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PROLOTHERAPY

IN

TEMPOROMANDIBULAR DISORDERS

PROLOTHERAPY IN TEMPOROMANDIBULAR DISORDERS

REGENERATIVE INJECTION THERAPY FOR
PAIN, DYSFUNCTION AND STRUCTURAL HEALING



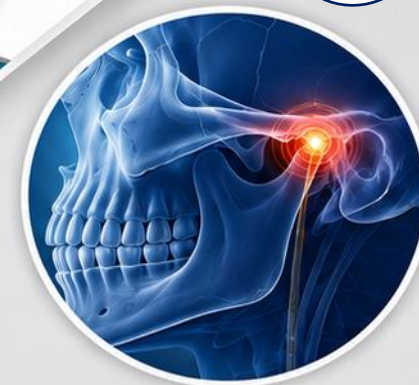
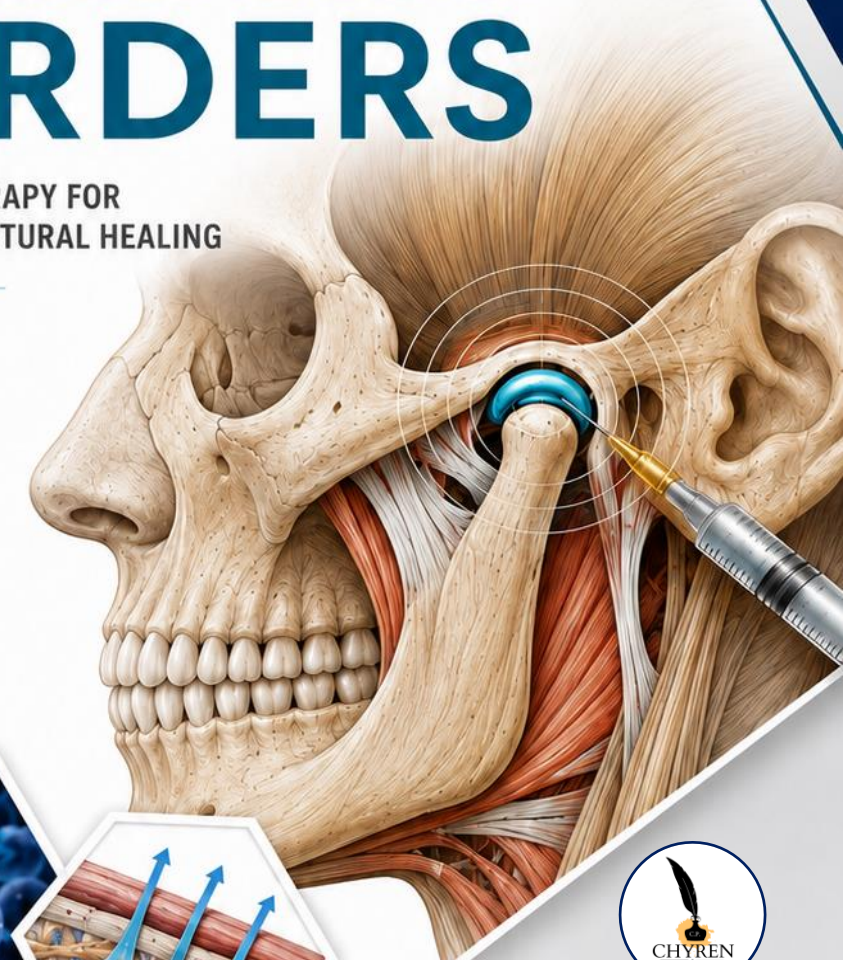
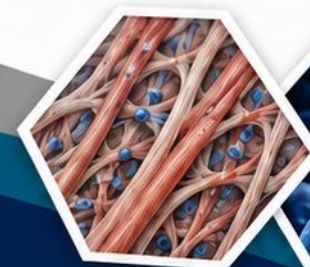
STIMULATES
NATURAL HEALING



STRENGTHENS
LIGAMENTS



RESTORES JOINT
FUNCTION



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PREFACE

Temporomandibular disorders (TMDs) constitute one of the most common and clinically challenging conditions encountered in maxillofacial practice, affecting a substantial proportion of the population and manifesting as orofacial pain, joint sounds, and restricted mandibular movement. Despite decades of clinical experience and an expanding body of literature, the management of TMDs remains largely empirical and symptom-directed. Conventional therapeutic modalities, including pharmacological agents, physiotherapy, occlusal splints, and, in refractory cases, surgical intervention, offer variable and often temporary relief, addressing the manifestations of joint dysfunction without necessarily restoring the structural integrity of the compromised articular and periarticular tissues.

It is against this backdrop of therapeutic uncertainty that prolotherapy has emerged as a promising, minimally invasive, regenerative alternative. By inducing a controlled local inflammatory response through the injection of an irritant solution, most commonly hypertonic dextrose, into lax or degenerated connective tissue, prolotherapy is proposed to stimulate collagen synthesis, strengthen ligamentous support, and restore biomechanical stability to the temporomandibular joint. Its disease-modifying potential, favourable safety profile, and cost-effectiveness distinguish it from purely palliative interventions and have generated growing clinical and academic interest in recent years.

This book - 'PROLOTHERAPY IN TEMPOROMANDIBULAR DISORDERS' compiles and critically appraises the existing body of knowledge on prolotherapy in the management of temporomandibular disorders. The text begins by revisiting the anatomy, functional biomechanics, and pathophysiology of the temporomandibular joint, followed by a review of the epidemiology and conventional management approaches for TMDs. Subsequent chapters examine the scientific rationale, technique, and clinical application of prolotherapy, its documented advantages and limitations, and the future directions this therapy may take as research in the field continues to evolve.

It is hoped that this compilation will serve as a comprehensive, evidence-oriented reference for postgraduate students, clinicians, and researchers seeking to understand the evolving role of regenerative injection therapy in the contemporary management of temporomandibular disorders.

ACKNOWLEDGEMENT

The completion of this book stands as a testament to the guidance, encouragement, and goodwill of many individuals, to whom I owe a profound debt of gratitude.

I am deeply indebted to my guide, Dr. M. Srinivasa Raju, Professor and Head of the Department, Department of Oral Medicine and Radiology, St. Joseph Dental College & Hospital, Eluru, for his exemplary guidance, unfailing support, and sharp professional insight. His invaluable assistance, coupled with his constructive criticism, shaped this work at every stage of its preparation.

I wish to express my heartfelt appreciation to my esteemed teachers, Dr. Mrudula Raju. B, Professor and Dr. M. Swathi, Reader, Department of Oral Medicine and Radiology, St. Joseph Dental College, Eluru, whose wisdom, patience, and generous mentorship have left an indelible mark on my academic journey. Their astute insights and unwavering encouragement have been instrumental in bringing this book to fruition.

I am equally grateful to my batchmate and seniors, whose camaraderie, wisdom, and moral support enriched this endeavour and made the journey a truly memorable one.

My sincere thanks to our Principal and Management, for graciously granting permission to utilize the outstanding facilities of St. Joseph Dental College & Hospital, Eluru, without which this work would not have been possible.

Above all, I owe an immeasurable debt of gratitude to my parents, sibling and friends, whose boundless love, patience, and unwavering faith in me have been the true foundation of this achievement. It is to them that I dedicate this work, with heartfelt reverence and love.

This book is based on the dissertation submitted to Dr. NTR University of Health Sciences (Dr. NTRUHS) in partial fulfilment of the requirements for the degree of Master of Dental Surgery (MDS) in Oral Medicine and Radiology.

With regards,

Dr. G. Vyshnavi Durga

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ABBREVIATIONS

Abbreviation	Full Form
AAOP	American Academy of Orofacial Pain
ADAMTS	A Disintegrin and Metalloproteinase with Thrombospondin Motifs
BTX-A	Botulinum Toxin Type A
CBCT	Cone Beam Computed Tomography
CGRP	Calcitonin Gene-Related Peptide
CGF	Concentrated Growth Factor
COX	Cyclooxygenase
COPC	Chronic Overlapping Pain Conditions
DAMP	Damage-Associated Molecular Pattern
DC/TMD	Diagnostic Criteria for Temporomandibular Disorders
DDwR	Disc Displacement with Reduction
DDwoR	Disc Displacement without Reduction
DJD	Degenerative Joint Disease
ECM	Extracellular Matrix
EGF	Epidermal Growth Factor
FGF	Fibroblast Growth Factor
GH	Growth Hormone
HA	Hyaluronic Acid
HMGB1	High-Mobility Group Box 1 Protein

HRQoL	Health-Related Quality of Life
IGF-1	Insulin-like Growth Factor-1
IL	Interleukin
JFLS	Jaw Functional Limitation Scale
L-PRF	Leukocyte and Platelet-Rich Fibrin
L-PRP	Leukocyte-Rich Platelet-Rich Plasma
LP-PRP	Leukocyte-Poor Platelet-Rich Plasma
LT	Low-Level Laser Therapy
MMP	Matrix Metalloproteinase
MMO	Maximum Mouth Opening
MRI	Magnetic Resonance Imaging
MSC	Mesenchymal Stem Cell
NF-κB	Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells
NRS	Numerical Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OA	Osteoarthritis
OHRQoL	Oral Health-Related Quality of Life
OHIP	Oral Health Impact Profile
OPPERA	Orofacial Pain: Prospective Evaluation and Risk Assessment
P2G / PGG	Phenol-Glycerine-Glucose Solution
PDGF	Platelet-Derived Growth Factor
PMID	PubMed Identifier

PRF	Platelet-Rich Fibrin
PRP	Platelet-Rich Plasma
RCT	Randomized Controlled Trial
RDC/TMD	Research Diagnostic Criteria for Temporomandibular Disorders
SVF	Stromal Vascular Fraction
TENS	Transcutaneous Electrical Nerve Stimulation
TGF-β	Transforming Growth Factor Beta
TML	Temporomandibular Ligament
TMD	Temporomandibular Disorder
TMDs	Temporomandibular Disorders
TMJ	Temporomandibular Joint
TNF-α	Tumor Necrosis Factor Alpha
TRPV1	Transient Receptor Potential Vanilloid 1
VAS	Visual Analogue Scale
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization

SECTION 1
INTRODUCTION

Pain arising from the orofacial region constitutes one of the most diagnostically complex and therapeutically challenging categories of chronic musculoskeletal pain encountered in dental and medical practice. Among the diverse conditions responsible for orofacial pain, temporomandibular disorders (TMDs) occupy a position of particular clinical significance, accounting for the majority of non-odontogenic orofacial pain presentations and representing a major source of disability, functional impairment, and healthcare utilization worldwide.^{[1][2]}

Temporomandibular disorders are broadly defined as a cluster of related disorders involving the temporomandibular joint, the masticatory musculature, and the associated hard and soft tissue structures of the craniofacial region. They are characterized by a cardinal symptom triad of -

- (1) orofacial pain localized to the preauricular area and masticatory muscles,
- (2) joint sounds including clicking, popping, and crepitus, and
- (3) mandibular movement disorders including limited opening, deviation, and deflection. The clinical spectrum of TMDs extends from mild, self-limiting acute conditions to severe, debilitating chronic pain syndromes with profound biopsychosocial consequences.^[3]

The epidemiological burden of TMDs is substantial. An estimated 5–12% of the general population worldwide experiences TMD symptoms significant enough to warrant clinical attention, with subclinical signs detectable in an even larger proportion of the population.^{[1][2]}

Despite the high prevalence of TMDs and the significant suffering they impose, the management of these conditions remains largely empirical, heterogeneous, and insufficiently evidence-based. Conventional therapeutic approaches—including pharmacological interventions such as NSAIDs, muscle relaxants, and tricyclic antidepressants; physical modalities including physiotherapy, occlusal splint therapy, and electrophysical treatments; and, in refractory cases, surgical interventions including arthrocentesis, arthroscopy, and open joint surgery—address TMD symptoms through diverse but often palliative mechanisms that do not fundamentally restore the structural integrity of the compromised articular and periarticular connective tissues.^[4]

Prolotherapy—derived from the Latin 'proles' (offspring, growth) combined with 'therapy' (treatment)—represents a distinct approach to chronic

musculoskeletal pain management that harnesses the body's intrinsic healing mechanisms through the deliberate induction of a controlled local inflammatory response. By injecting an irritant solution (most commonly hypertonic dextrose) into degenerated, lax, or injured connective tissues, prolotherapy initiates a regenerative cascade that culminates in the synthesis of new collagen fibres, restoration of tissue architecture, and recovery of biomechanical function. This regenerative rationale distinguishes prolotherapy fundamentally from conventional symptomatic treatments and positions it as a potentially disease-modifying intervention for appropriate TMD subtypes.^{[5][6]}

Definition of temporomandibular disorder:

The term 'temporomandibular disorder' was formally introduced by Bell in 1982 to supplant the diverse and often confusing nomenclature that had previously been applied to these conditions, including Costen syndrome (named after the otolaryngologist James Costen who first described the clinical entity in 1934), myofascial pain dysfunction syndrome, craniomandibular disorders, and cervicofacial pain dysfunction.^{[7][8]}

In contemporary usage, TMDs are defined as a collective term embracing a number of related disorders of the masticatory system sharing certain common symptoms but involving distinct pathophysiological mechanisms, anatomical substrates, and clinical presentations. The American Academy of Orofacial Pain (AAOP) defines TMDs as 'a collective term embracing a number of clinical problems that involve the masticatory muscles, the temporomandibular joint (TMJ) and associated structures, or both.'^[9]

The Diagnostic Criteria for Temporomandibular Disorders (DC/TMD), published in 2014 by Schiffman et al. through the International RDC/TMD Consortium Network, provides the current gold standard classification framework.

The DC/TMD employs a dual-axis diagnostic approach:

- (1) Axis I addresses physical diagnoses, categorizing TMDs into pain disorders (myalgia, headache attributed to TMD) and intra-articular disorders (disc displacement disorders, degenerative joint disease, subluxation);
- (2) Axis II evaluates pain-related disability and psychological status through validated instruments including the Patient Health Questionnaire (PHQ-4), the Graded Chronic Pain Scale (GCPS), and the Jaw Functional Limitation Scale (JFLS).^[10]

From a pathophysiological standpoint, TMDs arise from a complex interplay of predisposing (biomechanical, genetic, hormonal, psychological), precipitating (microtrauma, macrotrauma, acute overloading), and perpetuating (parafunctional habits, maladaptive pain behaviours, central sensitization) factors that converge to disrupt the homeostatic balance of the masticatory system. The multifactorial nature of TMD aetiology necessitates a comprehensive, biopsychosocial approach to both diagnosis and management.^{[11][12]}

SECTION II
ANATOMY OF
TEMPOROMANDIBULAR
JOINT

A thorough comprehension of the normal anatomy, functional biomechanics, and physiological mechanisms of the temporomandibular joint is indispensable for understanding the pathophysiology of TMDs and the rationale for prolotherapy-based regenerative interventions. The TMJ is among the most anatomically complex and biomechanically sophisticated joints in the human body, characterized by a unique combination of rotational and translational movement, a fibrocartilaginous articular surface, and the presence of an interposed articular disc that transforms a potentially incongruent articulation into a dynamically congruent one.^{[13][14]}

Osseous architecture:

Mandibular condyle:

The mandibular condyle is an ovoid bony projection arising from the superior extremity of the mandibular ramus. Its long axis is oriented mediolaterally, with a mean mediolateral dimension of 15–20 mm and an anteroposterior diameter of 8–10 mm. The condylar head presents a convex articular surface in both sagittal and coronal planes—a geometry specifically adapted to facilitate the complex translational and rotational kinematics of mandibular movement. Considerable individual variation exists in condylar morphology: the condyle may be ovoid (most common), convex, angled, rounded, or flat, with implications for the distribution of intra-articular loading forces.^[15]

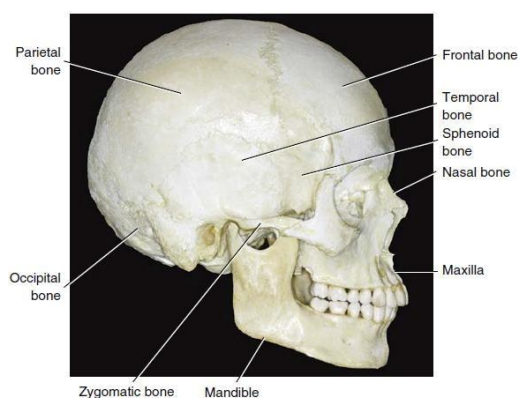


Figure 1: The lateral view of the cranium and the mandible.^[3]

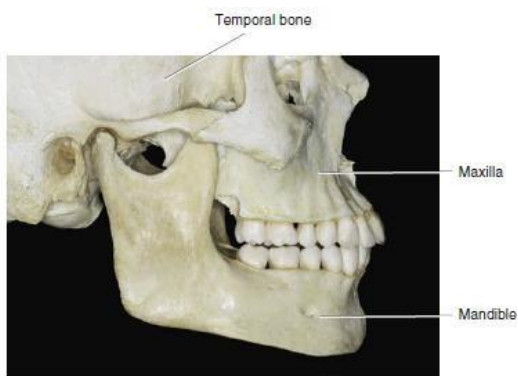


Figure 2: Skeletal components that make up the masticatory system-maxilla, mandible and temporal bone.^[3]



Figure 3: The Condyle (anterior view)
The medial pole (MP) is prominent than lateral pole (LP).^[3]

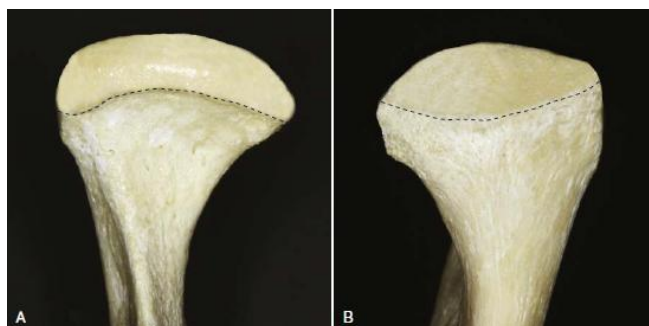


Figure 4: The Condyle A) Anterior and B) Posterior view. A dotted line marks the border of the articular disc surface. The articular surface of the posterior aspect of the condyle is greater than on the anterior aspect.^[3]

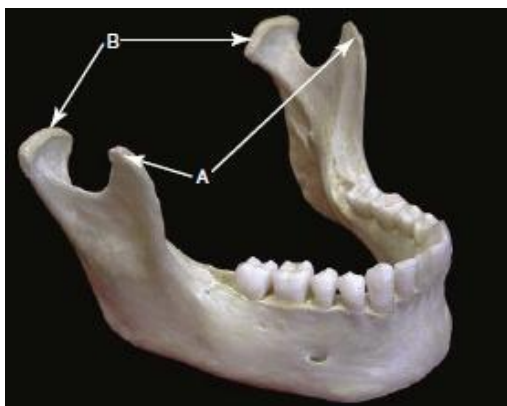


Figure 5: The ascending ramus extends upward to form the coronoid process (A) and the condyle (B).^[3]

The articular surface of the condyle is covered by a dense layer of fibrocartilage—predominantly type I collagen with smaller contributions from type II collagen—rather than the hyaline cartilage that lines most synovial joint surfaces. This fibrocartilaginous articular layer, ranging from 0.4 to 0.6 mm in thickness, is organized into four histological zones from superficial to deep:

- (1) the articular zone (dense fibrous tissue),
- (2) the proliferative zone (undifferentiated mesenchymal cells),
- (3) the fibrocartilaginous zone (chondrocyte-like cells embedded in a collagenous matrix),
- (4) the calcified cartilage zone (transitioning to the subchondral bone plate). The fibrocartilaginous nature of the TMJ articular surface confers superior adaptive and regenerative capabilities compared to hyaline cartilage.^[16]

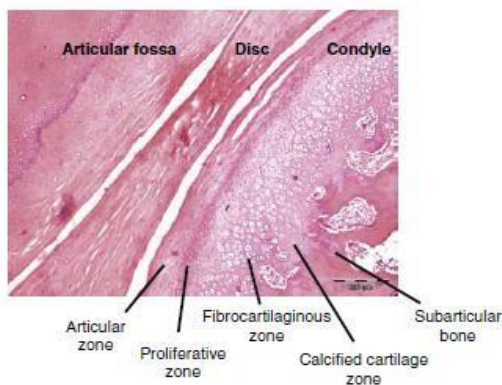


Figure 6: A histological section of a healthy mandibular condyle showing 4 zones: articular zone, proliferative zone, fibrocartilaginous zone and the calcified zone.^[3]

The condylar neck, a narrowed cylindrical region connecting the condylar head to the mandibular ramus, is the site of mandibular condylar fractures, which are among the most frequent mandibular fracture patterns. The pterygoid fovea, a small depression on the anteromedial aspect of the condylar neck, serves as the principal insertion site for the inferior head of the lateral pterygoid muscle.^[17]

Temporal articular surface:

The temporal component of the TMJ articulation is formed by the squamous part of the temporal bone and comprises two anatomically distinct but functionally integrated regions: the mandibular (glenoid) fossa and the articular eminence (articular tubercle). The mandibular fossa is a concave depression of variable depth located posterior to the articular eminence and anterior to the external acoustic meatus. In the closed mouth position, the condyle is seated in the posterior part of the fossa, with the articular disc interposed between the condylar head and the fossa roof.^[18]

The articular eminence is a convex, transversely oriented ridge of compact cortical bone located at the anterior margin of the mandibular fossa, forming the posterior root of the zygomatic arch. It constitutes the primary functional load-bearing surface of the temporal component during dynamic jaw movements, particularly during mastication and wide mouth opening when the condyle-disc complex translates forward and articulates against its posterior slope. The inclination of the articular eminence—ranging from approximately 30° to 60° to the Frankfort horizontal plane—is an important determinant of condylar movement patterns and articular loading characteristics.^[19]

The articular surface of the temporal bone is lined by a thin layer of fibrocartilage comparable to that covering the condyle. The roof of the mandibular fossa, however, is remarkably thin (as little as 0.5 mm in some regions), explaining the potential for condylar impaction into the middle cranial fossa following severe mandibular trauma.^[20]

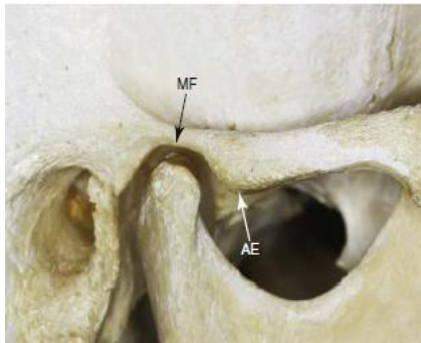


Figure 7: Bony structures of temporomandibular joint (lateral view)
MF-mandibular fossa
AE-articular eminence.^[3]

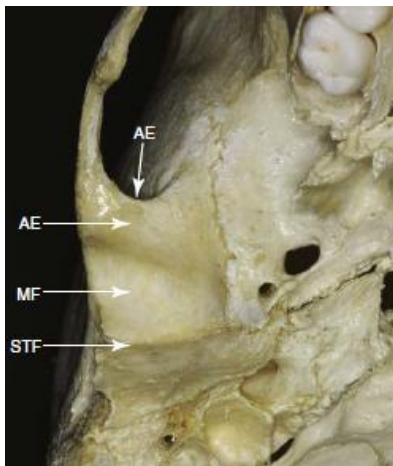


Figure 8: Articular fossa (inferior view)
AE-articular eminence
MF-mandibular fossa
STF-squamotympanic fissure.^[3]



Figure 9: An inferior view of surface of the cranium and mandible. The condyles seems to be slightly rotated so that if an imaginary line were drawn through the lateral and medial poles it would extend medially and posteriorly toward the anterior border of the foramen magnum.^[3]

Articular disc:

The articular disc (intra-articular meniscus) is a biconcave, elliptical fibrocartilaginous structure interposed between the mandibular condyle and the temporal articular surface. Its biconcave geometry is specifically adapted to accommodate the convex geometries of both articular surfaces, converting an otherwise incongruent ball-and-socket articulation into a functionally congruent

one across the full range of mandibular movement. The disc is conventionally divided into three anteroposterior zones:

- (1) the anterior band (approximately 2 mm thick),
- (2) the intermediate zone (thinnest region, 1–2 mm thick, located between the condylar head and the articular eminence in the intercuspals position), and
- (3) the posterior band (thickest region, approximately 3 mm thick).^[21]

the disc divides the TMJ cavity into two distinct compartments:

