osteoclast deficiency leads to bone mass formation in TMJA require further investigation. Some researchers have suggested that chondrocytes can transdifferentiate into osteoblasts or osteocytes during remodeling deficiency, leading to soft callus ossification and high-density calluses. To further test this hypothesis, Zhou et al. cloned a green fluorescent protein reporter gene in the chondrocytes and found that 60% of chondrocytes transdifferentiated into mature osteoblasts during fracture healing. These findings suggest that chondrocyte-mediated bone formation might be a crucial participant during endochondral ossification. In addition, previous studies have suggested that endochondral ossification is the main bone formation
mode in TMJA. Furthermore, our serial studies showed that large amounts of cartilage tissue and fibrocartilage tissue exist in the radiolucent zone, even in the bone tissues of ossifying ankylosis. Thus, we assumed that because osteoclast deficiency may result in remodeling suppression, some of the chondrocytes in the cartilage area of the ankylosed bone mass might be transdifferentiated into osteoblasts or osteocytes to directly ossify the cartilage, thus contributing to the hypertrophy of the ankylosed bone and high bone density. However, this hypothesis needs further exploration.

Macrophages are osteoclast progenitor cells that exert important functions in bone resorption. These cells are present during the inflammatory phase of fracture healing in both humans and animals and play a critical role in initiating fracture repair. Macrophages eliminate pathogenic microorganisms, cell debris, and necrotic tissues and induce high expression of inflammatory factors such as interleukin 1, interleukin 6, and tumor necrosis factor-alpha after injury. Previous studies have shown that reducing macrophages or diminishing macrophage-related inflammation factors from the time of injury may compromise fracture healing. Xing et al. found that C-C motif chemokine receptor 2 (CCR2) knockout dramatically reduced the number of macrophages, vascularization, maturation of cartilage, and callus size compared with the control group at 7 days after injury; at 21 days after injury, however, the CCR2 knockout group had a larger callus size and more bone formation than the control group. Another study showed that callus formation was wholly abolished when macrophage depletion was initiated at the time of surgery in macrophage Fas-induced apoptosis transgenic mice. In studies of TMJA, our results showed that the number of macrophages was highest in ankylosis early-stage tissues among control condyle and ankylosis late-stage tissues. Interestingly, once the macrophages were diminished at the time of TMJA model surgery, the severity of ankylosis was alleviated and the ankylosis bone mass formation was limited with reduced cartilage size and decreased expression of cartilage-related genes. Consistent with these studies on fracture healing, macrophage depletion during fracture healing has been shown to reduce callus formation and cartilage size, while macrophage colony-stimulating factor 1 increased the number of macrophages and soft callus formation. These studies suggest that macrophages might have an essential role in initiating fracture healing and the TMJA process and are closely related to the callus and ankylosis bone mass size.

**Molecular studies of TMJA**

*Molecular studies of bone formation.* MSCs mediate bone formation during fracture healing mainly by directly differentiating into osteoblasts for bone formation or differentiating into chondrocytes for the endochondral ossification process accompanied by high-level expression of osteogenic or chondrogenic genes. A previous preclinical study suggested down-regulation of osteogenic and angiogenic cytokines, such as Wingless-Int1 (Wnts), BMP-4, BMP-7, and angiopoietin 2, in hypertrophic bone nonunion compared with normal fracture healing. To further explore the features of bone formation during TMJA progression, we analyzed samples from animals with TMJA and found lower expression of Wnt5a, β-catenin, lymphocyte-enhancing factor, runt-related transcription factor 2, osterix, SRY-box transcription factor 9, collagen type X alpha 1, alkaline phosphatase, osteocalcin, and BMP-4 in fibrosis and bony ankylosis compared with condylar fracture undergoing the regular healing process. Additionally, our results...
suggested that Wnt signaling might be involved in the formation of traumatic TMJA. Consistent with this, Pilmane and Skagers also found that high transforming growth factor-β1 expression and persistent msh homeobox 2 expression led to persistent bone formation and limited programmed cell death in TMJA. Thus, many MSCs are recruited to the TMJ injury site once the condyle has fractured and the TMJ fossa has sustained severe injury for slow but consistent bone formation of TMJA bone mass.

Molecular studies of angiogenesis. The occurrence of angiogenesis coupled with osteogenesis has been widely accepted. Rich angiogenesis may accelerate fracture healing, while angiogenesis deficiency leads to atrophic bone nonunion. Thus, rich angiogenesis might be involved in the TMJA bone mass formation process. Liang et al. found that the angiogenic-related gene expressions of hypoxia-inducible factor 1-alpha, vascular endothelial growth factor, angiopoietin 1, cysteine-rich angiogenic inducer 61, and matrix metalloproteinases were higher in bony ankylosis than fibrous ankylosis. These results suggest that the increased angiogenesis in the TMJA bone mass might be an important factor for consistent supplies of blood, nutrition, and osteoprogenitors.

Conclusion

Increasing numbers of studies have suggested that the pathological mechanisms of the bone mass formation process of traumatic TMJA are similar to those of the callus formation of hypertrophic nonunion. Recent studies have provided relevant evidence from different aspects that have uncovered more detailed mechanisms of traumatic TMJA. This review might be used by oral and maxillofacial surgeons to further understand the characteristics and pathological processes of TMJA.

Authors’ contributions

L.H. He and Z.Y. Zhang contributed to the study conception and design, data acquisition, and drafting of the manuscript; E. Xiao contributed to the data analysis and interpretation and critical revision of the manuscript; Y. He contributed to the data analysis and critical revision of the manuscript; and Y. Zhang contributed to the study conception and design and critical revision of the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Ethics approval

The ethics review committee of Peking University School and Hospital of Stomatology waived the requirement for ethics approval because this study was a narrative review.

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