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Perspective Article

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Pathophysiology and epidemiology of TMJ

S.B. Milam

Department of Oral and Maxillofacial Surgery, University of Texas Health Science Center, San Antonio, TX, USA

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Painful disorders involving the temporomandibular joint (TMJ) and associated soft tissues are relatively common with prevalences ranging from 16-59% for reported symptoms and 33-86% for clinical signs[1]. Approximately 25% of those individuals experiencing temporomandibular pain will eventually seek treatment[2]. Severe degenerative temporomandibular joint disorders may reduce posterior vertical support of the mandible resulting in gross facial disfigurement and airway compromise. Alternatively, traumatic injuries or inflammatory conditions affecting the temporomandibular joint can lead to joint ankylosis yielding significant compromise to the individual's ability to sustain adequate nutrition and maintain oral health. Estimated treatment costs associated with these disorders have exceeded $10 billion annually.

A strong female preponderance (as high as a 9:1 female/male ratio) has been observed in studies of patients who seek treatment for painful temporomandibular disorders. Recent studies have implicated estrogens in the pathogenesis of some degenerative TMJ diseases and in joint nociception, providing some explanation for the apparent female predisposition to these disorders[3-10]. Estrogen receptors have been identified in tissues of primate and human TMJs[3-5]. Recent animal studies have implicated estrogens as potential contributors to extracellular matrix catabolism in the TMJ[11].

Sex hormones may also regulate neural responses to injury of the TMJ and associated structures. For example, more brainstem neurons express c-fos following noxious stimulation of the TMJ region in intact female rats compared to ovariectomized female animals or males[12,13]. Perhaps this offers some explanation to the observation that postmenopausal women receiving estrogen replacement therapy totaling 185 mg or more per year are 1.77 times more likely to be referred for treatment of a painful temporomandibular disorder than postmenopausal women who do not receive estrogen replacement therapy[8].

Unique features of the human temporomandibular joint

The temporomandibular joint is a load-bearing, synovial-lined articulation formed by the mandibular condyle and squamous portion of the temporal bone. The unique structure of the TMJ permits both hinge and sliding movements. Furthermore, the TMJ is the only load-bearing articulation that is connected to its contralateral counterpart by a single bone (i.e., the mandible connects both TMJs). This unique anatomic relationship forces dependent movements of the TMJs.

The articular surfaces of the TMJ are composed of fibrocartilages that are distinct from the hyaline cartilages of articulations of the appendicular skeleton[14-18]. Several studies have provided a partial characterization of the extracellular matrices of both normal and diseased TMJs[17,19-30] (see Table 1). The unique biochemical composition of these articular tissues is reflected by material properties that are also distinct from those of other load-bearing articulations[31].

During human embryologic development, two distinct sets of articulations form between the cranium and mandible, termed primary and secondary TMJs[32]. The primary TMJ forms from cellular elements of Meckel's cartilage and the first branchial arch serving as a limited hinge articular until 16 weeks of postnatal life. This articulation will ultimately become the joint between the incus and the malleus. The secondary TMJ develops from condensed mesenchyme located lateral to Meckel's cartilage beginning at six weeks of development[33-35]. This structure will mature to the complex articulation that is characteristic of the human TMJ.

Molecular events that underlie development of the temporomandibular joint appear to be distinct from those of other load-bearing, synovial joints. For example, a 22-base pair frame shift mutation of the cartilage derived morphogenetic protein-1 gene has been identified as the primary derangement of the Hunter-Thompson chondrodysplasia[36].