- (1) the superior (temporodiscal) compartment between the temporal articular surface and the superior disc surface, and
- (2) the inferior (condylodiscal) compartment between the condylar head and the inferior disc surface. These compartments are functionally distinct: translation of the condyle-disc complex occurs primarily in the superior compartment, while rotation of the condyle beneath the disc occurs in the inferior compartment.^[22]

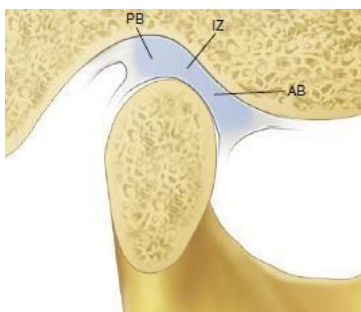


Figure 10: Articular disc, fossa and condyle (lateral view). The condyle is normally situated on the thinner intermediate zone (IZ) of the disc. The anterior border of the disc (AB) is considerably thicker than the intermediate zone, and the posterior

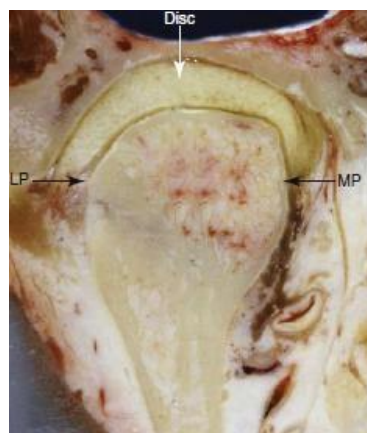
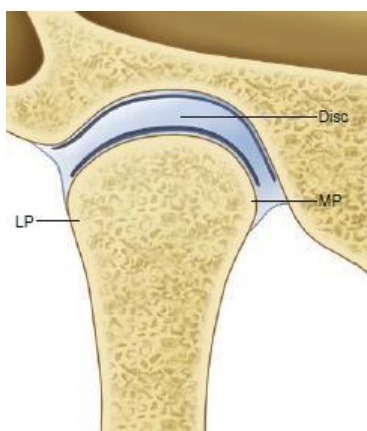


Figure 11: Articular disc, fossa and condyle (anterior view).^[3]

Histologically, the articular disc is composed of densely interwoven collagen fibres—predominantly type I collagen (approximately 70–80% dry weight)—embedded in a ground substance of proteoglycans, glycosaminoglycans, and water. The collagen fibres in the central load-bearing zone are oriented perpendicular to the articular surface to resist compressive forces, while peripheral fibres are arranged obliquely or parallel to the disc margin to resist tensile and shear forces. Elastin fibres, though present in small quantities, contribute to the viscoelastic properties of the disc.^[23]

A small number of chondrocyte-like cells are present within the disc matrix, particularly in the posterior and anterior bands. These cells are responsible for synthesizing and maintaining the disc ECM and are sensitive to mechanical stimuli transmitted through the collagen fibre network. Cyclic mechanical loading within physiological ranges promotes anabolic disc cell activity, while excessive static or impact loading triggers catabolic responses including upregulation of matrix metalloproteinases and inflammatory cytokines.^[24]

Disc attachments:

The articular disc has well-defined peripheral attachments that govern its position and movement relative to the condyle and temporal bone. Anteriorly, the disc is attached to the joint capsule and to a tendinous extension of the superior head of the lateral pterygoid muscle—the so-called discal tendon—which exerts an anteromedial traction force on the disc during jaw opening. Medially and laterally, the disc is attached to the condylar poles through the medial and lateral discal (collateral) ligaments, which tether the disc to the condyle and restrict mediolateral disc displacement relative to the condyle. These discal ligaments, when elongated or torn, predispose to disc displacement—the most common form of articular TMD.^[21]

Posteriorly, the disc merges with the bilaminar zone (posterior attachment or retrodiscal tissue), a loose, highly vascularized and richly innervated connective tissue structure that fills the space between the posterior disc margin and the posterior wall of the mandibular fossa. The bilaminar zone consists of a superior elastic stratum (attaching to the tympanic plate) and an inferior collagenous stratum (attaching to the condylar neck), separated by a venous plexus. The elastic recoil of the superior stratum provides a posterior traction force on the disc that counterbalances the anterior pull of the lateral pterygoid during translational movement, contributing to disc-condyle co-

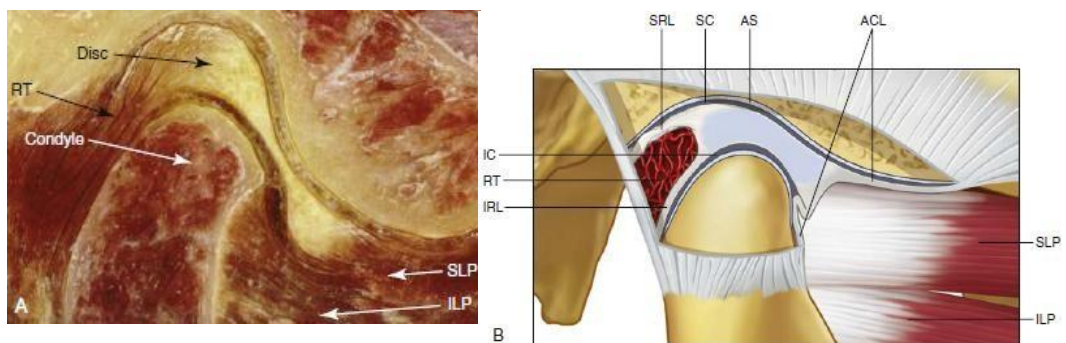


Figure 12: Temporomandibular joint. A) lateral view and B) diagram showing anatomic components

ACL-Anterior capsular ligament

RT- retrodiscal tissues

SC and IC- superior and inferior joint cavity

SLP and ILP- superior and inferior lateral pterygoid muscles

SRL- superior retrodiscal lamina (elastic).^[3]

ordination.^[20]

Capsular and ligamentous structures:

Joint capsule:

The TMJ capsule is a fibrous connective tissue sleeve that completely envelops the joint, attaching superiorly to the margins of the articular fossa and eminence (above the fibrocartilaginous articular surface) and inferiorly to the condylar neck, just below the articular fibrocartilage. The capsule consists of an outer fibrous layer and an inner synovial layer. The synovial membrane, composed of a thin layer of specialized synoviocytes (type A macrophage-like cells and type B fibroblast-like cells), lines the superior and inferior joint compartments of the retrodiscal tissue—but NOT the central articular surfaces, which are avascular and aneural in health.^[25]

The synoviocytes produce synovial fluid—an ultrafiltrate of blood plasma enriched with hyaluronic acid (hyaluronan), lubricin (proteoglycan-4), and various growth factors including IGF-1, TGF- β , and PDGF. Synovial fluid serves the critical functions of joint lubrication (reducing articular surface friction to nearly zero under physiological loading conditions) and articular nutrition (providing oxygen and metabolic substrates to the avascular articular fibrocartilage through diffusion). Disruption of synovial fluid homeostasis—as

occurs in TMJ inflammatory arthropathies—impairs both lubrication and articular nutrition, contributing to progressive fibrocartilage degeneration.^[25]



Figure 13: Capsular ligament (lateral view). Note that it extends anterior include the articular eminence and encompass the entire articular surface of the joint.^[3]

Temporomandibular ligament:

The temporomandibular ligament (TML), also designated the lateral capsular ligament or lateral temporomandibular ligament, is the primary intrinsic ligament of the TMJ and the principal passive restraint against abnormal condylar displacement. It is composed of two functionally distinct portions:

- (1) the oblique outer portion, arising from the lateral surface of the articular tubercle and inserting obliquely downward and backward into the condylar neck and posterior condylar surface; and
- (2) the horizontal inner portion, arising from the lateral surface of the articular tubercle and inserting horizontally into the posterolateral aspect of the condylar head and disc.^[26]

The oblique outer portion functions to limit the extent of condylar rotation and prevent excessive inferior displacement of the condyle. It determines the hinge arc through which the mandible opens without translation (approximately the first 20–25 mm of interincisal opening). The horizontal inner portion limits posterior displacement of the condyle and disc, protecting the retrodiscal tissue from compression during mandibular retraction movements. Elongation or mechanical failure of the TML, whether through acute macrotrauma or chronic microtrauma from parafunction, compromises these protective functions and predisposes to articular hypermobility, retrodiscal impingement, and chronic TMD pain.^[17]

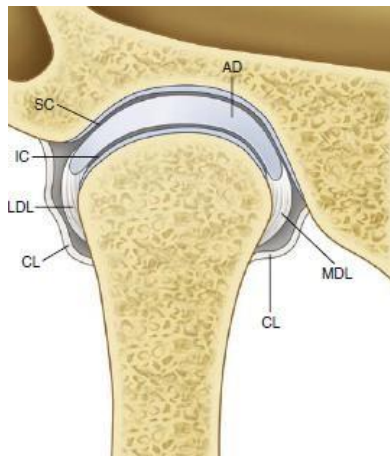


Figure 14: Temporomandibular joint (Anterior view).

AD-Articular Disc

CL-Capsular Ligament

IC-Inferior joint Cavity

LDL-Lateral Discal Ligament

MDL- Medial Discal Ligament

SC- Superior joint Cavity.^[3]

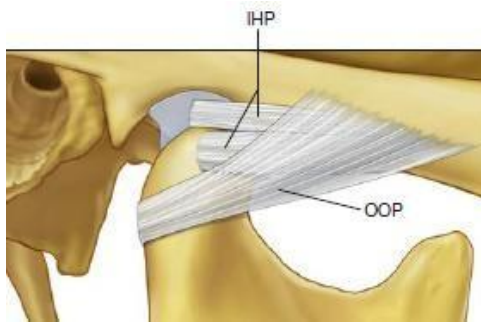


Figure 15: Temporomandibular ligament (lateral view).

OOP-Outer Oblique Portion

IHP-Inner Horizontal Portion

The OOP limits posterior movement of the condyle and disc.^[3]

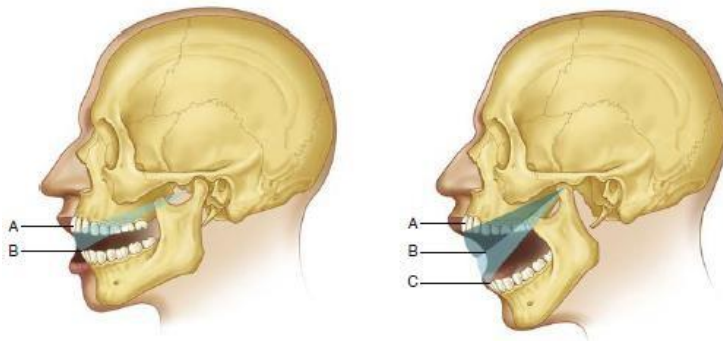


Figure 16: Effect of the Outer Oblique Portion of the Temporomandibular ligament. As the mouth opens, the teeth can be separated about 20-25 mm (from A to B) without condyles moving from the fossae. At B the TM ligaments are fully extended. As the mouth opens wider, they force the condyles to move downward and forward out of the fossae. This creates a second arc of opening (from B to C).^[3]

Accessory ligaments:

The sphenomandibular ligament arises from the angular spine of the sphenoid bone and the adjacent petrotympanic fissure and descends to insert into the lingula of the mandibular foramen on the medial surface of the ramus. It plays a role in guiding mandibular rotation during wide mouth opening and may contribute to the force distribution during mandibular movements. The stylomandibular ligament, a thickening of the deep cervical fascia, runs from the tip and anterior border of the styloid process to the posterior border and angle of the mandible, serving as a posterior restraint to excessive mandibular protrusion.^[17]

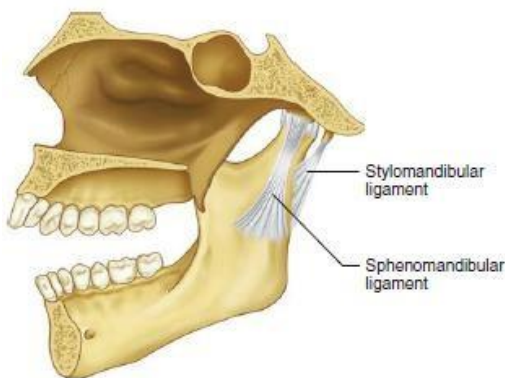


Figure 17: The mandible, temporomandibular joint and accessory ligaments.^[3]

Masticatory musculature:

Masseter:

The masseter is a powerful quadrilateral masticatory muscle located on the lateral aspect of the mandibular ramus and body. It arises from the lower border and medial surface of the zygomatic arch and inserts into the lower half of the lateral surface of the ramus and angle of the mandible. The masseter consists of a superficial portion with obliquely oriented fibres primarily responsible for jaw elevation and minor protrusion, and a deep portion with more vertically oriented fibres contributing to jaw elevation and mandibular retraction.^[27]

The masseter is the most accessible masticatory muscle for palpation and is the primary site of myofascial trigger points in myofascial pain dysfunction syndrome. Its morphology can be evaluated with high-resolution ultrasound, providing non-invasive assessment of muscle thickness, echogenicity, and the presence of trigger point lesions. Masseter hypertrophy, a consequence of chronic

bruxism, contributes to increased TMJ loading and is an important clinical indicator of parafunctional mandibular activity.^[28]

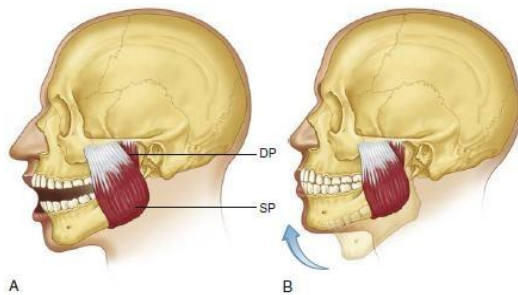


Figure 18: A) Masseter muscle DP-deep portion SP-superficial portion B) Function- elevation of mandible.^[3]

Temporalis:

The temporalis muscle is a large, fan-shaped muscle originating from the entire temporal fossa, bounded by the temporal lines on the parietal and frontal bones. Its fibres converge into a thick tendon that passes deep to the zygomatic arch to insert into the coronoid process and the anterior border of the mandibular ramus, extending as far down as the retromolar fossa. The anterior fibres, directed vertically, produce powerful mandibular elevation; the posterior fibres, directed nearly horizontally, produce mandibular retraction. The temporalis is a primary postural muscle of the mandible, maintaining intercuspal position and generating significant forces during habitual masticatory function.^[29]

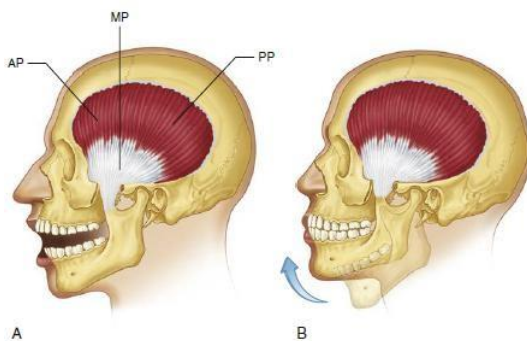


Figure 19: A) Temporal muscle AP-anterior portion MP-middle portion PP-posterior portion B) Function- elevation of mandible The exact movement by the location of the fibers or portion being

Lateral pterygoid:

The lateral pterygoid muscle, the most functionally critical muscle of mandibular movement from a TMJ mechanics perspective, consists of two distinct heads with different functional roles and potentially different pathological involvements in TMDs. The superior (sphenoidal) head arises from

the infratemporal surface of the greater wing of the sphenoid bone and inserts predominantly into the articular disc (approximately 70%) and the condylar neck (30%). The inferior (pterygoid) head arises from the lateral surface of the lateral pterygoid plate and inserts entirely into the pterygoid fovea of the condylar neck.^[30]

The inferior head of the lateral pterygoid contracts during jaw opening and protrusion, pulling the condyle-disc complex forward and downward along the articular eminence. The superior head, contrary to earlier concepts, contracts primarily during jaw closing and bruxist activities (co-contraction with the elevator muscles) to control disc positioning and resist posterior condylar displacement. Dysfunction of the superior lateral pterygoid—whether from chronic hyperactivity, muscle splinting, or altered proprioceptive feedback—has been implicated in the pathogenesis of anterior disc displacement through its excessive anterior traction on the disc.^[31]

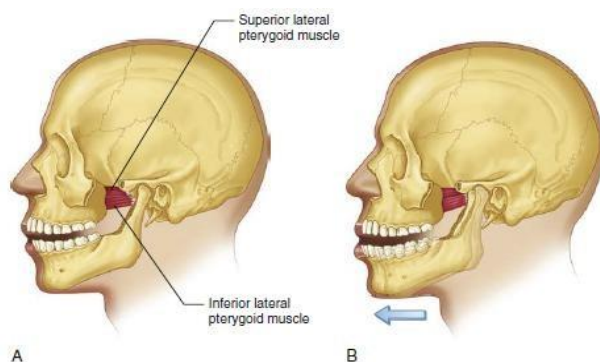


Figure 20: A) Inferior and superior lateral pterygoid muscles. B) Function of inferior lateral pterygoid—protrusion of mandible.^[3]



Figure 21: A) When the condyle is in a normal relationship in the fossa, the attachments of the superior and inferior lateral pterygoid muscles create a medial and anterior pull on the condyle and disc (arrows). B) As the condyle moves anteriorly from the fossa, the pull becomes more medially directed (arrows).^[3]

Medial pterygoid:

The medial pterygoid originates from a deep head (medial surface of the lateral pterygoid plate and pyramidal process of the palatine bone) and a superficial head (maxillary tuberosity and adjacent pyramidal process). It inserts into the medial surface of the mandibular ramus and angle. The medial pterygoid works in concert with the masseter to form a 'muscular sling' that suspends and elevates the mandible. Together with the lateral pterygoid, it mediates lateral excursion (contralateral medial pterygoid) and protrusion (bilateral medial pterygoid) movements.^[27]

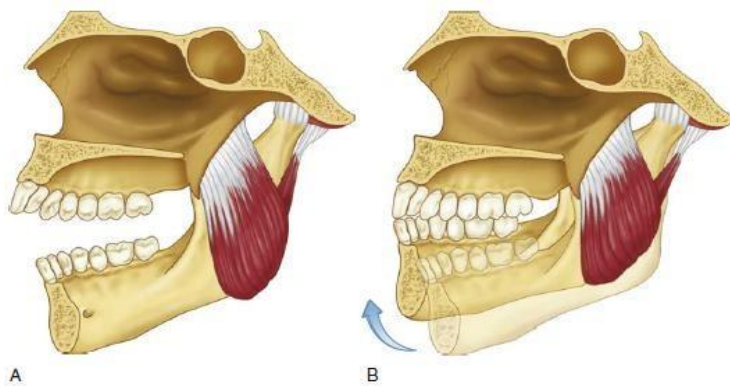


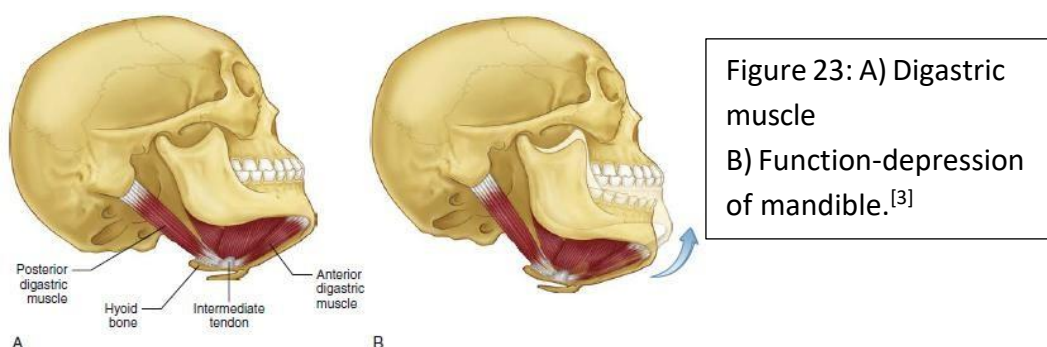
Figure 22: A) Medial pterygoid muscle
B) Function-elevation of mandible.^[3]

Digastric muscle:

Although the digastric is not generally considered a muscle of mastication, it does have an important influence on the function of the mandible. It is divided into two portions or bellies. The posterior belly originates from the mastoid notch, just medial to the mastoid process; its fibers run forward, downward, and inward to the intermediate tendon attached to the hyoid bone. The anterior belly originates at a fossa on the lingual surface of the mandible, just above the lower border and close to the midline; and its fibers extend downward and backward to insert at the same intermediate tendon as does the posterior belly. When the right and left digastrics contract and the hyoid bone is fixed by the suprahyoid and infrahyoid muscles, the mandible is depressed and pulled backward and the teeth are brought out of contact. When the mandible is stabilized the digastric muscles with the suprahyoid and infrahyoid muscles elevate the hyoid bone, which is a necessary function for swallowing.^[3]

The digastrics are one of many muscles that depress the mandible and raise the hyoid bone. Generally, muscles that are attached from the mandible to the hyoid bone are called suprahyoid and those attached from the hyoid bone to the

clavicle and sternum are called infrahyoid. The suprahyoid and infrahyoid muscles play a major role in coordinating mandibular function. So also do many of the other numerous muscles of the head and neck. It can be quickly observed that a study of mandibular function is not limited to the muscles of mastication. Other major muscles, such as the sternocleidomastoid and the posterior cervical muscles, play major roles in stabilizing the skull and enabling controlled movements of the mandible to be performed. A finely tuned dynamic balance exists among all of the head and neck muscles, and this must be appreciated for an understanding of the physiology of mandibular movement to occur. As a person yawns, the head is brought back by contraction of the posterior cervical muscles, which raises the maxillary teeth. This simple example demonstrates that even normal functioning of the masticatory system utilizes many more muscles than just those of mastication. With an understanding of this relationship, one can see that any effect on the function of the muscles of mastication also has an effect on other head and neck muscles.^[3]



Neurovascular supply:

Nerve supply:

The sensory innervation of the TMJ is provided primarily by the auriculotemporal nerve (a branch of the mandibular division of the trigeminal nerve, V3) and supplemented by branches of the masseteric nerve and the deep temporal nerves (also branches of V3). The auriculotemporal nerve provides the principal sensory innervation to the posterior and lateral aspects of the joint capsule and retrodiscal tissue, where free nerve endings serving nociceptive, thermoreceptive, and autonomic functions are concentrated.^[32]

The periarticular connective tissues—capsule, ligaments, and retrodiscal tissue—contain a rich assortment of mechanoreceptors (Ruffini endings, Pacinian corpuscles, Golgi tendon organ-like endings) and free nociceptors (type

III and IV afferents) that collectively provide afferent information about joint position, movement velocity, intra-articular pressure, and noxious stimuli to the central nervous system. This proprioceptive and nociceptive sensory network is clinically important for understanding both the pain mechanisms in TMDs and the potential neurogenic analgesic effects of prolotherapy.^[32]

Blood supply:

The TMJ receives its arterial supply from multiple branches of the external carotid artery, including the superficial temporal artery (posterior and lateral capsule), the maxillary artery and its branches including the anterior tympanic artery (retrodiscal tissue and anterior capsule), the ascending pharyngeal artery, and the masseteric and pterygoid arteries. The retrodiscal tissue contains a venous plexus capable of considerable distension that accommodates changes in joint space volume during mandibular translation, acting as a hydraulic cushion.^[33]

SECTION III

FUNCTIONAL BIOMECHANICS

OF TEMPOROMANDIBULAR

JOINT

Kinematics of jaw opening:

The unique biarthrodial character of the TMJ—its simultaneous bilateral function as paired joints coupled through the rigid mandible—means that movements at one TMJ necessarily affect the contralateral joint. Mandibular opening involves a complex combination of rotation (hinge-like movement) and translation (gliding movement) that proceeds in a predictable kinematic sequence governed by the morphology of the articular eminence, the tautness of the temporomandibular ligament, and the coordinated action of the masticatory muscles.^[34]

In the initial phase of mouth opening (approximately 0–20 mm interincisal distance), the condyle rotates around a transverse axis located approximately through the mandibular foramina, with minimal translational displacement. This rotational movement occurs in the inferior joint compartment between the condylar head and the inferior surface of the articular disc, which remains in close apposition to the condyle. As mouth opening progresses beyond approximately 20–25 mm, the elevator muscles relax sufficiently and the oblique portion of the TML becomes taut, triggering translation of the condyle-disc complex anteriorly and inferiorly along the posterior slope of the articular eminence. This translational movement occurs in the superior joint compartment. Maximum mouth opening (40–55 mm interincisally) involves the condyle positioned over the articular eminence or at its crest.^[19]

