Temporomandibular Joint and Airway Disorders

A Translational Perspective

G. Gary Demerjian
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Editors

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Foreword

The book will be structured as per NIH and AHRQ recommendations of the intertwined nature of translational research and translational effectiveness as it pertains specifically to TMD and airway issues. In the first part of the work (translational research), topics such as the molecular proteomic and interactomic signature of the synovial and salivary inflammasome in TMD with internal derangement will be described. This Part I will make the point that, from the clinical perspective, extracting synovial fluid in the dental clinical setting and testing for the inflammasome signature in individual patients by means of simple commercially available kits that can be run in collaboration with an academic center (i.e., practice-based research network model, such as our EBD-PBRN) can offer useful patient-centered diagnostic tools and intervention recommendations for treatment (i.e., NIH translational research). The second part of the book will be dedicated to discussing the clinical effectiveness of treatment interventions from an EBD perspective: how to correct for malocclusal conditions that lead to TMD and airway issues, and how these interventions can benefit a variety of systemic symptoms in individual patients (i.e., AHRQ translational effectiveness). To optimize effectiveness of this Part II of the book, it will be helpful to consider the inclusion of representative videos of the patient-clinician encounter before, during, and following intervention; in that regard, a link of such videos will be included with the book, so that the reader can follow the evolution of treatment in a variety of patients and cases.

Los Angeles, CA

G. Gary Demerjian
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Preface

There is a vast body of research available to students, researchers, and professionals in the broader field of dentistry. The purpose of this content is to discuss translational research and translational effectiveness to verify and confirm aspects from prior results of data collected. The following chapters discuss how repetitive neural inflammation and microtrauma can be relieved with an oral appliance, giving the temporomandibular joint (TMJ) orthopedic support, ameliorating temporomandibular joint disorders (TMD), airway and neurological disorders.

Los Angeles, CA

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Acknowledgments

This project would not have been completed without the help of many people. I want to thank God for bringing the right people, lining up opportunities and orchestrating everyone involved, to allow this book to be published. My parent's prayers have been a source of comfort and strength. I want to thank Dr. Francesco Chiappelli as a co-editor for being open minded, foreseeing this project the first day that we met and for mentoring me through the process. He is a true scientist, who questions the existing knowledge and has pushed me to explore new frontiers. My other co-editor is Dr. André Barkhordarian, a true researcher and scientist whose thirst for knowledge and perseverance is inspiring. We have worked on several research projects together. He has believed in my work and has expanded my knowledge through our work together. Our assistant editor, Kelcie Berg, has been a source of energy and inspiration as she took on the position spending many hours in helping put this manuscript together. The authors and coauthors have been a pleasure to work with. Martial arts has been a part of my life from a young age. I want to thank all of my teachers and students for allowing me to share in the arts through training. A special thank you to a man who has touched me, as an example of a man in pursuit of perfection of character, is my Karate Master Anthony C. Marquez. Most important are my loving wife Flora, son Haig, and daughter Rachel-Marie, who have patiently put their lives on hold at times to allow me the privilege to put this body of work together. It is my hope that this book will help inspire you to think outside the box and to grow your skills and knowledge.

Introduction

The TMJ is used throughout the day as we eat, speak, chew, and brux. To understand how a mal-relationship or disorder of the TMJ can affect neurological disorders, it is important to understand the neuroanatomy of the trigeminal nerve and its central connections to other portions of the nervous system. Overload of the trigeminal nerve and its firing can cause central sensitization and neuroinflammation in the central nervous system (CNS).

Oral orthotics suppress certain neurological conditions by decompressing irritated afferent fibers of the auriculotemporal (AT) nerve in the patient's TMJ, thus reducing aberrant excitatory input to the reticular formation (RF) and cerebellum. The oral orthotics alter the relationship of the TMJ by altering the space between the teeth. The TMJ is placed into centric relation rather than centric occlusion. By creating more space between the mandibular condyle and infra-temporal fossa, the aberrant sensory input of the AT nerve through the trigeminal network to the RF in the CNS is reduced. This can evoke systemic effects in patients with neurological disorders, such as neuropathic pain, sleep disorders (parasomnias), neurologic disorders (cervical dystonia, strabismus, hemifacial spasm, nystagmus, blepharospasm, Tourette's syndrome, complex regional pain syndrome, Parkinson's disease, and trigeminal neuralgia), or psychological stress.

Contents

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Part I

Translational Research

1 Neuroanatomy of the Trigeminal Nerve and Proximal Innervation of the TMJ

G. Gary Demerjian, André Barkhordarian, and Francesco Chiappelli

Abbreviations

AT	Auriculotemporal
CNS	Central nervous system
RF	Reticular formation
TMJ	Temporomandibular joint
VPM	Ventralis posteromedialis

1.1 Introduction

The temporomandibular joint (TMJ) is the most superior joint in the body. The TMJ moves similarly to a ball and socket joint; however, a fibrocartilage articular disc in the TMJ separates the bones of the mandible from the temporal bone of the skull. The TMJ has an upper compartment that is translational, whereas the lower compartment is rotational.

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Branches of the mandibular nerve innervate the TMJ. While a person is speaking, or chewing, a mal-relationship within this joint can cause afferent nociceptive and proprioceptive signals to be sent through the trigeminal network system into the central nervous system (CNS). Sharp neurologic pain is seen clinically when (1) a patient has pain on opening or closing the TMJ or (2) when the joint makes a clicking sound, causing a disc displacement with reduction. These signals can also be aberrant subthreshold, without the generation of pain.

It is very important to understand the neuroanatomy of the trigeminal nerve and its central connections to other portions of the CNS. Trigeminal drive can cause a peripheral overload into the CNS causing central sensitization and neuro-inflammation, which can evoke systemic effects in patients such as neurological disorders. Oral orthotics suppress certain neurological conditions by decompressing irritated afferent fibers of the auriculotemporal nerve in the TMJ. The reducing aberrant excitatory input to the reticular formation (RF), cerebellum, and thalamus will cause a reduction or suppression of neurologic symptoms.

1.1.1 Neuroanatomy of the Temporomandibular Joint

The temporomandibular joint (TMJ) is where the mandibular condyle and the temporal bone of the

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cranium articulate. The TMJ has two distinct compartments, created by the articular disc. The lower compartment of the TMJ is a hinge-type movement (relationship of the mandibular condyle to the articular disc). The upper compartment is a translational-type movement of the disc (formed by the gliding of the disc against the surface of the glenoid fossa). The TMJ is innervated by three branches of the mandibular branch of the trigeminal nerve. The auriculotemporal (AT) nerve provides sensory fibers to the surrounding region of the TMJ from the posterior extending medially and laterally. The masseteric nerve supplies sensory fibers to the capsule on the anteromedial region, while the posterior deep temporal nerve supplies the anterior lateral [1]. The neuroanatomy of the trigeminal nerve will be discussed in detail in this chapter.

1.1.1.1 Temporomandibular Joint and Trigeminal Nerve Connections

The three divisions of the trigeminal nerve run in close proximity to other cranial nerves. Any sensory dysfunction in the head and neck may be a symptom in patients with neurological dysfunction and movement disorders. The trigeminal spinal nucleus is located at all levels of the brainstem down to the level of C-3, and the central pathways connect this nucleus with the ascending up to the thalamus and sensory cortices [2]. Therefore, abnormalities or injuries of the TMJ can often accompany and cause neurologic syndromes in the central nervous system. An understanding of the relevant anatomy and neurology will help clinicians to better understand and treat patients with temporomandibular joint dysfunction and correlated neurological disorders. This chapter covers trigeminal system anatomy and physiology of the trigeminal nerve system and how the TMJ may affect the trigeminal nerve and its central connections.

1.1.2 Anatomy and Physiology of the Trigeminal Nerve and Its Central Connections

The trigeminal nerve exits the pons and travels anterior to the Gasserian ganglion (GG). The Gasserian ganglion is anatomically similar to spinal root ganglia [3–5]. The site of formation of the three divisions is separate but runs closely together within the ganglion. The GG contains the cell bodies of all the trigeminal sensory neurons, whereas the motor root does not enter the ganglion.

Somatic sensory impulses converge to the GG from the deep and superficial structures of the head and face via three major divisions (ophthalmic division, maxillary division, mandibular division) of the trigeminal nerve [2]. These three divisions represent an afferent system, which will be described anatomically, from the GG to the peripheral branches and their connections in the periphery. The mandibular nerve is the only division of the trigeminal nerve that contains a motor root in the trigeminal system. The trigeminal nerve also contains some peripheral branches of sympathetic and parasympathetic fibers that supply the salivary, sweat, or other glands of the face, eyes, and mouth [6].

1.1.3 Ophthalmic Nerve

The ophthalmic nerve (V1) is the first division of the trigeminal nerve and is purely sensor. It is the smallest of the three divisions and supplies sensation to the forehead, eyeball, lacrimal gland, and lacrimal sac. It also supplies the upper eyelids, the frontal sinuses, and the side of the nose. As V1 arises from the Gasserian ganglion [7], it immediately enters the cavernous sinus inferiorly, where it lies below the trochlear nerve [8]. V1 gives off connections within the cavernous sinus to the oculomotor, trochlear, and abducens nerves, thereby supplying sensation to the muscles innervated by these nerves [9]. At this level, it also gives off recurrent branches that cross, adhering to the trochlear nerve, and are distributed to the tentorium cerebelli and dura. As V1 leaves the cavernous sinus, it divides into three branches, which are the lacrimal nerve, frontal nerve, and nasociliary nerve. All three branches enter the orbit through the superior orbital fissure [10].

Branches of V1 are as follows (Fig. 1.1): (a) tentorial nerve innervates the dura of the anterior fossa, tentorium cerebelli, falx cerebri, and the

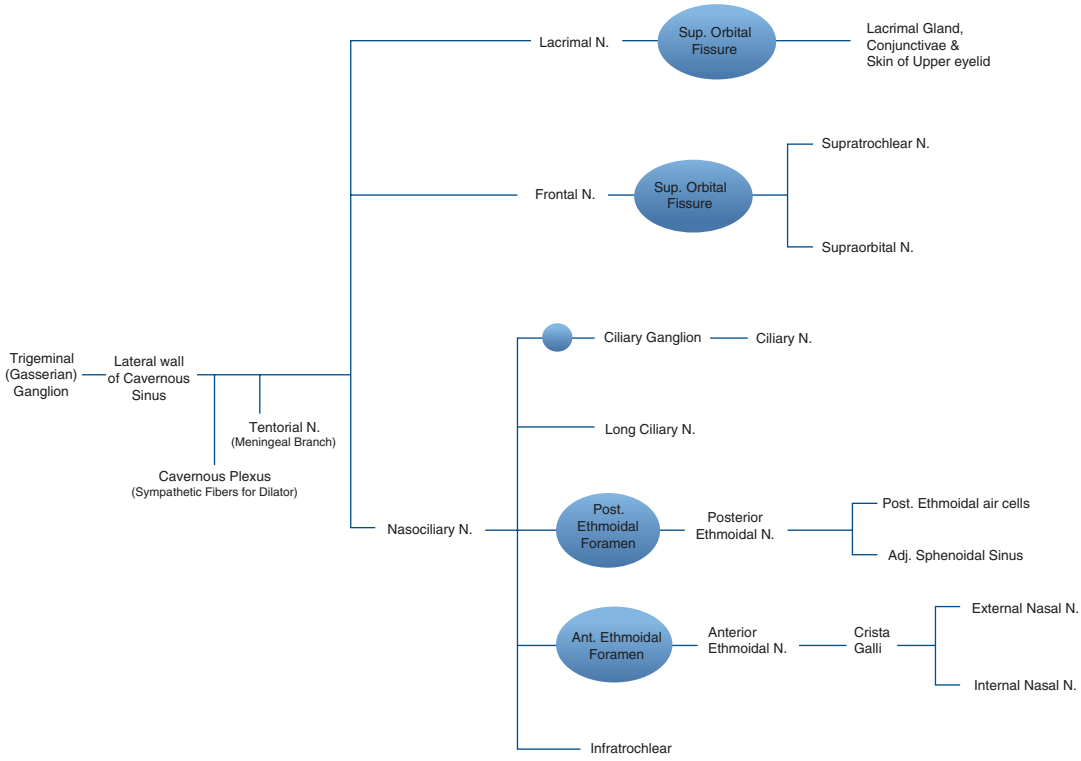

Fig. 1.1 Ophthalmic nerve. A diagram of the branches, pathways, and areas of innervation of the ophthalmic division of the trigeminal nerve. Supplied by Ms. Rachel-Marie Demerjian

superior sagittal sinuses. In animal studies, the ophthalmic division has minor contribution from the maxillary division and innervates the vessels in the circle of Willis [11, 12]. (b) Frontal nerve enters the orbit from above the superior rectus and the levator palpebrae superioris muscles. Around the middle of the orbit, the supratrochlear nerve branches off, and at this point it becomes the supraorbital nerve. The supraorbital nerve exits the orbit through the supraorbital notch (with the supraorbital artery) and proceeds superiorly giving minor branches to the frontal sinus and eyelids [13]. It innervates the skin near the midline of the forehead, the upper eyelid (skin and conjunctiva), frontal sinuses, and the skin on the side of the nose. (c) The lacrimal nerve enters the orbit through the superior orbital fissure and divides into two divisions. The superior division provides sensory innervation to the lacrimal gland, the conjunctiva, and the upper eyelid. The lower division of the lacrimal nerve anastomoses with the maxillary division. (d) Nasociliary nerve is the sensory innervation to the eye and the nose as it passes through the cranial cavity and enters the orbit through the annulus of Zinn (common tendinous ring) between the two divisions of the oculomotor nerve and courses under the superior rectus muscle. It exits the orbit via the anterior ethmoidal foramen and reenters the cranial vault. It enters the nasal cavity through the nasal fissure, which is located on the side of the crista galli. At this point, it divides into three terminal branches. Two of the branches terminate in the anterior nasal cavity (medial and lateral internal nasal nerves), and the branch continues anterior to the end of the nose (external nasal nerve) [13].

1.1.4 Maxillary Nerve

The maxillary nerve (V2) of the trigeminal nerve is also a pure sensory division. It innervates the skin of the midface (small part of the temporal

area, lower eyelid, cheek, upper lip, side of the nose, part of the mucous membrane of the nose, nasopharynx, maxillary teeth, maxillary sinus, soft palate, tonsil, and palate of the mouth).

V2 arises from the GG and enters the cavernous sinus beneath V1. The middle meningeal nerve is an intracranial branch of V2 that innervates the dura mater of the middle cranial fossa. V2 passes through the foramen rotundum (in the medial aspect of the greater wing of the sphenoid bone) [14] to the pterygopalatine fossa [15]. At this point, V2 gives off three branches: (*A*) pterygopalatine nerves, which enter the pterygopalatine ganglion and then divides into branches that supply portions of the nasal cavity and nasopharynx (posterior superior nasal, posterior inferior nasal) and hard and soft palate (nasopalatine nerve, greater palatine nerve, lesser palatine nerve, pharyngeal branch (Fig. 1.2). The pterygopalatine ganglion receives parasympathetic impulses from the genticulate ganglion of the facial nerve and sympathetic impulses from the superior cervical ganglion via the deep petrosal nerve (internal carotid artery). (*B*) Posterior superior alveolar nerves pass through the pterygomaxillary fissure to provide sensation to the maxillary gingiva and molar teeth; and (*C*) zygomatic nerve passes through the inferior orbital fissure into the orbit. When in the orbit, zygomatic nerve has connections with the lacrimal nerve. This zygomatic nerve then divides into two branches: (*a*) zygomaticofacial nerve that passes through the zygomatic foramen innervates the skin of the face, over the zygomatic bone, and (*b*) zygomaticotemporal nerve innervates the skin on the temporal side of the zygomatic bone.

As the V2 nerve passes through the inferior orbital fissure and becomes the infraorbital nerve

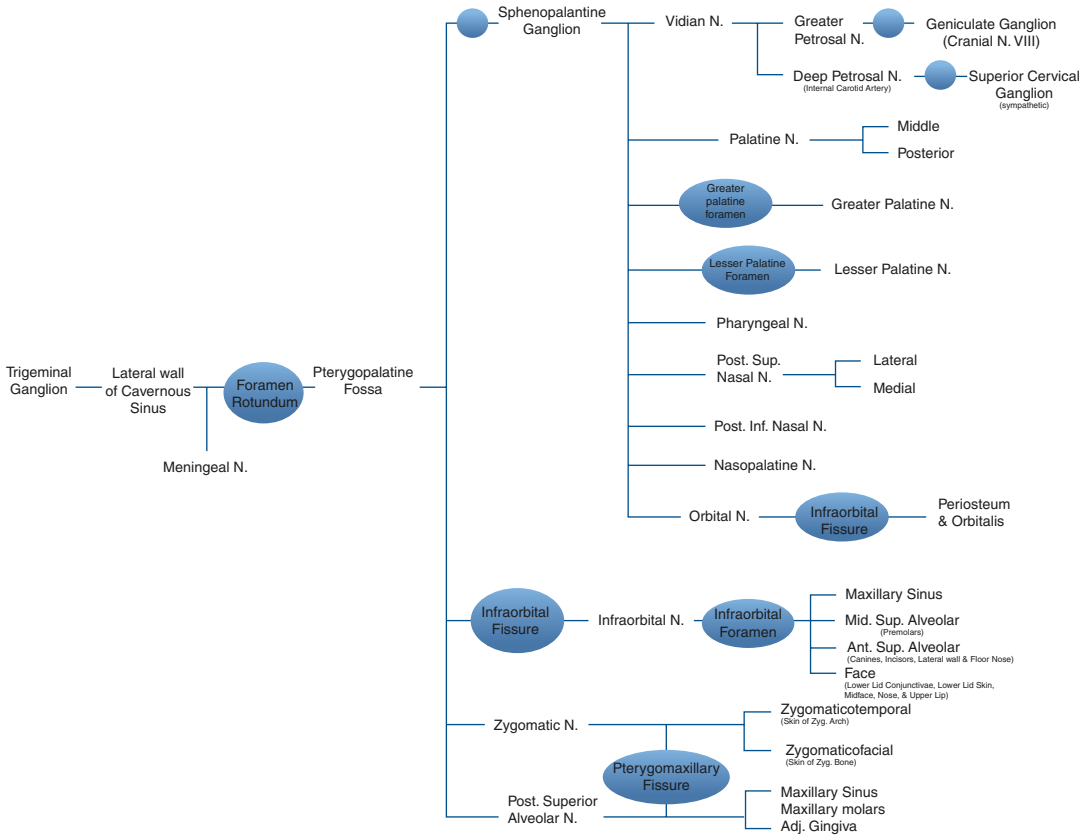

Fig. 1.2 Maxillary nerve. The maxillary nerve supplies innervation to the midface. This figure demonstrates the pathways, branches, and arears of innervation such as the teeth. Supplied by Ms. Rachel-Marie Demerjian

as it enters the orbit. The infraorbital nerve is the terminal branch of the V2. It passes through the orbital floor into the infraorbital canal. While in the infraorbital canal, it innervates the maxillary bicuspids and anterior teeth. The infraorbital nerve innervates the skin of the face from an area below the eye to the upper lip adjacent to the nose (Figs. 1.2). [16–18].

1.1.5 Mandibular Nerve

The mandibular nerve (V3) contains a large sensory and small motor root. The sensory root from the Gasserian ganglion passes inferiorly through the motor root. The motor root supplies muscles that derive from the first branchial arch of mammalian embryos [6]. The two roots are in close proximity in the middle cranial fossa and travel through the foramen ovale to the infratemporal fossa. There they become one trunk. The foramen ovale sits in the posteromedial aspect of the greater wing of the sphenoid bone [14]. At the infratemporal fossa, V3 gives off two branches: (*a*) nervus spinosus nerve which accompanies the middle meningeal artery through the foramen spinosum and innervates the dura mater on the temporal side of the cranium [19] and (*b*) **medial pterygoid nerve**, which passes through or by the otic ganglion to the tensor veli tympani and tensor veli palatini muscles [6]. V3 then divides into anterior (primarily motor) and posterior (primarily sensory) divisions.

1.1.6 Otic Ganglion

The otic ganglion is located medial to V3, as it exits the skull through the foramen ovale from the skull. [20]. The preganglionic parasympathetic fibers arise from the glossopharyngeal nerve (via tympanic plexus and the lesser petrosal nerve) and the facial nerve (via chorda tympani nerve) [20, 21]. Preganglionic sympathetic fibers from the superior cervical ganglion via the middle meningeal artery pass through the otic ganglion. Postganglionic fibers exit the otic ganglion via the auriculotemporal nerve to innervate the parotid gland [22].

1.1.6.1 Anterior Division of V3

The anterior division of V3, being mostly motor root, innervates the muscles of mastication. It travels downward and forward, medial to the lateral pterygoid muscle, and separates into three branches: (*a*) lateral pterygoid nerve (innervates lateral pterygoid muscle); (*b*) masseteric nerve (innervates master muscle) passes superior border to the lateral pterygoid muscle and over the mandibular notch and supplies a fiber to the retrodiscal tissue of the temporomandibular joint; (*c*) temporal nerve (anterior temporal nerve and posterior temporal nerve) passes to the temporalis muscle; and (*d*) the buccinator nerve passes between the two heads of the lateral pterygoid muscle to reach the masseter and buccinator muscle [2] (Fig. 1.3).

1.1.6.2 Posterior Division of V3

The posterior division of V3 has three major subdivisions, all with dual functions [6]: (a) the auriculotemporal (AT) nerve can have 1–5 root variations and can start from the mandibular nerve or the inferior alveolar nerve. When a bifurcation of the inferior alveolar nerve occurs, the AT nerve roots could start from the anterior or posterior rami of the inferior alveolar nerve trunk. Regardless of the number of primary roots, the AT nerve trunk is finally formed by the merging of the roots. Over 80% of the dissections, the medial meningeal artery passed between the first and second branches of the auriculotemporal nerve, which are then combined into a single nerve [23].