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Corresponding author: Stephen B. Milam, D.D.S., Ph.D., Professor & Chair, Department of Oral & Maxillofacial Surgery, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78284, USA
E-mail: milam@uthscsa.edu

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Species	Specimen	Biochemicals	Ref.
Human	Synovial fluid	aggrecan	[64, 65]
Pig	Fibrocartilage	aggrecan	[66]
Primate	TMJ	alpha5 betal 1 integrin	[17]
Rat	AD	biglycan	[24, 27]
Human	Synovium, AD	BMP-2	[67]
Human	Synovial fluid	cartilage oligomeric matrix protein	[64, 65]
Primate	TMJ	chondroitin sulfate	[17, 68]
Rat	AD	chondroitin sulfate	[27]
Cow	AD	chondroitin sulfate	[69, 70]
Human	AD	chondroitin-6-sulfate	[23]
Rat	AD	decorin	[24, 27]
Human	AD	decorin	[71]
Primate	AD	dermatan sulfate	[72]
Human	Synovium	FGF-2, FGFR-I	[73]
Primate	TMJ	fibronectin	[17]
Primate	TMJ	hyaluronic acid	[17]
Human	AD	keratan sulfate	[23]
Primate	TMJ	keratan sulfate	[17]
Cow	AD	keratan sulfate	[28]
Primate	TMJ	laminin	[17]
Rat	Synovium	laminin	[74]
Primate	TMJ	link protein	[17]
Human	TMJ	tenascin	[22, 75, 76]
Primate	TMJ	tenascin	[17]
Human	TMJ	TGF-β	[22]
Pig	Fibrocartilage	TGF-β	[77]
Rabbit	AD	TIMP-1	[11, 20, 78]
Rabbit	AD	TIMP-2	[11, 78]
Rabbit	AD	type I collagen	[79]
Cow	AD	type I collagen	[80]
Primate	TMJ	type I collagen	[17, 72]
Rat	TMJ	type I collagen	[26, 29, 81]
Rabbit	AD	type II collagen	[79]
Rat	AD	type II collagen	[21, 26, 29]
Cow	AD	type II collagen	[80]
Primate	TMJ	type II collagen	[17, 68]
Mouse	Synovium	type VI collagen	[30]
Cow	AD	type IX collagen	[80]
Cow	AD	type XII collagen	[80]
Human	TMJ	VEGF	[82, 83]
Pig	Fibrocartilage	versican	[66]

Table 1. ECM molecules identified in TMJ tissues and fluids.

Species	Specimen	Biochemicals	Ref.
Human	Synovial fluid	CGRP	[42, 43, 60, 84]
Human	AD	CGRP	[47]
Rat	TMJ	CGRP	[38, 48, 51, 85-89]
Sheep	TMJ	CGRP	[90, 91]
Human	Synovial fluid	neurokinin A	[42, 60]
Rat	Synovial fluid	neurokinin A	[45]
Human	Synovial fluid	NPY	[42, 60]
Human	AD	NPY	[47]
Rat	Synovium	NPY	[38, 45, 51, 92]
Sheep	TMJ	NPY	[90]
Human	Synovial fluid	substance P	[42, 60]
Human	AD	substance P	[47]
Human	Retrodiscal	substance P	[46]
Rat	TMJ	substance P	[38, 48, 51, 92, 93]
Sheep	TMJ	substance P	[90]
Human	AD	VIP	[47]
Human	Synovial fluid	VIP	[60]
Rat	Synovium	VIP	[38]

Table 2. Neuropeptides identified in TMJ fluids and tissues.

Individuals afflicted with this rare genetic disorder are of short stature with gross deformities involving all joints of the appendicular skeleton. However, the temporomandibular joints appear to develop normally in these unfortunate individuals[37]. In addition, some clinical anomalies, such as idiopathic condylar hyperplasia, are only known to affect the temporomandibular joint. These observations suggest that genetic regulation of the development of the temporomandibular joint is distinct from that of synovial joints of the appendicular skeleton[37].

The temporomandibular joint is the only load-bearing joint that is innervated by a cranial nerve (i.e., the trigeminal nerve). Using retrograde labeling methods, some investigators have provided evidence that the TMJ also receives significant innervation from neurons located in C2-C5 DRG, as well as from the superior cervical, stellate, sphenopalatine, and otic ganglia[38-41]. Neuropeptides, including substance P, calcitonin gene-related peptide (CGRP), neuropeptide Y (NPY), and vasoactive intestinal polypeptide (VIP) have been identified in TMJ synovial tissues and synovial fluid obtained from symptomatic patients[38,42-51] (see Table 2). Some of these neuropeptides produce inflammatory effects when released into peripheral tissues from stimulated nerve terminals (i.e., neurogenic inflammation). Neurogenic mechanisms have been proposed in some models of degenerative temporomandibular joint disease[18].