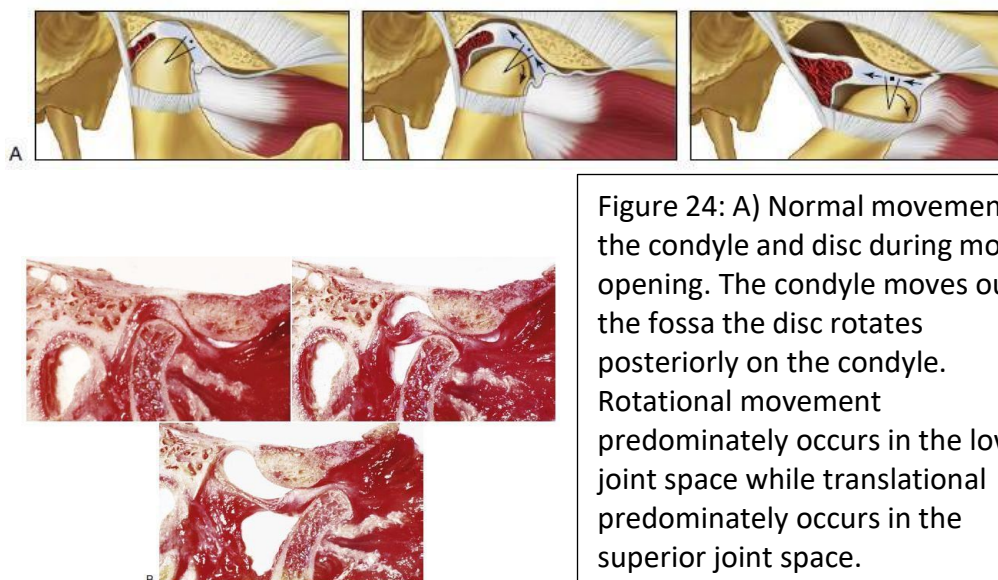


Figure 24: A) Normal movement of the condyle and disc during mouth opening. The condyle moves out of the fossa the disc rotates posteriorly on the condyle. Rotational movement predominately occurs in the lower joint space while translational predominately occurs in the superior joint space. B) The same movements are shown in the cadaver specimen.^[3]

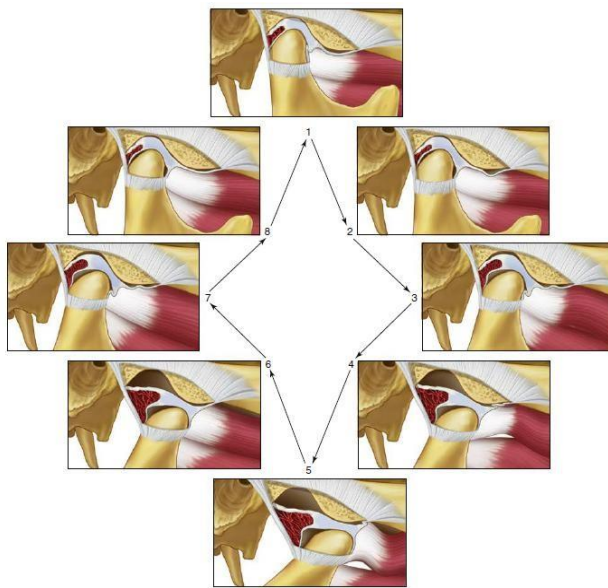


Figure 25: Normal functional movement of the condyle and disc during the full range of opening and closing. The disc is rotated posteriorly on the condyle as the condyle is translated out of the fossa. The closing movement is the exact opposite of opening. This is pressure between the articular surfaces of the joint.^[3]

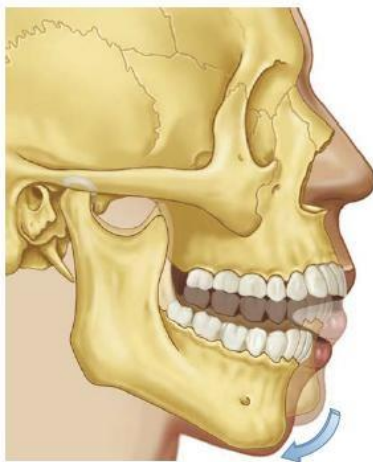


Figure 26: Rotational movement about a fixed point in the condyle.^[3]

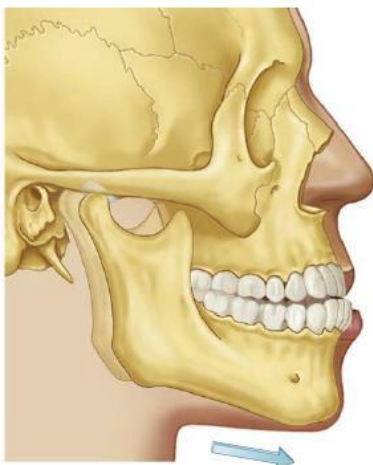


Figure 27: Translational movement of the mandible.^[3]

Joint lubrication mechanisms:

The near-frictionless lubrication of the TMJ articular surfaces is achieved through two complementary mechanisms. Boundary lubrication, the primary mechanism during slow mandibular movements, is provided by lubricin (proteoglycan-4), a glycoprotein secreted by synoviocytes that adsorbs to the articular surface and prevents direct surface-to-surface adhesion. Hydrodynamic lubrication, operative during rapid mandibular movements and high articular loading, involves the development of a pressurized fluid film between the articular surfaces that prevents contact and distributes loads across a wider area. The viscoelastic properties of hyaluronic acid in the synovial fluid are critical for maintaining the integrity of the hydrodynamic lubrication film.^[35]

Load distribution:

During mastication, significant compressive, tensile, and shear forces are transmitted across the TMJ articular surfaces. Experimental studies using pressure-sensitive films and force transducers have demonstrated that peak articular contact stresses during maximum voluntary clenching can reach 0.5–1.5 MPa on the load-bearing region of the articular eminence. The articular disc serves a critical load-distributing function, spreading these contact forces over a larger surface area (thereby reducing peak stress concentrations) and protecting the underlying articular fibrocartilage from concentrated mechanical insult.^[36]

Disruption of normal articular disc positioning, as in anterior disc displacement, fundamentally alters the load distribution pattern within the joint, concentrating mechanical stress on the posterior slope of the condyle and the posterior wall of the articular fossa—regions covered by thinner fibrocartilage poorly adapted to sustained compressive loading. This mechanical consequence of disc displacement is an important pathomechanical driver of progressive condylar remodelling and degenerative joint disease.^[37]

SECTION IV
PATHOPHYSIOLOGY OF
TEMPOROMANDIBULAR
DISORDERS

Myogenous pathophysiology:

Myofascial pain dysfunction, the most prevalent TMD subtype, involves complex interactions between peripheral and central sensitization mechanisms. At the peripheral level, sustained or repetitive masticatory muscle contraction—driven by bruxism, clenching, or postural muscle hyperactivity—produces ischemia within muscle fibres, with accumulation of adenosine, bradykinin, substance P, 5-hydroxytryptamine, and hydrogen ions that sensitize group III (A δ) and group IV (C) muscle afferents, reducing their activation thresholds and producing spontaneous pain.^[28]

Central sensitization in myofascial TMD involves neuroplastic changes in the trigeminal dorsal horn, including upregulation of NMDA receptors, increased production of substance P and CGRP, and reduction in GABAergic inhibitory tone, that amplify pain signals from the masticatory muscles and expand the area of pain referral beyond the primary afferent territory. The development of myofascial trigger points—hyperirritable foci within taut bands of masticatory muscle fibres, characterized by localized twitch responses to needle stimulation and characteristic referred pain patterns—is a hallmark of chronic myofascial TMD.^[38]

Articular and discal pathophysiology:

Anterior disc displacement is the most prevalent form of articular TMD pathology. It arises from progressive elongation and mechanical failure of the lateral and medial discal (collateral) ligaments and the posterior discal attachment (bilaminar zone), which normally tether the disc to the condyle and prevent anterior displacement. The resulting loss of disc-condyle coupling allows the anteriorly directed forces exerted by the superior lateral pterygoid muscle to gradually displace the disc anteromedially relative to the condyle. In the early stages, the elastic recoil of the superior stratum of the bilaminar zone may still be sufficient to recapture the disc onto the condylar head during opening—the stage of disc displacement with reduction. With progressive elongation and degeneration of the elastic fibres, the disc can no longer be recaptured, culminating in disc displacement without reduction.^[39]

The posterior discal ligaments and bilaminar zone, once subjected to compressive loading from the displaced condyle in the closed mouth position, undergo inflammatory degeneration, fibrosis, and eventual replacement by fibrous scar tissue (a process termed 'pseudo-disc formation' that may partially restore comfortable joint function in longstanding DDwoR). The rich

innervation of the bilaminar zone makes compression of this tissue an important and often underappreciated source of chronic retrodiscal pain in disc displacement disorders.^[39]

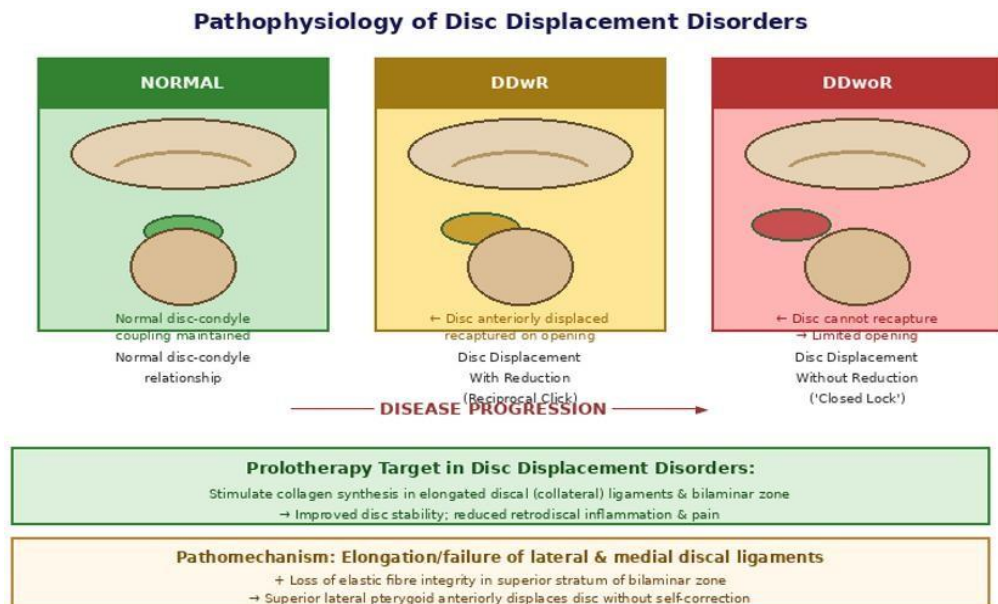


Figure 28: Stages of temporomandibular disc displacement from normal disc-condyle relationship through disc displacement with reduction (DDwR) to disc displacement without reduction (DDwoR), with the underlying pathomechanism and prolotherapy rationale.^[39]



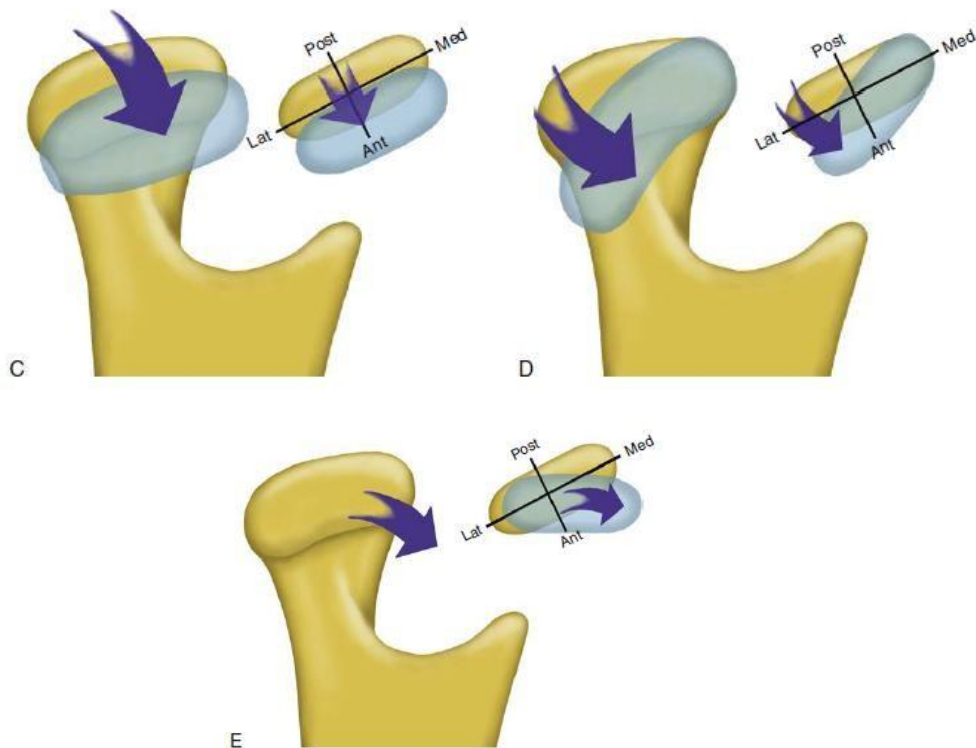


Figure 29: A) In the closed joint position the pull of the superior lateral pterygoid muscle is in an anteromedial direction (arrows).

B) When the mandible translates forward into a protrusive position, the pull of the superior head is even more medially directed (arrows). In this protruded position the major directional pull of the muscle is medial and not anterior. The disc may have the opportunity to be displaced in several directions.

C) From the superior view, the disc may be displaced anteriorly from the condyle.

D) The disc may be displaced anteromedially with the lateral pole being exposed first.

This is likely the most common direction of disc displacement since it is the directional pull of the superior lateral pterygoid muscle.

E) The disc may be displaced anterolaterally with the medial pole being exposed first. Since there are no functional forces being applied to the disc in this direction, it is the least likely disc displacement.^[3]

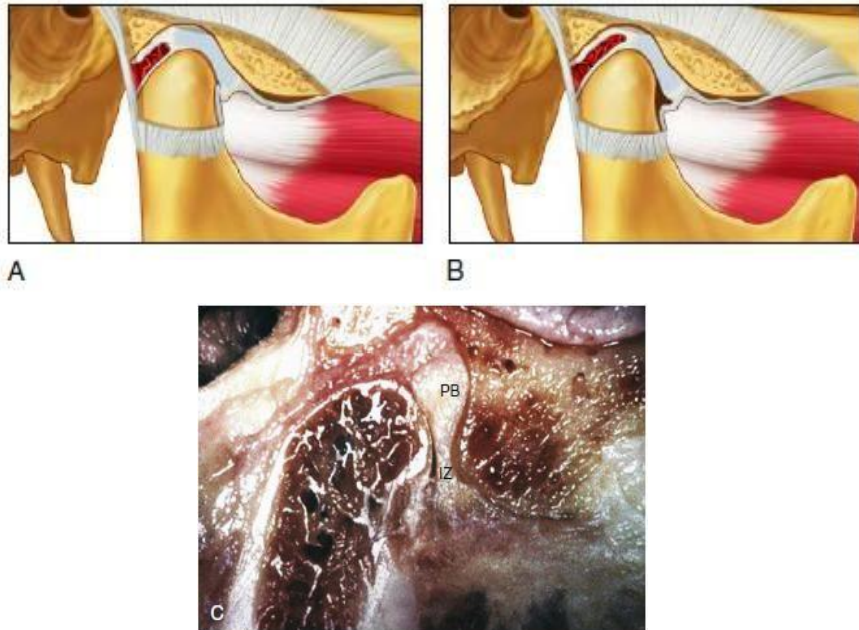


Figure 30: A) Normal position of the disc on the condyle in the closed joint position. B) Functional displacement of the disc. Its posterior border has been thinned and the discal and inferior retrodiscal ligaments are elongated, allowing activity of the superior lateral pterygoid to displace the disc anteriorly (and medially). C) In this specimen the condyle is articulating on the posterior band (PB) of the disc and not on the intermediate zone (IZ). This depicts an anterior displacement of the disc.^[3]

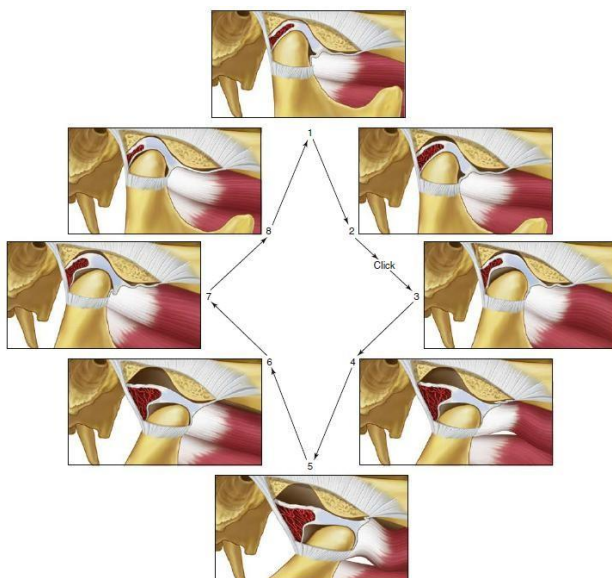


Figure 31: Disc Displacement with a Single Click. Between positions 2 and 3 a click is felt as the condyle moves across the posterior border into the intermediate zone of the disc. Normal condyle-disc function occurs during the remaining opening and closing movement. In the closed joint position (1) the disc is again displaced forward (and medially) by activity of the superior lateral pterygoid.^[3]

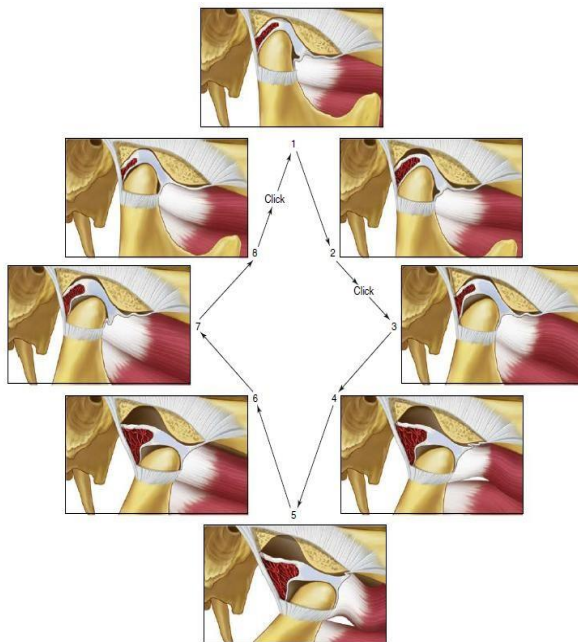


Figure 32: Disc Displacement With a Reciprocal Clicking. Between positions 2 and 3 a click is felt as the condyle moves across the posterior border of the disc. Normal condyle-disc function occurs during the remaining opening and closing movement until the closed joint position is approached. Then a second click is heard as the condyle once again moves from the intermediate zone to the posterior border of the disc (between 8 and 1).^[3]

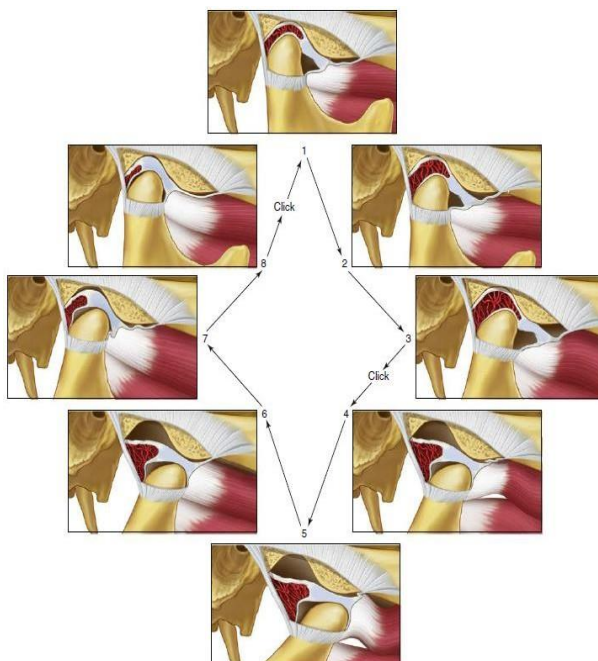


Figure 33: Disc Displacement With Reduction. During opening, the condyle passes over the posterior border of the disc onto the intermediate area of the disc, thus reducing the anterior displaced disc. This discal movement can lead to momentary mechanical catching or locking. When this is present, the condition is called disc displacement with intermittent locking.^[3]

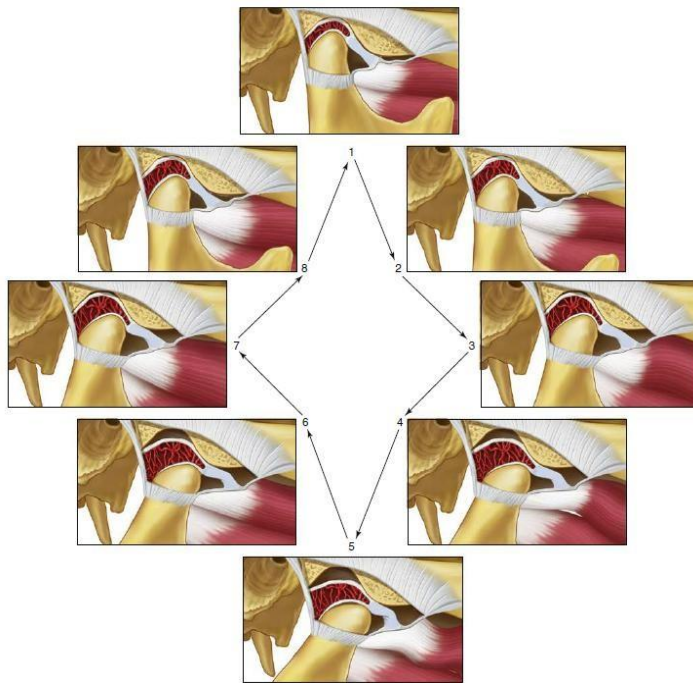


Figure 34: Disc Displacement Without Reduction (Closed Lock). The condyle never assumes a normal relationship on the disc, but instead causes the disc to be maintained in front of the condyle. This condition limits the distance it can translate forward.^[3]

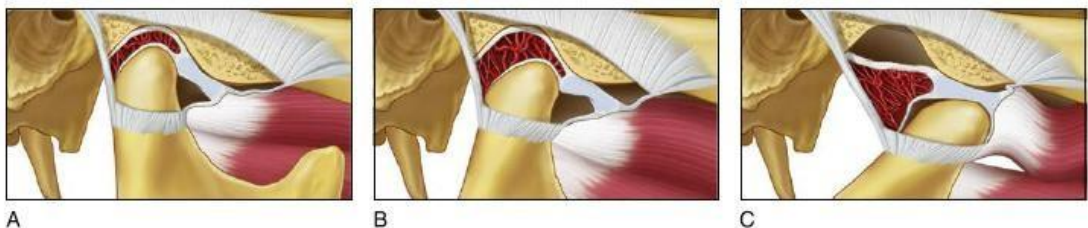


Figure 35: Anteriorly Displaced Disc With Reduction.

A) Resting closed joint position.

B) During the early stages of translation, the condyle moves up onto the posterior border of the disc. This can be accompanied by a clicking sound.