This nerve supplies the external auditory meatus (ear canal), auricle (ear), external part of the tympanic membrane (ear drum), temporal skin, and parotid gland (secretomotor fibers) to the sides of the head. Several articular branches are also carried with the nerve, which supply blood to the temporomandibular joints [6, 24, 25]. The auriculotemporal nerve is the primary nerve to supply the TMJ, together with the masseteric nerve branches and the deep temporal. It is the primary sensory supply to the TMJ with contributions also from the masseteric (anterior lateral) and deep temporal nerves (anterior medial) [Fig. 1.4]. The auriculotemporal nerve

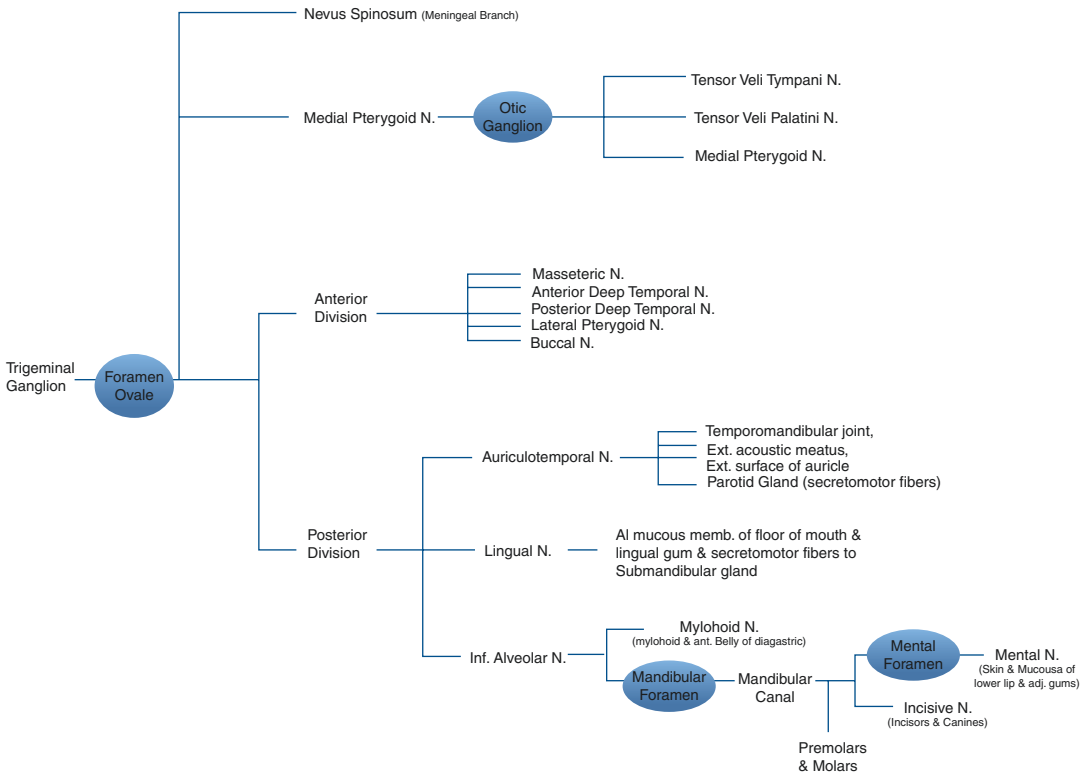

Fig. 1.3 Mandibular nerve. The mandibular nerve has sensory and motor branches. This figure demonstrates the pathways and branches of the mandibular nerve. Supplied by Ms. Rachel-Marie Demerjian

has the majority of nerve endings that are located in the vascular connective tissue, on the posterior aspect of the disc called the retrodiscal tissue (bilaminar zone) [26, 27]. There are three types of nerve receptors in the TMJ: Ruffini corpuscles (unencapsulated), Pacinian corpuscles (encapsulated), and free nerve endings. The function of these receptors is perception of pain and to relay the position of the joint. There are no receptors on the articular surfaces of the disc [1, 26]. (b) The lingual nerve supplies innervation to the mandibular gingiva and anterior portion of the tongue. The chorda tympani of the facial nerve joins the lingual nerve, to supply taste fibers for the anterior two-thirds of the tongue. The lingual nerve sends parasympathetic fibers to the submandibular ganglion; then postganglionic fibers exit the submandibular ganglion and return to the lingual nerve before entering the salivary glands. (c) The inferior alveolar nerve gives off branch, mylohyoid nerve (a motor branch that innervates the mylohyoid muscle and the anterior belly of the digastric muscle) before entering the mandible through the mandibular foramen. In the mandible, it sends branches to the inferior dental plexus, which innervate the mandibular teeth and gingiva. The lingual never exits the mandible through the mental canal and becomes the mental nerve and innervates the skin and mucous membrane of the lower lip and gums and the chin (Fig. 1.4).

1.1.7 Trigeminal Afferent Fibers

The Gasserian ganglion contains the cell bodies of the afferent sensory trigeminal fibers, which enter the lateral pons. There they split into a short ascending and a long descending branch. The descending branch forms the trigeminal spinal tract, at the medulla oblongata, which continues medially into the trigeminal spinal nucleus.

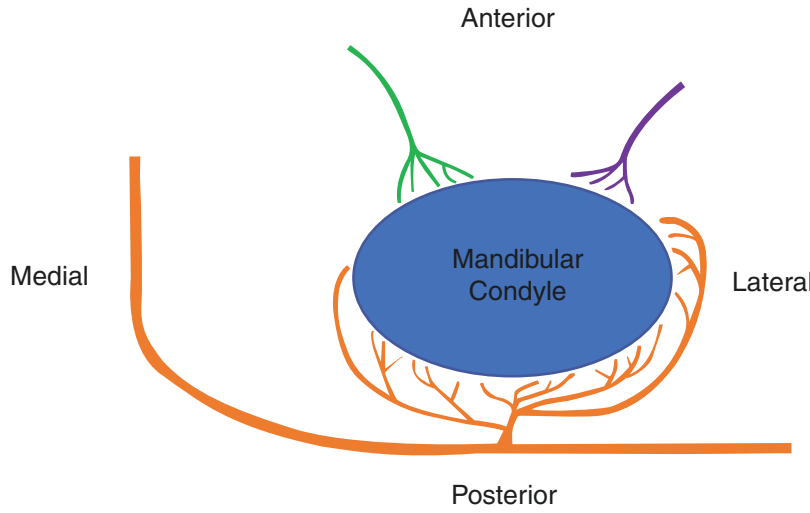

Fig. 1.4 Afferent nerve innervations of the TMJ. As the auriculotemporal nerve passes by the TMJ from the posterior, it supplies branches innervating the surrounding tissues as it wraps around the mandibular condyle from medial to lateral (yellow). The black arrow is pointing to the retrodiscal tissue. The posterior deep temporal nerve (green) supplies a branch to the anterior lateral section of the condyle and the masseteric nerve (blue) innervated the anterior medial portion. Adapted from Saleem N et al.

Investigations of the trigeminal spinal nucleus show that the afferent fibers of all divisions extend and diminish caudally at the level of C3 [4]. The most caudal portion of the trigeminal spinal nucleus is involved in the transmission of pain perception as it contains the fibers from V3.

As the motor root of V3 enters the pons, it is composed of axons with terminals in the muscles of mastication and oral cavity. They bypass the trigeminal motor nucleus and end in the midbrain. The cells of origin of the motor root of V3 and the mesencephalic nucleus are found throughout the mesencephalic tegmentum and rostral pontine.

1.1.8 Gasserian (Trigeminal, Semilunar) Ganglion

The motor root of the trigeminal nerve originates from the mesencephalic nucleus and accompanies the sensory root. The sensory and motor divisions exist the pons as two separate roots, where the motor root exits just superior to the point of entrance of the sensory root. The trigeminal nerve exits the pons and travels anterior to the Gasserian ganglion. The motor root is underneath the Gasserian ganglion in Meckel's cave. It is surrounded by arachnoid and dura, located in the middle cranial fossa [28]. The Gasserian ganglion is similar to a spinal root ganglion [3–5]. Formation sites for the three divisions of the trigeminal nerve are separate. However, all three divisions of the nerve run closely together. The Gasserian ganglion contains the cell bodies of all the trigeminal sensory axons. The motor root of the trigeminal nerve does not enter the ganglion.

1.1.9 Trigeminal Nerve Nuclei

The trigeminal system has four nuclei: three *sensory* nuclei, which are the trigeminal main sensory nucleus, trigeminal mesencephalic nucleus, and the trigeminal spinal nucleus, and one *motor* nucleus, the trigeminal motor nucleus [9].

1.1.9.1 Main Sensory Nucleus

The trigeminal main sensory nucleus is located in the midpons [29]. The main sensory nucleus provides tactile and pressure sensation from

the head to the brainstem. Most of its neurons project to the contralateral ventralis posteromedialis (VPM) nucleus and ascend to the thalamus [30].

1.1.9.2 Mesencephalic Nucleus

Mesencephalic nucleus consists of unipolar, primary afferent cells similar to sensory ganglion cells [31]. Their cell bodies remain within the central nervous system and are derived from neural crest cells. Most of these neurons within the mesencephalic nucleus are proprioceptive in function [32, 33], with receptor terminals in the muscles of mastication, which respond to stretch. Neurons of this nucleus are unipolar cells that receive proprioceptive information input to the main sensory and trigeminal motor nucleus and reticular formation and send projections to the trigeminal motor nucleus to mediate a reflex response.

1.1.9.3 Spinal Trigeminal Nucleus

The spinal trigeminal nucleus extends down the spinal cord as far as the second cervical root and merges with the substantia gelatinosa [29]. The spinal trigeminal nucleus is divisible into three sections: (*a*) the spinal trigeminal nucleus oralis, (*b*) the spinal trigeminal nucleus interpolaris, and (*c*) spinal trigeminal nucleus caudalis [31]. The ophthalmic division is located most ventrally and those from the mandibular located most dorsally. The nucleus of the spinal trigeminal nucleus is primarily involved in the transmission of pain and temperature impulses [34].

1.1.9.4 Trigeminal Motor Nucleus

The trigeminal motor nucleus is located medial to the main sensory nucleus at the level of the pons. It contains interneurons and the cell bodies of alpha and gamma motor/branchiomotor neurons. The motor fibers join the mandibular division of the trigeminal nerve and are distributed to the muscles (masseter, temporalis, medial pterygoid, lateral pterygoid, mylohyoid, anterior belly of the digastric, tensor veli tympani, and tensor veli palatini muscles) [9].

1.1.10 Spinal Trigeminal Nuclei Connections

Many neurons of the spinal trigeminal nucleus send axons into the longitudinal axon plexus, which consists of bundles of interconnected myelinated and unmyelinated axons. These bundles run through the entire length of the nucleus within the spinal tract, containing ascending and descending axons. The axons give off collateral fibers that effectively connect the different levels of the nucleus [35, 36].

The trigeminal sensory nucleus is connected to the motor nuclei (ocular, trigeminal, facial, vestibular, glossopharyngeal, vagal, and hypoglossal) in the brainstem via short neurons in the tegmentum. Ascending impulses are conducted by multi-synaptic pathways via the dorsal section of the hypothalamus to the ventromedial nuclei of the thalamus. Then the thalamus will distribute the signals to cerebral cortex. The trigeminal nucleus also has collateral axons that send impulses to the superior colliculus, cerebellar cortex, and deep cerebellar nuclei [37, 38].

The ascending pathway of the spinal trigeminal nucleus and main sensory nucleus forms the trigeminothalamic tract also known as the ventral trigeminal tract. This tract transmits impulses of pain and temperature, arising from all levels of the spinal trigeminal nucleus.

Incoming pain impulses from the face are relayed to the thalamus via the trigeminothalamic tract. The trigeminal spinal nucleus and the spinal trigeminal tract extend to the level of the second cervical vertebrae. The pain impulses from the neck enter the spinal cord at the level of C1 and C2. Second-order neurons in the spinal trigeminal nucleus relay the pain impulses to the thalamus via the lateral spinothalamic tract. Investigators have followed the overlapping zones of the descending trigeminal system and cervical root fibers of C1, C2, and C3 to cervical levels down to the level of C6 [39]. A microelectrode study showed that there were some convergent fiber neurons from the trigeminal and cervical roots. As stimuli were delivered to the peripheral branches of the trigeminal and cervical roots, the

same neurons were triggered. Kerr stated that stimulation of the dorsal root of the first dorsal cervical segment produces referred pain to the back of the eye, to the forehead, and, occasionally, to the vertex; rarely is pain evoked in the back of the head (ref). Therefore, he estimated that 25–30% of the neurons responded to the stimuli from either the face or neck regions [9].

1.1.11 Reticular Formation

The reticular formation (RF) forms the central core of the brainstem and is described as a diffuse structure that has no distinct cytoarchitectural boundaries, which houses over 100 identified nuclei. The RF forms the central gray matter of the midbrain, pons, and medulla. The spinal cord contains an analogue of the RF throughout its entire length, known as the intermediate zone of gray matter. The RF contains fibers oriented in all planes and appears as an interlacing structure that fills the area among various ascending and descending pathways (cranial nerve nuclei and gray matter) in histological sections [40]. It is continually receiving information of activity occurring in the nervous system and responding by influencing the skeletal muscle activity (motor), sensations (somatic and visceral), activity of the autonomic nervous system, endocrine function, reciprocal hypothalamus connections, consciousness levels, and biological rhythm [2].

RF neurons have elaborate dendritic trees, which branch out and radiate in all directions. They give rise to an ascending or descending axons and numerous collateral branches. The dendrites are in perpendicular orientation to the long axis of the brainstem. The axons, radiating dendritic trees, and collateral branches facilitate the ability of the neurons to collect and transmit information to and from various nuclei (e.g., oculomotor, trigeminal, facial, glossopharyngeal nuclei) via ascending and descending fibers along the brainstem. The RF integrates incoming information and then influences outgoing information to nerve cell activity at all levels of the CNS [41, 42].

The RF is divided into four longitudinal zones (columns) on the basis of their mediolateral locations in the brainstem: median zone (midline raphe), paramedian zone (located lateral to the midline), medial zone, and lateral zone [2, 43].

The medial zone (motor zone, efferent zone) consists of large neurons. The medial zone nuclei contain neurons with bifurcate axons that give rise to long ascending and descending branches, each with collateral branches. The ascending fibers course in the central tegmental tract to terminate in the hypothalamus (controls the autonomic nervous system) and thalamus (function in arousal). The descending fibers extend inferiorly to the spinal cord by joining the pontine and medullary reticulospinal tracts. The pontine and rostral medullary RF of the medial zone give rise to the reticulobulbar tract (motor control and modulation of sensory information transmission), which terminates in the motor and sensory cranial nerve nuclei [2].

The lateral zone (sensory zone, afferent zone) consists of small-sized interneurons, which are the most numerous type of cells in the RF. These small-sized interneurons contain short ascending and descending branches that are localized in the medial zone. Some interneurons terminate in the cranial nerve motor nuclei. It receives sensory information from the cerebrum, cranial nerves, cerebellum, and spinal cord via collateral branches of various somatosensory (touch, pressure, pain, temperature, and general proprioception) pathways. The lateral zone receives sensory information, integrates, and then relays the information to the medial zones [2, 44, 45].

1.1.12 Thalamus

The thalamus, a large sensory nucleus, is found between the cerebral cortex and the brainstem. It is located between the corpus striatum from above and the midbrain and hypothalamus from below. It is completely covered by the cerebral hemispheres. The posterior ventral nucleus of the thalamus sends impulses to the cerebral cortex and has connections to the basal ganglia. These projections to the cerebral cortex lead to the

paracentral and postcentral gyri. It relays all sensory information from the external environment, except olfaction to the cerebral hemispheres for processing [9].

1.1.13 Auriculotemporal Nerve Connection to Systemic Neuropathology

The neural innervation of the TMJ was discussed previously by the auriculotemporal nerve, masseteric nerve, and the posterior deep temporal nerve [1, 46]. Tissue damage or inflammation can produce an excitability of the nociceptors at the site nerve injury. This is called peripheral sensitization [46–50]. Prolonged excitation can cause changes in the CNS termed neural plasticity resulting in the release of neuropeptides such as calcitonin gene-related peptide (CGRP) and substance P (SP) into the synapse from the primary afferent neurons. These neuropeptides act on the macrophages, mast cells, and platelets causing inflammatory mediators (cytokines, histamine, serotonin and bradykinin). These inflammatory mediators can cause an increase in excitability while acting on the nociceptive afferent nerve endings. An increase excitability of the nociceptors causes spontaneous activity, lower threshold activation, and an increased response to subsequent stimuli. These neuropeptides are transported in the trigeminal spinal nucleus [46, 51–54]. An increase in the nociception activity can lead to increase afferent signals into the CNS causing central sensitization. Sensory neurons at all three levels of the trigeminal spinal nucleus have relay neurons to the thalamus either directly or indirectly via the reticular formation [46, 49, 53, 55, 56].

Nerve damage or injury leads to an increase activity and repair, causing neuronal regeneration and sprouting [46]. Neuromas are sensitive to chemical, mechanical, and thermal stimulation. Neuromas transmit spontaneous stimulation into the CNS [56]. This spontaneous neural activity originates from the cell body in the Gasserian ganglion. The increase of neural activation arising from the neuroma and the Gasserian ganglion results in hypersensitivity and hyperexcitability of the CNS. Prolonged tissue and neural innervation can cause changes in the CNS leading to neural plasticity [46].

The trigeminal nerve has a tonic regulator (inhibitory), called the reticular formation. The reticular formation exerts control over the sensorimotor circuits within the brainstem [57]. The specific network for locomotor and postural control in humans is transmitted via the pontomedullary reticular formation and integrated through multisensory input at different levels within the midbrain [58].

Research has shown that stimulation along the trigeminal nerve causes a motor activity in the sternocleidomastoid and splenius muscles of the neck [58, 59]. Therefore, stimulation of the primary sensory afferent fibers of the auriculotemporal nerve traveling via the trigeminal nerve to the brainstem activates the reticular formation [60, 61]. Siegel found movements of the head and neck were caused by neural stimulation of the reticular formation on the ipsilateral side [62]. The nucleus raphe of the reticular formation gets direct input from the trigeminal spinal tract when trigeminal nerves are excited. Excessive neuronal stimulation can cause an interference with impulse conduction from the cerebral cortex via the reticular formation and produce stimulation causing involuntary movements such as balance disorders [63]. The cerebellum gets afferent impulses from the vestibular nuclei, cerebral cortex, spinal cord, reticular formation, and trigeminal nuclei via the trigeminocerebellar tract. Damage to, or a lesion within, any of these pathways primarily produces a change of muscle tone or postural reflexes [57].

Conclusion

The TMJ is a complex joint, where the relations can be affected by several ways, such as macro-trauma (direct injury of the joint) or micro-trauma (clenching or bruxism). This complex joint is the only joint in the body that has a hard end point (dentition) that dictates the relationship of the joint. Furthermore, if one of the temporomandibular joints does not function properly such as an internal derange-

ment, it will affect the TMJ on the other side causing a compensation of the opposing TMJ. Any mis-relationship that affects either TMJ or the dental relationship can start a chain of events due to the afferent signal conducted through the trigeminal network system into the CNS. Oral orthotics suppresses certain neurological conditions by reducing the aberrant excitatory input into the RF. Therefore, signals to the thalamus and cerebellum are reduced. The type of orthotic or splint is not relevant; however the proper mechanical force being put on TMJ and relieving the excitatory input into the CNS is most relevant.

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2 Neuroanatomy and Neurophysiology of the Trigeminal Network System

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Abbreviations

AT	Auriculotemporal
CGRP	Calcitonin gene-related peptide
CN	Cranial nerve
CNS	Central nervous system
CS	Cavernous sinus
CSF	Cerebrospinal fluid
GG	Gasserian ganglion
GP	General proprioception
GSA	General somatic afferent
GSE	General somatic efferent
GVA	General visceral afferent
GVE	General visceral efferent
NS	Nociceptive-specific
OG	Otic ganglion
PCG	Postcentral gyrus
PD	Parkinson's disease
PDL	Periodontal ligament
RA	Rapid adapting
SA	Slow adapting
SOF	Superior orbital fissure
SP	Substance P
SSA	Special somatic afferent
SVA	Special visceral afferent
SVE	Special visceral efferent
TCR	Trigeminocardiac reflex
TMD	Temporomandibular joint disorder
TMJ	Temporomandibular joint
TNR	Tonic neck reflex
VN	Vestibular nuclei
VPM	Ventral posterior medial
WDR	Wide dynamic range

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2.1 Cranial Nerve Involvement in TMD

Temporomandibular disorders (TMD) are a group of pathologies affecting the temporomandibular joint (TMJ), masticatory muscles, and related ligaments causing joint dysfunction. TMD are considered to be among the most complex and yet common conditions involving orofacial pain. Early investigations have indicated that 1–75% of population showed at least one objective TMD sign, and 5–33% reported subjective symptoms with the highest prevalence among women, between ages 20 and 40 [1–3]. TMD is

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most often manifested as an internal derangement. Pain is a common symptom of TMD, due to the sensory innervations of the joint, followed by inflammation as a result of the stress on the surrounding neurons (neuronal damage) and tissues. However, not all TMD patients experience pain and little is known about pathological pathways involving pain development.