The temporomandibular joint possesses a remarkable remodeling capacity that may be required for adaptation to mandibular growth and changes in dentition[52]. Dramatic examples of this capacity consisting of extensive remodeling of joint structures following subcondylar fractures of the mandible in children and young adults have been observed clinically. The molecular events that underlie temporomandibular joint remodeling and adaptation are poorly understood.

Mechanisms of disease

Studies of potential mechanisms of degenerative temporomandibular joint disorders have been hampered by the lack of well-characterized, suitable animal models. Human studies have been enhanced with the clinical introduction of minimally invasive techniques that permit acquisition of biological fluids and tissues from normal and diseased temporomandibular joints. Several molecular species have been identified in these human specimens, including matrix degradation products[53,54], matrix metalloproteinases[55,56], cytokines[57-59], and neuropeptides[43,44,60] (see Tables 2,3,4). In general, contemporary models of degenerative TMJ disease(s) stress the importance of mechanical loading and subsequent activation of molecular cascades leading to excessive catabolism of articular tissues, ultimately culminating in a dysfunctional (i.e., disease) state[18,61].

There is evidence from animal studies that some degenerative conditions may result from a genetic predisposition. For exam-

Species	Specimen	Biochemicals	Ref
Rat	Synovium	cathepsin B	[94]
Rat	Synovium	cathepsin D	[94]
Rat	Synovium	cathepsin L	[95]
Rabbit	AD	MMP-1	[11, 20, 78]
Rabbit	AD	MMP-2	[20, 78]
Rat	Synovium	MMP-2	[96]
Human	Fibrocartilage	MMP-2	[97]
Human	Synovial fluid	MMP-2	[56]
Human	AD	MMP-2	[98]
Rat	Synovium	MMP-3	[96]
Rabbit	AD	MMP-3	[11, 20, 78]
Human	Synovial fluid	MMP-3	[55]
Human	Synovial fluid	MMP-9	[56]
Rabbit	AD	MMP-9	[20, 78]
Rat	Synovium	MMP-9	[96]
Rat	AD, fibrocartilage	MMP-9	[99]

Table 3. Proteases identified in TMJ tissues and fluids

Species	Specimen	Biochemicals	Ref
Human	Synovium	COX-1	[100]
Human	Synovium	COX-2	[101]
Human	Synovial fluid	PGE2	[102]
Human	Synovial fluid	LTB4	[102]
Rat	AD, fibrocartilage	IL-1	[99, 103]
Human	Synovial fluid	IL-1B	[57]
Human	Synovium	IL-1B	[58]
Rabbit	Synovium	IL-1B, IL-1ra	[104]
Human	Synovium	IL-6	[59, 83]
Human	Synovial fluid	IL-6	[57]
Human	Synovium	IL-8	[105]
Human	Synovium	iNOS	[106, 107]
Rat	Synovium	iNOS	[108]
Rats	Synovial fluid	ROS	[109]

Table 4. Inflammatory molecules identified in TMJ fluids and tissues.

ple, heterozygous offspring of the Del1 mouse exhibit severe structural defects in the TMJ that are similar to those observed in progressive degenerative joint disease[62]. These mice harbor multiple copies of a deletion mutation affecting the Col2a1 gene. However, a recent study of 494 monozygotic or dizygotic twins failed to demonstrate that genetic factors significantly influence TMJ pain, joint noises, jaw clenching or bruxism[63].

Summary

Painful TMJ disorders are common. They affect predominantly young women and can produce significant physical derangement of the jaw. The mechanisms that underlie these degenerative joint diseases are poorly understood at

the present time. Future studies are needed to delineate basic mechanisms of disease and identify risk factors that contribute to TMJ disease susceptibility.

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