C) During the remainder of opening, the condyle assumes a more normal position on the intermediate zone of the disc as the disc is rotating posteriorly on the condyle. During closure the exact opposite occurs. In the final closure, the disc is again functionally displaced anteromedially. Sometimes this is accompanied by a second (reciprocal) click.^[3]

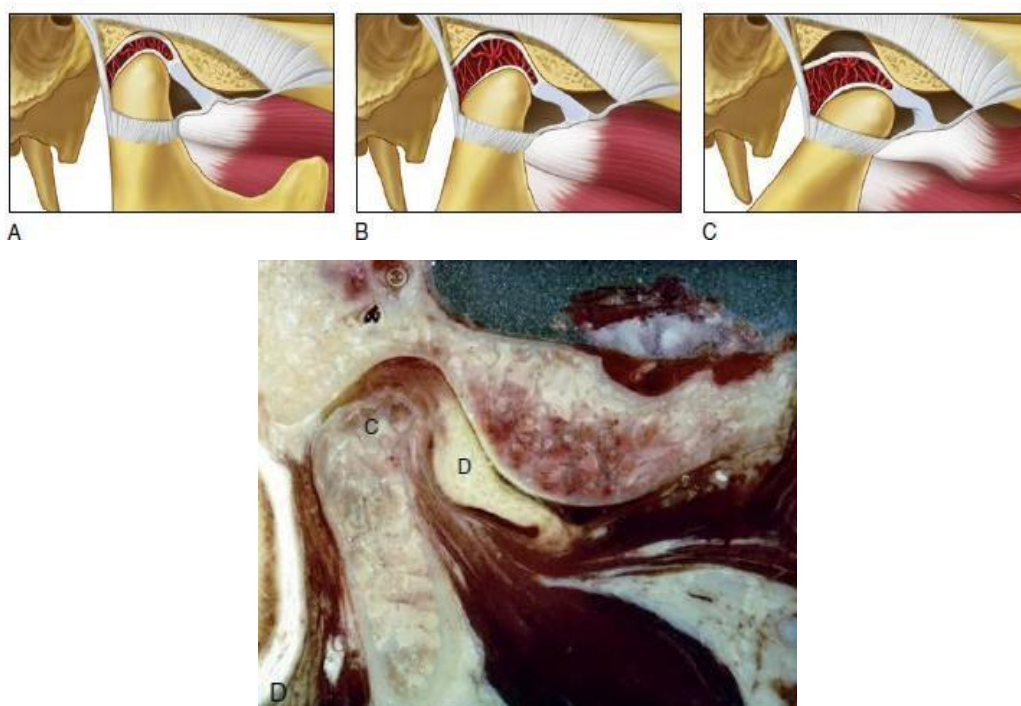


Figure 36: Anteriorly Displaced Disc Without Reduction.

A) Resting closed-joint position.

B) During the early stages of translation, the condyle does not move onto the disc but instead pushes the disc forward.

C) The disc becomes jammed forward in the joint, preventing the normal range of condylar translatory movement. This condition is referred to clinically as a closed lock.

D) In this specimen the disc (D) is displaced anterior to the condyle (C).^[3]

Degenerative joint disease:

Osteoarthritis of the TMJ is characterized by the progressive breakdown of articular fibrocartilage and subchondral bone remodelling, driven by an imbalance between anabolic and catabolic processes. The pathogenesis involves mechanical, biochemical, and inflammatory components: excessive or abnormal mechanical loading activates chondrocyte and disc cell mechano-transduction pathways, stimulating the synthesis of pro-inflammatory cytokines (IL-1 β , IL-6, TNF- α), matrix metalloproteinases (MMP-1, -3, -13), and ADAMTS enzymes (primarily ADAMTS-4 and -5) that degrade collagen and aggrecan—the principal structural components of the articular fibrocartilage and disc.^[40]

Synovitis, characterized by hyperplasia of the synovial membrane and increased production of inflammatory cytokines and prostaglandins, amplifies the catabolic processes and contributes to joint effusion, increased intra-articular pressure, and retrodiscal tissue inflammation. Subchondral bone undergoes microarchitectural remodelling—initially with sclerosis and later with cyst formation and osteophytosis—in response to altered biomechanical loading and inflammatory mediators. Clinically, this manifests as condylar flattening, erosion, osteophyte formation, and radiographic evidence of reduced joint space on CBCT imaging.^[41]

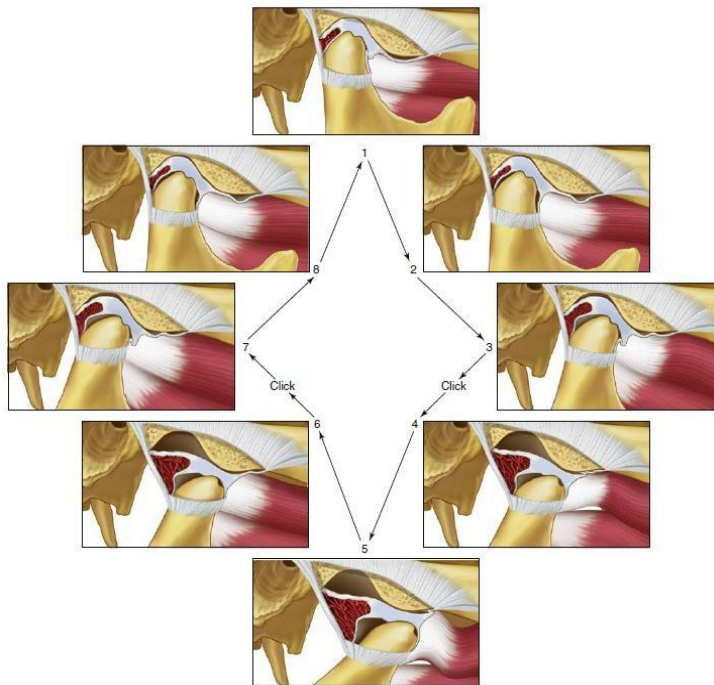


Figure 37: In position 1 the structural defect (alteration in form) in the condyle and disc. Between positions 3 and 4, the condyle moves out of the defect, resulting in a click. The condyle returns to this defect between positions 6 and 7. Note that the opening and closing click occurs at the same degree of opening.^[3]

Inflammatory arthropathies:

Systemic inflammatory arthritis including rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis, and juvenile idiopathic arthritis (JIA) may involve the TMJ as part of their polyarticular presentation. TMJ involvement in RA occurs in 50–75% of patients with advanced disease and is characterized by synovial pannus formation, progressive cartilage degradation, condylar erosion, and potentially severe structural joint destruction with consequent anterior open bite deformity. In JIA, TMJ involvement during the period of active condylar growth can lead to mandibular growth retardation, micrognathia, and severe malocclusion.^[42]

Acute TMJ synovitis and capsulitis present with acute-onset preauricular pain, joint tenderness on palpation, limited mouth opening, and ipsilateral posterior open bite (due to joint effusion displacing the condyle inferiorly). Retrodiscitis—inflammation of the vascularized and innervated bilaminar zone—is specifically precipitated by posterior condylar displacement from trauma, dental procedures under anaesthesia, loss of posterior occlusal support, or aggressive lateral condylar displacement during dental treatments.^[40]

SECTION V
**REVIEW
OF
LITERATURE**

Systemic search strategy:

The literature review presented in this chapter was conducted using a structured, comprehensive bibliographic search strategy to identify all relevant publications on prolotherapy for temporomandibular disorders and related musculoskeletal conditions. Electronic databases searched included PubMed/MEDLINE, Scopus, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar, and EMBASE. The search was conducted without date restrictions but emphasised publications from 1990 to October 2024.^[43]

Primary search terms applied to PubMed included: ('prolotherapy' OR 'dextrose prolotherapy' OR 'proliferative injection therapy' OR 'regenerative injection therapy' OR 'hypertonic dextrose injection') AND ('temporomandibular joint' OR 'temporomandibular disorder' OR 'TMJ' OR 'TMD' OR 'jaw pain'). Secondary searches included broader musculoskeletal prolotherapy terms to capture comparative and mechanistic evidence applicable to the TMJ context. A total of 347 potentially relevant citations were identified; after title and abstract screening and full-text review, over 200 publications were included in this review.^[44]

Landmark RCTs and Key Studies:

1) Reeves and Hassanein (2000) – Foundational RCT:

The randomized, double-blind, placebo-controlled trial by Reeves and Hassanein, published in the Journal of Alternative and Complementary Medicine in 2000, remains the landmark Level I evidence study for dextrose prolotherapy in TMJ hypermobility. Thirty-nine adult patients with documented chronic TMJ hypermobility (defined as condylar translation beyond the articular eminence with or without pain, confirmed clinically and radiographically) and a minimum 6-month history of symptoms unresponsive to conservative management were enrolled.^[45]

Patients were randomized 1:1 to receive three monthly intra-articular injections of either 10% dextrose with 0.2% lidocaine (prolotherapy group, n=20) or 0.2% lidocaine alone (control group, n=19). Blinding was maintained through identical injection procedures and labelling. Primary outcomes (pain VAS, MMO, subluxation frequency) were assessed at 1-year post-treatment by a blinded assessor. The prolotherapy group demonstrated statistically significant ($p < 0.01$) superior outcomes on all primary measures. The number needed to treat

(NNT) for clinically significant pain improvement (>50% reduction) was 2.7, indicating a high treatment effect size.^[45]

2) Comert Kilic and Gungormus (2016) -Three-Arm RCT for TMJ Osteoarthritis:

This prospective, randomized, double-blind, placebo-controlled three-arm trial, published in the International Journal of Oral and Maxillofacial Surgery, enrolled 60 patients with clinically and CBCT-confirmed TMJ osteoarthritis and randomized them equally to: Group 1 (prolotherapy: 25% dextrose, 1 mL per joint, three sessions at 4-week intervals); Group 2 (corticosteroid: methylprednisolone acetate 40 mg, 1 mL per joint, three sessions); Group 3 (placebo: normal saline 1 mL per joint, three sessions). Assessments were conducted at 1-, 3-, and 6-months post-treatment.^[46]

The prolotherapy group demonstrated statistically significant and clinically meaningful improvements in VAS pain scores at all assessment time points compared to both the corticosteroid and placebo groups, achieving a 72.3% mean reduction in pain intensity at 6 months compared to 55.1% in the corticosteroid group and 32.4% in the placebo group. MMO improved significantly in both active treatment groups, with no statistically significant difference between prolotherapy and corticosteroids in MMO improvement. Crucially, the corticosteroid group demonstrated partial regression of pain improvement from the 1-month to the 6-month assessment, while the prolotherapy group maintained and further improved its outcomes over the same period.^[46]

3) Refai, Altahhan and Elsharkawy (2011) – Prospective study for TMJ Hypermobility:

This prospective clinical investigation by Refai, Altahhan, and Elsharkawy, published in the Journal of Oral and Maxillofacial Surgery, enrolled 20 patients with clinical and radiographic evidence of TMJ hypermobility defined by condylar translation beyond the crest of the articular eminence. All patients received three intra-articular injections of 25% dextrose solution (1.5 mL per session) at 4-week intervals into the upper joint space and the lateral capsule. Outcomes were assessed at 3, 6, and 12 months.^[47]

At 12-month follow-up, 17 of 20 patients (85%) reported complete resolution of subluxation episodes, compared to 4 of 20 (20%) at baseline who had subluxation infrequently. Significant reductions in pain intensity (mean

VAS reduction of 6.2 points on a 0–10 scale) and improvements in MMO (mean increase of 9.7 mm from a baseline of 38.2 mm) were documented. Post-treatment panoramic and tomographic imaging demonstrated improved condyle-fossa relationships and increased thickness of the articular eminence posterior slope in the majority of patients, suggesting structural adaptive changes in response to the increased functional demands following prolotherapy-induced joint stabilization.^[47]

4) Hauser et al – Multiple Retrospective and Case series studies:

Hauser and colleagues have published multiple retrospective analyses and case series evaluating Hackett-Hemwall dextrose prolotherapy for chronic TMDs and associated cervical conditions. A representative retrospective cohort study examined outcomes in 52 consecutive chronic TMD patients (mean symptom duration 4.8 years) who had failed previous conservative treatments including physiotherapy, splint therapy, and pharmacological management. Patients received Hackett-Hemwall prolotherapy (25% dextrose injected into the TMJ upper space, lateral capsule, and associated cervical ligaments) at 4–6-week intervals for a mean of 6.1 sessions.^[49]

Significant improvements were documented at final follow-up (mean 14.2 months): mean VAS pain reduction from 7.4 to 2.6 (65% improvement); MMO improvement from 28.3 mm to 41.7 mm; resolution of subluxation in 88% of patients who had presented with this feature; and clinically significant reduction in jaw functional limitation scores. Patient-reported satisfaction was high, with 90% of patients reporting they would undergo prolotherapy again and 85% recommending it to other TMD patients. No serious adverse events were documented.^[50]

5) Garg, Singh and colleagues – Indian clinical studies:

Several Indian investigators have published studies evaluating prolotherapy for TMJ disorders in South Asian patient populations. A prospective clinical study from a tertiary dental institution compared intra-articular dextrose prolotherapy (12.5% dextrose, 1 mL, three sessions at 4-week intervals) with intra-articular hyaluronic acid injections in 30 patients with TMJ osteoarthritis per group. Both modalities produced significant improvements in VAS pain scores, MMO, and OHIP-14 scores at 6-month follow-up, with no statistically significant difference between groups—suggesting comparable efficacy of prolotherapy and HA for TMJ osteoarthritis in the short term.^[51]

A retrospective audit of prolotherapy outcomes in 48 patients with chronic articular TMD attending an oral medicine department in India reported a mean VAS pain reduction of 61.3% after a mean of 4.8 sessions over 5.2 months. Patients with TMJ hypermobility demonstrated the greatest improvements (72.4% pain reduction), followed by those with disc displacement disorders (63.1%), and those with early osteoarthritis (54.8%). Post-injection soreness was the most common adverse effect (reported by 73% of patients at some point during treatment), with all cases self-limiting within 5 days.^[52]

Comparative Studies with Conventional Therapies:

1) Prolotherapy versus Arthrocentesis:

Arthrocentesis, through the hydraulic distension and lavage of the upper joint space, shares certain mechanical effects with intra-articular prolotherapy (relief of intra-articular negative pressure, lysis of adhesions, removal of inflammatory mediators). A prospective comparative study by Saber and colleagues randomized 45 patients with disc displacement without reduction to either arthrocentesis (Ringer's lactate lavage) or dextrose prolotherapy (three sessions). Both modalities significantly improved MMO and reduced pain, with no statistically significant between-group difference at 3-month follow-up. However, the prolotherapy group demonstrated superior maintenance of improvement at 6 months, suggesting a more durable treatment effect attributable to its regenerative structural mechanism.^[53]

2) Prolotherapy versus Occlusal splints:

Occlusal splint therapy (stabilization splints) is the most universally prescribed conservative TMD intervention. A randomized study by Dahlström and colleagues comparing prolotherapy with stabilization splint therapy in 42 patients with chronic articular TMD found comparable efficacy for pain reduction and functional improvement at 3 months in both groups. At 12-month follow-up, the prolotherapy group demonstrated significantly superior functional outcomes (MMO, JFLS scores) compared to the splint group, while pain reduction was comparable. The authors concluded that prolotherapy may provide additional functional benefits beyond those achievable with splint therapy alone, particularly for the articular component of TMDs.^[54]

3) Prolotherapy versus Hyaluronic acid injections:

Hyaluronic acid (HA) is the most widely studied comparator for TMJ prolotherapy. Multiple studies have compared these modalities for TMJ

osteoarthritis. A prospective RCT by Altman and colleagues randomized 64 patients with TMJ osteoarthritis to three intra-articular injections of either 25% dextrose or sodium hyaluronate (Synvisc® equivalent). Both groups demonstrated significant improvements in VAS pain scores, MMO, and Patient Global Assessment at 6-month follow-up. No statistically significant between-group differences were observed, suggesting clinical equivalence. The lower cost of dextrose compared to commercial HA preparations provides a practical advantage for prolotherapy in resource-limited settings.^[157]

4) Prolotherapy versus PRP for TMJ Disorders:

Several studies have directly compared dextrose prolotherapy and PRP injections for TMJ disorders. Çelik and colleagues randomized 60 patients with chronic TMD (both disc displacement and osteoarthritis subtypes) to receive three intra-articular injections of either 12.5% dextrose or leucocyte-poor PRP (LP-PRP) prepared by double centrifugation. Patients with osteoarthritis-predominant TMD showed greater improvements with PRP, while those with hypermobility or disc displacement-predominant disease showed comparable improvements with both modalities. PRP was associated with more frequent immediate post-injection discomfort (due to platelet activation) but with comparable post-session pain profiles after 48 hours.^[55]

5) Prolotherapy in combination with Physiotherapy:

A prospective randomized study by Kamath and colleagues assigned 40 TMD patients with mixed articular and myofascial presentations to prolotherapy alone (three intra-articular dextrose sessions) versus prolotherapy combined with a supervised physiotherapy programme (jaw exercises, manual therapy, postural correction). At 6-month follow-up, the combination group demonstrated significantly greater improvements in JFLS scores, MMO, and patient-reported quality of life compared to prolotherapy alone, confirming the additive benefit of physiotherapy in optimizing and sustaining prolotherapy outcomes.^[56]

Systemic reviews and Meta- analyses:

1) Prolotherapy for TMDs:

A systematic review by Dagenais, Yelland, and Del Mar specifically examining prolotherapy for TMJ disorders identified six studies (including three RCTs) meeting inclusion criteria and concluded that the available evidence supports the efficacy of dextrose prolotherapy for pain reduction and functional improvement in chronic articular TMDs, with a safety profile superior to

corticosteroid injections. The quality of evidence was rated as moderate, with the principal methodological limitations being small sample sizes, variable follow-up durations, and heterogeneous injection protocols.^[57]

2) Prolotherapy for Musculoskeletal Conditions broadly:

Broader systematic reviews and meta-analyses of prolotherapy for musculoskeletal pain across multiple joints provide important supporting evidence applicable to the TMJ context. Hauser and colleagues' systematic review of 32 studies on dextrose prolotherapy for chronic musculoskeletal pain (including knee, shoulder, spine, and hip conditions) found consistent evidence of significant pain reduction and functional improvement across diverse anatomical sites, with a favourable safety profile and no serious adverse events reported in any included study.^[5]

A Cochrane systematic review by Yelland and colleagues, examining prolotherapy for low back pain, concluded that while the evidence was insufficient to definitively support prolotherapy as a standalone treatment, several high-quality RCTs demonstrated significant benefit when prolotherapy was combined with spinal manipulation and exercise. The authors noted that the quality of prolotherapy evidence had significantly improved over the review period, with more recent studies demonstrating more rigorous methodology.^[58]

3) Evidence for PRP in TMDs (Comparative Context):

Given the frequent comparative context in which PRP is evaluated alongside dextrose prolotherapy for TMJ disorders, a brief summary of the PRP evidence base is warranted. A systematic review by Machado and colleagues identified 12 studies evaluating intra-articular PRP for TMJ disorders, encompassing both disc displacement and osteoarthritis subtypes. The pooled evidence demonstrated significant improvements in pain and mouth opening with PRP, with an acceptable safety profile. The review identified LP-PRP as the preferred formulation for intra-articular TMJ applications, based on superior outcomes and reduced risk of post-injection inflammatory flare compared to L-PRP.^[158]

A multicentre RCT by Hegab and Bhatt randomized 96 patients with TMJ osteoarthritis to receive either LP-PRP or sodium hyaluronate (HA) injections (three sessions each). Both groups demonstrated significant improvements in pain, MMO, and Joint Vibration Analysis parameters. PRP demonstrated superior outcomes compared to HA at 12-month follow-up,

suggesting that the growth factor-mediated regenerative mechanism of PRP may provide more durable benefits than the visco-supplementation mechanism of HA for advanced TMJ osteoarthritis.^[59]

Evidence Gaps and Methodological Limitations:

A comprehensive appraisal of the prolotherapy literature for TMDs identifies the following significant evidence gaps that limit the strength of current clinical recommendations:

- (1) insufficient number of adequately powered, multicentre RCTs with large sample sizes;
- (2) heterogeneity of dextrose concentrations, injection volumes, injection sites, and treatment frequencies across studies;
- (3) variability in patient selection criteria and TMD subtype composition;
- (4) limited use of standardized, validated outcome measures (DC/TMD physical examination, GCPS, JFLS, OHIP-14);
- (5) inadequate long-term follow-up beyond 12 months in most studies; and
- (6) absence of structural outcome measures (post-treatment MRI, CBCT) to objectively document the claimed connective tissue regenerative effects.^[60]

The absence of methodological standardization—particularly regarding injection protocols—constitutes the most significant barrier to evidence synthesis and the derivation of clear, evidence-based clinical guidelines. The prolotherapy community has recognized this limitation, and international consensus efforts to develop standardized reporting guidelines for prolotherapy clinical trials (analogous to the CONSORT statement for RCTs) are underway.^[61]

Study done by	Study Type & Participants	Therapy Administered	Outcome
Reeves & Hassanein, 2000, USA ^[45]	RCT, 39 patients (20 prolotherapy, 19 control), TMJ hypermobility	10% dextrose + 0.2% lidocaine, 1 ml intra-articular; 3 monthly sessions vs lidocaine alone	Pain VAS, MMO, subluxation frequency; assessed at baseline and 12 months → VAS decreased by >50% in 74% vs 26% in control
Comert Kilic & Gungormus, 2016, Turkey ^[46]	3-arm RCT, 60 patients, (20/group), TMJ osteoarthritis	Group 1: 25% dextrose, 1 mL; Group 2: methylprednisolone acetate 40 mg, 1 mL; Group 3: saline 1 mL; 3 sessions at 4-week intervals	Pain VAS, MMO; assessed at 1, 3, 6 months → VAS decreased by 72.3% (prolotherapy), decreased by 55.1% (steroid), decreased by 32.4% (placebo)
Refai, Altahhan & Elsharkawy, 2011, Egypt ^{[47][48]}	Prospective study, 20 patients, TMJ hypermobility	25% dextrose, 1.5 mL intra-articular + lateral capsule; 3 sessions at 4-week intervals	Pain VAS, MMO, subluxation frequency, imaging; assessed at 3, 6, 12 months → 85% resolution of subluxation; VAS decreased by 62%; MMO increased by 9.7 mm

Hauser et al., 2001-2010, USA ^{[49][50]}	Retrospective cohort, 52 patients, Chronic TMD (mixed articular + cervical involvement)	Hackett-Hemwall prolotherapy: 25% dextrose into TMJ upper space, lateral capsule, cervical ligaments; mean 6.1 sessions at 4–6 week intervals	Pain VAS, MMO, subluxation, JFLS; assessed at mean 14.2 months → VAS decreased by 65%; MMO increased by 13.4 mm; 88% resolution of subluxation
Garg, Singh et al., 2014, India ^[51]	Prospective study, 60 patients, (30/group), TMJ osteoarthritis	12.5% dextrose, 1 mL vs hyaluronic acid; 3 sessions at 4- week intervals	Pain VAS, MMO, OHIP-14; assessed at 6 months → Both groups VAS decreased by ~60%; MMO increased by ~10 mm; OHIP-14 improved
Garg et al., 2015, India ^[52]	Retrospective audit, 48 patients, Chronic articular TMD (hypermobility, disc displacement, early OA)	Mean 4.8 sessions of intra-articular 12.5% dextrose prolotherapy over 5.2 months	Pain VAS, subgroup analysis; assessed at ~6 months → Mean VAS decreased by 61.3%; hypermobility decreased by 72.4%, disc displacement decreased by 63.1%, early OA decreased by 54.8%
Saber et al., 2012, Egypt ^[53]	Prospective comparative study, 45 patients, Disc displacement without reduction	Arthrocentesis (Ringer's lactate lavage) vs prolotherapy (3 dextrose sessions)	Pain VAS, MMO; assessed at 3 and 6 months → Both improved; prolotherapy maintained superior outcomes at 6 months

Dahlström et al., 2006, Sweden ^[54]	RCT, 42 patients, Chronic articular TMD	Prolotherapy (dextrose injections) vs occlusal splints	Pain VAS, MMO, JFLS; assessed at 3 and 12 months → Comparable at 3 months; prolotherapy superior in MMO and JFLS at 12 months
Altman et al., 2008, USA ^[157]	RCT, 64 patients, TMJ osteoarthritis	25% dextrose vs sodium hyaluronate (Synvisc® equivalent), 3 intra-articular sessions	Pain VAS, MMO, Patient Global Assessment; assessed at 6 months → Both improved ~65% pain reduction; MMO increased by ~10 mm
Çelik et al., 2019, Turkey ^[55]	RCT, 60 patients, Mixed TMD (OA + hypermobility/disc displacement)	12.5% dextrose vs leucocyte-poor PRP (LP-PRP), 3 sessions	Pain VAS, MMO; assessed at 1, 3, 6 months → OA cases: PRP superior (pain decreased by ~70% vs 55%); hypermobility/disc displacement: comparable
Kamath et al., 2020, India ^[56]	RCT, 40 patients, Mixed articular + myofascial TMD	Prolotherapy alone vs prolotherapy + physiotherapy (jaw exercises, manual therapy, posture correction)	Pain VAS, MMO, JFLS, QoL; assessed at 6 months → Combination group: JFLS decreased by ~75% vs 55%; MMO increased by ~12 mm vs 8 mm

Dagenais, Yelland & Del Mar, 2007, Australia ^[57]	Systematic review, 6 studies, Chronic articular TMDs	Review of prolotherapy in TMDs	Pain VAS, MMO; follow-up varied (3–12 months) → Moderate evidence; pain decreased by ~60–70%; functional improvement consistent
Hauser et al., 2011, USA ^[5]	Systematic review, 32 studies, Musculoskeletal conditions (including TMJ)	Review of musculoskeletal prolotherapy	Pain VAS, MMO; follow-up varied (6–12 months) → Pain decreased by 50–70% across joints; functional improvement; safe profile
Yelland et al., 2004, Cochrane Review ^[58]	Systematic review, multiple RCTs, Low back pain (comparative musculoskeletal context)	Prolotherapy for low back pain	Pain VAS, function; follow-up varied (3–12 months) → Standalone benefit limited; combined therapy → pain decreased by ~50%
Machado et al., 2020, Brazil ^[158]	Systematic review, 12 studies, TMJ disorders (OA + disc displacement)	PRP for TMJ disorders	Pain VAS, MMO; follow-up 6–12 months → Pain decreased by ~65–75%; MMO increased by ~10–12 mm; LP-PRP superior

Hegab & Bhatt, 2021, Multicentre RCT ^[59]	RCT, 96 patients, TMJ osteoarthritis	LP-PRP vs sodium hyaluronate, 3 sessions	Pain VAS, MMO, Joint Vibration Analysis; assessed at 12 months → PRP superior (pain decreased by ~70% vs 55%; MMO increased by ~12 mm vs 8 mm)
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Table 1: Describing the studies explained in review of literature

SECTION VI

**TEMPOROMANDIBULAR
JOINT DISORDERS**

Classification of TMDs:

The classification of temporomandibular disorders has undergone profound revision over the past five decades, progressively evolving from simplistic anatomical or symptom-based taxonomies toward operationalized, evidence-based frameworks that account for the multidimensional biopsychosocial complexity of these conditions. Understanding the current classification is essential for appropriate patient selection for prolotherapy and for interpreting the evidence from published studies.^[62]

Historical classification systems:

The earliest clinical classifications of jaw joint disorders focused primarily on anatomical and mechanistic features. Costen (1934) attributed a cluster of auricular and facial symptoms to mandibular overbite and overclosure, attributing the pathology to mechanical impingement of the chorda tympani and auriculotemporal nerves by the posteriorly displaced condyle. Schwartz (1955) introduced the concept of 'temporomandibular joint pain-dysfunction syndrome,' emphasizing the role of masticatory muscle spasm. Laskin (1969) reformulated this as 'myofascial pain dysfunction (MPD) syndrome,' emphasizing psychophysiological mechanisms and distinguishing it from true articular pathology.^{[63][64]}

Bell's 1982 classification introduced the term 'temporomandibular disorders' and organized TMDs into primary (direct joint structural problems) and secondary (referred pain and systemic disorders manifesting in the TMJ region) categories. The subsequent development of the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) by Dworkin and LeResche in 1992 represented a landmark advance, providing operationalized, dual-axis diagnostic criteria with demonstrated reliability and validity across multiple languages and cultural contexts.^[65]

DC/TMD Classification (Current Standard):

The Diagnostic Criteria for Temporomandibular Disorders (DC/TMD), published in 2014 by Schiffman and an international consortium of 50 expert investigators, represents the current internationally accepted standard for clinical and research diagnosis of TMDs.