TMD exist in conjunction with other disorders [4]. These include orofacial morbidities such as headaches [5], hearing loss, and tinnitus [5] but can also include bodily disorders such as irritable bowel syndrome [6–10], ulcers [5], high blood pressure, allergies [5], cardiovascular disease [9], fibromyalgia [8], chronic fatigue syndrome [6, 8], arthritis [11], and neck and back pain [12]. Other medical conditions such as Ehlers-Danlos syndrome, dystonia, Lyme disease, endometriosis, interstitial cystitis, Meniere's disease, sleep disorders, and scleroderma have also been observed as possible comorbidities in patients with TMD [4]. Recent studies show that neurological disorders, such as torticollis, Parkinson's disease, dystonia, Tourette's syndrome, and even tics, may have a root cause in TMJ-related disorders [13]. The problems may be due to an undiagnosed TMJ disc dislocation, subsequent distal condylar displacement, and associated compression and irritation of the auriculotemporal (AT) nerve. This may be due to bone loss, trauma, grinding, and other pathological etiologies [13, 14]. Hence, any and all aspects of AT neural interaction can be affected, leading to a very broad array of disorders (e.g., neurologic, dystonic, and neuromuscular disorders).

It is possible that TMD and its related comorbidities are simply a reflection of the TMJ neural integration within the brainstem centers via the sensorimotor system. This connection is intertwined with the neural networks controlling body balance and coordination. For this reason, TMD can be just one physical manifestation of a more extensive set of remote or systemic problems [15].

Loss of motor control in the TMJ can be attributed to the lack of coordination among agonist and antagonist muscle co-activation [16]. It is this coordination of agonist and synergist muscles, and not strength that is pivotal in injury resistance [17]. Such coordination is dependent on the nervous system. Any defects or functional inefficiencies of normal neural orchestration may result in prominent symptoms such as local muscle stiffness or joint pain. These symptoms, as well as the accumulation of injuries and motor coordination imbalances, are superficial presentations of an underlying etiological problem that can be traced back to other issues [18].

Abnormalities in either peripheral afferent input to the brain or the brain's response to sensory input can interfere with motor programs in the cortical motor areas. Therefore, dysfunctional sensorimotor integration can significantly disturb motor control [19]. For example, an error in proprioceptive afferent information may contribute to the abnormal movements characteristic of those with Parkinson's disease [20]. Dystonic patients also display reduced perception of kinesthetic sensations induced by muscle vibration, suggesting dysfunction along the Ia afferent pathways [18].

This afferent input provides our central nervous system with the information necessary to act with respect to the pull of gravity [21]. In addition to impairments in the visual, vestibular, and skeletal systems, mandibular positions may also contribute to balance disorders. Further connections exist between proprioceptive afferents of the neck and body and the vestibular nuclei (VN). Neurons in the caudal part of the trigeminal mesencephalic nucleus also project to the VN [22]. Changes in masticatory muscle function and the interdental occlusal plane have been shown to parallel changes in the plantar arch of the feet through connection from afferent proprioceptive impulses of plantar arch muscle configuration to the trigeminal motor nucleus innervating the masticatory muscles [23]. Evidence suggests an intimate neurological integration between the masticatory system and the somatosensory innervations of the body as a whole [18].

In general, various functional components of the cranial nerves are described as:

The *afferent* or sensory input fibers—they are impulses from periphery toward the central nervous system (CNS) carried by ascending fibers.

The *efferent* motor output fibers—they are impulses carried away from CNS to muscles and glands by descending fibers.

Based on derivation, structures of the body innervated by afferent and efferent nerves are divided into three categories:

(a) The somatic structures are derived from embryonic somites, a bilaterally paired block of paraxial mesoderm that forms in developing embryo of segmented animals, and in vertebrates are subdivided into the sclerotomes, myotomes, and dermatomes. Embryonic somites give rise to the vertebrae of the vertebral column, the rib cage, part of the occipital bone, skeletal muscle, cartilage, and tendons [24].
(b) The visceral structures are derived from the gut, genitourinary, cardiovascular and respiratory systems, and their associated glands.
(c) The branchial structures are derived from the branchial arches. Neuronal modalities carried by spinal nerves and cranial nerves are referred to as *general* and components that are only carried by cranial nerves are referred to as *special*. Therefore, there are seven classical neuroanatomic classifications for functional components based on tissue origins.
    1. General somatic afferent (GSA): General sensation afferent fibers carry touch, pressure, pain, temperature, and proprioception from visceral and somatic structures of the head and neck. GSA fibers input impulses to the trigeminal spinal nucleus via CN V, CN VII, CN IX, and CN X. General proprioception (GP): afferent neurons carry proprioceptive/kinesthetic sensations (muscle, tendon, and ligament stretch) from muscles (tendons) of mastication/eye movement and periodontal ligaments (PDL).
    2. General somatic efferent (GSE): General motor innervation to skeletal muscles of head and face (CN III, CN IV, CN VI, CN IX).
    3. General visceral afferent (GVA): General sensation from viscera (CN VII, CN IX, CN X).
    4. General visceral efferent (GVE): Parasympathetic motor innervation to viscera (CN III, CN VII, CN IX, CN X).
    5. Special somatic afferent (SSA): Special sensory input from the eye (CN II) and from the ear (CN VIII).
    6. Special visceral afferent (SVA): Special sensory input from the viscera conveying the special sense of smell (CN I) and taste (CN VII, CN IX, CN X).
    7. Special visceral efferent (SVE): Motor innervation to skeletal muscles of branchial arch origin (CN V, CN VII, CN IX, CN X) [25].

2.2 The Somatosensory Receptors of the Human Oral Tissues

The human oral tissue is richly innervated by receptors that send signals to the brain transmitting information about mechanical (touch), thermal (heat, cold, warmth), and noxious events (pain) from the periphery. The somatosensory receptors of the oral tissues are generally divided into mechanoreceptors, nociceptors, and thermoreceptors.

2.2.1 Mechanoreceptors

Mechanoreceptors convey information regarding mechanical sensory events, including touch, pressure, vibration, and proprioception that can be classified according to their morphology, and rate of adaptation. Most mechanoreceptive signals are carried by the A-beta and some C fibers.

There are four principal types of mechanoreceptors:

- The tactile corpuscles (Meissner corpuscles, rapidly adapting type I) respond to light touch and adapt rapidly to changes in texture.
- The bulbous corpuscles (Ruffini endings, slowly adapting type II) detect tension deep in the skin and fascia.
- The Merkel nerve endings (Merkel discs, slowly adapting type I) detect sustained pressure.
- The lamellar corpuscles (Pacinian corpuscles, rapidly adapting type II) in the skin and fascia detect rapid vibrations.

There are mechanoreceptors in the cochlea of the inner ear called stereocilia that transduce sound to the brain. The free nerve endings detect touch, pressure, stretching (polymodal receptors) and the baroreceptors are activated by the stretch of the blood vessels.

Based on rate of adaptation, there is slow-adapting (SA) versus rapid-adapting (RA) receptors. SA fibers continue to respond during a static mechanical stimulus, while RA fibers show only an initial response at stimulus onset and perhaps when the stimulus ends.

Differences in the density of sensory afferent endings cause different qualities of tactile sensations, such as light touch and sustained pressure [26–30].

Superficial mechanoreceptors are mostly fast adapting. The deeper mechanoreceptors are slowly adapting with high response thresholds conveying proprioceptive rather than tactile information [31].

Mechanoreceptors are also present in the periodontal ligament (PDL) of teeth. These mechanoreceptors are involved in regulating forces applied in occlusion, mastication, and biting [28, 32].

There are two key classes of PDL receptors [26]: (1) the Ruffini-like receptors projecting into the mesencephalic trigeminal nucleus. These receptors are fast adapting with directional sensitivity and respond according to the amount of force applied to the tooth. They are unlike most Ruffini-like receptors that are normally slow adapting and are therefore involved in jaw-jerk reflex response [33]. (2) Receptors that innervate more superficial structures of the PDL are both fast-and slow-adapting mechanoreceptors, which connect to the sensory trigeminal nucleus [28, 34].

2.2.2 Nociceptors

Generally nociceptive fibers are smaller in diameter and have free nerve ending with lower conduction velocity than mechanoreceptive fibers. Based on afferent fiber morphology, they are divided into two types:

- A-delta fibers that are thinly myelinated and relatively fast-conducting (although slower than mechanoreceptors). They are responsible for fast, sharp sensations.
- C fibers that are unmyelinated and slow-conducting. They are responsible for dull, slow aching pain.

Free nerve endings are unencapsulated and have simple sensory structures. They are the most common type of nerve ending and can be of different types such as rapidly adapting, intermediately adapting and slowly adapting. The A-delta type II fibers are fast adapting while A-delta type I and C fibers are slowly adapting.

Most A-delta and C fibers end as free nerve endings that can detect temperature, mechanical stimuli (touch, pressure, stretch), or nociception. Polymodality is the characteristic of a receptor responding to multiple modalities such as responding to mechanical (touch, pressure, stretch), pain (nociception), or temperature stimuli.

Most primary nociceptive afferents innervating the oral tissue carry sensory inputs to the trigeminal spinal nucleus, which extends from the pons to the upper cervical cord and is subdivided into subnucleus oralis, subnucleus interpolaris, and subnucleus caudalis [35]. The A-delta and C afferent neurons from the oral tissues synapse in the subnucleus caudalis, (most caudal of the three nuclei) then connect to the brain through secondary neurons [36]. From the subnucleus caudalis, three types of neurons project to the thalamus: (1) wide dynamic range (WDR) neurons, responding to both noxious and non-noxious stimuli, (2) nociceptive-specific (NS) neurons, and (3) low-threshold mechanoreceptors, which do not receive nociceptive input [37]. Many of the secondary neurons that carry sensory information from the head, face, and oral cavity to the thalamus have small receptive fields [36], but there are other NS and WDR neurons that have large receptive fields and respond to noxious thermal and mechanical stimulation, as well as non-noxious mechanical stimuli carrying crude touch, conscious proprioception, pain, and temperature sensations [28, 37]. There are some secondary neurons that show an overlap in their characteristics responding both as A-beta as well as C-polymodal neurons. Other

WDR neurons that respond to stimuli from TMJ, dental pulp, masticatory muscles, and superficial skin can be involved in the process of referred pain and have an increase in size for receptive fields [36, 38–40].

2.2.3 Thermoreceptors

A thermoreceptor is a nonspecialized receptive portion of a sensory neuron that codes absolute and relative changes in temperature within the innocuous range. The warmth receptors in the human peripheral nervous system consist of unmyelinated C fibers that have low conduction velocity. Furthermore, cold receptors have both C fibers and thinly myelinated A-delta fibers that are fast conductors. A warm stimulus increases the rate of action potentials in the warm receptors, whereas cooling decreases it. For cool receptors, cooling increases their action potential discharge, and warming decreases the rate of the discharge.

In the oral cavity temperature, changes are frequent. They can be noxious or non-noxious in nature. The secondary neurons of the trigeminothalamic tract receive A-delta or C-fiber inputs. These fibers respond more frequently to warming in the noxious range of above 45 °C than the non-noxious range of 35–45 °C with an increase in number of neurons recruited and responding at an increasing temperature [28, 36].

2.3 Gasserian Ganglion

The Gasserian ganglion (GG) is a thin semilunar-shaped structure [41, 42] positioned at the anterior, inferior, and lateral aspects of the Meckel cave [42–44]. The Meckel cave is an enclosed structure that is formed by two layers of dura, dura propria (internal layer) and intracranial periosteum (external layer) [42, 45, 46]. The GG has a convex surface, which faces the anteroinferolateral wall of the Meckel cave and merges with the dural wall of the sinus. Its concave surface faces the cerebrospinal fluid (CSF) side and the trigeminal cistern, which is an upward extension of the subarachnoid space of the prepontine cistern [41, 42, 45]. A group of small sensory rootlets called the pars triangularis (fan-shaped rootlets) emerge from the concave surface. They anastomose with each other and extend posteriorly to form the sensory root of the fifth cranial nerve [42, 47–49].

The convex surface of GG gives rise to V1, V2, and V3 branches within the Meckel cave [50]. The GG has a size ranging from 14 to 22 mm in length and thickness of 4 to 5 mm. Considering the semilunar shape of the ganglion, its thickness is really about 1.5–2 mm [41, 42, 45, 51]. The GG is only partially within the trigeminal cistern. The convex anteroinferior surface merges to the dura of the Meckel cave and temporal fossa and is considered to be outside the trigeminal cistern [41, 42, 45, 46]. The motor root of CN V passes inferior to the GG attached to the basal wall of the Meckel cave in its distal portion [42, 51].

The V1 courses anteriorly in the lateral wall of the cavernous sinus and exits the intracranial cavity through the superior orbital fissure (SOF), V2 exits through the foramen rotundum, and V3 exits through the foramen ovale [49, 52–55].

2.4 Branches of Trigeminal Nerve

2.4.1 Ophthalmic Nerve

The ophthalmic nerve (V1) passes by the dura close to its medial surface which forms the lower part of the lateral wall of the cavernous sinus and splits into the lacrimal, frontal, and nasociliary nerves as it passes through the superior orbital fissure (SOF) [56–59]. The lacrimal nerve innervates the lacrimal gland and the upper eyelid, whereas the nasociliary nerve divides into the anterior and posterior ethmoid nerves, innervating part of the paranasal sinuses, dura of the anterior cranial fossa, and also anterior and middle third of the falx cerebri [58, 60–62].

The frontal nerve innervates the conjunctiva of the eye and forms the cutaneous branches: supraorbital nerve and supratrochlear nerves.

The supraorbital nerve passes the supraorbital foramen and supplies palpebral filaments of the upper eyelid and conjunctiva as well as the skin of the scalp up to the lambdoid suture. The supratrochlear nerve comes out of the frontal notch

between the trochlea and the supraorbital foramen and courses to the forehead to supply the conjunctiva and the skin of the upper eyelid.

2.4.2 Maxillary Nerve

The maxillary nerve (V2) passes through the foramen rotundum and enters the infraorbital canal. It connects to the pterygopalatine ganglion and provides parasympathetic and sensory branches to the paranasal sinuses. Some of its fibers pass through the orbit and exits through the infraorbital foramen to give rise to the zygomatic nerve and infraorbital nerve branches [56–58, 61, 63].

The infraorbital nerve branches into:

- Palpebral branches (supply the skin of the lower eyelid)
- Nasal branches (supply the skin of the side of the nose and of the movable part of the nasal septum)
- Superior labial branches (supply the skin of the cheek anterior part and upper lip) [58, 61, 64]

The zygomatic nerve divides into the zygomaticofacial nerve and zygomaticotemporal nerve. The zygomaticofacial nerve exits the skull through the zygomaticofacial foramen. It pierces the orbicularis oculi muscle supplying the skin of the cheek. The zygomaticotemporal nerve courses through the zygomaticofacial canal to the anterior part of the temporal fossa. It passes between the bone and the temporalis muscle, piercing the temporal fascia above the zygomatic arch and innervates the skin of the temple [58, 61].

2.4.3 Mandibular Nerve

The mandibular nerve (V3) exits the cranium through the foramen ovale and divides into anterior and posterior branches. The anterior branches are masseteric nerve (motor), deep temporal nerve (has anterior and posterior divisions (motor)), buccal nerve (sensory), and lateral pterygoid nerve (motor).

The posterior branches are auriculotemporal nerve (sensory), lingual nerve (sensory), and inferior alveolar nerve (motor and sensory—it gives rise to mylohyoid nerve).

Three main sensory branches of V3 are buccal, mental (a terminal branch of the inferior alveolar nerve), and auriculotemporal nerves [56–58, 61, 63]. The buccal nerve courses behind the ramus of the mandible and passes in front of the masseter to innervate the anterior skin and the buccinator muscle. The mental nerve exits the mandible through the mental foramen and supplies the skin of the lower lip. Furthermore, the auriculotemporal nerve innervates the posterior tissue of the temporomandibular joint and the superior surface of the parotid gland. It courses along temporalis superficialis to innervate the tragus and the adjoining part of the auricle of the ear and the posterior part of the temple [58, 61].

From the main trunk, the mandibular nerve gives rise to:

- Meningeal branches—nervus spinosus (sensory)
- Muscular branches—nerve to medial pterygoid (motor)

From the anterior division:

- Masseteric nerve (motor)
- Anterior and posterior deep temporal nerve (motor)
- Buccal nerve (sensory)
- Lateral pterygoid nerve (motor)

From the posterior division:

- Auriculotemporal nerve (sensory)
- Lingual nerve (sensory)
- Inferior alveolar nerve (motor and sensory: to mylohyoid and supplies anterior belly of digastric muscle)

2.4.3.1 Auriculotemporal (AT) Nerve

The auriculotemporal nerve is branching posteriorly from the mandibular nerve trunk and runs along the lateral pterygoid muscle. Then, it turns and crosses the posterior border of the mandible and divides into branches. It innervates the TMJ capsule, the tympanic membrane, the skin lining of the external acoustic meatus, the upper part of the auricle, the tragus of the ear, the temporal

region, the parotid gland and the region of scalp above the auricle. The posterior part of the cheek, the buccal, and labial gland is also innervated by AT nerve as well as the skin over the angle of mandible, the parotid gland, and its fascia (through its connections to great auricular nerve).

AT nerve entrapment is a common condition among patients with TMD. It plays a key role in the pathogenesis of TMJ pain syndromes, headaches, pain, or parasthesias within the external acoustic meatus and auricle. The symptomology of headaches and regional pain may be due to the anatomical relationships that exist between the AT nerve, the muscles of mastication, temporomandibular joint, and surrounding vessels in the infratemporal fossa.

In most anatomical textbooks and atlases, AT nerve starts with two roots from the posterior margin of the mandibular nerve below its exit through the foramen ovale. In the case of two-nerve root variation, the roots surround the middle meningeal artery and run between the lateral pterygoid muscle and the posterior parts of tensor veli palatini. They later fuse and form a short trunk extending laterally from the sphenoid spine and sphenomandibular ligament to the TMJ. Then the nerve trunk gives off numerous branches, which include branches communicating with the facial nerve, articular branches, branches to the external acoustic meatus, anterior auricular nerve, superficial temporal branch, parotid branches, vascular branches, and branches communicating with the otic ganglion and the mandibular nerve [65–77].

Some authors have pointed out the high variability of AT nerve describing a one, two, three, and four (sometimes five) root variation that affects the nerve entrapment [66, 71, 74] (Fig. 2.1).

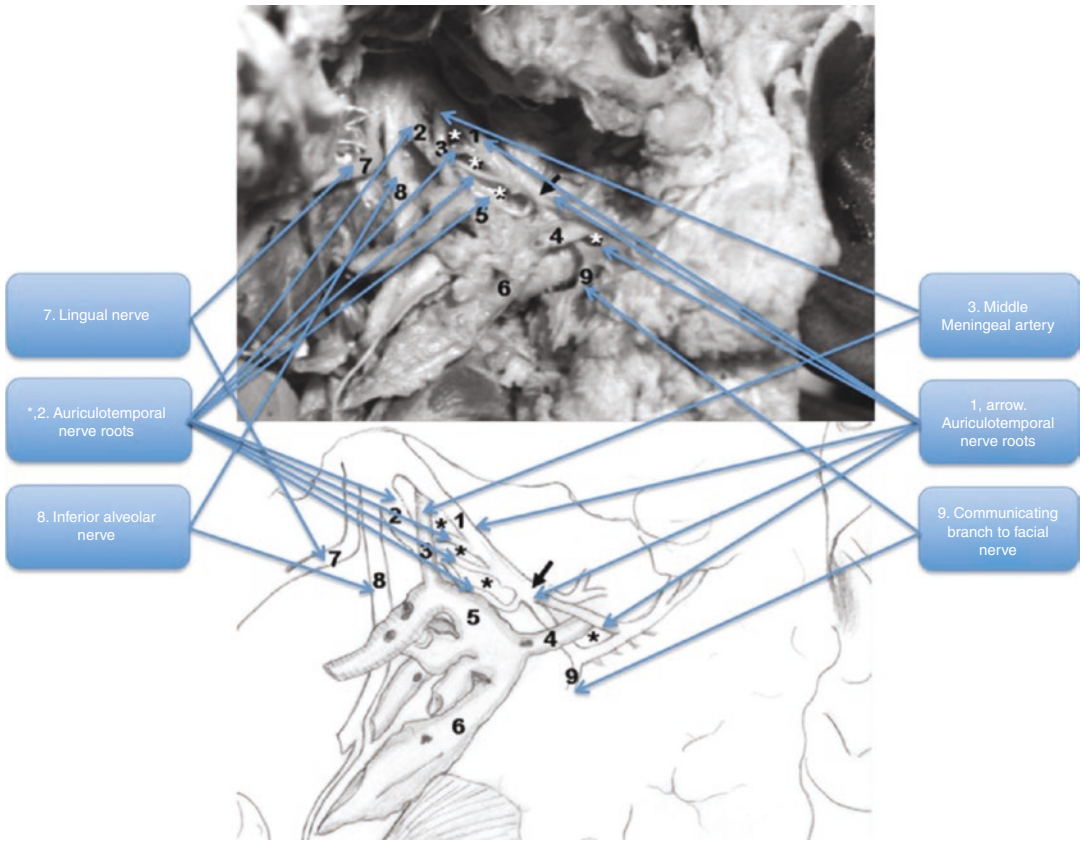


Fig. 2.1 Dissection picture and diagrammatic representation of the left infratemporal fossa showing multiple auriculotemporal nerve roots (*, arrow, 1 and 2). The middle meningeal artery (3), superficial temporal artery (4), maxillary artery (5), external carotid artery (6), lingual nerve (7), inferior alveolar nerve (8), communicating branch to the facial nerve (9) (Adapted from Simmi et al. 2009 [74])

According to Komarnitki [72] there are two main factors that determine the presence of AT nerve entrapment within the infratemporal fossa. The first is anatomical variation, and the second is the presence of various types of dysfunction within the masticatory system. A dysfunction within the masticatory system such as a small functional or structural change within the stomatognathic system can initiate a series of morphological changes and ultimately leads to entrapment and pain syndromes [72].