The DC/TMD **Axis I** taxonomy organizes TMDs into three major groups:^[66]

Group I — Pain Disorders:

These include

(a) Myalgia, subdivided into-

local myalgia (pain localized to palpation site),

myofascial pain (pain spreading beyond palpation site but not beyond temporalis boundaries), and

myofascial pain with referral (familiar pain reported at a site beyond muscle boundaries)

(b) Headache attributed to TMD; and

(c) Arthralgia (pain from the joint proper).

Group II — Intra-articular Disorders:

Disc displacement disorders are subclassified into- disc displacement with reduction (DDwR, with or without intermittent locking),

Disc displacement without reduction with limited opening (closed lock), and disc displacement without reduction without limited opening.

Hypomobility disorders and hypermobility disorders (subluxation, dislocation) complete this group.

Group III — Degenerative Joint Disease:

This encompasses osteoarthritis (DJD with pain) and osteoarthrosis (DJD without pain), diagnosed on the basis of characteristic crepitus and radiographic evidence of structural bony changes.

Axis II taxonomy evaluates pain-related disability and psychological status through validated instruments including the Patient Health Questionnaire (PHQ-4), the Graded Chronic Pain Scale (GCPS), and the Jaw Functional Limitation Scale (JFLS).^[66]

Clinical features of TMDs:

Pain characteristics:

Pain is the predominant symptom driving TMD patients to seek care and constitutes the primary therapeutic target. TMD-associated pain is classically described as a dull, aching, chronic discomfort arising in the preauricular region,

with a characteristic pattern of exacerbation during jaw function—mastication, maximum mouth opening, yawning, prolonged speaking—and improvement with rest. The pain may radiate to the temporal region, ear, cheek, mandible, neck, and shoulder, frequently defying simple anatomical explanations and reflecting the convergence and referral patterns of the trigeminal sensory system.^[67]

A subset of TMD patients presents with acute, severe pain associated with sudden restricted mouth opening, representing an acute closed lock from disc displacement without reduction or condylar dislocation. Inflammatory TMJ pain, as in synovitis, capsulitis, or retrodiscitis, is characteristically more constant, severe, and associated with palpable joint tenderness, while myofascial pain is typically more diffuse, variable in intensity, and associated with masticatory muscle tenderness.^[68]

Chronic TMD pain involves peripheral and central sensitization mechanisms that amplify and perpetuate the pain experience beyond the initial tissue injury. Patients with chronic TMD-associated pain demonstrate reduced pressure pain thresholds at both local (masticatory region) and remote (forearm, tibialis anterior) sites compared to healthy controls, indicating generalized pain sensitivity consistent with central sensitization. The OPPERA study demonstrated that reduced pressure pain threshold, heightened response to cold pressor stimuli, and high somatic awareness are significant predictors of TMD chronification.^[69]

Joint sounds:

Joint sounds in TMDs encompass three distinct phenomena with different pathomechanical correlates. Clicking or popping (reciprocal click) is the pathognomonic joint sound of disc displacement with reduction. The opening click arises from the abrupt recapture of the anteriorly displaced disc by the advancing condylar head as the mandible opens, while the reciprocal closing click occurs as the disc re-displaces anteriorly relative to the retracting condyle during closing. The temporal relationship of these sounds during the opening-closing cycle is characteristic: the opening click typically occurs earlier in the opening arc when the disc displacement is less severe and later as displacement progresses.^[70]

Crepitus—a grating, grinding, or gravel-like sound appreciated on auscultation with a stethoscope or through direct palpation—is pathognomonic of degenerative joint disease. It arises from the articulation of roughened, eroded

articular surfaces or the presence of articular debris and fibrous adhesions within the joint space. Fine crepitus may occur in mild degenerative changes, while coarse crepitus indicates more advanced articular surface destruction. The presence of crepitus should prompt thorough radiographic evaluation with CBCT to assess the extent of condylar bony changes.^[13]

Mandibular movement disorders:

Normal maximum mouth opening (MMO) in adults ranges from 40 to 55 mm (interincisal distance), with values below 40 mm considered restricted and below 35 mm indicating clinically significant limitation. Normal lateral excursion is 7–10 mm and protrusion 5–8 mm. In clinical assessment, MMO is evaluated as passive (examiner-assisted) and active (patient-initiated) measurements, with both measured in millimetres with a ruler or a Boley gauge.^[67]

Mandibular deflection during opening—a progressive deviation of the midpoint toward the affected side that persists at maximum opening—is characteristic of unilateral disc displacement without reduction (closed lock), as the unaffected condyle translates fully while the ipsilateral condyle of the closed-locked joint is mechanically impeded. Mandibular deviation—a midline shift during opening that corrects toward the midline before maximum opening—typically reflects asymmetric muscular activity or disc displacement with reduction (where the opening click corresponds to disc recapture and midline correction).^[67]

Diagnostic modalities:

Clinical examination protocol:

The DC/TMD examination protocol provides a standardized, validated framework for the clinical evaluation of TMDs. It encompasses:

- (1) pain history including location diagram, pain characteristics, and temporal pattern;
- (2) mandibular range of motion measurements (MMO, lateral excursion right and left, protrusion) with and without pain;
- (3) joint sound assessment (clicking, crepitus) during opening, closing, and lateral movements using palpation and, when available, a stethoscope;
- (4) masticatory muscle palpation (masseter superficial and deep, anterior/middle/posterior temporalis, medial and lateral pterygoids, digastric)

- using a standardized 1 kg force (1 cm² fingertip pressure);
- (5) TMJ palpation (lateral pole in closed and open positions); and
- (6) headache provocation testing.^[71]

Magnetic resonance imaging:

MRI remains the gold standard for evaluating the soft tissue components of the TMJ, providing unparalleled resolution of disc position, disc morphology, retrodiscal tissue integrity, synovial changes, and bone marrow signal. The standard TMJ MRI protocol includes bilateral sagittal and coronal proton density (PD) weighted and T2-weighted sequences acquired in both the closed (intercuspal) and maximum open mouth positions, using a dedicated TMJ surface coil. Slice thickness is typically 2–3 mm with minimal interslice gaps.^[72]

Normal disc position is defined as the posterior band of the disc at the 12 o'clock position (direct superior) relative to the condylar head on a true sagittal section in the closed mouth position. A disc position between 11 and 1 o'clock ($\pm 30^\circ$ from superior) is considered within the range of normal variation. Disc displacement with reduction is diagnosed when the disc is anteriorly positioned in the closed mouth view (posterior band anterior to 11 o'clock) but assumes a near-normal relationship in the open mouth view. Disc displacement without reduction shows anterior disc positioning in both closed and open views.^[73]

MRI also enables evaluation of disc morphology changes (biconcave, biconvex, thickened, biplanar, folded), disc signal changes (loss of uniform low signal indicating fibrocartilage degeneration), joint effusion (high T2 signal in the joint compartments indicating synovitis and increased vascular permeability), bone marrow edema (high T2/low T1 signal in the condyle or temporal bone indicating early osteoarthritis or avascular necrosis), and synovial pannus (low T1/T2 signal mass in the superior compartment in inflammatory arthropathies).^[74]

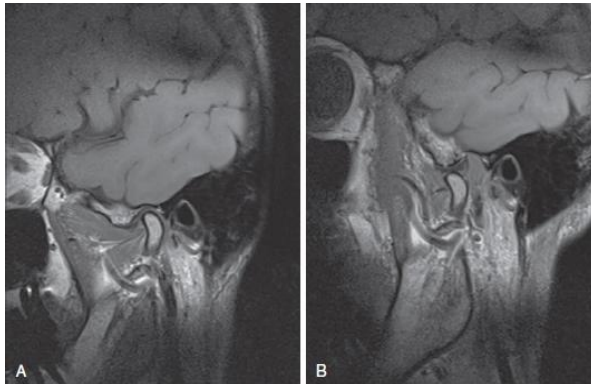


Figure 38: Magnetic Resonance Image.
A) Normal TMJ with the disc properly positioned between the condyle and fossa. B) During opening the disc is maintained between the condyle and fossa.^[3]

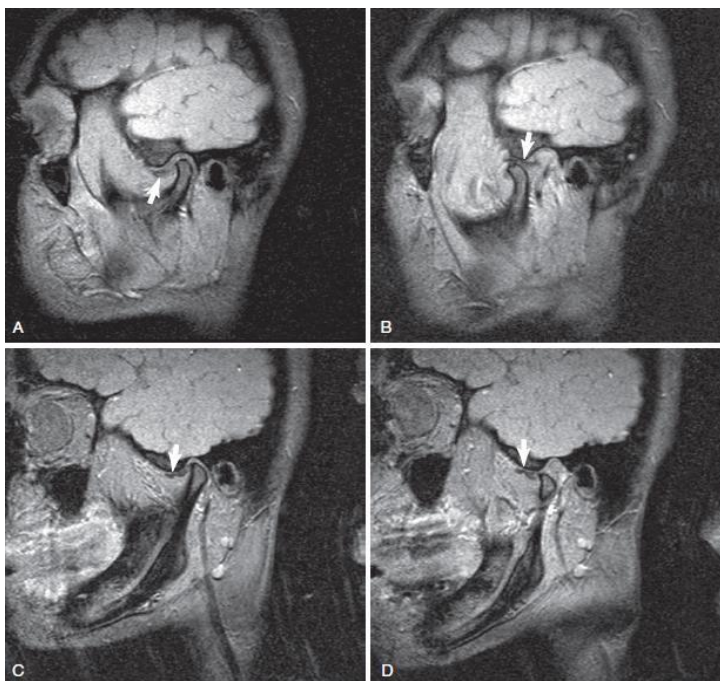


Figure 39: These MRI images depict the disc position with mandibular movement.

A) In this patient with the mouth closed, the MRI reveals the disc to be anteriorly displaced (dark area).

B) When this patient is asked to open the mouth, the disc is reduced to its normal position.

C) In this patient the disc is also noted to be in an anteriorly displaced position, but when this patient opens the mouth, the disc is not reduced.

D) This is a closed lock condition.^[3]

Cone Beam Computed Tomography:

CBCT has become the preferred radiographic modality for evaluating the osseous components of the TMJ, offering isotropic voxel resolution (typically 0.1–0.4 mm), three-dimensional multiplanar reconstruction capability, and substantially lower effective radiation doses compared to multislice CT (estimated effective dose of 20–100 μSv for TMJ CBCT versus 300–500 μSv for multislice CT). CBCT is specifically indicated for the assessment of degenerative osseous changes, condylar morphology abnormalities, post-traumatic bony changes, and pre-surgical planning.^[75]

The Petersson radiographic staging system and its modifications provide standardized criteria for grading degenerative condylar changes:

Stage 0 (no visible osseous changes),

Stage 1 (flattening),

Stage 2 (subchondral erosion),

Stage 3 (osteophyte formation),

Stage 4 (gross destructive changes with condylar resorption).

CBCT-based assessment of joint space dimensions—superior, anterior, and posterior—has been proposed as an indirect indicator of disc position, though its diagnostic accuracy is inferior to MRI.^[76]

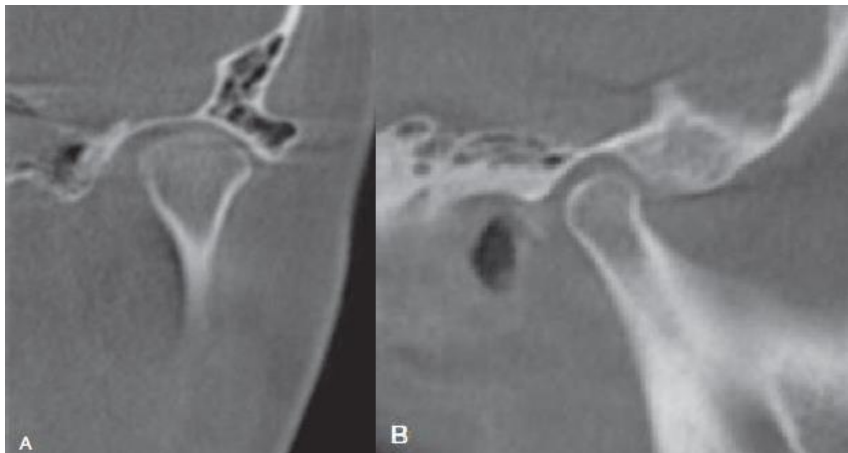


Figure 40: Normal Condylar Images With CBCT.

A) anterior view of the TM joint in the closed position.

B) lateral view TM joint.^[3]

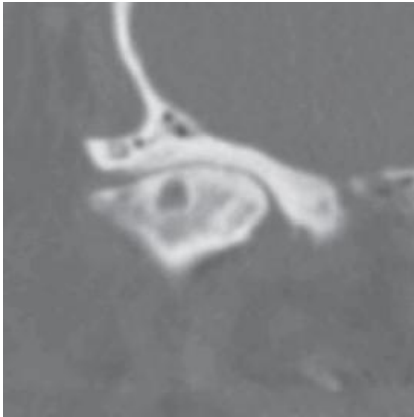


Figure 41: Anterior CBCT view of condyle with a subchondral bone cyst.^[3]

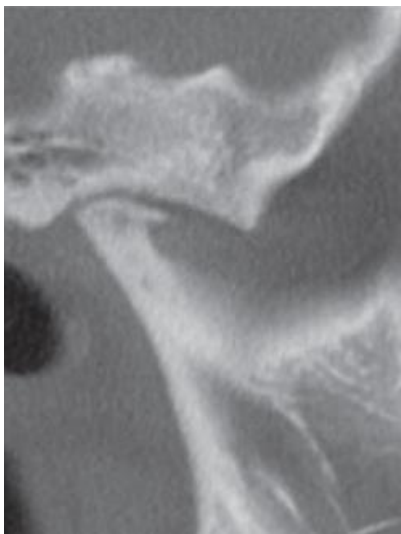


Figure 42: CBCT view of Flattening of the Articular Surface of the Condyle.^[3]

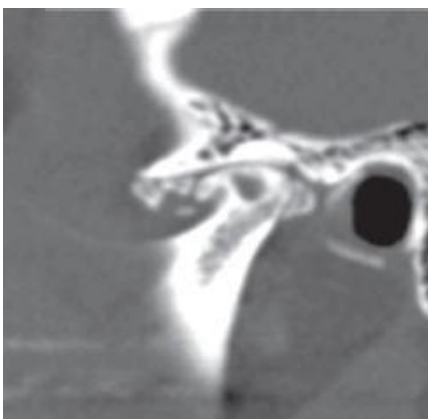


Figure 43: CBCT view showing Significant osteophytes.^[3]

Ultrasonography:

High-resolution diagnostic ultrasonography (typically 10–15 MHz linear transducers) offers a valuable radiation-free, real-time, dynamic imaging alternative for TMJ assessment, with particular utility in evaluating joint effusion, disc echogenicity, condylar surface irregularity, and synovial hypertrophy. Power Doppler ultrasonography enables visualization of increased vascularity in the synovial membrane during active inflammatory arthropathy, providing a non-invasive means of monitoring inflammatory disease activity.^[77]

The principal limitations of TMJ ultrasonography include its inability to visualize deep intra-articular structures due to acoustic shadowing from the condylar cortex, significant operator dependency requiring specialized training, and limited standardization of examination protocols across institutions. Despite these limitations, ultrasonography is increasingly employed as a complementary bedside tool for dynamic TMJ assessment, guided injection procedures, and monitoring treatment response.^[78]

Electromyography and Jaw Tracking:

Surface electromyography (sEMG) of the masticatory muscles provides objective data on muscle electrical activity, enabling quantification of muscle hyperactivity, asymmetry of bilateral muscle function, and the effectiveness of treatment interventions in reducing masticatory muscle co-contraction. Computer-assisted jaw movement tracking systems (electrognathography, jaw tracking devices) provide precise kinematic analysis of mandibular movement patterns, detection of movement irregularities indicative of disc displacement or condylar hypomobility, and quantification of movement velocity and acceleration.^[79]

Impact on quality of life:

Chronic TMDs impose a profound burden on multiple dimensions of health-related quality of life (HRQoL). Oral health-related quality of life (OHRQoL), measured with the Oral Health Impact Profile-14 (OHIP-14) and the Jaw Functional Limitation Scale (JFLS), is severely compromised in TMD patients, with significant impairments in functional limitation (eating, speaking), orofacial pain, psychological discomfort (worry, embarrassment), social disability (avoiding social activities), and handicap (inability to function).^[80]

Sleep disturbance is an especially significant HRQoL domain impacted by chronic TMDs. TMD pain interferes with sleep onset and maintenance, while

sleep bruxism—a sleep-related movement disorder closely associated with TMDs—perpetuates masticatory muscle pain and articular loading during sleep, creating a bidirectional relationship between poor sleep quality and TMD pain severity. Patients with both TMDs and comorbid sleep disorders demonstrate significantly greater pain severity, disability, and healthcare utilization.^[81]

The psychological burden of chronic TMDs is considerable. A systematic review by Reiter and colleagues found significantly elevated rates of depression (29–56%), anxiety (26–49%), and somatization in TMD patients compared to the general population. These psychological comorbidities not only contribute to greater pain severity and disability but also moderate treatment outcomes, with patients with high psychological distress demonstrating poorer responses to conventional TMD therapies. The biopsychosocial model of TMD management recognizes the necessity of addressing these psychological dimensions alongside physical treatment.^[82]

SECTION VII
EPIDEMIOLOGY OF
TEMPOROMANDIBULAR
DISORDERS

Prevalence and incidence:

The prevalence of TMDs varies considerably in the published literature, reflecting differences in diagnostic criteria, study populations, sampling methods, and the distinction between sign-based and symptom-based case definitions. Using the Research Diagnostic Criteria for TMD (RDC/TMD), the landmark OPPERA (Orofacial Pain: Prospective Evaluation and Risk Assessment) study—the largest prospective cohort study ever conducted on TMD—reported a first-onset annual incidence of 3.9% and a period prevalence of approximately 13% for chronic TMDs in a community-based cohort of 3,258 adults.^[83]

A systematic review by Manfredini and colleagues, encompassing 27 epidemiological studies from diverse geographical regions, reported population-based TMD prevalence estimates ranging from 6% to 68% for signs and 14% to 59% for symptoms, depending on the diagnostic system employed. The wide range highlights the critical influence of case definition on prevalence estimates.^[84]

The prevalence of specific TMD subtypes varies: myofascial pain accounts for 40–60% of TMD diagnoses in clinical samples, disc displacement with reduction for 20–30%, disc displacement without reduction for 5–10%, and osteoarthritis for 5–15%. Mixed presentations involving both muscular and articular components constitute a substantial proportion of clinical TMD presentations.^[85]

Sex and age distribution:

A striking and consistent epidemiological characteristic of TMDs is their disproportionate predilection for females, with female-to-male ratios ranging from 3:1 to 9:1 in treatment-seeking populations. This sex disparity has been attributed to multiple factors including hormonal influences (the association between estrogen and pain sensitivity, as evidenced by the exacerbation of TMD symptoms during hormonal fluctuations associated with the menstrual cycle, pregnancy, and menopause), sex differences in pain processing and central sensitization, higher rates of psychological comorbidities including anxiety and depression in women, and sociocultural factors influencing help-seeking behavior.^{[86][87]}

The age distribution of TMDs demonstrates a peak prevalence in the second to fifth decades of life, corresponding to the period of peak reproductive

and economic activity. Pediatric TMDs, while less prevalent, are increasingly recognized as a clinically significant entity, with studies reporting TMD signs in 15–40% of children and adolescents. In elderly populations, degenerative TMJ disease (osteoarthritis/osteoarthrosis) predominates, while myofascial pain and disc displacement disorders are more characteristic of younger adults.^[88]

Socioeconomic impact:

The socioeconomic burden of TMDs is profound and multidimensional. Chronic TMD pain interferes with fundamental activities of daily living including mastication, deglutition, phonation, and social interaction, imposing significant functional and psychosocial burdens on affected individuals. TMD patients demonstrate substantially higher rates of healthcare utilization, including more frequent dental and medical consultations, diagnostic investigations, and pharmacological prescriptions, compared to pain-free controls.^[89]

Work absenteeism and presenteeism (reduced productivity while at work due to pain-related impairment) are significant indirect costs of chronic TMDs. A study by Von Korff and colleagues found that TMD-related work disability was comparable in magnitude to that associated with back pain, with affected individuals losing an average of 7.2 workdays per year due to TMD-related pain. The total annual direct and indirect economic cost of chronic TMDs in the United States alone has been estimated to exceed USD 4 billion.^[89]

TMDs are frequently comorbid with other chronic pain conditions including headache disorders (particularly migraine and tension-type headache), fibromyalgia, irritable bowel syndrome, interstitial cystitis, and chronic widespread pain—collectively referred to as chronic overlapping pain conditions (COPCs). The OPPERA study demonstrated that the presence of COPCs significantly increased the risk of TMD onset, highlighting shared pathophysiological mechanisms involving central sensitization, altered pain modulation, and autonomic nervous system dysregulation.^[90]

SECTION VIII
CONVENTIONAL
MANAGEMENT
APPROACHES OF TMDs

Pharmacological management:

Pharmacological agents constitute the first line of management for acute TMD pain and play an adjunctive role in chronic TMD management. Non-steroidal anti-inflammatory drugs (NSAIDs), particularly ibuprofen (400–800 mg three times daily), naproxen sodium (500 mg twice daily), and diclofenac (50 mg three times daily), are the most widely prescribed agents for TMD pain due to their dual analgesic and anti-inflammatory mechanisms mediated through cyclooxygenase (COX-1 and COX-2) inhibition. A Cochrane systematic review by Mujakperuo and colleagues concluded that there is moderate evidence supporting the short-term efficacy of NSAIDs for TMD pain reduction.^[91]

Low-dose tricyclic antidepressants (TCAs), particularly amitriptyline (10–75 mg nightly) and nortriptyline, have been employed for their analgesic, sleep-modulatory, and antidepressant effects in chronic TMD management. TCAs modulate central pain processing through inhibition of norepinephrine and serotonin reuptake, potentiation of descending inhibitory pain pathways, and blockade of sodium and N-methyl-D-aspartate (NMDA) channels. Several controlled trials have demonstrated superior pain reduction with amitriptyline compared to placebo in chronic myofascial TMD.^[92]

Serotonin-norepinephrine reuptake inhibitors (SNRIs), particularly duloxetine and venlafaxine, represent alternative centrally acting analgesics for chronic TMD with a more favourable side-effect profile compared to TCAs. Muscle relaxants—including cyclobenzaprine, tizanidine, and methocarbamol—are employed for myofascial pain-predominant TMDs to reduce masticatory muscle hyperactivity. Clonazepam, benzodiazepine with muscle relaxant and analgesic properties, has demonstrated efficacy in reducing nocturnal masticatory muscle activity in bruxism-related TMDs.^[93]

Intra-articular corticosteroid injections—typically triamcinolone acetonide (10–40 mg) or methylprednisolone acetate (20–40 mg)—are employed for acute inflammatory arthropathies of the TMJ, providing potent localized anti-inflammatory effects. However, the chondrotoxic potential of repeated corticosteroid injections—evidenced by progressive articular fibrocartilage degradation, subchondral bone loss, and accelerated osteoarthritis—limits their repeated application and makes them unsuitable as long-term management strategies for chronic articular TMD.^{[94][95]}

Botulinum toxin type A (BTX-A) injections into hypertrophic masticatory muscles, particularly the masseter (25–50 units per side) and

temporalis (20–40 units per side), have emerged as an effective pharmacological intervention for bruxism-related myofascial pain, masseteric hypertrophy, and chronic masticatory muscle pain syndromes refractory to conventional therapies. By selectively inhibiting acetylcholine release at the neuromuscular junction, BTX-A reduces muscle contractile force and hyperactivity, thereby reducing masticatory muscle pain and bruxism-related TMJ loading.^[96]

Physiotherapy and Conservative Physical Modalities:

Physical therapy constitutes a cornerstone of conservative TMD management, encompassing a broad spectrum of interventions targeting masticatory muscle pain, restricted mandibular mobility, postural dysfunction, and neuromuscular coordination deficits. The therapeutic rationale for physiotherapy in TMDs is grounded in the recognition that many TMD presentations involve dysfunctional neuromuscular patterns, adaptive postural changes, and movement coordination deficits that respond to targeted physical rehabilitation.^{[97][98]}

Therapeutic exercises for the masticatory system include passive and active range-of-motion exercises, mandibular proprioceptive training, and neuromuscular coordination exercises. These interventions aim to restore normal mandibular movement patterns, reduce pain-related movement avoidance, and improve proprioceptive feedback from the periarticular structures. A systematic review by Armijo-Olivo and colleagues demonstrated that therapeutic exercises significantly improved pain and maximum mouth opening in TMD patients.^[99]

Manual therapy techniques applicable to TMDs include intraoral and extraoral joint mobilization, soft tissue manipulation of masticatory and cervical muscles, myofascial release techniques, and cervical spine manipulation. The anatomical and functional relationship between the cervical spine and the TMJ—mediated through shared neural pathways, the trigemino-cervical nucleus, and muscular connections—provides the rationale for addressing cervical dysfunction in TMD management.^[100]

Electrophysical modalities employed in TMD management include transcutaneous electrical nerve stimulation (TENS), which reduces masticatory muscle hyperactivity and provides analgesic effects through gate control and endorphin-mediated mechanisms; ultrasound therapy, which promotes tissue heating, increases collagen extensibility, and reduces inflammatory mediator concentrations; and low-level laser therapy (LLLT), which exerts biomodulatory effects including mitochondrial stimulation, enhanced ATP

synthesis, and anti-inflammatory cytokine modulation. A systematic review by Petrucci and colleagues found moderate evidence supporting LLLT for TMD pain reduction.^[101]

Occlusal splint therapy, particularly stabilization splints fabricated as full-arch hard acrylic appliances, remains one of the most widely prescribed reversible conservative interventions for TMDs. The proposed mechanisms of splint action include redistribution of occlusal loading forces, reduction of masticatory muscle EMG activity, promotion of condylar repositioning, and cognitive awareness modification that reduces parafunctional habits. A Cochrane review by Friction and colleagues concluded that stabilization splints are more effective than no treatment for myofascial pain reduction.^[102]

Surgical management:

Surgical interventions for TMDs occupy the apex of the treatment hierarchy and are reserved for patients with specific structural intra-articular pathologies refractory to comprehensive conservative management. The principle of maximum reversibility dictates that irreversible surgical procedures should be considered only after exhaustion of conservative and reversible options. The spectrum of TMJ surgical procedures ranges from minimally invasive arthrocentesis to complex total joint replacement.^[103]

Arthrocentesis of the TMJ, described by Nitzan, Dolwick, and Martinez in 1991, is the simplest and most commonly performed TMJ surgical procedure. It involves the continuous irrigation of the superior joint space with physiological saline or Ringer's lactate solution under local anaesthesia through a dual-needle technique, with the objectives of removing inflammatory mediators, lysing fibrous adhesions, removing by-products of cartilage breakdown, and restoring negative intra-articular pressure and disc mobility. Multiple randomized controlled trials have demonstrated the efficacy of arthrocentesis for improving mouth opening and reducing pain in disc displacement without reduction and early degenerative joint disease.^{[104][105]}

TMJ arthroscopy, a minimally invasive endoscopic procedure, permits direct visualization of the superior joint compartment, enabling lysis of adhesions, disc repositioning, lavage, debridement of diseased tissue, and biopsy under magnification. Open joint procedures including disc repositioning (discoplasty), discectomy with or without disc replacement using autogenous or alloplastic materials, condyloplasty, eminectomy, and total alloplastic joint

replacement are reserved for advanced structural joint pathology.^[106]

Introduction to Prolotherapy as a Regenerative treatment modality:

Against the background of the limitations of conventional TMD therapies, prolotherapy emerges as a biologically grounded, minimally invasive alternative that directly addresses the structural connective tissue deficiencies underlying many chronic articular TMDs. The fundamental premise of prolotherapy is that chronic pain arising from ligamentous laxity, fibrocartilaginous degeneration, and articular instability can be ameliorated—and potentially reversed—by stimulating the body's intrinsic tissue repair machinery through the controlled induction of a local healing response.^[60]

Prolotherapy involves the percutaneous injection of a proliferant solution—most commonly hypertonic dextrose (10–25%)—into the insertion points of ligaments and tendons, periarticular connective tissues, and intra-articular spaces. The injected solution acts as a chemical irritant, provoking cellular damage at the injection site that triggers the classical phases of wound healing: inflammation, proliferation, and remodelling. The net result, achieved over multiple treatment sessions, is the synthesis of new collagen fibres that augment the cross-sectional area, tensile strength, and biomechanical resilience of the treated connective tissues.^{[107][108]}

In the context of the TMJ, this regenerative mechanism holds particular relevance for conditions involving capsular laxity (predisposing to hypermobility and subluxation), elongated posterior discal ligaments (predisposing to disc displacement), degeneration of the retrodiscal bilaminar zone (causing chronic retrodiscal pain), and early degenerative changes of the articular fibrocartilage. By augmenting the structural integrity of these compromised tissues, prolotherapy aims to restore articular stability, normalize condyle-disc-fossa relationships, and eliminate the biomechanical triggers of chronic TMD pain.^[109]

SECTION IX
PROLOTHERAPY

Historical background and evolution of Prolotherapy: Ancient and pre-modern precursors:

The conceptual antecedents of prolotherapy extend to antiquity. Hippocrates (460–370 BC) is reported to have treated shoulder joint instability in javelin throwers by introducing a hot cautery probe into the joint to induce scar tissue formation that would restrict excessive movement—a crude but conceptually analogous precursor to the prolotherapy principle of inducing connective tissue proliferation to restore joint stability. Similarly, the ancient practice of 'firing' (applying hot irons to the tendons and ligaments of injured horses to induce scar formation and ligament strengthening) reflects an empirical understanding of the healing-promoting properties of controlled tissue injury.^[110]

Modern development by Hackett, Hemwall and collaborators:

The scientific foundation of modern prolotherapy was laid by Earl Gedney, an osteopathic physician, who in the 1930s described the use of sclerosing agents to strengthen hypermobile joints and lax ligaments in osteopathic athletes. Gedney's work attracted the attention of George Stuart Hackett (1895–1969), an American general surgeon practicing in Canton, Ohio, who systematically investigated the relationship between ligamentous insufficiency and chronic musculoskeletal pain over more than two decades of meticulous clinical observation.^[111]

Hackett introduced the concept of 'ligamentous relaxation'—a state of ligament insufficiency characterized by elongated, weakened fibres unable to provide normal articular restraint—as a primary etiological mechanism for chronic back, neck, and extremity pain. He developed a systematic injection technique targeting the entheses (ligament-to-bone attachment points) of specific spinal and appendicular ligaments with proliferant solutions, publishing his landmark monograph 'Ligament and Tendon Relaxation Treated by Prolotherapy' in 1956. Hackett documented significant clinical improvements in pain and function in over 1,800 patients treated over 15 years, establishing the clinical basis for prolotherapy practice.^[112]

Gustav Hemwall (1909–1998), a Swedish-American family physician from Oak Park, Illinois, became Hackett's most dedicated student and collaborator, ultimately treating more than 10,000 patients with prolotherapy over a 40-year career. Hemwall refined Hackett's injection techniques, extended their application to diverse musculoskeletal conditions, and made significant contributions to prolotherapy education through teaching seminars and

workshops. The Hackett-Hemwall Foundation, established in their honour, continues to advance prolotherapy education and research internationally.^[113]

C. Everett Koop, who later served as Surgeon General of the United States (1981–1989), received prolotherapy treatments from Hemwall for his own chronic back pain in the 1970s and became a prominent advocate for the technique. His endorsement brought prolotherapy to wider medical attention and provided a degree of mainstream medical credibility to a therapy that had been regarded with scepticism by the established medical community.^[114]

Development of Dextrose as the primary injectant:

The original Hackett-Hemwall prolotherapy formulation employed a combination of dextrose, glycerine, and phenol (Ongley's solution, also referred to as P2G solution), which produced a robust proliferative response but was associated with significant post-injection pain, tissue necrosis at high concentrations, and potential systemic toxicity from phenol absorption. The progressive refinement of prolotherapy injectants led to the identification of hypertonic dextrose as an effective, safe, and physiologically metabolized proliferant that could produce comparable regenerative effects with a substantially improved safety profile.^[115]

The work of Reeves and Hassanein in the late 1990s and early 2000s, producing the first randomized controlled trials of dextrose prolotherapy for peripheral joint conditions, established the scientific evidence base for dextrose as the reference-standard prolotherapy injectant and provided the methodological template for subsequent TMJ prolotherapy research. The parallel development of 'perineural injection therapy' (neural prolotherapy) by Lyftogt, employing low-concentration dextrose solutions for neurogenic pain via subcutaneous injection adjacent to sensitized peripheral nerves, expanded the clinical applications of dextrose and elucidated its neurogenic analgesic mechanisms.^[116]

Application to temporomandibular joint:

The application of prolotherapy to the temporomandibular joint emerged in the clinical literature in the late 1990s and early 2000s, motivated by the recognized limitations of existing articular TMD therapies and the biological plausibility of collagen-stimulating effects in the capsular and ligamentous structures of the TMJ. Reeves and Hassanein's 2000 randomized controlled trial provided the first level I evidence for the efficacy of dextrose prolotherapy in TMJ hypermobility, establishing a clinical research precedent that subsequent

investigators have built upon.^[117]

Mechanism of action: Cellular and Molecular basis

Phase 1: Osmotic cellular perturbation and initiation of inflammatory cascade:

When a hypertonic dextrose solution (10–25%) is injected into the target tissue, the osmotic gradient between the injectant and the intracellular fluid causes rapid dehydration of cell membranes—particularly the plasma membranes of fibroblasts, tenocytes, chondrocytes, and synoviocytes at the injection site. This osmotic cellular stress disrupts membrane integrity, triggers release of intracellular contents (including adenosine triphosphate, potassium ions, and cytosolic proteins), and activates mechanosensitive and osmosensitive signalling pathways including the MAPK/ERK pathway, the p38 pathway, and the NF- κ B transcription factor cascade.^[118]

The cellular damage at the injection site releases damage-associated molecular patterns (DAMPs) including high-mobility group box 1 (HMGB1) protein, heat shock proteins (HSPs), and fragmented extracellular matrix components that activate toll-like receptor (TLR) signalling on resident macrophages, mast cells, and dendritic cells. Mast cell degranulation releases preformed vasoactive mediators including histamine and tryptase, initiating the classical vascular response of the inflammatory phase: arteriolar vasodilation, increased capillary permeability, plasma protein extravasation, and leukocyte adhesion molecule upregulation.^[119]

Phase 2: The inflammatory Phase (Days 0-5):

The inflammatory phase of prolotherapy-induced healing parallels the classical wound healing inflammatory response. Neutrophils are the first circulating leucocytes to arrive at the injection site (within hours), executing phagocytosis of cellular debris and secreting neutrophil elastase, collagenase, and reactive oxygen species that further remodel the injected tissue matrix and amplify the inflammatory signal. Neutrophil-derived extracellular traps (NETs) may also contribute to the early inflammatory response by providing a scaffold for subsequent cellular events.^[120]

Monocytes, arriving by 24–48 hours, differentiate into tissue macrophages that assume the central coordinating role in the transition from the inflammatory to the proliferative phase. Macrophage polarization is a critical determinant of healing outcomes: M1 macrophages (classically activated)

produce pro-inflammatory cytokines (IL-1 β , IL-6, TNF- α) and reactive oxygen/nitrogen species that orchestrate the acute inflammatory response; M2 macrophages (alternatively activated), emerging as the inflammatory phase resolves, produce anti-inflammatory cytokines (IL-10, TGF- β 1) and pro-resolution lipid mediators (lipoxins, resolvins) that transition the tissue toward the regenerative proliferative phase.^[121]

Phase 3: Proliferative phase – Fibroblast activation and collagen synthesis (Day 3-21):

The proliferative phase is characterized by fibroblast recruitment, activation, and robust collagen synthesis—the key cellular events mediating the structural benefit of prolotherapy. Growth factors released at the injection site—particularly PDGF (from activated platelets and macrophages), TGF- β 1 (from platelets, macrophages, and newly activated fibroblasts), FGF-2 (from tissue macrophages and injured endothelial cells), and VEGF (promoting neovascularization)—create a potent chemoattractant and mitogenic environment that drives fibroblast migration from adjacent connective tissue into the healing zone.^[122]

Activated fibroblasts differentiate toward myofibroblasts under the influence of TGF- β 1, acquiring α -smooth muscle actin (α -SMA) expression that enables them to exert contractile forces on the ECM—important for wound closure in the early proliferative phase. These activated cells synthesize the structural proteins of the provisional and permanent ECM, including type III collagen (predominant in the early proliferative phase, providing elasticity), type I collagen (increasingly dominant as remodelling progresses, providing tensile strength), fibronectin, tenascin-C, and decorin and biglycan (small leucine-rich proteoglycans that regulate collagen fibrillogenesis and collagen fibre diameter).^[123]

The NF- κ B signalling pathway, activated by dextrose-induced cellular stress and cytokine receptor signalling, plays a central regulatory role in the fibroblast proliferative response, promoting the transcription of genes encoding growth factors, adhesion molecules, and extracellular matrix proteins. Laboratory studies have demonstrated that exposure of fibroblasts to dextrose concentrations equivalent to those used in prolotherapy (15–25%) significantly increases the production of TGF- β 1, PDGF, and connective tissue growth factor (CTGF/CCN2)—key autocrine and paracrine stimuli for fibroblast activation and collagen synthesis.^{[118][124]}

Phase 4: Remodelling phase – Collagen maturation and tissue strengthening (3 weeks - 12 months):

The remodelling phase, which extends well beyond the completion of active collagen synthesis, is responsible for the maturation and reorganization of the newly deposited collagen matrix into a biomechanically functional connective tissue. Key processes during remodelling include:

- (1) collagen fibril cross-linking by lysyl oxidase enzymes, which catalyse the formation of covalent bonds between lysine and hydroxylysine residues on adjacent collagen molecules, dramatically increasing the tensile strength of the fibril network;
- (2) progressive conversion of type III to type I collagen by fibroblast-mediated protease-remodelling;
- (3) realignment of collagen fibrils along lines of tensile stress through mechano-transduction signals; and
- (4) reduction in cellularity and synthetic activity as the tissue matures.^[125]

Mechanism of Action of Dextrose Prolotherapy

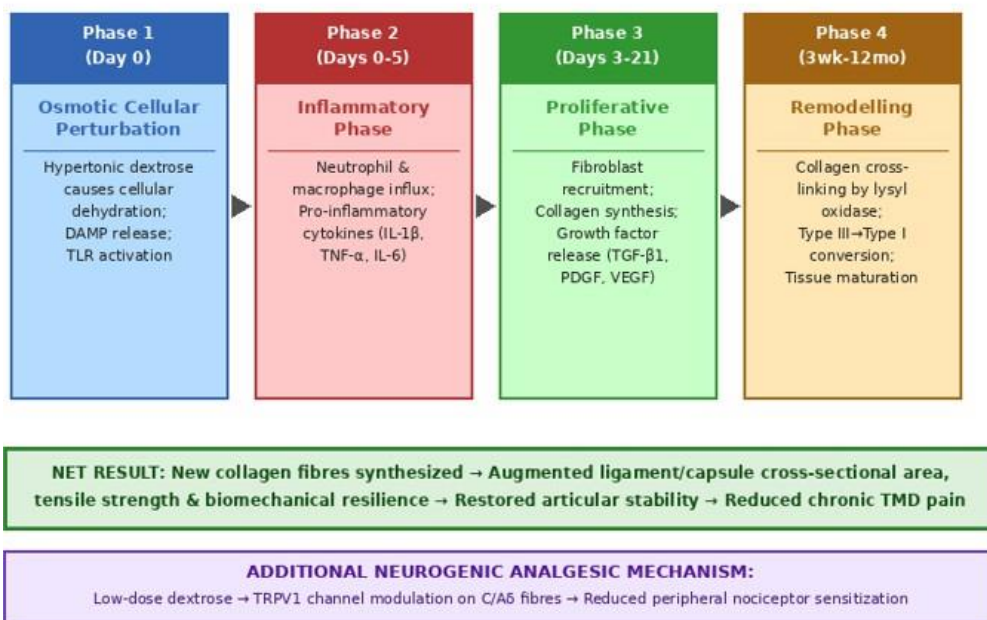


Figure 44: Cellular and molecular mechanism of action of dextrose prolotherapy showing four phases of healing:

- (1) Osmotic cellular perturbation,
- (2) Inflammatory phase,
- (3) Proliferative phase with collagen synthesis and
- (4) Remodelling phase with tissue maturation.^[118]

Histological studies in animal models of prolotherapy have directly demonstrated these remodelling changes. A landmark study by Liu and colleagues in rabbit medial collateral ligaments demonstrated that prolotherapy injection produced statistically significant increases in ligament mass (by 30–44%), ligament thickness, and the strength at the bone-ligament junction compared to saline control injections, accompanied by histological evidence of increased collagen fibril density and organization.^[107]

Neurogenic analgesic mechanisms:

Beyond the classic inflammation-proliferation-remodelling mechanism, prolotherapy with lower-concentration dextrose solutions (5–15%) has been proposed to exert direct neurogenic analgesic effects through mechanisms distinct from the proliferative response. Lyftogt's perineural injection therapy hypothesis posits that hyperosmolar dextrose injected subcutaneously adjacent to sensitized peripheral nociceptive nerve fibres exerts a transient blockade of transient receptor potential vanilloid 1 (TRPV1) channel—polymodal nociceptors expressed on small-diameter C and A δ fibres that are sensitized by inflammatory mediators and contribute to peripheral sensitization in chronic pain states.^[126]

The osmotic modulation of TRPV1 channel function may reduce the spontaneous activity and sensitization of peripheral nociceptors, providing rapid (often within minutes of injection) analgesic effects that precede the slower collagen-synthesis-mediated structural benefits of prolotherapy. This dual-mechanism model—rapid neurogenic analgesia combined with delayed structural regeneration—may explain the clinical observation that some TMD patients experience immediate post-injection pain improvement, even before the proliferative phase is well underway.^[127]

Additionally, prolotherapy may restore impaired proprioceptive function in hypermobile TMJs by reducing the mechanical stimulus that sensitizes joint mechanoreceptors during abnormal condylar translation, and—through

structural ligamentous strengthening—by improving the quality of proprioceptive afferent signals from newly matured collagen fibre mechanoreceptors. Improved proprioceptive feedback in turn refines neuromuscular control of mandibular movement, potentially contributing to more stable condylar positioning and reduced articular loading during function.^[128]

Injectants used in prolotherapy:

Hypertonic dextrose (D-Glucose):

Hypertonic dextrose is the most extensively researched, most commonly employed, and best-characterized prolotherapy injectant. Dextrose solutions for prolotherapy are typically prepared by diluting pharmacy-grade 50% dextrose (for intravenous use) with a combination of local anaesthetic (1–2% lidocaine or 0.5% bupivacaine) and/or normal saline to achieve the desired final concentration. The most commonly employed dextrose concentrations in TMJ prolotherapy studies range from 10% to 25%, with 12.5% (a 1:1 mixture of 25% dextrose and 1% lidocaine) and 25% (1:1 mixture of 50% dextrose and 2% lidocaine) being the most frequently reported preparations.^[129]

The physiological metabolism of dextrose—through glycolysis and the citric acid cycle—ensures complete clearance from the injection site without accumulation of toxic metabolites, contributing to the excellent safety profile of dextrose prolotherapy. The local anaesthetic component (lidocaine) serves to reduce the immediate post-injection pain associated with tissue distension and the osmotic cellular injury, improving patient comfort during and immediately following the procedure.^[130]

Phenol – Glycerine – Glucose (P2G / Ongley’s solution):

The original Hackett-Hemwall prolotherapy formulation, known as P2G solution or Ongley's solution, contains phenol (2.5%), glycerine (25%), glucose (25%), and lidocaine (1.5%) in sterile water. Phenol, a hydroxybenzene compound, acts as a potent tissue irritant and protein precipitant, inducing more intense and prolonged inflammatory stimulation than dextrose alone. Glycerine provides osmotic cellular disruption, while glucose contributes additional osmotic and metabolic stimuli.^[131]

P2G solutions were widely used in early prolotherapy practice and remain employed by a minority of practitioners, particularly for spinal and large joint prolotherapy where a more robust proliferative stimulus is desired.