2.5 Innervation of Cranial Dura Mater and Trigeminal Nerve

The cranial dura mater, supratentorial dura mater, falx cerebri, tentorium cerebelli, major dural sinuses, proximal part of the intracranial internal carotid, basilar and middle cerebral arteries and the posterior cranial fossa dura are all innervated by the trigeminal nerve branches, the first three cervical spinal nerves, and the cervical sympathetic trunk. The arachnoid and pia matter do not contain nerve fibers.

The dura of the anterior cranial fossa is innervated by meningeal branches of the anterior and posterior ethmoidal nerves of V1 (branches following the middle meningeal artery) and meningeal branch of the V2 and V3 (nervus spinosus) divisions of the trigeminal nerve. The nerve of Arnold (nervus tentorii), a recurrent branch of the V1, bilaterally innervates the tentorium cerebelli, dura of the parieto-occipital region, posterior third of the falx, transverse sinus, and posterior third of the superior sagittal sinus. It originates from V1 within the lateral wall of the cavernous sinus (CS), runs caudally to the trochlear nerve entering the tentorium to follow the tentorial vessels such as the artery of Bernasconi–Cassinari.

The mid-meningeal nerve (nervus meningeus medius) of V2 and the nervus spinosus of V3 innervate the middle cranial fossa and the lesser wing of the sphenoid bone. The mid-meningeal nerve innervates the dura in the parietal area, whereas the nervus spinosus enters the cranial cavity mostly through the foramen spinosum and in some cases through the foramen ovale. It courses along the middle meningeal artery dividing into anterior and posterior branches that follow the main divisions of the artery and supply the dura mater in the middle cranial fossa and lateral convexity [50, 58, 60–62, 78, 79].

The dura mater of the posterior fossa is innervated by the upper three cervical nerves (that give off ascending meningeal branches), glossopharyngeal, hypoglossal, vagus and trigeminal nerves.

Nerves from C1 and C2 innervate the dura mater in the lateral and posterior parts of the posterior cranial fossa, and nerves from C3 innervate the dura mater in the anterior part of the posterior cranial fossa. A branch of the vagus nerve starting from the superior ganglion follows the posterior meningeal artery and supplies the dura of posterior fossa. The hypoglossal nerve exits the hypoglossal canal and courses rostrally to supply the dura of the anterior walls and floor of the posterior fossa and dura of the inferior petrosal sinuses. Animal studies using horseradish peroxidase tracing have shown trigeminal nerve innervation of the dura of posterior fossa [58, 61, 62, 79, 80].

2.6 Trigeminal Innervation of Major Intracranial Vessels

Many human and animal studies have shown that the pterygopalatine and Gasserian ganglia play a role in cerebrovascular innervations. The trigeminal innervations such as the ones in the vessels of the circle of Willis and their distal branches have shown that these innervations are present throughout the thickness of the adventitia (the connective tissue covering a vessel), but they never reach the smooth muscle cells.

There is a dense nervous plexus present in the lateral wall of the CS, located mainly around the abducent nerve and medial to the ophthalmic nerve and numerous interconnections exist between these nerves. Fibers from the CS plexus and the abducent nerve leave to move onto the internal carotid artery (ICA) and enter the anterior circle of Willis. Other fibers with the abducent nerve (VI) join the basilar artery and get distributed to the posterior circle of Willis and vertebral arteries [58, 61, 81–83].

2.7 Trigeminal Nerve (CN V) Pathways

Most trigeminal sensory (afferent) pathways consist of first, second, and third order neurons with the exception of the mesencephalic nucleus. The general somatic afferent (GSA) neurons in the trigeminal sensory pathway transmit touch, pressure, pain, and thermal sensations from the periphery to the CNS. The cell bodies of these pseudounipolar (first order) neurons are located in the Gasserian ganglion. Their peripheral processes course through the trigeminal nerve divisions (V1, V2, and V3) terminating in the sensory receptors of the orofacial regions. The central processes of CN V enter the pons and terminate in the trigeminal sensory nuclei (main/chief/principal sensory nucleus and spinal trigeminal nucleus) and synapse with second order neurons that have their cell bodies in these nuclei. The input from CN V is then relayed by the second order neurons through the ventral or dorsal trigeminal lemnisci to the ventral posterior medial (VPM) nucleus of the thalamus and synapse with the third order neurons. The second order neurons that join the ventral lemniscus cross before connecting to the VPM of thalamus, whereas the fibers joining the dorsal lemniscus do not. Third order neurons from the VPM take the sensory information to the postcentral gyrus for further processing.

Some sensory fibers of the trigeminal system are A-beta discriminatory touch fibers. They are non-adapting, meaning they keep responding to stimuli even when there is no change in muscle length. The trigeminal A-beta fibers are highly myelinated medium to large diameter (6–12 μm) fast-conducting (33–75 m/s) neurons that peripherally terminate in the secondary receptors of muscle spindles and cutaneous mechanoreceptors of the orofacial regions [25, 84–86].

The central processes of CN V pseudounipolar (first order) neurons enter the pons via the trigeminal spinal tract, which consists of ipsilateral nerves. They bifurcate into fibers that synapse with second order neurons that have their cell bodies located in the main sensory nucleus as well as subnucleus oralis and subnucleus interpolaris of the spinal trigeminal nucleus. Through the ventral trigeminal lemniscus (ventral trigeminothalamic tract), some second order neurons from the main sensory nucleus ascend and cross the midline to terminate in the contralateral VPM nucleus of the thalamus. The remaining second order neurons of the main sensory nucleus join the dorsal trigeminal lemniscus (dorsal trigeminothalamic tract) where they do not cross and terminate ipsilaterally in the VPM nucleus of the thalamus. Second order neurons from subnucleus oralis and subnucleus interpolaris cross the midline and ascend in the ventral trigeminal lemniscus to the contralateral VPM nucleus of the thalamus. The VPM nucleus of thalamus houses the cell bodies of the third order neurons, and this is where the second and third order neurons synapse. From the VPM nucleus, the third order neurons take the sensory information to the postcentral gyrus (PCG) of the cerebral cortex for processing [25, 84–86]. Other primary afferent sensory fibers of the trigeminal branches are similar to the A-delta and C fibers of the spinal nerves. A-delta fibers are thinly myelinated and are considered the smallest of the myelinated nerves. They are 2–5 μm in diameter and are fast conductors with a velocity of 3–30 m/s. They are activated by mechanical and thermal stimuli and their activation results in short-lasting, pricking-type pain. The C fibers are polymodal (mechanical, thermal, chemical), unmyelinated, and have less than 2 μm of diameter with a slow conduction velocity of 0.5–2 μm/s. Activation of C fibers results in dull, poorly localized, burning-type pain. These neurons are stimulated by physical stimuli (mechanical injury) and tissue damage by-products (cytokines, neuropeptides released from afferent nociceptors substance P (SP), calcitonin gene-related peptide (CGRP), neurokinins). The peripheral processes of these neurons terminate in rapidly adapting free nerve endings.

There are classically four types of free nerve endings. Type 1 is described as a spherical or oval-shaped corpuscle with one or two layers of capsules and ramified endings such as Ruffini corpuscle. Type 2 is cylindrical or conical-shaped corpuscle with ten or more layers

of capsules such as the Vater-Pacini. Type 3 is a spindle-shaped corpuscle with ramified endings and 1–3 layers of corpuscles such as Golgi-Mazzoni corpuscle. Type 4a is an unmyelinated network of intersecting nerves and free nerve endings; it is a pain receptor. Type 4b is unmyelinated nerve ending and is a vasomotor receptor. According to Ishibashi, Vater-Pacini corpuscles, Golgi-Mazzoni corpuscles, Ruffini corpuscles, non-corpuscle complex endings, and free nerve endings are found in the TMJ capsule [25, 84–87].

Pseudounipolar neurons of CN V enter the pons through the trigeminal spinal tract and synapse in the subnucleus caudalis of the trigeminal spinal nucleus. The subnucleus caudalis is involved in the transmission of pain and thermal sensation from orofacial structures. Some of the second order fibers of the subnucleus caudalis cross the midline joining the ventral trigeminal lemniscus and synapse the third order neurons in the contralateral VPM. Others do not cross and join the dorsal trigeminal lemniscus synapsing the third order neurons in the ipsilateral VPM nucleus of thalamus. The thalamus receives indirect trigeminal nociceptive (dull, aching pain) input via the reticular formation and through the interneuronal connections between subnucleus oralis, subnucleus interpolaris, and the main sensory nucleus. The synaptic activity is modulated and the somatosensory information from the trigeminal system is relayed by the ascending third order neurons through the posterior limb of the internal capsule to the PCG of the somatosensory cortex for further processing.

GSA fibers carry touch, pressure, pain, and temperature sensations innervating parts of the scalp, two-third of the dura mater, conjunctiva and cornea of the eye, face, nasal cavities, paranasal sinuses, temporomandibular joint, lower jaw, gingival, palate, teeth, and anterior two-thirds of the tongue through the trigeminal nerves.

GVA and GSA sensory neurons of facial, glossopharyngeal, and vagus nerves are also carried by the trigeminal spinal tract and terminate in the spinal trigeminal nucleus. They synapse with the second order neurons in these nuclei.

Other trigeminal sensory pathways consist of the GP afferent pseudounipolar neurons. They are proprioceptive large diameter myelinated A-alpha and A-beta nerve fibers that have their cell bodies located in the mesencephalic nucleus. Their peripheral processes course through CN V [(V1), (V2) and (V3)] and CN III, CN IV, and CN VI, carrying proprioceptive stretch sensations from muscles of mastication and related tendons, extraocular muscles, and PDL to the CNS. The central processes of GP neurons synapse in the main sensory nucleus, motor nucleus, and reticular formation.

The trigeminal motor (efferent) pathway consists of the SVE branchiomotor neurons, which carry motor innervations to the skeletal muscles of branchial arch origin (CN V, CN VII, CN IX, CN X). They form the motor root of the trigeminal while exiting the pons, entering the Gasserian ganglion, joining the mandibular division of the trigeminal, and are distributed to innervate muscles of mastication (temporalis, masseter, medial pterygoid, lateral pterygoid), and mylohyoid (eight muscles), anterior belly of the digastric, tensor veli tympani, and tensor veli palatini muscles. The cell bodies of these neurons are located in the trigeminal motor nucleus [25, 84–86].

The trigeminal system has four nuclei (one motor nucleus and three sensory nuclei):

Motor nucleus

Sensory nuclei:

- Main (chief, principal) nucleus of the trigeminal
- Mesencephalic nucleus of the trigeminal
- Spinal nucleus of the trigeminal (with three subnuclei):
  - Subnucleus oralis
  - Subnucleus interpolaris
  - Subnucleus caudalis

2.7.1 Motor Nucleus of the Trigeminal

The trigeminal motor nucleus is situated medially to the sensory complex at about the level of the principal trigeminal sensory nucleus. It is

mainly composed of the cell bodies of multipolar alpha and gamma motor (branchiomotor) neurons whose axons form the motor root of the CN V as they exit the pons. The branchiomotor fibers join the mandibular division of the trigeminal nerve to innervate the masticatory muscles as well as the mylohyoid muscles, anterior belly of the digastric, tensor veli tympani, and tensor veli palatini muscles as mentioned above. The motor neurons that innervate the jaw-closing muscles are located dorsolaterally in the rostral and middle thirds of the motor nucleus, whereas, the jaw-opening motor neurons are found ventromedially, in the caudal third of the nucleus [88, 89].

2.7.2 Sensory Nuclei

The sensory information from the orofacial structures is transmitted to the thalamus by the trigeminal sensory nuclei. It consists of cells that have the shape of a long cylinder extending from the mesencephalon to the level of the first few cervical spinal cord. The main sensory nucleus and the trigeminal spinal nucleus receive inputs from the first order pseudounipolar afferent neurons whose cell bodies are housed in the trigeminal ganglion. These nuclei are considered the first sensory relay station of the trigeminal system.

2.7.3 Main Nucleus

The main nucleus is located in the midpons, lateral to the motor nucleus. It is involved in transmitting discriminatory (fine) tactile and pressure sense information received from the mechanoreceptors of the orofacial region.

2.7.4 Mesencephalic

The mesencephalic nucleus is truly a sensory ganglion located in the CNS which houses the cell bodies of sensory first order pseudounipolar neurons. Peripherally, these large-diameter myelinated neurons accompany the motor root of the trigeminal to exit the pons and innervate the muscle spindles of the muscles of mastication. The mesencephalic first order neurons follow the orbital branches of the V1 to innervate the muscle spindles of the extraocular muscles and follow the dental branches of the V2 and V3 to the sensory receptors of the PDL of the maxillary and mandibular teeth. In the CNS, the mesencephalic nucleus synapses bilaterally with the main sensory nucleus and motor nucleus and connects to the reticular formation to mediate reflex responses.

2.7.5 Spinal Trigeminal Nucleus

The spinal trigeminal nucleus is the largest of the sensory nuclei and extends caudally to the outer lamina of the dorsal horn (substantia gelatinosa) of the upper three to four cervical spinal segments. It consists of three subnuclei:

- Subnucleus oralis (pars oralis)—most rostral
- Subnucleus interpolaris (pars interpolaris)—intermediate
- Subnucleus caudalis (pars caudalis)—most caudal

The subnucleus oralis is joined with the trigeminal main sensory nucleus. It receives inputs from pseudounipolar (first order) afferent neurons and transmits discriminative (fine) tactile sense from the orofacial region to the VPM of thalamus.

The subnucleus interpolaris also receives inputs from pseudounipolar (first order) afferent neurons of the orofacial region and transmits tactile sensations (dental pain) to the VPM of the thalamus.

The subnucleus caudalis is situated as the most caudal nucleus of the three and extends from the level of the medulla to the C3 or C4 of the spinal cord. It is associated with the substantia gelatinosa and has similar cellular morphology, synaptic connections, and functions.

The subnucleus caudalis receives inputs from pseudounipolar (first order) afferent neurons (A-delta and C fibers) of the orofacial region transmitting nociception (pain) and thermal sensations to the thalamus.

The trigeminal nerve is anatomically associated with the parasympathetic ganglia of other oculomotor, facial, and glossopharyngeal nerves by carrying their autonomic fibers to their destination [25, 84–86].

2.8 Trigeminal Nerve-Related Cranial Nerve Pathways

1. Major cranial sensory ganglia are:
   Gasserian
   Geniculate
   Cochlear (spiral)
   Vestibular (Scarpa's)
   Superior glossopharyngeal
   Inferior glossopharyngeal
   Superior vagal
   Inferior vagal (nodose)
2. Major cranial parasympathetic ganglia are:
   Ciliary ganglion: located inside the orbit
   Pterygopalatine ganglion: located in the pterygopalatine fossa
   Otic ganglion: located in infratemporal fossa
   Submandibular ganglion: located in submandibular fossa

2.8.1 Facial Nerve

The facial nerve consists of two parts: facial nerve proper (motor root) and the nervus intermedius. The facial nerve proper consists of the axons of SVE (branchiomotor) neurons with their cell bodies residing in the facial nucleus. The nervus intermedius carries GVE neurons with their cell bodies residing in the superior salivatory nucleus. Through its connection to the geniculate ganglion, it carries first order pseudounipolar SVA, GSA, and GVA neurons, which all have their cell bodies located in the geniculate ganglion.

The three important intratemporal branches of facial nerve are:

(a) Greater petrosal nerve
(b) Nerve to the stapedius muscle (stapedius muscle is responsible for "dampening down" loud noises protecting the middle and inner ear structures)
(c) Chorda tympani nerve

The GVE preganglionic parasympathetic fibers from superior salivatory nucleus exit the brainstem via the nervus intermedius and are distributed by greater petrosal nerve and the chorda tympani nerve. They pass through the geniculate ganglion and greater petrosal nerve, where they continue through the pterygoid canal, to enter the pterygopalatine fossa and synapse in the pterygopalatine ganglion with postganglionic parasympathetic fibers. These postganglionic parasympathetic fibers provide secretory innervations to the lacrimal gland and the glands of the nasal and oral cavity.

GVE preganglionic fibers join the lingual nerve through the geniculate ganglion and the chorda tympani nerve. The lingual nerve is a branch of the mandibular division of the trigeminal nerve that carries preganglionic parasympathetic fibers to the submandibular ganglion, where they synapse with postganglionic parasympathetic neurons of submandibular and sublingual glands providing them with secretomotor innervation.

The geniculate ganglion houses the cell bodies of the SVA neurons, which transmit taste sensations from the anterior two-thirds of the tongue. The chorda tympani nerve carries peripheral fibers from the anterior two-thirds of the tongue via the lingual nerve of the mandibular division. Its central processes enter the brainstem via the nervus intermedius to join the ipsilateral solitary tract and terminate in the solitary nucleus.

The greater petrosal nerve carries the peripheral end of GVA pseudounipolar sensatory neurons, which have their cell bodies in the geniculate ganglion from the nasal cavity and the soft palate. The central processes of the GVA neurons course through the nervus intermedius joining the ipsilateral solitary tract and terminating in the solitary nucleus. The GSA pseudounipolar neurons of the geniculate ganglion carry temperature, touch, and pain sensation from the pinna and the external auditory meatus. These fibers course through nervus intermedius and join the spinal

trigeminal tract and terminate in the spinal trigeminal nucleus.

The facial nerve exits the facial canal via the stylomastoid foramen and enters the parotid gland, where it starts dividing at the pes anserinus giving off several extratemporal branches supplying structures of the face such as:

- Temporal—frontalis, muscles of the external ear
- Zygomatic—remainder of frontalis, two parts of orbicularis oculi and adjacent muscles
- Buccal—upper half of orbicularis oris, buccinator, and dilator muscles inserting into the upper lip
- Marginal mandibular—muscles of the lower lip
- Cervical—platysma and other branches including the posterior auricular (supplying posterior auricular muscles) and the posterior belly of digastric as well as the stylohyoid [25, 84–86]

2.8.2 Glossopharyngeal Nerve

The glossopharyngeal nerve is cranial nerve nine (CN IX). It originates at the medulla oblongata as a group of rootlets that collect to form the main trunk. CN IX emerges from the anterior aspect moving laterally in the posterior cranial fossa and exits the cranium through the jugular foramen. Right after leaving the cranium, it forms the superior and inferior ganglia that contain the cell bodies of the first order pseudounipolar neurons. Anatomically, it splits into several nerves and branches: tympanic nerve, nerve to stylopharyngeus, pharyngeal branch, tonsillar branch, lingual nerve (glossopharyngeal lingual, not to be confused with lingual nerve), and carotid body (sinus branch). The superior ganglion contains the cell body of GSA, and the inferior ganglion contains the cell bodies of GVA and SVA neurons.

The GSA neurons of the superior ganglion of CN IX provide touch, pain, and temperature innervations peripherally to the pinna of the ear and the external auditory meatus (as well as some sensory inputs to oral structures including pharyngeal wall and posterior one-third of the tongue). Their central processes enter the brain through glossopharyngeal nerve root, joining the spinal tract of the trigeminal nerve and terminating in the spinal nucleus of the trigeminal nerve.

The cell bodies of the SVA neurons, which carry taste sensation, are housed in the inferior ganglion of the glossopharyngeal nerve. They connect peripherally to the tongue, supplying the posterior one-third of the tongue and neighboring pharyngeal wall with taste sensation. The central processes of CN IX terminate in the solitary nucleus.

The inferior ganglion of the glossopharyngeal nerve houses the cell bodies of the first order GVA neurons as well. The peripheral processes are carried by the main trunk of the nerve innervating the mucosa of the posterior one-third of the tongue, tonsil and neighboring pharyngeal wall, tympanic cavity, and auditory tube. Its central processes enter the solitary tract and synapse in the nucleus ambiguus. CN IX supplies sensory innervation to the oropharynx by GVA neurons; therefore it carries the afferent information for the gag reflex. The efferent nerve of this reflex process is provided through the vagus nerve (CN X). SVE branchiomotor nerve cell bodies of both CN IX and CN X are located in the nucleus ambiguous. Some nerves exiting the brainstem via the CN IX innervate the stylopharyngeus muscle. Others convey through CN X to innervate most of the laryngeal and pharyngeal muscles with the exception of the stylopharyngeus and the tensor veli palatini muscles.

GVA fibers carry information of blood pressure and oxygen saturation from the carotid body and carotid sinus via the carotid sinus nerve to the CNS. Their central processes terminate in the solitary nucleus relaying sensory inputs to the reticular formation, general visceral efferent motor nuclei, and intermediolateral horn of the spinal cord, which is involved in controlling the blood pressure.

CN IX provides parasympathetic innervations to the parotid gland. The cell bodies of preganglionic parasympathetic GVE neurons are located in the inferior salivatory nucleus. Preganglionic fibers exit the brain through the CN IX and branch off as the tympanic nerve to form the tympanic plexus in the middle ear and continue as the

lesser petrosal nerve, which enters the otic ganglion. In the otic ganglion, they synapse with postganglionic parasympathetic neurons and join the auriculotemporal branch of the trigeminal nerve to provide parotid gland with secretomotor innervation [25, 84–86].

The otic ganglion (OG) is one of the most difficult parasympathetic ganglia to study due to its small size and cumbersome access for anatomical dissection and visualization.

Otic ganglion is located in the infratemporal fossa immediately below the foramen ovale. It surrounds the origin of the medial pterygoid nerve and is laterally related to the medial surface of the mandibular nerve trunk bordering the tensor veli palatine nerve and anteriorly the middle meningeal artery [90].

The OG is a small oval-shaped flattened lens or spider-like structure of about 3.5–4.5 mm long, 3 mm wide, and 1.5 mm thick with yellowish-brown or reddish-gray color [90, 91].