However, their use for intra-articular TMJ injections is generally discouraged due to the risk of phenol-mediated tissue necrosis at higher concentrations, the intense and prolonged post-injection inflammatory response, and the availability of safer dextrose-only formulations with demonstrated efficacy. The potential for phenol systemic absorption through vascular injection, with associated neurotoxic and cardiotoxic risks, further limits the application of P2G solutions.^[131]

Platelet Rich Plasma (PRP):

Platelet-rich plasma is an autologous biological concentrate prepared by differential centrifugation of venous blood to produce a small volume of plasma containing supra-physiological concentrations of platelets (typically 3–8× baseline whole blood concentrations), platelet-derived growth factors, and bioactive proteins. PRP formulations are broadly classified by their leucocyte content (leucocyte-rich L-PRP versus leucocyte-poor LP-PRP or pure PRP) and their activation state (liquid PRP versus activated gel form activated with thrombin and/or calcium chloride).^[132]

The alpha granules of concentrated platelets contain potent growth factors including PDGF-AA, PDGF-BB, PDGF-AB, TGF- β 1, TGF- β 2, VEGF, EGF, insulin-like growth factor-1 (IGF-1), and hepatocyte growth factor (HGF)—a cocktail of regenerative signals that directly stimulates fibroblast, chondrocyte, and tenocyte proliferation and ECM synthesis without requiring the intermediary step of osmotic cellular injury that characterizes dextrose prolotherapy. LP-PRP is generally preferred for intra-articular applications to minimize the catabolic effects of neutrophil-derived enzymes and reactive oxygen species from leucocytes on the articular cartilage and disc.^[133]

Platelet Rich Fibrin (PRF):

Platelet-rich fibrin (PRF), developed by Choukroun and colleagues in 2001, is a second-generation platelet concentrate prepared without the addition of anticoagulants or exogenous activators, producing a three-dimensional fibrin scaffold that serves as a slow-release reservoir for platelet-derived growth factors. The fibrin architecture of PRF provides a natural carrier matrix for growth factor delivery, with sustained release profiles extending over 7–14 days compared to the more rapid release of growth factors from activated liquid PRP.^[134]

Advanced PRF formulations including injectable PRF (i-PRF) and concentrated growth factor (CGF) have been developed for application in joint

regeneration contexts. Intra-articular injection of i-PRF for TMJ osteoarthritis and disc displacement disorders has demonstrated promising preliminary results, with improvements in pain, function, and, in some studies, disc morphology on post-treatment MRI assessment.^[59]

Sodium Morrhuate and Other Injectants:

Sodium morrhuate, a mixture of sodium salts of saturated and unsaturated fatty acids derived from cod liver oil, is a potent sclerosant and proliferant that has been employed in prolotherapy, particularly for the treatment of varicose veins and, historically, for musculoskeletal conditions. Its mechanism involves direct cellular membrane disruption and protein denaturation, producing a robust but somewhat unpredictable inflammatory response. The relatively higher rate of adverse tissue reactions—including post-injection necrosis and allergic reactions—compared to dextrose has limited its contemporary application in TMJ prolotherapy.^[131]

Ozone (O₃) therapy, involving the intra-articular injection of oxygen-ozone gas mixtures (typically 5–20 µg/mL ozone concentration), has been investigated as a regenerative and anti-inflammatory intervention for TMJ disorders. Ozone exerts its effects through the production of reactive oxygen species that modulate inflammatory cytokine production, stimulate antioxidant defences, and potentially promote angiogenesis and collagen synthesis. Several studies have compared intra-articular ozone with corticosteroids and arthrocentesis for TMJ disorders, demonstrating comparable efficacy with a favourable safety profile.^[135]

Comparison of Prolotherapy with other Regenerative Therapies: Prolotherapy versus PRP: Biological comparison:

Dextrose prolotherapy and PRP share the fundamental objective of stimulating tissue regeneration but employ fundamentally different biological mechanisms. Dextrose acts indirectly by inducing controlled cellular damage and the subsequent wound healing cascade, using the body's endogenous growth factor synthesis capacity to drive regeneration. PRP acts directly by delivering exogenous, supra-physiological concentrations of platelet-derived growth factors that immediately engage fibroblast, chondrocyte, and tenocyte regeneration machinery without requiring the intermediate inflammatory damage signal.^[48]

This mechanistic distinction has clinical implications. Dextrose

prolotherapy may be more suitable for conditions where the primary deficit is connective tissue laxity or degeneration (hypermobility, discal ligament elongation) that requires robust collagen synthesis through the full proliferative cascade, while PRP may be preferred where the predominant pathology involves fibrocartilage degeneration (early osteoarthritis) that benefits more from direct growth factor stimulation of chondrocyte-like disc cells. In practice, the two modalities are not mutually exclusive and have been explored in combination protocols.^{[136][137]}

Prolotherapy versus Corticosteroid injections: A Fundamental distinction:

The philosophical and mechanistic contrast between prolotherapy and corticosteroid injection represents the most clinically relevant comparison in TMJ articular disorder management. Corticosteroids suppress the inflammatory cascade by binding to intracellular glucocorticoid receptors, thereby inhibiting NF- κ B activation, reducing cytokine production, decreasing prostaglandin synthesis, and inhibiting leucocyte migration. This anti-inflammatory action produces rapid and potent pain relief by eliminating the cytokine-mediated sensitization of nociceptors—an effect ideally suited for acute inflammatory arthropathy.^[5]

Prolotherapy, by contrast, deliberately initiates the inflammatory cascade as the first step in stimulating connective tissue regeneration. Its analgesic mechanism is not achieved by suppressing inflammation but by inducing the healing process that ultimately resolves the structural source of chronic pain. The long-term consequences of this mechanistic distinction are clinically significant: repeated corticosteroid injections have been demonstrated to produce chondrocyte apoptosis, inhibit fibroblast collagen synthesis, degrade articular cartilage matrix, and promote subchondral bone loss—progressive structural damage that contrasts sharply with the tissue-strengthening effects of prolotherapy.^[94]

SECTION IX - CHAPTER 1
**PROLOTHERAPY IN
TEMPOROMANDIBULAR
JOINT DISORDERS**

Principles of Patient selection:

Optimal patient selection is the most critical determinant of prolotherapy outcomes in TMDs. The appropriate selection of candidates requires a thorough clinical and radiographic evaluation to identify the specific TMD subtype, ascertain the structural basis of the patient's symptoms, assess prior treatment history, and screen for contraindications. The fundamental principle guiding selection is that prolotherapy should be considered when the primary clinical problem involves structural connective tissue insufficiency—laxity, degeneration, or inadequate healing of the capsular ligaments, discal ligaments, retrodiscal tissue, or articular fibrocartilage—that is amenable to stimulation of regenerative tissue repair.^[138]

Primary indications:

1) TMJ Hypermobility and Recurrent Subluxation: Patients with excessive condylar translation beyond the articular eminence (subluxation) or complete dislocation (luxation) arising from capsular laxity, ligamentous insufficiency, or a steep articular eminence represent the most well-established indication for prolotherapy in the TMJ. The regenerative strengthening of the joint capsule and lateral temporomandibular ligament by prolotherapy directly addresses the structural cause of hypermobility, providing a non-surgical alternative to eminectomy or eminoplasty for eligible patients.^[138]

2) Chronic Articular Pain with Early-to-Moderate Degenerative Changes: Patients with chronic preauricular pain, crepitus, and radiographic evidence of early degenerative changes (condylar flattening, early erosion) who have failed conservative management including NSAIDs, physiotherapy, and occlusal splint therapy for a minimum of 3–6 months are appropriate candidates for prolotherapy. The growth factor-mediated stimulation of fibrocartilaginous repair and the analgesic modulation afforded by dextrose may halt disease progression and provide durable symptomatic relief.^[104]

3) Disc Displacement Disorders with Pain: Patients with symptomatic disc displacement—with or without reduction—in whom pain is attributable to retrodiscal tissue inflammation and loading (due to posterior condylar displacement against the inflamed bilaminar zone) may benefit from targeted injection of the posterior joint space and retrodiscal region. By stimulating collagen synthesis in the elongated posterior discal ligaments and bilaminar zone fibrous tissues, prolotherapy may improve disc stability and reduce retrodiscal pain.^[46]

4) Post-traumatic TMD: Patients presenting with TMD symptoms following mandibular whiplash injuries (cervical hyperextension-hyperflexion trauma), direct chin trauma, intubation-related condylar displacement, or forceful dental procedures may present with acute capsular and ligamentous injury followed by chronic pain and hypermobility. Prolotherapy may accelerate connective tissue healing and prevent the chronification of post-traumatic TMD.^[47]

Contraindications:

Absolute contraindications to prolotherapy include: active local or systemic infection involving or adjacent to the injection site; documented allergy or hypersensitivity to dextrose, lidocaine, or other components of the injectant; uncontrolled or poorly controlled diabetes mellitus (a concern both due to impaired wound healing and the glucose content of the injectant, which may cause unpredictable glycaemic excursions in insulin-dependent patients); known bleeding diathesis or therapeutic anticoagulation with INR >2.5 (risk of haemarthrosis); and active malignancy involving the joint region.^[139]

Relative contraindications include: advanced degenerative joint disease with severe structural joint destruction requiring surgical reconstruction; avascular necrosis of the mandibular condyle; active inflammatory systemic arthropathy requiring disease-modifying antirheumatic drug (DMARD) therapy; pregnancy (due to the uncertain effects of repeated intra-articular injections and local anaesthetic exposure); and significant psychological comorbidity (severe untreated depression, anxiety disorders, or somatization) that may impair realistic expectations and compliance.^[140]

Injection technique and protocol:

Pre-Procedural preparation:

Prior to prolotherapy, a detailed pre-procedural assessment is performed to document baseline clinical parameters including pain intensity (VAS or NRS), maximum mouth opening (MMO), lateral and protrusive excursion, joint sound characteristics, and masticatory muscle tenderness. Relevant imaging—including recent CBCT (within 6 months) and/or MRI—is reviewed to confirm the diagnosis and identify anatomical variations that may affect injection technique. Standardized photographs or diagrams documenting the distribution of pain and palpation tenderness are recorded for monitoring treatment response.^[141]

Patients are counselled to discontinue NSAID medications for a minimum of 5–7 days before each injection session, as NSAIDs inhibit prostaglandin synthesis and cyclooxygenase-mediated inflammatory pathways—the very cascade that prolotherapy aims to activate. Acetaminophen (paracetamol) may be used for pain management in the peri-procedural period as it does not significantly inhibit the peripheral inflammatory response. Patients on anticoagulant therapy are assessed on a case-by-case basis, with bridging protocols or treatment modification considered in consultation with the treating physician.^[108]

Anatomical landmarks and approach:

The standard approach for TMJ prolotherapy is a preauricular percutaneous approach. With the patient supine or reclined at approximately 45° and facing straight ahead, the operator stands at the head of the table or to the side of the treated joint. The anatomical landmarks are identified by palpation: the tragus of the ear, the posterior border of the condyle (palpable just anterior to the tragus with the mouth slightly open), and the posterior slope of the articular eminence (palpable approximately 10–12 mm anterior to the condylar head with the mouth open 10–15 mm).^[138]

For the upper joint compartment injection, the patient is asked to open the mouth to approximately 10–15 mm (sufficient to translate the condyle anteriorly and open the upper joint space without excessive tissue tension). The injection point is located approximately 10 mm anterior to the tragus and just inferior to the zygomatic arch, at the level of the posterior slope of the articular eminence. A 25-gauge, 1.5-inch (38 mm) needle is introduced perpendicular to the skin surface and directed superiorly and anteriorly toward the posterior slope of the articular eminence at approximately 45° to the coronal plane.^[49]

Needle advancement is guided by anatomical landmarks and the characteristic tactile sensation of the needle entering the joint space (a slight 'give' on penetration of the fibrous capsule). In the upper joint compartment, a modest decrease in injection resistance (loss of resistance technique) may be perceived. Aspiration prior to injection is mandatory to confirm absence of intravascular needle placement. If blood is aspirated, the needle is repositioned before injection. If clear synovial fluid is aspirated, it confirms correct intra-articular placement and may be gently withdrawn to relieve the pressure of any effusion.^[138]

Additional injection sites:

In addition to the upper joint space, prolotherapy protocols for the TMJ may include injection into the following structures depending on the clinical presentation:

- (1) the lateral capsule and TML insertion, targeting the area just anterior and inferior to the condylar head with the mouth closed, directing the needle toward the lateral condylar neck and the fibrous capsule;
- (2) the posterior joint space, targeting the retrodiscal bilaminar zone with the condyle in the closed position, directing the needle posteriorly along the posterior condylar margin;
- (3) pericapsular injections at the insertions of the capsular ligaments into the temporal bone and condylar neck.^[45]

For patients with combined TMJ hypermobility and masticatory muscle pain, trigger point injections of the masseter and temporalis muscles with low-concentration dextrose (5–10%) may be incorporated into the treatment session.

This comprehensive approach—addressing both articular and myofascial components simultaneously—is consistent with the Hackett-Hemwall tradition of treating the entire injured region rather than focusing on a single anatomical target.^[142]

Injectant volume and concentration:

The volume of injectant injected into the upper joint compartment per session ranges from 0.5 to 2.0 mL in published studies, with most contemporary protocols employing 1.0–1.5 mL. The maximum safe volume for the upper joint compartment is limited by the capacity of the space (approximately 1.5–2.0 mL when distended) and by the risk of excessive intra-articular pressure if over-distension occurs. Lateral capsule and pericapsular injections use smaller volumes (0.25–0.5 mL per injection point) with a 'peppering' technique—multiple small aliquots deposited at slightly different depths along the needle tract as it is slowly withdrawn.^[46]

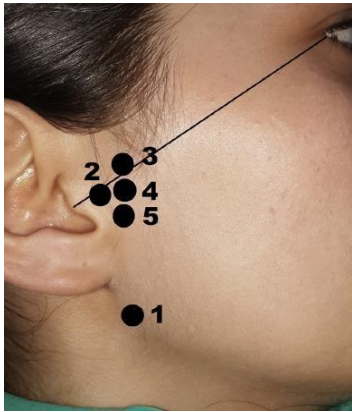


Figure 45: Injection points:
 1) stylomandibular ligament;
 2) posterior disc attachment;
 3) superior capsular attachment;
 4) superior joint space;
 5) inferior capsular attachment.^[46]



Figure 46: Injection at superior capsular attachment.^[47]



Figure 47: Injection into superior joint space.^[47]



Figure 48: Injection at inferior capsular attachment.^[47]

Post – Injection Management:

Immediately following injection, the patient is monitored for 15–20 minutes for adverse reactions including vasovagal syncope, allergic reactions, and signs of intravascular injection. Post-injection instructions include:

- (1) apply a clean ice pack to the preauricular region for 10–15 minutes immediately after the procedure to reduce local swelling;
- (2) avoid NSAIDs and aspirin for 5–7 days post-injection;
- (3) soft diet for 24–48 hours to reduce articular loading during the acute post-injection inflammatory phase;
- (4) gentle jaw range-of-motion exercises (passive and active) beginning 48 hours post-injection to prevent stiffness and to guide collagen remodelling along functional stress lines.^[6]

Follow-up assessments are scheduled at 4–6 week intervals coinciding with each subsequent injection session, with standardized re-evaluation of pain, MMO, jaw function, and patient-reported global improvement. Documentation of objective clinical measurements at each visit provides the framework for monitoring treatment response and adjusting the treatment plan accordingly. The treatment protocol is typically completed after 3–6 sessions, depending on clinical response.^[49]

Clinical evidence for pain reduction:

Randomized controlled trials:

Reeves and Hassanein's landmark 2000 randomized, double-blind, placebo-controlled trial assigned 39 patients with chronic TMJ hypermobility and pain to receive either 10% dextrose/0.2% lidocaine prolotherapy or 0.2% lidocaine control injections (three sessions at monthly intervals). At 12-month follow-up, the prolotherapy group demonstrated statistically significant reductions in pain VAS scores (mean reduction of 56% vs 20% in controls, $p < 0.01$), significant improvements in MMO (mean increase of 11.3 mm vs 3.2 mm), and marked reduction in subluxation frequency. This study established level I evidence for dextrose prolotherapy in TMJ hypermobility.^[45]

Cömert Kiliç and Güngörmüş conducted a three-arm RCT ($n=60$) comparing intra-articular prolotherapy (25% dextrose), corticosteroid (methylprednisolone acetate 40 mg), and saline placebo injections in patients

with TMJ osteoarthritis confirmed by CBCT. Three injections were administered at 4-week intervals. At 6-month follow-up, the prolotherapy group showed the greatest and most durable reductions in VAS pain scores and improvements in MMO. The corticosteroid group demonstrated superior early (1-month) pain reduction but partial regression by 6 months, while the placebo group showed modest spontaneous improvement. The authors concluded that prolotherapy provides more durable benefits than corticosteroid injection for TMJ osteoarthritis.^[46]

A randomized pilot trial by Refai, Altahhan, and Elsharkawy enrolled 20 patients with radiographically confirmed TMJ hypermobility and randomized them to receive three intra-articular dextrose prolotherapy sessions or arthrocentesis. Both modalities demonstrated significant improvements in pain and mandibular movement. The prolotherapy group showed superior improvements in condyle-fossa relationships on post-treatment imaging and a higher rate of subluxation resolution (85% vs 65% at 12 months) compared to arthrocentesis.^[47]

Prospective cohort studies:

Hauser, Hauser, and Baird reported a retrospective study of 26 chronic TMD patients who received a mean of 5.3 Hackett-Hemwall dextrose prolotherapy sessions over 7.2 months. VAS pain scores improved from a mean baseline of 7.2 to 2.4 at final follow-up (67% reduction), and MMO improved from 32.5 mm to 42.8 mm (10.3 mm improvement). Of 26 patients, 92% reported improvement in overall condition and 77% stated that prolotherapy had met their treatment expectations. No serious adverse events were documented.^[49]

Ko, Lee, and colleagues conducted a prospective observational study of 34 patients with chronic TMD (mixed articular and myofascial presentations) receiving three intra-articular dextrose prolotherapy sessions. significant improvements in vas pain scores (52.3% reduction), MMO (8.7 mm improvement), and Jaw Functional Limitation Scale (JFLS-20) scores were observed at 3-month follow-up, with maintained improvements at 6 months. Patients with predominantly articular presentations (disc displacement, osteoarthritis) demonstrated greater pain reduction than those with myofascial predominance.^[143]

Study done by	Study Type & Participants	Therapy Administered	Outcome
Reeves & Hassanein, 2000, USA ^[45]	RCT, 39 patients (20 prolotherapy, 19 control), TMJ hypermobility	10% dextrose + 0.2% lidocaine, 1 mL intra-articular; 3 monthly sessions vs lidocaine alone	Pain VAS, MMO, subluxation frequency; assessed at baseline and 12 months → VAS decreased by 56% vs 20% control; MMO increased by 11.3 mm vs 3.2 mm; marked reduction in subluxation
Cömert Kiliç & Güngörmüş, 2016, Turkey ^[46]	3-arm RCT, 60 patients, (20/group), TMJ osteoarthritis	Group 1: 25% dextrose, 1 mL; Group 2: methylprednisolone acetate 40 mg, 1 mL; Group 3: saline 1 mL; 3 sessions at 4-week intervals	Pain VAS, MMO; assessed at 1, 3, 6 months → Prolotherapy group showed greatest and most durable pain decreased; corticosteroid group early improvement regressed by 6 months; placebo modest spontaneous improvement
Refai, Altahhan & Elsharkawy, 2011, Egypt ^[47]	Randomized pilot trial, 20 patients, TMJ hypermobility	25% dextrose, 1.5 mL intra-articular + lateral capsule; 3 sessions at 4-week intervals vs arthrocentesis	Pain VAS, MMO, subluxation, imaging; assessed at 3, 6, 12 months → Both improved; prolotherapy superior in condyle-fossa relationship and subluxation resolution (85% vs 65%)

Hauser, Hauser & Baird, 2001, USA ^[49]	Retrospective cohort, 26 patients, chronic TMD patients	Hackett-Hemwall prolotherapy: 25% dextrose into TMJ upper space, lateral capsule, cervical ligaments; mean 5.3 sessions over 7.2 months	Pain VAS, MMO, patient satisfaction; assessed at final follow-up (~7 months) → VAS decreased by 67% (7.2 → 2.4); MMO increased by 10.3 mm; 92% reported improvement; 77% met expectations; no adverse events
Ko, Lee et al., 2005, Korea ^[143]	Prospective observational study, 34 patients, chronic TMD (mixed articular and myofascial presentations)	Three intra-articular dextrose prolotherapy sessions (concentration not specified, typical 12.5–25%)	Pain VAS, MMO, JFLS-20; assessed at 3 and 6 months → VAS decreased by 52.3%; MMO increased by 8.7 mm; JFLS-20 improved; articular-predominant cases showed greater pain reduction

Table 2: Describing clinical evidence of pain reduction studies

Functional outcomes: Mouth opening and Jaw function:

Improvement in maximum mouth opening (MMO) is the most consistently reported functional outcome in TMJ prolotherapy studies. Across the published literature, mean improvements in MMO following a complete prolotherapy course (3–6 sessions) range from 5.2 to 14.6 mm, with higher baseline restriction predicting greater absolute improvement. The mechanisms underlying MMO improvement with prolotherapy include: reduction in articular pain reducing protective muscle guarding and trismus; improved articular mechanics from disc stabilization; and resolution of intra-articular adhesions through the hydraulic distension effect of the injection.^[143]

Jaw Functional Limitation Scale (JFLS-20) scores—assessing functional limitation across three domains: mastication, vertical jaw mobility, and verbal/emotional communication—have been employed as standardized

outcomes in several recent studies. Significant improvements across all JFLS-20 domains have been documented following prolotherapy, indicating clinically meaningful restoration of jaw function beyond the objective measurement of MMO alone. Patient-reported improvements in the ability to eat harder foods, sustain speaking, and perform social activities requiring jaw function are particularly meaningful endpoints that reflect real-world treatment impact.^[45]

Safety profile and adverse effects:

Commonly reported adverse effects:

Post-injection soreness is the most consistently reported adverse effect of TMJ prolotherapy, occurring in 60–85% of patients following each injection session. It typically manifests as increased preauricular pain, jaw stiffness, and limited comfortable mouth opening in the 24–72 hours following injection, corresponding to the acute inflammatory phase. This temporary exacerbation is an expected consequence of the intended inflammatory stimulus and is reliably self-limiting, resolving within 3–5 days in the majority of patients. Concurrent mild swelling and erythema in the preauricular region may accompany post-injection soreness.^[139]

Transient headache, dizziness, and a sensation of jaw tightness are occasionally reported in the immediate post-injection period, typically resolving within several hours. These symptoms likely reflect a combination of local anaesthetic effects, the brief osmotic cellular perturbation at the injection site, and the patient's psychological response to the procedure. Pre-emptive counselling of patients to expect these temporary reactions reduces procedure-related anxiety and improves compliance with subsequent sessions.^[6]

Rare and Theoretical complications:

Infection—specifically septic arthritis—is a theoretical risk of any intra-articular injection procedure. However, no cases of septic arthritis attributable to dextrose prolotherapy of the TMJ have been reported in the published literature, likely reflecting the bacteriostatic properties of hypertonic dextrose and the relatively avascular nature of the disc/capsular injection targets. Strict adherence to sterile injection technique—including pre-injection skin antisepsis with 2% chlorhexidine gluconate or povidone-iodine, use of sterile disposable needles and syringes, and sterile preparation of the injectant—is the primary preventive measure.^[108]

Injury to the auriculotemporal nerve, with consequent temporary

paresthesia or neuralgia in its sensory distribution (tragus, anterior auricle, and temporal region), is a potential complication of TMJ injection due to the proximity of this nerve to the standard injection site. Most reported cases of post-injection paraesthesia in the auriculotemporal territory following TMJ procedures resolve spontaneously within weeks to months. Facial nerve injury—though theoretically possible if the needle deviates posteriorly into the parotid gland—has not been reported in the context of TMJ prolotherapy.^[144]

SECTION IX - CHAPTER 2
ADVANTAGES AND
LIMITATIONS OF
PROLOTHERAPY IN
TMDs

Advantages of Prolotherapy in TMD Management:

1)Biologically Rational, Regenerative Mechanism:

The most notable advantage of prolotherapy is its alignment with the fundamental principles of tissue repair biology. Rather than suppressing pain symptoms pharmacologically or removing diseased tissue surgically, prolotherapy exploits the body's innate wound healing machinery to regenerate the specific connective tissue structures whose functional failure underlies chronic articular TMD. This approach respects the biological complexity of connective tissue repair, recruits the full complement of growth factors, cytokines, and cellular mediators that the body has evolved to deploy in healing responses, and ultimately produces new, biologically authentic collagen that integrates with the existing tissue matrix.^[60]

The evidence that prolotherapy genuinely increases collagen synthesis, collagen fibre density, and ligamentous cross-sectional area—documented in multiple preclinical animal studies—distinguishes it from symptomatic treatments that modulate pain perception without restoring tissue structure. The theoretical implication of this regenerative mechanism is disease modification: by restoring structural integrity to the lax capsular ligaments and elongated discal attachments, prolotherapy may interrupt the pathological cycle of abnormal articular mechanics, excessive loading, and progressive degeneration that drives the chronification and escalation of articular TMDs.^[107]