Its parasympathetic roots are formed by the preganglionic axons from the inferior salivary nucleus in the medulla oblongata. These axons join the glossopharyngeal nerve (or CN IX) and travel with the tympanic nerve for a short distance. Then they leave the tympanic nerve to form the lesser petrosal nerve. In most cases, the CN IX preganglionic fibers exit through the sphenopetrosal fissure to reach the posterior surface of the OG, enter, and synapse to the postganglionic fibers within the OG. However, in some cases they pierce the greater wing of the sphenoidal bone in the area of foramen spinosum through the innominate canal of Arnold and reach the OG. Within the OG, preganglionic fibers synapse with the postganglionic fibers (cell bodies located in the OG) and exit joining the auriculotemporal nerve of V3 via a communicating branch. The auriculotemporal nerve conveys the secretomotor fibers via an anastomosis to the facial nerve that brings them to the parotid gland and the small buccal and the labial glands [92, 93] (Fig. 2.2).

The plexus around the middle meningeal artery and deep petrosal nerve are the anterior border of the otic ganglion, and they give rise to the fibers of the sympathetic roots that enter the

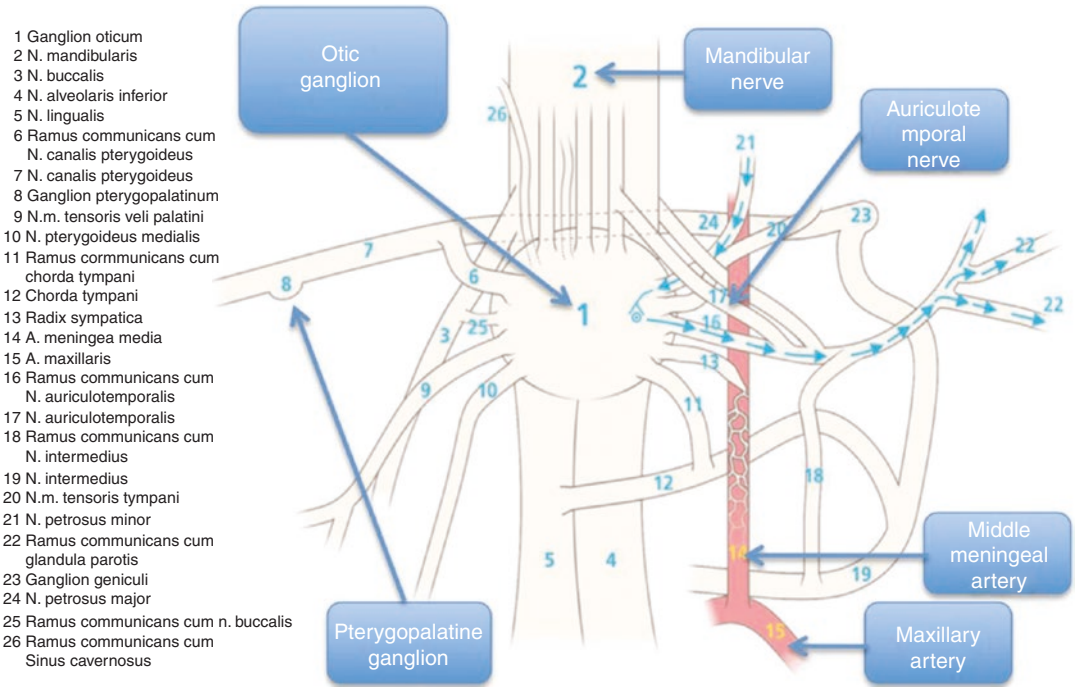


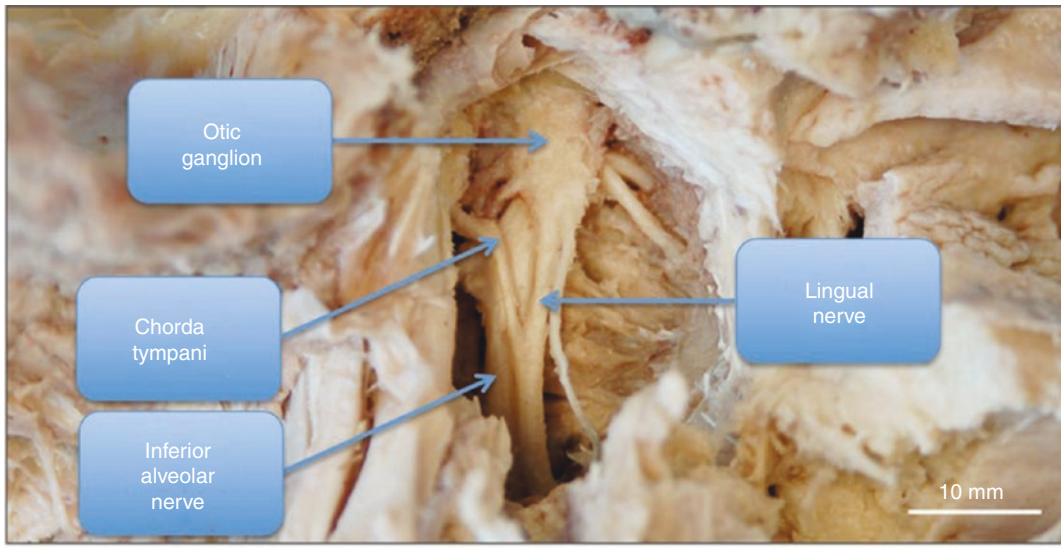
Fig. 2.2 Schematic drawing of otic ganglion (Adapted from Sengera M. et, al. 2014 [94])

otic ganglion from the ventrolateral direction. These postganglionic fibers originate from the superior cervical ganglion, pass through the OG without relaying synaptic connections, and run together with the parasympathetic fibers through the communicating branch to the auriculotemporal nerve. The sympathetic fibers are necessary for the parotid gland blood vessels [93, 95, 96].

The sensory root fibers course through the OG without synapsing to reach the medial pterygoid nerve, which innervates both the tensor veli palatini and the tensor veli tympani muscles [90, 93]. The sensory root also receives fibers from the glossopharyngeal nerve via the tympanic plexus and the lesser superficial petrosal nerve [97] (Fig. 2.3).

Branches of the OG: The facial nerve motor fibers pass through the otic ganglion to reach the levator veli palatini muscle. They course through the chorda tympani and enter the otic ganglion through a communicating branch. These facial motor fibers continue through the otic ganglion, without any synaptic connections, relaying fibers from the internal sphenoidal nervule (communicating branch) and pass through the pterygoid canal. There they anastomoses with the nerve of the pterygoid canal, Vidian nerve, which connects to the pterygopalatine ganglion for the levator veli palatini muscle [92, 93, 98].

In short, this is the pathway: facial nerve—chorda tympani—otic ganglion—internal sphenoidal nervule—pterygoid nerve—pterygopalatine



1 Ganglion oticum
2 N. lingualis
3 N. alveolaris inferior
4 Chorda tympani
5 Radix sympatica
6 R. communicans cum n. auriculotemporalis
7 A. meningea media
8 N.m. tensoris tympani
9 N. petrosus minor
10 N. mandibularis
11 R. communicans cum n. canalis pterygoideus
12 N. buccalis
13 N.m. tensoris veli palatini
14 N. pterygoideus medialis

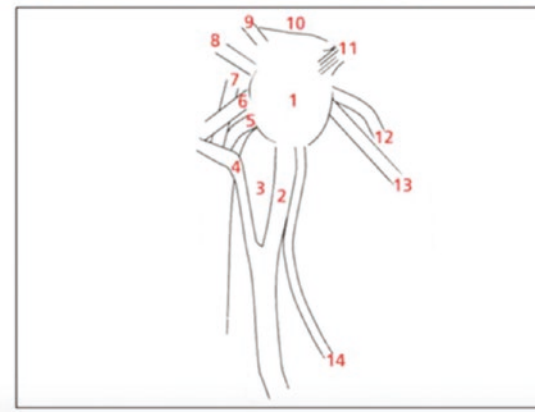


Fig. 2.3 Photograph and schematic drawing of left otic ganglion (Adapted from Sengera M. et, al. 2014 [94])

ganglion—lesser palatine nerve to the muscle [93, 99, 100].

The parasympathetic fibers of the Vidian nerve and the greater superficial petrosal nerve synapse in the pterygopalatine ganglion. The postganglionic fibers from the pterygopalatine ganglion follow the blood vessels arriving at the nasal mucous membrane, palate, rhinopharynx, pharynx, and lacrimal gland [98].

The auriculotemporal nerve carries postganglionic parasympathetic secretory fibers for the parotid gland (Jacobson's anastomosis—glossopharyngeal tympanic nerve to superficial part of the lesser petrosal nerve [93]). Postganglionic fibers from the otic ganglion enter all ramifications of the trigeminal mandibular nerve including the meningeal branch and lingual nerve [101]. The communicating branch to the greater petrosal nerve provides sensory and parasympathetic fibers to the lingual nerve and OG has a connection to the greater petrosal nerve via the lesser petrosal nerve [93, 102]. The sphenoidalis internus, arising from the otic ganglion, passes a small bony canal to the pterygoid canal and anastomoses with the Vidian nerve. Sphenoidalis internus seem to be accompanied by a small ganglionic cord (Sengera assumes it to be sphenoidalis externus) [94] along half of its course, which separates from it and continues toward the trigeminal ganglion [98].

The external sphenoidal nerve is a thin branch that enters the cavernous sinus through foramen Vesalii, or a small bony canal accompanied by a small vein. It has been shown that the external sphenoidal nerve is joined to the trigeminal ganglion from the medial side and reaches the cavernous sinus [93, 103]. There are connections, branches, and rami arising from the dorsal side of the otic ganglion to the trigeminal ganglion and to a small ganglion in the cavernous sinus [104]. This has also been shown in animal [105–108] and human dissection studies [23, 103] providing evidence that postganglionic otic fibers terminate on cerebral arteries [99]. Clara describes a communicating branch to the buccal nerve and assumes it to be a pathway for parasympathetic fibers to the buccal glands. According to Miriam Sengera [94], no other detailed information about this connection is found in the literature; however, they were able to find these communicating branches in their specimens.

2.8.3 Vagus Nerve (CN X)

Inferior to the CN IX and superior to the spinal accessory nerve (CN XI) in the medulla, a group of rootlets join to form two distinct bundles: the inferior (smaller) and the superior (larger) bundles that form the CN X. The inferior (smaller) bundle joins the CN XI for a short distance before it separates and rejoins the main trunk of CN X, to exit the cranium through the jugular foramen. Shortly after exiting the cranium, the CN X forms its superior (jugular) and inferior (nodose) ganglia. The CN X carries SVA, GVA, GSA, SVE, and GVE functional components that are also carried by the facial and glossopharyngeal nerves.

The cell bodies of pseudounipolar first order SVA neurons that carry taste sensations peripherally from the scant taste buds of the epiglottis are located in the inferior ganglion of the CN X. The fibers that are extended toward the brainstem enter to terminate in the solitary nucleus.

The cell bodies of pseudounipolar first order GVA neurons are located in the inferior ganglion. The peripheral processes transmit sensations from the mucous membranes of the soft palate, pharynx, larynx, esophagus, trachea, and GVA chemoreceptor fibers in the carotid body, which monitor blood carbon dioxide concentration carrying the information to the CNS. The central processes of the GVA neurons enter the brainstem through the solitary tract and terminate in the solitary nucleus. The cell bodies of pseudounipolar first order GSA neurons that convey pain, temperature, and touch sensations are located in the superior ganglion. Peripherally they carry information from the pinna of the ear, external auditory meatus, skin of the ear, tympanic membrane, and dura of the posterior cranial fossa. GSA neurons enter the brainstem centrally by joining the spinal tract of the trigeminal and terminate in the spinal trigeminal nucleus [25, 84–86].

The nucleus ambiguus houses the cell bodies of the SVE branchiomotor neurons which innervate the laryngeal and pharyngeal muscles, except for the stylopharyngeus muscle (innervated by SVE-CN IX) and tensor veli palatini muscle innervated by the medial pterygoid nerve, a branch of mandibular nerve. The tensor veli palatini muscle is the only muscle of the palate that is not innervated by the pharyngeal plexus, which is formed by the CN IX and CN X.

The cell bodies of preganglionic parasympathetic GVE neurons are located in the dorsal motor nucleus of the CN X. They exit the brainstem to supply parasympathetic innervation to the laryngeal mucous glands, the thoracic organs, and most of the abdominal organs.

The CN X has different anatomical pathways on right and left as it descends inferiorly. The important branches of vagus nerve are:

- *Meningeal branch* carries first and second cervical spinal nerves branching at the superior ganglion and supplies the dura in the posterior cranial fossa.
- *Auricular branch* arises from the superior ganglion joining a branch from the glossopharyngeal nerve and facial nerve communications. It supplies the auricle, the tympanic membrane, and the floor of the external auditory meatus.
- *Pharyngeal branches* form the pharyngeal plexus and supply all the muscles of the soft palate (except the tensor veli palatini muscle) and pharynx (except the stylopharyngeus muscle).
- *Superior laryngeal nerve* has two branches: (1) internal laryngeal nerve, which innervates the area above the vocal cords supplying the mucosa of epiglottis, (2) external laryngeal nerve, which innervates the inferior constrictor muscle and the cricothyroid muscle.
- *Recurrent laryngeal nerve*, on the right side, arises close to subclavian artery and courses posterior to the common carotid artery, then passes between trachea and esophagus while supplying them. It enters the larynx to conveying sensory information from the area below the vocal cords and muscles of larynx on the right (except the cricothyroid). On the left, it arises at the aortic arch and passes underneath, coursing behind the aorta close to the ligamentum arteriosum. Then, it ascends into the groove at the junction of trachea and esophagus giving off branches to the aorta, heart, and trachea. Both left and right recurrent laryngeal nerves enter the larynx supplying sensation to the area below the vocal cords giving cardiac branches to the deep cardiac plexus as well as branches to the trachea, esophagus, and inferior constrictor muscles.
- *Carotid branches* arise from either the glossopharyngeal nerve, superior laryngeal nerve, or the inferior ganglion.
- *Cardiac branches* arise from the superior or inferior cervical levels as two or three separate branches and merge with superficial and deep cardiac plexus.
- *Esophageal branches* provide innervation to the esophagus and the posterior aspect of the pericardium.
- *Pulmonary branches* supply the bronchi and related pulmonary tissue.
- *Gastric branches* supply the stomach. The left CN X supplies the anterior-superior region of the stomach, and the right CN X supplies the posteroinferior region.
- *Celiac branches* are derived mainly from the right CN X; form the celiac plexus and supply the pancreas, spleen, kidneys, adrenals, and intestine; and contribute to the hepatic plexus of the liver.
- *Renal branches* contribute to the renal plexus including the splanchnic nerves, which supply the blood vessels, glomeruli, and tubules [25, 84–86].

2.9 Neurophysiological Pathway Correspondence

The trigeminal nerve is the largest and most complex of the 12 cranial nerves. It has the greatest peripheral sensory distribution and the highest central brainstem representation [109]. Neurons at all levels of the trigeminal brainstem complex project to brainstem regions including

the reticular formation and motor nerve nuclei. Their connectivity to these particular regions provide the central substrate underlying autonomic and muscle reflex responses to craniofacial stimuli [109]. The ventro-basal nociceptive neurons communicate with the overlying somatosensory cerebral cortex. In contrast, nociceptive neurons medial in the nuclei (e.g., intralaminar nuclei; parafascicular nucleus) are generally corresponded with the anterior cingulate cortex. Neurological reflex studies can aid in our understanding of afferent and efferent pathways and are effective neurophysiological tools for the assessment of cranial nerve nuclei and the functional integrity of suprasegmental structures [110]. Information retrieved from analysis of the neurophysiology, central pathways, and normative data behind these reflexes can be used to understand various neurological abnormalities, including trigeminal pain and neuralgia, facial neuropathy, and brainstem lesions, and how best to treat the symptoms.

2.9.1 Trigeminofacial Reflex

The trigeminofacial reflexes including the blink reflex and corneal reflex are exteroceptive reflexes with a sensory afferent limb made up of cutaneous trigeminal fibers, exteroceptive and nociceptive A-beta, and A-delta and C fibers [109]. The efferent limb consists of motor fibers from the nucleus of the facial nerve. The afferent innervation of the cutaneous, intraoral, deep (i.e., joints, muscles, tendons) and cerebrovascular tissues project to the trigeminal brainstem complex [109]. This can be subdivided into the main or principal sensory nucleus and the spinal tract nucleus, with the latter being comprised of three subnuclei: oralis, interpolaris, and caudalis. The subnucleus caudalis is usually viewed as the principal brainstem relay site of trigeminal nociceptive information. The nociceptive inputs are conveyed predominantly at laminae I, II, V and VI. These nociceptive neurons have been categorized as nociceptive-specific (NS) neurons or wide dynamic range (WDR) neurons [109]. Many NS and WDR neurons in the subnucleus caudalis are only excited through natural stimulation of cutaneous or mucosal tissues and have properties consistent with a role in the detection, localization, and discrimination of superficial noxious stimuli [111]. The extensive convergent afferent input patterns that are characteristic of temporomandibular joint (TMJ) or myofascial activated NS and WDR neurons in the subnucleus caudalis can provide an explanation for the poor localization of deep pain, as well as the spread and referral of pain, which are typical of deep pain conditions involving the TMJ and associated musculature [109].

2.9.2 Trigeminocervical Reflex

Trigeminocervical reflexes are multisynaptic neck muscle withdrawal responses that are clearly identifiable in humans. These reflexes are mediated by neural circuits at the brainstem level, and degeneration of brainstem neural structures, as seen in progressive supranuclear palsy, results in significant impairment to the trigeminocervical reflexes. Other motor-related diseases such as Parkinson's disease (PD) are also often associated with degeneration in this area and, consequently, abnormal trigeminocervical reflexes [112].

2.9.3 Trigeminocardiac Reflex

The trigeminocardiac reflex (TCR) is defined as the sudden onset of parasympathetic arrhythmia, sympathetic hypotension, apnea, or gastric hypermotility upon stimulation of any sensory branches of the trigeminal nerve [113]. The trigeminal nerve and cardioinhibitory vagus nerve constitute the afferent and efferent pathway in this reflex arch. The proposed mechanism for the development of TCR begins with the sensory nerve endings of the trigeminal nerve sending neuronal signals via the Gasserian ganglion to the sensory nucleus of the trigeminal nerve, thus

forming the afferent pathway of the reflex arc [113]. Studies suggest that mechanical stimulation anywhere along the branches of the trigeminal nerve (central or peripheral) can elicit a TCR [113]. The reaction subsides with cessation of the stimulus. However, if patients have developed severe bradycardia, asystole, and arterial hypotension, intervention is required [13, 113]. This reflex involves multisynaptic neck muscle withdrawal responses that are mediated by neural circuits at the brainstem level. This reflex loop is absent or impaired in patients with PD or progressive supranuclear palsy due to the degeneration of brainstem neural structures [13, 110, 112]. Risk factors currently known to increase the incidence of TCR include hypercapnia, hypoxemia, light general anesthesia, age (more pronounced in children), the strength and duration of provoking stimuli, and drugs such as potent narcotic agents (sufentanil and alfentanil), beta-blockers, and calcium channel blockers [112]. The current treatment options for patients with TCR include (1) risk factor identification and modification, (2) prophylactic measures, and (3) administration of vagolytic agents or sympathomimetics [112].

2.9.4 Tonic Neck Reflex

The tonic neck reflex (TNR) is the earliest detectable reflex in the human embryo and is present at 7½ weeks of menstrual age [114, 115]. It is among other reflexes that allow the fetus to conform to the uterine cavity [115, 116]. The TNR originates in the mechanoreceptors of the upper cervical spine [115, 117] and plays the major role in orienting an organism in its environment and the maintenance of dynamic equilibrium [115, 118]. The TNR has a significant influence on jaw muscle activity and, in particular, muscles innervated by the trigeminal system via the trigeminal mesencephalic nucleus in the superior colliculus [119–121]. Trigeminocervical reflexes have been demonstrated to act through stimulation of motor neurons located in the subnucleus caudalis and in the dorsal horn of the upper cervical spine [115, 122].

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3 Neuroimmune and Systemic Manifestations of Neuroinflammation in the Temporomandibular Joint and Related Disorders

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Abbreviations

AD	Alzheimer's disease
BBB	Blood-brain barrier
CGRP	Calcitonin gene-related peptide
COX-2	Cyclooxygenase-2
DRG	Dorsal root ganglion
GG	Gasserian ganglion
iNOS	Inducible nitric oxide synthase
IP-10	IFN-β-induced protein 10
LPS	Lipopolysaccharide
MCP1	Monocyte chemotactic protein 1
M-CSF	Macrophage colony-stimulating factor
MHC	Major histocompatibility complex
MIF	Macrophage migration inhibitory factor
MIP-1-α	Chemokine macrophage inflammatory protein-1
MS	Multiple sclerosis
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
OPG	Osteoprotegerin
PAMPs	Pathogen-associated molecular patterns
PD	Parkinson's disease
PGE2	Prostaglandins E2
PKC	Protein kinase C
PRRs	Pattern recognition receptors
RAGE	Receptor for advanced glycation end products
RANK	Receptor activator of nuclear factor κB
RANKL	Receptor activator of nuclear factor κB ligand
RA-Rorγt	Retinoic acid-related orphan receptor γ thymus
SP	Substance P
STAT3	Signal transducer and activator of transcription-3
TLRs	Toll-like receptors
TMD	Temporomandibular disorders
TMJ	Temporomandibular joint
TRPV1	Transient receptor potential V1 receptor
VR1	Vanilloid receptor 1

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3.1 Introduction

The human temporomandibular joint (TMJ) is a bilateral articulation between the mandible and the temporal bone of the skull. The TMJ is a ginglymoarthrodial joint consisting of a hinge-type joint and a sliding arthrodial component [1]. The joint is encapsulated and stabilized by a fibrous membrane and is composed of the condylar process of the mandible that is separated from the glenoid fossa and the articular eminence of the temporal bone by a connective fibrous tissue disk that has a biconcave transversely oval shape [2]. Temporomandibular disorders (TMD are a group of pathologies affecting the TMJ, the muscles of mastication, and the related ligaments causing the joint dysfunction. TMD is most often manifested) as internal derangements and is considered to be among the most complex and yet common conditions involving orofacial pain. Pain is a common symptom, due to the sensory innervations of the joint and related muscles/ligaments, and is followed by inflammation as a result of damage and the stress upon the surrounding neurons and tissues.

Orofacial pain is a serious diagnostic and therapeutic problem. Symptoms usually occur as a result of compression of the nerves or nerve branches (such as the AT nerve) and vessels (such as the middle meningeal artery) by neighboring structures and muscles in the infratemporal fossa. Nerves may be compressed by normal anatomical structures or due to the pathological changes that affect them. The auriculotemporal (AT) nerve entrapment is an important cause of pain syndromes of the face and masticatory system [3–14].

3.2 Research and Findings

Inflammation has been identified as the underlying common denominator among TMD patients in the literature. Elevated levels of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) are found in the TMJ synovial fluid of TMD patients [15, 16]. Recently, our understanding of the inflammation process, immune surveillance, and signaling has changed, as new polarization states have been determined for T cells and osteoimmunology has been better recognized as a new emerging field.

In 2005 Harrington et al. and Park et al. established that TH17 cells were a true distinct linage of T cells. Eventually, retinoic acid (RA)-related orphan receptor γ thymus (Rorγt) was identified as the master transcription factor defining TH17 cells as a distinct lineage [17–19] secreting IL-17 cytokines with a primary role in sustained (chronic) inflammation and bone resorption.

The regulatory interaction between bone and immune cell pathways was established in a new field called osteoimmunology. Here the bone marrow provides the microenvironment that is critical for the development of the hematopoietic stem cells from which all cells of the mammalian immune system derive and in turn produce various immunoregulatory cytokines that influence the fate of bone cells. These influences are at molecular and cellular levels and ultimately determine (or alter) forms and functions. Bone metabolism consists of a complex series of finely regulated steps and events, which involve primarily the activity of bone-forming osteoblasts and of bone-destroying osteoclasts. The process of bone resorption is mediated through the receptor activator of nuclear factor κB (RANK), its ligand (RANKL), and osteoprotegerin (OPG), a decoy receptor for RANKL pathway. Activation of RANK/RANKL pathway results in maturation of preosteoclasts into mature osteoclasts resulting in an increase in the rate of bone resorption. Recently, additional polarization states such as TH9 cells are recognized providing a better picture of the inflammation, immune surveillance, and signaling processes [20].

3.3 Immune Surveillance and Signaling, Tissue Reaction, and Inflammation

In general, pathogens, toxins, traumatic events, and degeneration endanger the integrity of body tissues. In response, innate and adaptive immune cells, vascular cells, and neurons take actions to

maintain or restore tissue integrity. Innate immune cells, such as macrophages, are activated first. They respond in a nonspecific manner to exogenous signals (pathogens), or endogenous signals (ATP), which are released upon degeneration and cell damage [21].

The immune system functions under two principal branches of immunity: (a) innate immunity includes those immune processes that are triggered by the recognition of a novel pathogen. (b) Acquired immunity (i.e., antigen-dependent immunity) describes immune responses that are consequential to a previously encountered antigen. Both innate and acquired processes of immune surveillance are brought about principally either by humoral or cellular events. Humoral immunity provides protective immune surveillance by means of circulating soluble factors, such as cytokines, growth factors, complement factors, and antibodies. These factors are detected and measured in a variety of bodily fluids (e.g., blood serum, cerebrospinal fluid, saliva, synovial fluid). Humoral immune factors are produced by cells, which principally belong to the immune system per se. Certain cell populations that are not immune cells by functional definition (e.g., fibroblasts, astrocytes) contribute to the production of humoral factors at local sites of inflammatory and immune responses. Cellular immunity consists of immune surveillance events that are brought about by concerted, regulated myeloid and lymphoid cell populations. There are two principal families of innate immunity cells: the natural killer (NK) cells and the antigen-presenting cells, composed of myeloid derivatives, including dendritic cells and monocyte/macrophages. Cellular immune components of acquired immunity involve the lymphoid derivatives the T and B cells [22].

Immune cell populations are described and recognized by their functional status and their phenotype defined by glycoproteins that constitute the plasma membrane clusters of differentiation (CDs). In most but not all cases, CDs correspond to an identified function or functional structure, such as CD3 associated with the T-cell receptor defining all T cells. T cells express either CD4 or CD8 as their final stage of differentiation in the thymus. The majority of CD3+CD4+ cells are T cells endowed with the functional ability to assist cellular immunity to commence, expand, sustain, and control a fully developed acquired immunity response. CD4 T cells are often referred to as helper T cells, despite the fact that a small proportion of CD4 T cells can be cytotoxic. The cytotoxic immune function is primarily managed by CD8+CD3+ T cells, which also produce humoral factors and contribute to assisting cellular immune processes. The CD4 moiety recognizes and binds to the major histocompatibility complex (MHC) class II, whereas CD8 recognizes and binds to MHC class I. Because of the fact that MHC class I is ubiquitously expressed by every cell in the body, it follows that CD8 T cells provide immune surveillance of any cell that expresses foreign antigen on its membrane in association with MHC class I, such as a tumor cells and virally infected cells. Over the last decade, the known spectrum of CD4+ and CD8+ T-cell effect or subsets has become broader, including their particular cytokine commitment, stage of differentiation, role in local immunity, and specific functional activity. Discrete subsets of CD4 T cells (e.g., TH1, TH2, TH17, T regulatory cells [Tregs], CD45RA +CD4+ /CD8+, CD45R0 +CD4+/CD8 +, CD25+Foxp3 [forkhead box P3]+CD4+/CD8+) work in complementary synergy and with the M1 and M2 macrophage activation states to mediate an appropriate immune response [22].

The microenvironment is greatly dependent on the intricate, fluid relationships that exist between different subpopulations of CD3+ cells and the pattern of cytokines they produce. Two principal T cells-mediated cytokine patterns can be characterized on the basis of whether they foster T- or B-cell activation and proliferation. The human TH1 cytokines (e.g., IL-2, interferon gamma [IFN-γ], IL-12) predominantly favor T-cell activation, proliferation and maturation for cellular immunity toward parasites, virally infected cells and tumor cells, whereas the human TH2 cytokines (e.g., IL-4, IL-5, IL-10) favor the activation, proliferation and maturation of B cells enhancing humoral immunity and production of antibodies. A third T-cell

population blunts cellular immunity: the regulatory T-cell subpopulation (Tregs) characterized by tri-immunofluorescence flow cytometry to express either CD4 or CD8, the chain of the IL2 receptor, CD25, and FoxP3. Depending upon the microenvironment, TH1 populations might also engender a TH17 subpopulation, whose cytokine profile (e.g., IL-17A, IL-17F, tumor necrosis factor (TNF-α), IL-22, IL-23, and IL-9) lends to a state of sustained T cell-driven inflammation seen in autoimmune diseases and allergic reaction. TH2 cells may generate TH9 subpopulations characterized by elevated levels of IL-9 and IL-10, which downregulate TH1 activity. Tregs play a critical role in directing and regulating the dynamic plasticity required for balancing TH1/TH2 and the intimately related TH17/TH9 subpopulations.

Immune signaling is driven by a finely balanced and delicately regulated equilibrium of cytokines. The microenvironment dictates and regulates whether or not there is a predominant TH1 and TH17, or TH2 and TH9 pattern of cytokines, and controls cellular immune surveillance toward tumors and viral infections or in case of degeneration maintaining and restoring tissue integrity [22–25].

Myeloid derivatives, such as monocytes and macrophages, process foreign materials by phagocytosis, a process that has evolved in vertebrate immunology to recognize pathogens and damaged tissues through Toll receptors, which are pattern recognition receptors (PRRs) that recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). In a classic pattern of cellular immune surveillance, pathogens and cytohistological damaged tissues are detected through PAMP and DAMP within hours. This recognition event engenders a set of signals by resident macrophages. Levels of IFN-γ sharply rise, and immune surveillance commences. Macrophages either turn on their killing program "fight" against an invading pathogen or engage in a "fix" repairing, healing, and remodeling programs. Depending on the microenvironment, macrophages can either elicit responses that include nitric oxide and oxygen radical production—the destructive M1 response—or produce factors that promote proliferation, angiogenesis, and matrix deposition, the reparative M2 response [22, 25, 26]. IFN-γ produced by activated T cells may be the most potent stimulus for the inducible nitric oxide (NO) synthase pathway for arginine catabolism. Macrophages constitutively produce transforming growth factor-beta (TGF-β), which is inversely related to their NO production, thus suggesting that TGF-β may act as an autocrine regulator for NO formation and M1 activity [22, 26, 27].

The M1 and M2 states of macrophage activity represent a useful dichotomous functional classification that segregates the macrophage toxicity from its repairing physiological function. The M1 macrophage pattern reciprocally influences TH1 cytokines, including IL-12, which drives T cells toward sustained inflammation (i.e., TH17), activation, proliferation, and maturation; by contrast, the M2 state reciprocally favors TH2 patterns of cytokines to support humoral immunity, including B-cell proliferation and maturation and production of antibodies [22, 25–27].

The initial activation of monocytes/macrophages, which in turn release cytokines, targets the vascular system, particularly endothelial cells. While transient innate immune responses in the form of cytokines are beneficial to the host, the same essential spectrum of cytokines can lead to deregulation of homeostatic mechanisms, destruction of host tissues, and apoptosis [22, 28].

Macrophage-like cells have varied tissue distributions and have different names depending on their anatomical sites. In the central nervous system, macrophages are called microglial cells, whereas hepatic macrophages are referred to as Kupffer cells. In the lungs they are recognized as the alveolar macrophages, and in the skin, they are the Langerhans cells. Monocyte/macrophage subpopulations get activated and release large quantities of cytokines and chemokines in the central nervous system (CNS) following viral infection and degradation. Activated macrophages release a variety of pro-inflammatory proteins that include IL-1β, IL-6, IL-8, IL-15, IL-16, the chemokine macrophage inflammatory protein-1 (MIP-1)-α and MIP-1-β, monocyte chemotactic protein 1 (MCP1), macrophage colony-stimulating factor (M-CSF), macrophage migration inhibitory factor

(MIF), IFN-β-induced protein 10 (IP-10), and eotaxin.

Neuroinflammation, mediated in part by chemokine activity and the release of pro-inflammatory cytokines, contributes to the breakdown of CNS microvascular endothelial cells that constitute the blood-brain barrier (BBB), increasing the potential for continued pathogen and immune cell invasion into the brain. While most studies have focused on the inflammatory response of microglia and astrocytes, perivascular cells also play a key role in brain inflammation. Pericytes of the CNS are involved in recruitment of peripheral cells to the brain, which may directly induce neuronal damage or promote microglial hyper-activation and inflammation [22, 29].

3.4 Blood-Brain Barrier (BBB) Disruption and Inflammation

The BBB separates the brain from the circulatory system, thus maintaining a stable microenvironment. It is formed by specialized endothelial cells that are attached through tight junctions and adherence junctions. These function to separate the CNS from the circulation and restrict and prevent blood-borne molecules and peripheral cells from entering the CNS. Specialized endothelial cells line brain capillaries and form its structure. They transduce signals between the vascular system and brain. Both structure and function of the BBB are dependent upon the complex interplay between different surrounding cell types, including the endothelial cells, astrocytes, pericytes, and the extracellular matrix of the brain as well as the capillary blood. Tight junction proteins also provide BBB with two functionally distinct sides: the luminal side facing the circulation and the abluminal side facing the CNS parenchyma, which are highly sensitive to major cytokines produced during immune response, including TNF-α, IL-1β, and IL-6. Three sites have been identified with a physical barrier via tight junctions including the brain endothelium that forms the BBB; the arachnoid epithelium, which constitutes the middle layer of the meninges; and the choroid plexus epithelium, which secretes cerebrospinal fluid (CSF) [22, 30, 31].

The concerted cellular immune and inflammatory processes described above can disrupt the tight junctions of the BBB specialized endothelium thereby opening a gate, which enables the leakage and transvasation of activated immune cells and factors from the systemic circulation into the CNS and the brain parenchyma. A preliminary characterization of the molecular mechanisms of the BBB gateway proposes that it might be mediated in large part by nuclear factor kappa B (NF-κB) via the signal transducer and activator of transcription-3 (STAT3) activation. Inflammatory cytokines, including IL-17, can act as a trigger to NF-κB-mediated transcriptions, and IL-6, as a target of NF-κB, plays a critical role in opening the BBB gateway [31]. A role for certain other inflammatory modulators and chemokines has also been proposed in regulating the permeability of this BBB-gateway [31–33]. In animal models, exposure to an inflammatory stimulus at the time of an experimentally induced stroke leads to an identifiable Treg response, which modulates the TH1 response. An uncontrolled TH1 response to brain antigens is associated with higher neuropathologic scores [34–36]. IL-17 production by T cells contributes to ischemic brain injury up to 7 days following the stroke onset [37]. Based on current understanding of the role of TH17 and TH9, and specifically the TH17/TH9 balance in regulating immune surveillance mechanisms, and immune processes of chronic sustained inflammation in peripheral or central neuroinflammation, the "gateway theory" can be revised and expanded to involve and incorporate the role of TH17 and TH9 cytokines. Arima, Kamimura, Ogura, and collaborators, in their original description, characterized a rodent NF-κB-mediated "inflammation amplifier" mediated by IL-17, which was hypothesized to lead to a localized gateway through the BBB. Systemic inflammatory processes that involve macrophages in the M1 or the M2 states have differential effects upon the balance of TH17 and TH9 cytokines, regulated in part by TH1 and TH2 cytokines. Together, these factors act locally on the tight junction of the BBB endothelium and modulate the inflammation amplifier molecular

cascade. We hypothesize that the prevalence of M1 or M2 state of macrophage activation determines the porosity of the TH17/TH9 BBB gateway, which functions at the molecular level as the NF-κB-mediated gate theory of Arima, Kamimura, Ogura, etc. is described. In short, the TH17/TH9 BBB gateway is gated by the M1/M2 balance through its regulatory effects upon the molecular events of the inflammation amplifier and thus mediates the extent of systemic inflammation that can permeate into the central nervous system. By acting on the TH17/TH9 BBB gateway, novel patient-centered therapies may be developed to blunt NF-κB-mediated inflammation amplifier pathway and block inflammation of the brain consequential to a variety of neuroimmune pathologies, from cranial nerve neuropathies (e.g., trigeminal neuralgia) to neuropathologies (e.g., Alzheimer's disease, multiple sclerosis) to viral infections of the brain including neuroAIDS. In the same vein, the etiology of major depression has now been hypothesized to be associated with some form or some degree of neuroinflammation.

The degree to which CNS-specific TH17 cells contribute to injury in neurological disorders has yet to be explored. Nevertheless, should the hypothetical TH17/TH9 BBB gateway model be proven correct, it could open possibilities for new and timely therapeutic interventions in treating viral infections, which penetrate the CNS as well as other varied neuroimmune pathologies. They involve local brain immune responses following neurological injury, stoke and spectrum of neurological diseases, including central trigeminal neuralgia consequential to peripheral neuroinflammation [22, 31–33].

3.5 Neuroinflammation and Role of Neuropeptides

It is often believed that neuroinflammation is induced only by a pathological state, usually in the form of a microbial infection, exposure to toxins, or degeneration. However, many studies demonstrate that, in addition to the classical instigators of inflammation, enhanced levels of neuronal activity can trigger inflammatory reactions in peripheral tissues. This has long been known as "neurogenic inflammation".

Classical neurogenic inflammation in peripheral tissues is triggered by action potential-dependent release of substances from the peripheral terminals of peptidergic, sensory nerve fibers and involves vasodilation, plasma extravasations, recruitment of white blood cells, and mast cell degranulation. A number of studies have now shown that similar substances are released from synapses in the CNS in response to neuronal activity. These studies show that effective stimuli in rodent hind paws, such as direct electrical nerve stimulation at intensities sufficient to activate C fibers, cause selective activation of peptidergic primary afferents that express the transient receptor potential V1 (TRPV1) receptor by capsaicin and chemically induced inflammation. As in the periphery, activation of peptidergic primary afferent C fibers also leads to the spinal release of various mediators, including glutamate, substance P, calcitonin gene-related peptide (CGRP), and adenosine triphosphate (ATP). Receptors for these neurotransmitters and neuropeptides are present in the immune system, vascular cells, and higher-order neurons [21].

3.6 Substance P

Pain is in general a consequence of oral pathological conditions and orthotic procedures. Pain perception is partially due to activation of inflammatory pathways and accumulation of inflammatory molecules, a condition that is similar in other parts of the body. The sensory process of pain in the body involves neurons, receptors, channels, transmitters, and intracellular signaling molecules/effectors that play an important role in transduction, modulation, and propagation of peripheral stimuli to the CNS [38–41].

Primary sensory neurons are thin fibers containing unmyelinated C fibers and myelinated A-δ fibers that conduct pain signals from the periphery to the Gasserian ganglion (GG) and spinal cord then to the second-order neurons that convey the signals to the cortex through the thalamus [38].

Peripheral nociception terminals are specialized by expression of various receptors and

channels that are able to detect noxious chemicals and thermal and mechanical stimuli [38, 41].

Different types of injury result in the release of inflammatory mediators that act on the specific receptors expressed by nociceptive sensory neurons and result in production of secondary messengers and activation of protein kinases as well as phospholipases that regulate the activity of many receptors and channels leading to peripheral sensitization [41].

Neuropeptides are considered major inducers of pain and inflammatory process in peripheral tissues [42, 43].

Substance P (SP) is a neuropeptide that is produced in capsaicin selective sensory peripheral neuron cell bodies in the dorsal root ganglion and Gasserian ganglion and is involved in transmission of sensory stimuli to the CNS [44]. There are other neuropeptides besides SP that are present in the sensory peripheral neurons with pro-inflammatory activity such as calcitonin gene-related peptide (CGRP) and neurokinins A and B that are involved in neuroinflammation.

SP belongs to the same family as neurokinins (NK) A and B and shares the same carboxyl terminal sequence. It is encoded by the preprotachykinin-A gene in the perikaryon of primary afferent neurons in the GG and dorsal root ganglion (DRG), which is then transported to the central and peripheral processes of these neurons [45, 46]. A number of enzymes are involved in metabolism of SP. In periphery, endopeptidase and angiotensin-converting enzymes (EP and ACE) are mostly involved in cleavage of SP.

Several factors can activate and sensitize nociceptors at the site of injury to release neuropeptides in the periphery [44, 47].

The capsaicin vanilloid receptor (VR1) is an ion channel that is activated by vanilloid compounds, protons, and heat (<43 °C) [48]. VR1 is localized to mostly unmyelinated small and medium-sized neurons in GG supplying their peripheral receptive field with free nerve endings [49]. Activation of VR1 can result in opening of cation channels and calcium entry through voltage-gated calcium channels that induce depolarization and cause an increased SP release.

Vanilloid receptor 1-like receptor (VRL-1) is also a capsaicin receptor and is activated by higher temperature with a threshold of above 53 °C [48]. In GG, VRL-1 is localized to medium- to large-sized cell bodies with myelinated axons [50].

There are also other pathways that can have an effect in SP release and function. Bradykinin can bind to bradykinin B2 receptor on sensory neurons and cause protein kinase C (PKC) activation, which stimulates SP release from sensory endings. There are compounds that lower the threshold for firing of the sensory neurons such as prostaglandins. They are produced in the inflamed tissues and can bind to their receptor on sensory fibers lowering the firing threshold of neurons through protein kinase A [43].

There are three types of tachykinin receptors NK1, NK2, and NK3 that bind to substance P, neurokinin A, and neurokinin B preferentially [45, 51]. Endogenous tachykinins are not selective and can bind to these three receptors nonselectively at high peptide concentration or receptor availability.

Tachykinin receptors (NK1, NK2, NK3) are expressed in hard tissues, epithelial cells, periodontal ligaments, fibroblasts, endothelium, blood vessel walls, teeth, and supporting oral tissues.

SP mostly stimulates NK1 receptors and induces the release of secondary messengers such as inositol 1,4,5-trisphosphate (IP3) that cause elevation of calcium intracellularly [45].

Receptor activation by SP results in vasodilatation, increased blood flow, and blood vessel permeability, allowing for plasma extravasation and mast cell degranulation and release of histamine, which in turn activates nociceptors and further amplifies the process [52].

SP binds to its receptor on lymphocytes, granulocytes, and microphages and stimulates them to produce cytokines. Microphages will produce pro-inflammatory cytokines IL-1β, IL-6, and TNF-α as well as inflammatory mediators such as cyclooxygenase-2 (COX-2) an enzyme responsible for formation of prostanoids including prostaglandins E2 (PGE2) and thromboxane that in turn will sustain production of further SP neuropeptides and will keep feeding the cycle [45, 53, 54] both in the CNS and periphery [42, 55, 56].

3.7 VR1, VRL-1, and P2X3 Receptors in TMJ

The articular cavity of TMJ is enclosed by an articular capsule made up of fibrous tissue. The internal surface of TMJ and in particular the disk that lies between the condyle and the glenoid fossa of the temporal bone is covered with fibrous tissue. TMJ is innervated by primary nociceptive neurons that supply the capsule disk and the synovial membrane with free nerve endings and are connected to the CNS through their cell bodies in Gasserian ganglion.