2)Minimally invasive character:

Prolotherapy requires only a percutaneous needle injection—a procedure performable in the outpatient setting under local anaesthesia in 10–15 minutes—without the need for general anaesthesia, incision, joint distension under pressure (as in arthroscopy), or intraoperative fluoroscopic or endoscopic guidance. This minimal invasiveness translates into multiple clinical advantages: no recovery period beyond 24–48 hours of post-injection soreness; preservation of all TMJ structures (no risk of disc perforation, condylar surface damage, or nerve injury from surgical manipulation); no hospitalization costs; and ability to repeat treatment without cumulative surgical risk.^[130]

3)Cost – Effectiveness:

A complete dextrose prolotherapy course for TMDs (typically 3–6 sessions) represents a substantially lower cost than surgical interventions including TMJ arthroscopy (typically requiring day surgery facilities, general

anaesthesia, and arthroscopic equipment) or open joint procedures. The cost comparison with prolonged pharmacological therapy is also favourable when the long-term durability of structural improvement from prolotherapy is considered: patients who achieve structural stabilization and durable symptom relief through prolotherapy may require substantially fewer ongoing pharmacological prescriptions, physiotherapy sessions, and follow-up consultations.^[110]

4) Favourable safety profile:

The clinical safety record of dextrose prolotherapy, across thousands of published cases in musculoskeletal medicine, represents a major advantage over both pharmacological and surgical alternatives. The absence of the systemic adverse effects of chronic NSAID use (gastrointestinal ulceration, renal impairment, cardiovascular events), the chondrotoxic potential of repeated corticosteroid injections, the hepatotoxicity of acetaminophen overuse, and the potential morbidity of surgical interventions make dextrose prolotherapy one of the safest available interventions for chronic articular TMD in the medium to long term.^[145]

5) Compatibility with Concurrent Therapies:

Prolotherapy is compatible with—and potentially synergistic with—most other conservative TMD management modalities. Concurrent use of occlusal splints (which reduce parafunctional loading on the joint during the healing phase), physiotherapy (which restores neuromuscular coordination and guides collagen remodelling along functional stress lines), low-level laser therapy (which may enhance cellular proliferative responses), and psychological support (which addresses comorbid pain-related psychological distress) creates a multimodal management protocol that addresses the multiple pathophysiological dimensions of TMDs comprehensively.^[97]

6) Patient acceptance and satisfaction:

Patient-reported satisfaction with prolotherapy in published surveys and clinical studies is consistently high, with 80–92% of patients in different studies reporting overall improvement, willingness to repeat the treatment if necessary, and willingness to recommend prolotherapy to other TMD patients. The alignment of prolotherapy's regenerative philosophy with patients' preference for treatments that 'heal the cause' rather than 'mask the symptoms' contributes to positive patient engagement and treatment compliance. This patient-centred value proposition is an important practical advantage in a therapeutic area where

long-term patient engagement is essential for optimal outcomes.^[50]

Limitations of Prolotherapy:

1) Absence of Standardized Clinical Protocols:

The most significant barrier to the routine clinical adoption of prolotherapy for TMDs is the lack of standardized, evidence-based injection protocols validated through high-quality clinical trials. The current literature demonstrates substantial heterogeneity in dextrose concentration (ranging from 5% to 25%), injection volume (0.5–2.0 mL per session), number of injection sites (single upper joint space vs. multiple pericapsular sites), number of sessions (1–10), treatment intervals (2–8 weeks), and concurrent injection of masticatory muscles. This protocol variability makes it impossible to define a single optimal protocol from existing evidence and creates challenges for meaningful inter-study comparisons and meta-analytical pooling.^[60]

2) Evidence quality limitations:

While the evidence base for TMJ prolotherapy is broadly positive, it remains limited in methodological quality compared to the highest standards for clinical evidence. Most published studies are characterized by small sample sizes (typically 20–60 patients), limiting statistical power to detect moderate effect sizes and to explore subgroup differences (e.g., by TMD subtype or severity). Many studies lack a true placebo control—a particularly important limitation given the known non-specific effects of injection procedures including the attentional effects of clinical contact, the hydraulic joint distension from any injectant, and the placebo response to invasive procedures.^[146]

3) Requirement of Multiple sessions and Delayed response:

Unlike corticosteroid injections, which typically produce significant pain reduction within 24–72 hours, dextrose prolotherapy requires multiple sessions over a period of 2–6 months before maximum benefit is achieved, reflecting the time course of the proliferative healing cascade. The requirement for repeated injections, each associated with temporary post-injection soreness, represents a practical and psychological barrier for some patients—particularly those with high pain sensitivity, needle phobia, demanding occupational schedules, or logistical challenges related to clinic access.^[108]

4) Operator dependency:

The efficacy and safety of TMJ prolotherapy are significantly dependent

on the operator's anatomical knowledge, injection skill, and clinical judgment in patient selection. Unlike orally administered pharmacological treatments or standardized physiotherapy protocols, prolotherapy is inherently operator-dependent: the precision of needle placement within the intended target tissue, the volume and distribution of injectant within the joint space and pericapsular tissues, and the accuracy of anatomical targeting all require specialized training and procedural experience that may not be universally available in dental practice settings.^[108]

5) Absence of formal speciality guidelines:

The absence of formal clinical practice guidelines from major dental and orofacial pain specialty societies (AAOP, International Association for Dental Research, Royal College of Surgeons) endorsing or providing specific recommendations for prolotherapy in TMDs creates a regulatory and practice guidance vacuum that may discourage clinicians from adopting this modality and may expose practitioners who do offer it to medico-legal uncertainty. The development of evidence-based guidelines requires the accumulation of higher-quality evidence and formal endorsement processes that typically lag several years behind the publication of supporting clinical evidence.^[4]

6) Patient compliance challenges:

Achieving optimal prolotherapy outcomes requires sustained patient compliance across multiple sequential sessions, strict adherence to NSAID avoidance periods, initiation of recommended jaw exercises between sessions, and commitment to concurrent lifestyle modifications (bruxism management, stress reduction, dietary adjustments). Patients with significant pain-related psychological distress, poor health literacy, competing health concerns, or inadequate social support may struggle to maintain the level of engagement required for optimal prolotherapy outcomes, potentially resulting in incomplete treatment courses and suboptimal results.^[49]

7) Patient selection, Compliance and Psychosocial factors:

The biopsychosocial model of TMD management recognizes that patient psychological factors—including anxiety, depression, pain catastrophizing, fear-avoidance behaviour, and somatization—are major determinants of treatment outcomes. Patients with high pain catastrophizing (characterized by magnification of pain significance, rumination about pain, and helplessness in the face of pain) demonstrate consistently poorer outcomes across diverse TMD

treatment modalities, including prolotherapy. Pre-treatment psychological screening using validated instruments such as the PHQ-9 (depression), GAD-7 (anxiety), and the Pain Catastrophizing Scale (PCS) enables identification of patients requiring concurrent psychological support.^[82]

Motivational interviewing and patient education strategies focused on promoting realistic expectations, understanding the biological basis of prolotherapy's delayed regenerative effects, and framing temporary post-injection soreness as a positive sign of healing initiation are important components of the treatment process that may significantly improve patient compliance and treatment satisfaction. Collaboration with clinical psychologists and pain management specialists for patients with significant psychological comorbidity is an integral component of best-practice prolotherapy care.^[147]

SECTION IX - CHAPTER 3
FUTURE DIRECTIONS IN
PROLOTHERAPY FOR
TMDs

Emerging Injectants and Combination Biological Therapies:

1)Enhanced Prolotherapy: Dextrose combined with PRP:

The combination of hypertonic dextrose with platelet-rich plasma—sometimes designated 'enhanced prolotherapy' or 'dextrose-PRP prolotherapy'—represents one of the most immediately clinically translatable emerging approaches. The mechanistic rationale is compelling: dextrose activates the inflammatory cascade and stimulates endogenous growth factor synthesis, while the simultaneously injected PRP delivers an exogenous bolus of concentrated platelet-derived growth factors (PDGF, TGF- β , VEGF, IGF-1) that directly amplify the fibroblast proliferative response during the critical early proliferative phase.^[48]

Preclinical studies in rabbit anterior cruciate ligament models have demonstrated superior collagen synthesis and ligament biomechanical properties with dextrose-PRP combination injections compared to either modality alone. A proof-of-concept clinical series by Hauser and colleagues reported superior pain reduction and functional outcomes with enhanced prolotherapy compared to historical dextrose-only protocols, though the absence of a concurrent control group prevents definitive conclusions. Multicentre RCTs comparing dextrose-PRP combination therapy with dextrose alone and PRP alone in TMJ disorders are identified as a high-priority future research direction.^[59]

2)Platelet - Rich Fibrin (PRF) and Concentrated Growth Factor (CGF):

The sustained-release growth factor delivery characteristics of platelet-rich fibrin (PRF) make it an attractive candidate for single-injection protocols that provide prolonged biological stimulation of fibrocartilage repair without requiring repeated injections at short intervals. Injectable PRF (i-PRF), prepared by low-speed centrifugation to produce a liquid, injectable platelet concentrate with a high fibrinogen concentration, has demonstrated promising preliminary results for TMJ disc displacement and early osteoarthritis in several uncontrolled clinical series.^[134]

Concentrated growth factor (CGF), a third-generation autologous platelet concentrate produced by a specific variable centrifugation speed protocol, contains higher concentrations of TGF- β 1, PDGF, VEGF, and bone morphogenetic proteins (BMPs) compared to conventional PRP. Its application in TMJ regeneration contexts, while supported by compelling preclinical data, requires further clinical validation through well-designed RCTs.^[50]

3) Mesenchymal Stem Cell and Stromal Vascular Fraction Therapy:

Mesenchymal stem cell (MSC) therapy represents the leading edge of biological regenerative therapy for joint disorders. MSCs, harvestable from bone marrow (BM-MSCs), adipose tissue (AD-MSCs), or synovial membrane (SM-MSCs), possess both immunomodulatory properties—suppressing T-cell proliferation, modulating macrophage polarization toward an M2 anti-inflammatory phenotype, and inhibiting B-cell activation—and chondrogenic differentiation potential that enables them to contribute to fibrocartilage repair.^[148]

Stromal vascular fraction (SVF), the heterogeneous cell pellet obtained from enzymatic digestion and centrifugation of liposuctioned adipose tissue, contains AD-MSCs, pericytes, endothelial progenitor cells, and regenerative macrophages in a single autologous preparation obtainable on the same day as injection (unlike culture-expanded MSCs, which require a 2–4-week ex vivo expansion period). SVF has demonstrated significant anti-inflammatory and regenerative effects in preclinical models of osteoarthritis. Its application to TMJ regeneration in clinical settings is currently in the early investigation phase, with several ongoing pilot studies.^[149]

4) Exosome therapy:

Extracellular vesicles—particularly exosomes (40–150 nm vesicles) derived from MSCs—represent an emerging cell-free alternative to direct MSC therapy that retains many of the immunomodulatory and regenerative properties of the parent cells while avoiding concerns about direct cell transplantation (ectopic differentiation, immune rejection, malignant transformation). MSC-derived exosomes carry a cargo of microRNAs, mRNAs, proteins, and lipids that modulate the gene expression of recipient cells—particularly fibroblasts, chondrocytes, and macrophages—to promote anti-inflammatory and pro-regenerative phenotypes.^[150]

Preclinical studies have demonstrated that intra-articular injection of MSC-derived exosomes in rodent and rabbit models of osteoarthritis significantly reduces cartilage degradation, promotes chondrocyte proliferation and matrix synthesis, and reduces synovial inflammation. The clinical translation of exosome therapy to the TMJ requires the development of scalable exosome production and standardization protocols, regulatory frameworks for exosome-based products, and early-phase clinical trials to establish safety and preliminary efficacy in human TMJ disorders.^[150]

5) Gene therapy and Growth Factor Gene Delivery:

Gene therapy approaches employing viral and non-viral vectors to deliver therapeutic genes encoding anti-inflammatory cytokines (IL-1 receptor antagonist, IL-10), anabolic growth factors (TGF- β 1, IGF-1, BMP-7), or anti-catabolic agents (MMP inhibitors, ADAMTS inhibitors) to articular cells represent a futuristic but biologically compelling direction for TMJ regeneration. Adeno-associated virus (AAV) vectors have demonstrated effective and sustained intra-articular transduction in preclinical joint models.^[151]

Integration with Physiotherapy and Rehabilitation:

The Post – Prolotherapy Rehabilitation Window:

The period following prolotherapy constitutes a biologically defined rehabilitation window during which the newly synthesized collagen is maturing and can be mechanically directed along functional stress trajectories. Physiotherapy initiated 48–72 hours after each prolotherapy session—beginning with gentle passive range-of-motion exercises and progressively advancing to active jaw mobilization, resistance exercises, and functional training—aligns with the mechanobiological principle that mechanical stimulation guides collagen fibril alignment and crosslinking in regenerating connective tissue.^[6]

Structured post-prolotherapy rehabilitation protocols incorporating mandibular proprioceptive training, cervical stabilization exercises, scapular posture correction, and orofacial relaxation techniques have been proposed but not yet formally evaluated in prospective studies. The development and validation of standardized post-prolotherapy rehabilitation protocols for TMDs represents an important future research direction with the potential to significantly augment prolotherapy's structural and functional outcomes.^[97]

Biofeedback – Augmented Rehabilitation:

Biofeedback technologies—including surface EMG biofeedback, masseter kinesiography, and intraoral muscle activity monitors—enable real-time feedback of masticatory muscle activity to TMD patients, facilitating awareness and voluntary regulation of nocturnal and diurnal bruxism, masticatory muscle co-contraction, and jaw clenching habits. Integration of biofeedback-assisted bruxism management with prolotherapy may optimize outcomes by reducing the parafunctional articular loading forces that challenge the healing connective tissues during the prolotherapy treatment course.^[99]

Prolotherapy in Early Degenerative TMJ Disease: Disease Modification:

Perhaps the most clinically impactful future application of prolotherapy is its potential role as a disease-modifying intervention in early degenerative TMJ disease—the stage at which structural joint destruction is still limited, the articular fibrocartilage retains some regenerative capacity, and the condylar subchondral bone architecture is still amenable to remodelling in response to improved joint mechanics.^[13]

The ability to identify early TMJ degenerative disease before significant structural destruction has occurred is a critical prerequisite for this disease-modification strategy. Advances in quantitative MRI cartilage mapping—including T2 relaxometry (sensitive to collagen fibre disorganization), T1ρ relaxometry (sensitive to proteoglycan content), and diffusion tensor imaging (sensitive to tissue microstructure)—may enable the detection of subtle fibrocartilage compositional changes preceding visible morphological breakdown on conventional MRI, potentially providing a target for early prolotherapy intervention.^[152]

Synovial fluid biomarker profiling—measuring concentrations of collagen degradation products (C-terminal telopeptide of type II collagen, COMP), pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), and matrix metalloproteinases—may complement imaging in characterizing the stage and biological activity of TMJ degenerative disease, enabling the selection of patients most likely to benefit from regenerative intervention and providing biochemical outcome measures for future prolotherapy trials.^[153]

Need for high quality RCTs and Protocol Standardization: Design requirement for future trials:

Definitive evidence for the efficacy of prolotherapy in specific TMD subtypes requires the conduct of large-scale, methodologically rigorous multicentre RCTs adhering to the highest standards of clinical trial design as outlined in the CONSORT statement. Key design elements for future trials include:

- (1) DC/TMD-based patient selection with pre-specified TMD subtype stratification;
- (2) standardized injection protocols described in sufficient detail to enable replication;

- (3) sham injection placebo control arm (using normal saline or a procedure-matched placebo);
- (4) allocation concealment and operator blinding (evaluator blinded to treatment assignment); (5) pre-registered primary and secondary outcomes using validated instruments (VAS/NRS, MMO, JFLS-20, GCPS, OHIP-14, SF-36);
- (6) minimum 12-month follow-up with structural imaging endpoint; and
- (7) sample size calculations providing 80% power to detect clinically significant between-group differences.^[61]

International Collaboration and Data Sharing:

The relatively small number of TMD patients presenting to any single centre with appropriate clinical and research infrastructure necessitates international multicentre collaboration for adequately powered prolotherapy trials. The International RDC/TMD Consortium Network, which has previously coordinated the development of the DC/TMD diagnostic criteria across multiple countries and languages, provides an existing infrastructure for multicentre TMD research that could be leveraged for future prolotherapy trials. The establishment of shared data repositories with common data elements for prolotherapy clinical trial data would facilitate meta-analysis and evidence synthesis across studies.^[154]

Health Economics and Cost – Effectiveness Research:

Formal health-economic evaluations—including cost-effectiveness analyses, cost-utility analyses (measuring outcomes in quality-adjusted life years, QALYs), and budget impact analyses—are essential for informing healthcare resource allocation decisions and for supporting the integration of prolotherapy into publicly funded healthcare systems. The relative cost-effectiveness of prolotherapy compared to surgical interventions and long-term pharmacological therapy is a significant potential advantage that needs formal quantification through health-economic studies embedded in future clinical trials.^[155]

Artificial Intelligence and Precision Medicine Applications:

Emerging computational technologies including machine learning algorithms, artificial intelligence-based diagnostic systems, and radiomics analysis of TMJ imaging are beginning to transform the diagnostic and prognostic evaluation of TMDs. Machine learning models trained on large

clinical datasets have demonstrated the ability to predict TMD diagnosis, disease severity, and treatment response from clinical, psychological, and imaging variables with accuracy exceeding that of individual clinicians.^[156]

The application of precision medicine principles to prolotherapy—identifying the specific patient phenotype, TMD subtype, biomechanical profile, genetic background, and psychological context most associated with optimal prolotherapy response—represents a future direction with the potential to significantly improve the targeting and outcomes of prolotherapy treatment. Biomarker discovery studies identifying serum, salivary, or synovial fluid markers predictive of prolotherapy response would enable personalized patient selection and treatment optimization.^[12]

CONCLUSION

This topic has undertaken a comprehensive, critical, and synthesized review of the scientific literature pertaining to prolotherapy as a regenerative treatment modality for temporomandibular disorders. The review has encompassed the full spectrum of relevant scientific knowledge—from the fundamental anatomy, biomechanics, and pathophysiology of the temporomandibular joint, through the clinical classification and diagnosis of TMDs, to the historical evolution, biological mechanism, clinical evidence, comparative outcomes, advantages, limitations, and future directions of prolotherapy.^[5]

The principal conclusions arising from this review may be summarized as follows: Temporomandibular disorders represent a prevalent, multidimensional, and clinically complex group of conditions imposing significant individual and societal burdens that are inadequately addressed by existing symptom-directed therapeutic approaches. The structural connective tissue deficiencies—capsular laxity, ligamentous elongation, retrodiscal degeneration, and articular fibrocartilage breakdown—that underlie many forms of chronic articular TMD are not restored by pharmacological, physiotherapy, or even conventional surgical management, perpetuating the biomechanical dysfunction that drives symptom chronification.^[90]

Prolotherapy, through its well-characterized biological mechanism of osmotic cellular irritation, controlled inflammatory induction, fibroblast activation, and collagen synthesis, provides a scientifically rational and clinically evidenced regenerative intervention for precisely these structural deficiencies. The available clinical evidence—from three published RCTs, multiple prospective cohort studies, and numerous retrospective case series—consistently demonstrates statistically significant and clinically meaningful improvements in pain intensity, maximum mouth opening, jaw function, and patient-reported quality of life in TMD patients treated with dextrose prolotherapy.^[5]

The safety profile of dextrose prolotherapy for the TMJ is excellent: adverse effects are generally limited to expected, self-limiting post-injection soreness, and no serious adverse events attributable to the procedure have been reported in the published literature. This safety profile compares favourably with the chondrotoxic potential of repeated corticosteroid injections, the systemic

adverse effects of prolonged pharmacological therapy, and the inherent procedural risks of surgical TMJ interventions.^[139]

Evidence - based perspective:

From an evidence-based perspective, the current body of literature provides moderate-quality evidence (Level II to Level III in the Oxford Centre for Evidence-Based Medicine hierarchy) supporting the efficacy of dextrose prolotherapy for chronic articular TMDs—particularly hypermobility, disc displacement with pain, and early-to-moderate degenerative joint disease—in patients who have failed initial conservative management. The evidence is strongest for TMJ hypermobility (Level I: single RCT with low risk of bias) and adequate for degenerative TMJ disease (Level II: one well-designed RCT and multiple prospective cohort studies) and disc displacement disorders (Level III: prospective case series).^[140]

The limitations of the current evidence—small sample sizes, protocol heterogeneity, variable follow-up durations, and limited use of structural outcome measures—preclude definitive conclusions about the optimal protocol parameters and the relative contribution of prolotherapy's structural regenerative effects versus its non-specific analgesic effects. Clinicians offering prolotherapy should present the available evidence transparently to patients, employ a shared decision-making framework, and document their indication-specific rationale and clinical outcomes to contribute to the growing evidence base.^[60]

Clinical recommendations:

Patient Selection: Prolotherapy should be considered for patients with chronic articular TMD (hypermobility, disc displacement with pain, early-to-moderate degenerative joint disease) who have undergone thorough DC/TMD-based diagnostic evaluation, have failed a minimum 3–6 months of comprehensive conservative management, have no contraindications, and have realistic expectations about the nature and timeline of treatment response.

Injectant: Hypertonic dextrose (12.5–25%), prepared by diluting 50% pharmaceutical-grade dextrose with 1–2% lidocaine, represents the best-supported and safest injectant for routine clinical practice. PRP or LP-PRP may be considered for patients with advanced degenerative changes or for those in whom enhanced growth factor stimulation is specifically indicated.

Protocol: A standard protocol of 3–6 intra-articular upper joint space injections (1.0–1.5 mL per session) at 4–6-week intervals is recommended. Additional

pericapsular injections targeting the lateral TML and retrodiscal region should be considered based on the predominant structural pathology.

Multimodal Integration: Prolotherapy should be integrated within a comprehensive multimodal management programme including concurrent physiotherapy (initiated 48–72 hours post-injection), occlusal rehabilitation, psychological support for patients with significant comorbidities, and bruxism management strategies.

Operator Training: Prolotherapy for the TMJ must be performed by clinicians with advanced training in craniofacial anatomy, DC/TMD diagnosis, and intra-articular injection techniques, within an appropriate clinical setting with monitoring equipment and emergency protocols for adverse reactions.

Documentation and Follow-up: Systematic pre-treatment and post-treatment documentation of clinical parameters (VAS/NRS, MMO, lateral excursion, JFLS-20 scores) at each session is essential for monitoring treatment response, guiding clinical decisions, and contributing to the evidence base through clinical audit and research.

Future research priorities:

The following future research priorities are identified as most likely to advance the evidence base and clinical adoption of prolotherapy for TMDs:

- (1) Large-scale, multicentre, adequately powered RCTs with standardized DC/TMD patient selection, pre-specified treatment protocols, validated outcome instruments, sham controls, minimum 24-month follow-up, and structural imaging endpoints;
- (2) Protocol optimization studies systematically evaluating the effects of dextrose concentration, injection volume, number of sessions, and treatment interval on clinical outcomes;
- (3) Comparative trials evaluating dextrose prolotherapy versus PRP, LP-PRP, and combination dextrose-PRP;
- (4) Evaluation of prolotherapy in early degenerative TMJ disease as a disease-modifying intervention;
- (5) Biomarker studies identifying predictors of prolotherapy response; and
- (6) Formal health-economic evaluations and cost-effectiveness analyses.^[155]

Prolotherapy stands at an exciting juncture in its evolution as a clinical modality for TMD management. The convergence of a compelling biological rationale, a consistent body of supporting clinical evidence, an excellent safety record, and a cost profile that is competitive with existing alternatives positions prolotherapy as a legitimate and valuable component of the evidence-based TMD management armamentarium. The continued investment of the clinical research community in generating the high-quality evidence necessary to definitively establish its role—and to optimize its clinical application through protocol standardization and precision medicine approaches—offers the prospect of transforming prolotherapy from a promising emerging therapy into a standard-of-care option for patients with chronic articular TMDs who currently lack effective regenerative treatment alternatives.^[138]

In conclusion, this book affirms that prolotherapy—applied with appropriate patient selection, sound anatomical knowledge, a validated biological rationale, and within the framework of a multimodal management strategy—represents a scientifically grounded, clinically efficacious, safe, and cost-effective regenerative intervention that merits its role in the contemporary, evidence-based management of temporomandibular disorders.^[3]

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