P2X3 is an ATP-activated ligand-gated ion channel receptor present in small to large cell body neurons in the Gasserian ganglion (more on this in the next section) [57–59]. Neurons that contain VR1, VRL-1, and 2X3 receptors co-express CGRP and SP, and they project to superficial laminae of the medullary dorsal horn [49, 50]. The TMJ contains excess VR1 and P2X3 receptor in the articular capsule. They are seen around small and large blood vessels in synovial membrane and terminate as free nerve endings within the fibrous tissue of the joint. They are also seen in peripheral region of the articular disk. Therefore, VR1 and P2X3 receptors containing GG neurons innervate blood vessels in the articular capsule and disk, as well as the synovial membrane and the fibrous tissue around the condylar process.

According to a study by Ichikawa and colleagues in 2000 on rats, 25, 41, and 52% of primary sensory neurons of rats in the GG exhibit VR1, VRL-1, and P2X3 receptors, respectively, and 73%, 27%, and 44% of these respective receptors co-express CGRP [50].

3.8 Calcitonin Gene-related Peptide (CGRP)

The primary nociceptive neurons of the GG release neuropeptides and chemical agents in response to inflammatory or noxious stimuli and initiate peripheral neurogenic inflammation that results in sensitization of the trigeminal nociceptor neurons [60]. Activation of trigeminal neurons further progresses in activation of second-order neurons and glial cells that cause central sensitization, hyperalgesia, and allodynia [61]. This provides a possible pathway between peripheral inflammation and CNS activation.

CGRP is a 37 amino acid neuropeptide which is synthesized and released from the neurons of GG in response to a stimuli and is a major role player in TMD. Trigeminal nerve fibers that contain CGRP innervate the synovial membrane articular disk, periosteum, and joint capsule of the TMJ [62, 63]. An elevated level of CGRP in TMJ synovial fluid is an indication of impaired mobility and pain associated with arthritis [64] and inflammation [65]. Increased CGRP levels in TMJ can cause neurogenic inflammation by increasing the blood flow in the capsule, recruitment of immune cells, and activation of trigeminal nociceptors resulting in peripheral and central sensitization.

Chronically elevated levels of CGRP lead to excess bone resorption and osteoarthritis of the TMJ. Many studies including one that was done by Ryan Cady and colleagues in 2011 have shown that injection of CGRP into the TMJ capsule of rats will result in an increased expression of proteins that initiate and maintain peripheral and central sensitization by promoting local inflammation and pain, which in time will result in its transition from peripheral tissues to the CNS [61, 64, 66, 67]. The study showed that the CGRP stimulation of trigeminal neurons resulted in an increased expression of P38 and P-ERK in satellite glial cells in the GG. P38 and ERK are members of MAPK family of enzymes and are activated in response to inflammatory stimuli causing peripheral and central sensitization in primary and secondary neurons by increasing expression of ion channels and receptors associated with nociception [47, 68]. Elevated CGRP levels were also found to increase C-FOS expression in second-order neurons within the spinal trigeminal neurons, and it remained elevated until 24 h postinjection. An upregulation of OX-42, a biomarker of microglia activation [69], and GFAP a biomarker of both microglia and astrocyte activation [70, 71] was observed at 2 and 24 h postinjection. OX-42 is an antibody

designed to detect CD11b, which has been used as a marker of activated microglia in the brain. In the normal brain, microglia are the only cells that express CD11b. However, in the injured brain, neutrophils and monocytes, which also express CD11b, infiltrate the brain creating the misconception that rounded neutrophils and monocytes present in the injured brain are activated microglia [72, 73].

TMJ inflammation modulates excitability of cutaneous A-β neurons in GG through a paracrine secretion mechanism of substance P (SP) and causes TMD-associated inflammatory mechanical hyperalgesia and allodynia [74]. SP increases the severity of inflammation through astrocyte and glial cell production of pro-inflammatory cytokines such as IL-1β. IL-1β plays an important role in CNS functions including hypothalamic control of fever, sleep regulation, cardiovascular regulation, inflammatory and neuropathic pain [10, 75, 76], and generation of hyperalgesia [21, 77].

3.9 Peripheral Inflammation and CNS

Over the past two decades, many studies have shown that the systemic stimuli activate microglia and elicit a central response. Ever since this discovery, the peripheral to CNS pathways are becoming clearer.

In healthy systems and normal conditions, the activation of microglia will promote recovery, and the inflammatory response will resolve. Microglia will go back to its resting state monitoring the microenvironment of the brain. However, mounting evidence has shown that sustained systemic inflammation can initiate and start neurological diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS). The main cause is believed to be hypersensitive state that microglia can enter upon continuous stimulation which will result in excess production of pro-inflammatory mediators upon systemic inflammation or injury.

Our knowledge of microphage activation has evolved for the past few years from simplified M1 and M2 divisions to a broader spectrum of differentiation states that expand within different species [78, 79]. In general, the M1 pro-inflammatory state of the microglia is a defensive state that includes production of oxidative metabolites and pro-inflammatory cytokines upon stimulation by diverse set of ligands such as INF-γ, lipopolysaccharide (LPS), and other toll-like receptor (TLR) activators. Engagement of the receptor with the ligand leads to intracellular signaling through adaptive proteins such as MD88 and others. Activation of adaptor proteins leads to activation of kinases, phosphorylation of transcription factors, and an eventual genetic program induction that produces INF-γ, TNF-α, IL-1β, and IL-18 cytokines and chemokines. The pro-inflammatory activation is suppressed by glucocorticoids.

M1 pathway activation occurs by nod-like receptors (NLR) inflammasome and caspase-1 activation and conversion of pro-IL-1β and IL-18 into activated forms that are secreted into the cytoplasm. However, M2 functions as an anti-inflammatory response when macrophages and microglia are activated by IL-4, IL-1β, and other agonists. Alternative activation can vary depending on stimulus, and it is associated with helper T-cell responses such as allergy and immune resolution, eliminating parasites, tumor promotion, matrix deposition, tissue remodeling, and promotion of suppressive inflammatory cytokines such as IL-10 [80–82].

Microglia can be activated by systemic infection without the integrity of BBB being compromised. The circumventricular organs, which include the organum vasculosum of the lamina terminalis, the subfornical organ, the median eminence, and the area postrema, are sites where PAMPs in the blood can be detected. They are vascular regions and are loose capillary/endothelial cell junctions. At these regions large molecules can diffuse from capillaries into CNS.

The choroid plexus and leptomeninges are also densely vascularized. Microglia can become activated by inflammatory stimuli in the circulation. Initiation of an innate immune response happens in these regions and progresses into activation of resident microglia cells in the parenchyma of the brain [83].

Immune response in the brain differs from the peripheral immune response. Microglia activation in the brain becomes deleterious, and the balance between microglia phenotypes is determined by the type of neuroinflammation (acute versus chronic) associated with aging [84].

Microglia cells go through altered morphological changes during aging such as clustering [85]. These changes result in an increased expression of certain activation markers such as major histocompatibility complex II (MHC II) and receptor for advanced glycation end products (RAGE), which result in an increased pro-inflammatory cytokine production making microglia hypersensitive to inflammatory stimuli [86–88] and dysfunctional with age. Therefore, microglia activation can be both beneficial as the first line of defense and as a repair mechanism, but it may become destructive in case of excessive activation and hypersensitivity and will pose a start point for neurodegenerative disease processes [89, 90].

3.10 Microglia in CNS

For a long time, it was presumed that CNS is immune privileged and is not involved in the process of inflammation, but we know now that infection and neurological diseases elicit a local inflammatory response and activate the immune system. In the CNS this response is driven by the microglia cells, the resident immune cells in the brain region.

There are dynamic phenotypic changes that microglia goes through in the brain depending on the environment, aging, diseases stage, and presence of inflammatory factors such as cytokines and infiltrated microphages [91, 92].

Microglia cells are the first line of defense by sensing invading pathogens or host-derived ligands in case of tissue injury in the brain. They elicit a response by detecting the type of insult and directing the innate immune system to adaptive immune response. They become activated and clear the pathogen or damaged area by a process similar to phagocytosis, which is essential for reorganizing neuronal patters and repair mechanisms after injury [93, 94].

Microglia express specific receptors such as Toll-like receptors (TLR) to remove pathogenic organisms or apoptotic cell waste such as CD36 and integrins [94–96]. When microglia gets activated, it generates inflammatory cytokines, prostaglandins, inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and free radicals stimulating an adaptive response [94, 97].

There are monocyte-derived microphages and perivascular macrophages that besides phagocytic activities are responsible for antigen presentation to activate T cells that have been educated in the periphery to function in CNS [98].

Microphages are present in almost all organs of the body. They are cells produced by the differentiation of monocytes in tissues. They are cells of innate and are part of adaptive immunity. In the CNS, this specialized macrophage tissue is known as microglia. According to recent studies, the origin of microglia is derived from uncommitted F4/80-negative erythromyeloid progenitor subsets that enter and colonize the developing CNS during embryogenesis and become microglia [99–101]. Microglia is activated in CNS upon an invasion or an insult. Once activated, it starts the process of phagocytosis and releases effector molecules and cytokines for the purpose of recruitment of additional immune cells from blood into the CNS to control infection or invading pathogens. Microglia is also involved in the process of regeneration of damaged tissues in the CNS by secreting growth factors and anti-inflammatory molecules [54, 100]. Microglia exist in all regions of the brain with different densities, for example, 5% in the corpus callosum and 12% in the substantia nigra [100]. At the resting state, microglia are characterized by elongated processes and very small cell soma [102]. They have scavenger function for surveillance and control their immediate area. They do this by continually elongating and retracting their processes scanning the surrounding microenvironment [100]. Once microglia cells are activated, they can retract their processes and become mobile effector cells [103].

Activation of microglia is provoked by receptors such as Toll-like receptors (TLRs) and scavenger receptors as well as cytokine and chemokine receptors [100]. There are endogenous and exogenous signals that are essential to keep microglia in the resting state. A minor disturbance of these signals can result in spontaneous activation of microglia in the absence of any serious injury or infection in CNS, which in turn could jeopardize and damage neuronal integrity and function [100].

Microglia communicates with neurons and other glial cells through its surface molecule receptors. These receptors include cytokine receptors, scavenger receptors, pattern recognition receptors (PRRs), and chemokine receptors that recognize pro-inflammatory mediators. Activation of these receptors causes microglia to come out of its resting mode and become a moving effector cell that will induce and sustain inflammation [100]. There is also a small group of inhibitory receptors on the surface of microglia that inhibit pro-inflammatory activation of microglia.

3.11 Turn-off Mechanisms of Macrophages

In order for the host to survive, it is critical that the inflammatory process is turned off after activation. One of the pathways that have been identified to downregulate microglia activation is through the interaction between CD200 molecules on neurons in the brain and CD200 receptors on microglia that leads to an inhibitory signaling. Genetic knockout experiments have shown the importance of microglia downregulation, or turn-off pathway, in EAE and LPS models [104, 105]. Other ligand receptor pair interactions such as CD47-CD172α/51RPα and CX3CL1-CX3CR1 are also in part responsible for downregulation phenotype of microglia in healthy CNS. Interruption of these signaling pathways by loss of ligand due to impairment of neuronal integrity results in appearance of danger signals and may lead to microglia activation [80, 97, 106, 107].

CD200R is a receptor expressed only by microglia and microphages in the CNS. Its ligand CD200 is expressed by neurons, astrocytes, and oligodendrocytes. The interaction of CD200 and CD200R results in inactivation of microglia keeping it in its resting state.

There are receptors such as triggering receptor expressed on myeloid cells (TERM) 2 and purinergic receptors that are important inducers of the phagocytic, anti-inflammatory, and neuronal repair properties.

CX3CR1 is a seven-transmembrane chemokine receptor expressed in the CNS parenchyma by macrophages (microglia). Recent studies on animals with CX3R1 mutation have shown that the absence of this receptor or its dysfunction leads to harmful effects including decreased number of neuronal precursors and diminished adult neurogenesis and hippocampal circuit integrity [108]. These studies showed that an elevated level of hippocampal pro-inflammatory cytokines such as IL-1β secreted by microglia is toxic to developing neuronal progenitors. This supported the role of CX3CR1 as a "resting signal" to keep microglia in resting state. CD172a/Sirp alpha is an inhibitory signal on the surface of microglia that transmits a "do not eat me" signal through CD47 expressed by neuronal cells [63, 100, 109]. On the other hand, TERM2 is essential for phagocytosis. It expresses an "eat me" signal and is used by microglia to phagocytize apoptotic cell membranes. Colony-stimulating factor receptor 1 (Csfr1) is expressed by microglia, and it is essential for signaling cellular survival and development. It also controls development and survival of peripheral microphages.

Microglia also possess ionotropic receptors such as P2X4 and P2X7 as well as metallotropic receptors P2Y1, P2Y2, and P2Y12 on their surface that are essential for the maintenance of injured neurons (more on this in the next section) [110, 111].

When ATP is released in the parenchyma of CNS, for instance, after a neuronal injury, it activates microglia in the brain. The activation is signaled through the purinergic receptors that initiate microglial recruitment to the injured site and release of neurotropic factors. When microg-

lia is activated in the absence of an insult or infection, their function can be disruptive and harmful for neurons and neuronal networks resulting in developmental defects or neurological pathologies.

Substances that are released from primary afferent nerve fibers upon stimulation can directly activate glial cells. These include substance P acting on the neurokinin 1 receptor (NK1, also known as substance P receptor), ATP acting on P2X purinoceptor 7 (P2X7), and glutamate acting on metabotropic glutamate receptors (mGluRs). Consequently, markers of activation are upregulated in CNS microglia and astrocytes within minutes of enhanced neuronal activity.

3.12 Nucleotide Receptors P2X and P2Y

Extracellular nucleotides such as ATP serve as signals for variety of different biological and pathophysiological responses and disease states such as inflammation, bone remodeling, and neurological disorders and dysfunctions. They can be released at the site of injured tissue or in case of infection further stimulate related pathways through binding to P2 family of cytokine receptors.

Normally the extracellular levels of nucleotides are low in the body, but in case of trauma, damaged cells release high levels of nucleotides. There are two types of P2 family of cytokine receptors; the P2X ionotropic receptors that are ion-gated calcium channels and include P2X1–7 and the P2Y metallotropic seven-transmembrane spanning heterodimeric G protein-coupled receptors that include P2Y1, 2, 4, 6, 11, 12, 13, and 14 [81, 112–114].

P2X7 receptor is of particular interest and is expressed by several cell types including monocytes, macrophages, osteoclasts, osteoblasts, astrocytes, and most importantly microglia cells in CNS [52, 81, 115–117].

P2X7 receptor activation through ATP stimulates Ca^{2+}/Na^{+} influx and K^{+} efflux, mitogen-activated protein kinases (MAPKs), ERK1/2, P38, JNKs, the NADPH oxidase complex and reactive oxygen species (ROS) formation, phospholipase D, caspases, as well as nonspecific pore formation and stimulates inflammatory mediator release and apoptosis. It can also stimulate production and secretion of IL-1β, IL-8, cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and vascular endothelial growth factor (VEGF) [81, 118–121].

When P2X7 is activated for a longer period, it results in formation of reversible pores that lead to passage of small molecules that have been associated with apoptosis [81].

P2X7 receptors promote processing of the IL-1β into its biological active form through assembly of an inflammasome comprised of caspase-1; Nacht domain-, leucine-rich repeat-, and PYD-containing protein 3 (NALP-3); and apoptosis-associated speck-like protein containing CARD (ASC) that facilitates this process. The biosynthesis of IL-1β is comprised of two steps: (1) the synthesis of pro-IL-1β and (2) proteolytic cleavage of the pro-IL-1β by caspase-1 to make the active form. Once the P2X7 is activated, there is an efflux of K^{+} ion that stimulates cleavage of pro-caspase-1 to caspase-1, which ultimately converts more IL-1β to its active form [122, 123].

Extensive research on the subject of inflammation has shown that the inflammatory cycle including IL-1β and other pro-inflammatory cytokines is the main cause for many neuropathological disorders including multiple sclerosis and Parkinson's and Alzheimer's disease. It is believed that IL-1β affects many aspects of neurodegeneration including formation of β-amyloid precursor protein, activation of astrocytes, increase production of inducible nitic oxide synthase, and more.

It has been shown that P2X7 is involved in production and release of IL-1β and reactive oxygen species (ROS) from microglia, microphages, and other monocytic cells [124–126]. IL-1β causes expression of its own mRNA and P2X7 receptor in microglia and monocytes, which results in a positive feedback loop that causes sustained inflammation, activated glial cells, and astrocytes ultimately causing an increase in cell death and cell damage promoting more inflammation [125].

P2X7 regulates gene transcription by stimulating the expression and activation of Erg-1, Erg-2, Erg-3, the NFAT, NF-κB, CRE, CREB, AP-1, c-Fos, c-FosB, and JunB and promotes production of immune mediators such as VEGF, COX-2, IL-2, IL-6, and iNOS [115, 127–129].

COX-2 is a pro-inflammatory enzyme that catalyzes conversion of arachidonic acid into biologically active prostaglandins E2 (PGE2). P2X7 ligands promote the expression of COX-2 in osteoblast and blood mononuclear cells, and it appears that the production of PGE2 by osteoblast cells is ATP and P2X7 receptor dependent. Osteoblasts release PGE2, which is important in osteoclast maturation and differentiation, which in turn causes bone resorption.

Prolonged stimulation of the receptor results in formation of nonselective pores that involve the pannexin family of transmembrane channels and release of IL-1β.

3.13 P2X7, IL-1β, and Inflammasome

As mentioned earlier, innate immunity is triggered by relatively small determinants referred to as pathogen-associated molecular patterns (PAMPs) and is recognized by host inflammatory system. However, tissue damage also induces inflammation even in the absence of pathogens through molecules that are normally located inside of cells and are released after tissue injury. This is our body's defense system for surveilling and recognizing a possible danger. These molecules are termed damage-associated molecular patterns (DAMPs). Association of PAMPs and DAMPs elicits an immune response.

ATP is a common nucleotide that is available in every cell. It also plays an important role as the mediator for cellular communication, and it is considered a DAMP. A high concentration of ATP (5–10 μm) is present in cellular cytoplasm, whereas in healthy tissues, low concentrations of it (1–10 μm) can be found. ATP is released upon cell damage and is quickly inactivated by widespread ecto-ATPase enzyme. ATP is considered a neurotransmitter which points out its important role in the neuroinflammation theory, the P2X7 receptor, the inflammasome, and its induction of pro-inflammatory activity.

Accumulation of moderate amount of ATP in the pericellular space elicits a weak response where P2Y11 receptor activation causes partial maturation of dendritic cells (DCs) into TH2 phenotype. Pro-inflammatory cytokine and IL-12 secretions are inhibited, and IL-4 and IL-10 anti-inflammatory cytokines are promoted. However, the presence of high ATP concentrations results in P2X7 receptor stimulations and release of pro-inflammatory cytokines mainly IL-1β and IL-18 as well as mediators, and in case of sustained stimulation, cell death is ensued [130–132].

P2X7 receptor-driven IL-1β secretion is an active end result of intracellular processes that stimulates the release of this cytokine. IL-1β is accumulated in cell cytoplasm as pro-IL-1β since it lacks a leader sequence to be exocytosed by the exocytotic vesicles. Caspase-1 also known as IL-1β-converting enzyme (ICE) catalyzes maturation of pro-IL-1β.

Upon stimulation of cells with inflammatory stimuli, caspase-1 gets activated, which is otherwise inactive as pro-caspase-1 in quiescent cells [133, 134].

Two families of inflammasome scaffold proteins have been identified: (1) ICE protease activating factor (IPAF) and (2) NACHT-, LRR-, and PYD-containing proteins (NALPs). IPAF and NALP are part of the same complex. The inflammasome consists of a C terminal sequence that is rich in leucine referred to as LLR. This is the domain that interacts with bacterial products or chemical agents such as monosodium urate (MSU) and calcium pyrophosphate dihydrate (CPPD) and is released due to injury. The protein oligomerization domain (NACHT) and an N-terminal protein-binding motif are used for recruiting caspase-1 or caspase-5 (depending on species and inflammasome type). To recruit and modulate caspase activity, inflammasome scaffold protein uses three known motifs: (1) caspase recruitment domain (CARD) that mediates formation of large protein complexes via direct interaction between individual CARDs, (2) pyrin domain (PYD) that allows a pyrin domain-

containing protein to interact with other proteins that contain pyrin domain, and (3) baculovirus inhibitor of apoptosis repeat (BIR), a domain that is considered inhibitory. CARD derives caspase recruitment into the inflammasome complex. Caspase-1 is recruited by NALP-3 with the help of ASD that has both CARD and PYD. Binding of PAMPs or DAMPs to LRR sequences inhibits activation of inflammasome. This results in oligomerization by NACHT protein and recruitment of caspase-1 in case of NALP-1. In case of NALP-3 inflammasome, activation recruits ASC, which in turn binds to caspase-1 [135–140].

Studies have shown that P2X7 stimulation causes IL-1β release due to massive K+ efflux and that preventing K+ depletion prevents P2X7 receptor-mediated caspase-1 activation [139, 141–143]. However, cell-free studies that isolated pro-caspase-1 or apoptosome have shown that either Na+ or K+ inhibits activity suggesting that K+ efflux might have an indirect role in inflammasome stimulation [141].

In adaptive immunity, the body produces receptors (bound/soluble) that recognize and discriminate an infinite number of foreign or nonself antigens. However, innate immunity recognizes much more limited pathogen-associated molecular patterns (PAMPs) that stimulate and alert the immune system of the host from a wide range of potential unrecognized danger. In the body PAMPs are recognized by pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs). The retinoic acid-inducible gene (RIG)-like helicases (RLHs) and the nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) are two types of PRRs that survey the cytoplasm. RLHs are involved in antiviral immunity. However, NLRs are of our interest here, and they consist of NOD protein and IPAF, NAIP, and NALP inflammasome scaffold proteins.

Recent studies have shown that PRRs are not exclusive for PAMPs) and that DAMPs such as MSU and CPPD crystals as well as extracellular ATP can also activate them. This has brought about the concept of two-step mechanism of immune activation control. To avoid eliciting an unnecessary, costly, and harmful response, the immune system has evolved into a two-phase reaction. The first phase is the detection of foreign organisms by sensing the presence of PAMPs), which by itself is not enough to trigger an immune response. The cell will stay on standby until the body receives a second signal by detecting DAMPs, which are host-derived danger signals indicating there is a host cell danger. This elicits an inflammatory response by secretion of inflammatory cytokines, generation of reactive oxygen and nitrogen species, and recruitment of additional inflammatory cells. IL-1β activates the innate and adaptive immunity, and its oversecretion can cause chronic inflammatory diseases. In short, the IL-1β activation and release are controlled by two mechanisms: (1) detection of PAMPs, which causes IL-1β gene transcription and an inactive form of pro-IL-1β accumulation in the cell. (2) DAMPs such as ATP, a host cell damage signal, are detected, the P2X7 receptor is activated, and IL-1β is secreted [144–146].

Like glial cells, T cells express a large number of neurotransmitter receptors that can be activated in an antigen-independent fashion by substance P, CGRP, and neuropeptide Y all of which are released directly from primary afferents in response to neuronal activity [13, 58, 147]. In addition, T cells are activated by serotonin [58] and dopamine [148], substances that are also released in the spinal dorsal horn upon afferent stimulation [149, 150].

3.14 ATP and Its Effects on Regulatory CD4 T Cells

Naïve T cells get educated in the thymus, and once in the periphery, they get activated by encountering their cognitive antigen, which determines their response functionally. The nature of this response depends on the environment, mainly the accessory molecules and cytokines. T-cell response is sensed by cellular metabolisms such as inhibitor of mammalian target of rapamycin (mTOR), which functions as a sensor for cellular nutrients and energy and promotes CD8+ memory T-cell differentiation [151, 152]. mTOR also contributes to the generation of CD4+ CD25+ regulatory T cells (Tregs) that

express transcription factor forkhead box p3 (Foxp3) [153, 154].

Stimulation of the T-cell receptor (TCR) in CD4+ T cells results in an increased oxidative synthesis of ATP and its release through pannexin hemichannels [155]. As mentioned earlier, ATP binds to two classes of purinergic P2 receptors expressed in most eukaryotic cells: P2X ligand-gated ion channels and heterotrimeric guanine nucleotide-binding G protein-coupled protein P2Y receptors. P2X receptor autocrine activation of ATP plays an important role in sustained activation of MAPKs through T-cell receptor (TCR) and results in secretion of IL-2 that determines T-cell activation. Extracellular ATP stimulation of P2 receptor controls many pathways, and its innate immune system regulation has been widely studied [137–139, 156–160].

TCR stimulation of CD4+ cells causes ATP release and stimulation of P2 receptors which in turn regulate the set point of second messengers by affecting the cytosolic Ca^{2+} and cyclic AMP concentrations as well as protein kinesis activation. Therefore, Treg triggers a decrease in FoxP3 protein expression and derives the cell to convert to TH17 cells through P2X7 receptor indicating a role for autocrine ATP in regulation of Treg-mediated immunosuppression.

Pro-inflammatory cytokine IL-6 increases ATP synthesis and ERK phosphorylation in Tregs via P2X7 receptor activation, and this increased ATP synthesis and production of pro-inflammatory cytokines cause Tregs to lose their suppressive function as well as lineage stability. Activated ERK plays counter active role in the conversion of Tregs to effector T cells. Therefore, Tregs can differentiate into effector T cells in the presence of inflammation, and this conversion may lead to loss of tolerance to self at the meantime and may contribute to clearance of certain specific pathogens [161–165].

However, P2X receptor blocker and antagonist studies with stimulation of TCR have shown the activation of MAPKs with no effect on nuclear translocation of nuclear factor of activated T cells (NFAT) resulting cells entering into an anergic state of unresponsiveness [166].

Several studies have shown that Tregs are characterized by combined presence of CD 39 and CD 73 that degrade extracellular ATP to form adenosine [167, 168]. It was also hypothesized that P2X7 receptor sensitizes Treg to an ATP-mediated apoptosis. In addition, it was shown that Tregs could lose Foxp3 in both inflammatory and noninflammatory conditions to become effector cells [161, 169].

Ursula Schenk and her colleagues in 2011 showed that stimulation of P2X7 Treg receptor during chronic inflammation inhibited their immunosuppressive potential and resulted in Treg conversion to TH17 cells. They proposed that activation of T cells results in the release of ATP and that this endogenous ATP acts as a pro-inflammatory factor that shapes the T-cell function [166].

In pathological conditions, upon tissue injury, inflammatory reactions, hyperreactivity, and tumor cell growth, a large amount of ATP is released once cells start dying. ATP can also be released from T cells in response to physiological stimuli and can affect T cells through an autocrine and a paracrine mechanism of action. Inflammation and the immune response are regulated by this extracellularly generated ATP via purinergic receptors and through modulating B cells [170], monocytes and macrophages [171], eosinophils [172], as well as dendritic cells (DCs) [173–175].

In 2012 Sara Trabanelli and colleagues in their publication investigated the effect of extracellular ATP on CD4+ T cells. They showed that (1) low concentration of ATP at about physiological concentrations does not modulate proliferation or cell death of activated CD4+ T cells and Tregs, (2) intermediate extracellular ATP concentrations contribute to activation of CD4+ T cells, and (3) high concentration of ATP results in activated CD4+ T cells to turn off and instead Tregs to turn on [174].

The investigation showed that 250 nμ ATP induced activation of purinergic pathways in activated CD4+ T cells and resulted in secretion of IL-2, CD49, and CD54 (ICAM-1) expression. IL-2 is a cytokine that has an important role in survival and proliferation of lymphocytes. CD54

(ICAM-1) is a protein that is expressed on leukocytes and endothelial cells and facilitates leukocyte endothelial transmigration. ICAM-1 has a binding site for leukocyte function-associated antigen-1 (LFA-1) an integrin adhesion protein expressed by all leukocytes. Binding of ICAM-1 to LFA-1 facilitates transmigration of leukocytes across vascular endothelia in processes such as extravasation and the inflammatory response. It has been shown that increased concentration of extracellular ATP modulates an increase in CD54 and CD49d expression [176–178] in CD4+ T cells, thus facilitating transendothelial migration of CD4+ T cells into the inflamed tissue. Stimulation of purinergic receptors of activated CD4+ T cells with 1 nμ ATP causes a decrease in expression of CD54, CD49d, and CD25 the alpha chain of IL-2 receptor indicating an ATP-dependent inhibition of CD4+ T-cell activation and decreased survival and proliferation. High ATP concentration results in engagement of P2X7 and P2X4 subtype receptor and T-cell apoptosis [179, 180]. P2X7 derives nonselective membrane pore formation and results in cell death. A 250 nμ extracellular ATP concentration does not affect function of Tregs, whereas 1 nμ concentration stimulates their proliferation and chemotaxis through P2Y2 receptor activation, adhesion of monocytes, and their immunosuppressive ability. A possible in vivo scenario of what happens is that within a physiological range of ATP concentration (1–50 nμ), CD4+ T-cell proliferation is unaffected. In case of tissue damage and increase of concentration of extracellular ATP, CD4 T cells receive a danger signal and get activated and contribute to an inflammatory response. At this stage Tregs are not involved, but as ATP concentration increases, a feedback loop may occur where activated T cells go through apoptosis or their function may be inhibited by Tregs, which are proliferated and are recruited to the site of inflammation to avoid hyper-inflammation. Therefore, different concentrations of extracellular ATP modulate CD4+ T cells according to their activated/regulatory status, and any escape from this modulatory controlling pathway may result in an activated immune response that may last for a long time [174].

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4 Lubricin: Toward a Molecular Mechanism for Temporomandibular Joint Disorders

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Abbreviations

CRISPR	Clustered regularly interspaced short palindromic repeats
CRSWBCT	Cluster Randomized Stepped Wedge Blinded Controlled Trial
IPR&A	Individual patient research and analysis
RANKL	Receptor activator of nuclear factor-κ ligand
TMDs	Temporomandibular joint disorders

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4.1 Molecular Characterization of Lubricin

As discussed previously, the temporomandibular joint (TMJ) is the synovial ginglymoarthrodial articulation of the mandible with the maxillary bone of the frontal aspect of each the right and the left side of the facial skeleton. Wear and tear due to age, as well as trauma, contribute to alter the thickness of the disc, which brings about thinning of the cartilage in its central part and related chondropathology, progressively compromise the normal movement of the joint, and can lead to osteoarthritis of the joint and related osteopathology. TMJ disorders (TMDs) include disc displacement. Associated synovial inflammation; local pain and myalgias of the face, head, neck, and shoulders; and migraine-type headaches are often observed.

Osteoimmunology is a relatively new interdisciplinary domain of biological research, which focuses on the constellation of interactive processes that cross-modulate cellular immune surveillance and bone metabolism. The field originated as the elucidation of the immune regulation of osteoclasts, but it encompasses today a wider scope that extends from molecular and cellular interactions, to genomic and interactomic operational events [1, 2].

In brief, and as noted in Chap. 5 above, cartilage metabolism are highly dynamic and complex processes that are modulated in part in response to mechanical loading, such as tooth grinding and

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normal chewing. The cellular mechanisms that regulate bone formation and resorption involve the stimulation of osteoclast and osteoblast populations and the participation of bone marrow mesenchymal stem cells. Osteoclast differentiation is determined by the ratio of the receptor activator of nuclear factor-κ ligand (RANKL) to the soluble decoy receptor osteoprotegerin. Inflammatory cytokines including IL6 and hormones including parathyroid hormone, 1,25-dihydroxyvitamin D, glucocorticoids, and estrogen work in concert to control bone metabolism. The recognition that the continuous formation and resorption of bone is regulated by neuroendocrine and cellular immune events led to the establishment of osteo-(neuroendocrine) immunology as a rich interdisciplinary domain with obvious and direct implications for TMD [1]. Recent evidence further indicates that bone is more than just a structural scaffold: osteoblasts and osteoclasts work together in response to exercise and presumably other bone loading situations (e.g., chewing and grinding) to secrete endocrine factors, such as osteocalcin, sclerostin, and lubricin, which can act as a circulating hormone systemically to promote insulin sensitivity and reduce body fat mass, among other metabolic outcomes of significance. Osteocalcin, sclerostin, and lubricin are but examples of factors now recognized as "osteokine" that contribute to systemic homeostasis [3].

Osteocalcin, gamma-carboxyglutamic acid-containing protein, is a non-collagenous vitamin K-dependent protein found in bone and dentin. It is encoded by the BGLAP gene in osteoblasts and is secreted into body fluids, including saliva and blood serum, and presumably synovial fluid as well. In the circulation, osteocalcin acts as an osteokine and contributes to the regulation of glucose homeostasis by stimulating insulin release in the pancreas and directing adipocytes to release adiponectin, which in turn increases insulin sensitivity. Taken together, the concerted evidence to this date suggests that osteocalcin promotes bone formation, bone mineralization, and calcium ion homeostasis and simultaneously regulates energy metabolism systemically. Higher serum osteocalcin levels are relatively well correlated with increases in bone mineral density during treatment with anabolic bone formation drugs for osteoporosis such as teriparatide. Osteocalcin has strong potential as a timely and critical biomarker for establishing the effectiveness of treatment interventions aimed at promoting bone formation. In point of fact, osteocalcin is an important marker of bone activity and is increasingly routinely used to diagnose joint disease and to evaluate the effects of pharmaceuticals on bone metabolism [3–6].

In an experimental setting, adult male Sprague-Dawley rats were injected with 50 μL of complete Freud's adjuvant bilaterally into the anterosuperior compartment of the TMJ and monitored for signs of local TMJ inflammation at 1–4 weeks posttreatment. Enhanced osteoclast activity, expanded bone marrow cavity, increased RANKL/osteoprotegerin ratio in the cartilage and subchondral bone, and upregulation of osteocalcin peaked 2 weeks following injection. Meanwhile, TMD symptoms also increased in the 2-week complete Freud adjuvant-injection [7]. Taken together, these molecular data show the putative role of osteocalcin in the intimate interactive relationship between muscle action and bone in the joints [8] such as the TMJ.

Sclerostin, a glycol-protein secreted mainly, but not exclusively, by osteocytes, is encoded by the SOST gene. At the molecular level, sclerostin binds to LRP5/6 receptors and inhibits the Wnt signaling pathway, thus contributing to decreased bone formation. It expressed relatively late during osteoblast differentiation temporally coinciding with the expression of osteogenic marker osteocalcin. Sclerostin production by osteocytes is inhibited by the parathyroid hormone, mechanical loading, and inflammatory cytokines, but it is upregulated by calcitonin. Sclerostin deficiency is associated with high bone mass phenotype, but elevated serum sclerostin levels appear to be predictive of prediabetic metabolic condition. Increased serum sclerostin levels appear to be predictive of bone resorption. In brief, whereas sclerostin may not be a typical osteokine, it clearly emerges as a clinically significant biomarker for bone resorption [3, 9].

Based on this molecular knowledge base, preclinical and early clinical studies (i.e., clinical trials phases I and II) have gathered promising data in support of the efficacy of monoclonal human-

ized neutralizing antibodies (e.g., romosozumab, AMG 785 [Amgen], blosozumab [Elli Lilly], BPS804 [Novartis]) in a new treatment paradigm toward bone rebuilding for the management of patients with osteoporosis [10].

As described in a previous chapter (cf., Chap. 3), Lubricin is a 345 kDa proteoglycan (i.e., proteoglycan-4) encoded by the PRG4 human gene. It acts as a joint lubricant in synovial fluid and on the surface and the superficial layer of articular cartilage. It is synthesized by chondrocytes located at the surface of articular cartilage and by fibroblastoid synovial lining cells [11, 12]. Preclinical phase I trials indicate that intra-articular lubricin treatment retards progression of cartilage degeneration in early osteoarthritis. This anti-inflammatory effect of lubricin is obtained mechanistically by its binding to toll-like receptors 2 and 4 [13]. Toll-like receptors (TLRs) are a class of molecular receptors primarily found on white blood cells of the innate immune system, including monocytes/macrophages and dendritic cells, and principally function to induce cell-mediated immune activation. Related experimental research has established that inflammatory cytokines of the Th17 family (i.e., IL17) significantly up-regulates the expression of toll-like receptors 2, 3, and 4 in fibroblast-like synoviocytes from patients with rheumatoid arthritis and osteoarthritis by a molecular mechanism that specifically involves the signal transducer and activator of transcription 3 (STAT3). Another cytokine of the same Th17 family, IL23, augments the IL17-induced expression of these toll-like receptors by fibroblast-like synoviocytes obtained from patients with rheumatoid arthritis. Treatment of fibroblast-like synoviocytes from these patients in vitro with the STAT3-specific inhibitor, S3I-20, which selectively prevents the phosphorylation and activation of STAT3, blunts this IL17 effect [14]. Toll-like receptor 3 had been previously shown to promote osteoclastogenesis in rheumatoid arthritis synovium by inducing RANKL production by the fibroblast-like synoviocytes, which in turn favors the differentiation of osteoclasts in the arthritis synovium [15]. It follows that targeting the TLR3 pathway may be a promising approach to preventing inflammatory bone destruction in arthritic pathologies that evolve as complications of TMD.

In brief, the 340–350 kDa protein lubricin, often referred to as proteoglycan 4, is present in synovial fluid and on the superficial layer of articular cartilage and plays an important role in joint lubrication and synovial homeostasis. Lubricin is synthesized by chondrocytes located at the surface of articular cartilage and by fibroblastoid synovial lining cells. Lubricin's glycosylated region—the mucin domain—renders it hydrophilic, which permits its interaction with galectin-3 and promotes its lubricating property. Its remaining non-glycosylated regions interact with cartilage proteins and aid in lubricin's boundary lubricating ability [12, 16, 17]. A large family of enzymes, immune factors, including cytokines and chemokines, peptides and other modulators of physiological processes contribute to regulate lubricin biosynthesis. The importance of these interactomic sets of physiologic feedback loops is exemplified by the profound pathophysiological phenotypes of osteoarthritis observed in animal models and human patients. Indeed, recent findings implicate inflammatory factors in the attenuation of lubricin-mediated synovial lubrication in osteoarthritic pathologies [18].

Taken together with observations of increased levels of pro-inflammatory cytokines in the synovial fluid of osteoarthritic joints reported in a systematic review [19], as well as our own data [20, 21], we propose the hypothesis that lubricin is a key modulator of the psychoneuroendocrine-osteoimmune interactome. Our corollary hypothesis states that the regulation of synovial lubricin levels by TH17 cytokines has clinically relevant implications for novel treatments of osteoarthritic pathologies, involving, for example, CRISPR/Cas9-mediated genomic modification.

4.2 Experimental Model and Observations

The initial phase of experiments toward testing this hypothesis involved primary cultures of plastic adherent human synovial fibroblasts (Human Fibroblast-Like Synoviocytes, HFLS Aldrich) maintained under exponential growth condition in serum-free SCMF001 culture medium (Millipore)

at 37° C in a 5% CO_2 atmosphere. Stock cultures were maintained in 75 cm^2 plastic flasks (Falcon) and subcultured by standard trypsinization (0.1% trypsin in Dulbecco's phosphate-buffered saline, PBS, 37° C, 5 min) into 24-well plastic plates (Falcon) containing a tissue culture-treated sterilized glass coverslip at 10^5, 2.4×10^5 or 5×10^5 cells/well depending on the experiment, 24 h before testing. Cell density and morphology was verified by phase contrast microscopy. Cell counts were obtained by standard hemacytometer independently by two standardized cell culturists.

In vitro modulation of lubricin expression was tested under experimental conditions by supplementing the growth medium during the last 24 h, including experimental culture period with spent medium from related cultures, including myeloid (THP-1) and lymphoid cell lines (Jurkat) maintained in serum-free AIM-V medium (Gibco) and activated as needed [22], and other cell culture growth supplements, as required by the specific experimental conditions.

The experimental outcome was the immunoreactive form of lubricin, as detected by immunocytochemistry [23] using a polyvalent rabbit antihuman lubricin antibody (MABT401, Millipore) in a standard immunocytochemistry experimental protocol (13). In brief, cultures were fixed in 3.7% formaldehyde in PBS (room temperature, 10 min) with or without simultaneous permeabilization (0.1% triton X-100 in the formalin solution). Following copious washes in PBS (room temperature, 30 min), the cultures were incubated in the antibody solution at diverse dilutions (1/50–1/500, depending on the experimental conditions, PBS) (60–120 min, room temperature to overnight, 4° C). Following a second set of copious washes (room temperature, 30 min), the cultures were incubated in a 1/250 PBS dilution of biotin-conjugated goat anti-rabbit polyvalent antibody (Sigma) (60 min, room temperature), immediately followed by incubation with avidin-biotin complex (ABC) kit (Vector Laboratory) as per the protocol recommended by the manufacturer. Horseradish peroxidase precipitable color development was obtained with diaminobenzidine (DAB) substrate and H_2O_2 cofactor with a commercially available kit (BioRad). The coverslips were mounted on glass slides for preservation, and microphotography (Nikon), with or without phase contrast (20× objective × 10× eyepiece and as needed 100× oil immersion × 10× eyepiece) [23].

Microphotographs in grayscale were quantified by fractal analysis as described [23] by the box counting method with the Fractalyse software (Fractl-yse, fractalyse.org). Values of total cell dimensionality varied over a range of 1.25–1.75, depending on the stage of the cell cycle a given cell under examination was traversing, with cells in G_2 typically being considerably larger than cells in G_1 (Fig. 4.1).

The anti-lubricin reactive domain within the cytoplasmic compartment was also analyzed for

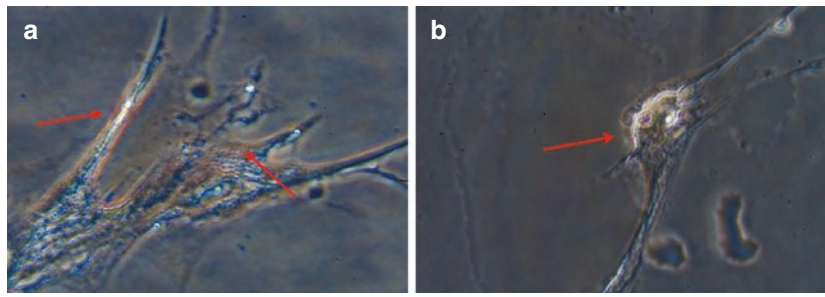

Fig. 4.1 Lubricin immunostaining in a representative G_2 human synovial fibroblast. Phase contrast microphotograph (20× objective × 10× eyepiece) is a representative mixed culture of human synovial fibroblasts exhibiting typical G_2 morphology in panel A and typical G_1 morphology in panel B. The luminescence corresponds to lubricin immunostaining as detected by horseradish peroxidase staining and viewed under bright light (not shown). The arrows underscore the localization of lubricin: filamentous and membrane-associated in G_2 cells vs. cytoplasmic in G_1 cells. It is possible and even probable that the translocation of the immunoreactive lubricin is regulated and controlled by the cytoskeletal network

Table 4.1 Estimation of lubricin immunostaining in a representative G_2 human synovial fibroblast

	Lubricin immunostaining (lubricin-stained fractal dimension)	Inverted microphotograph in contrasted grayscale of stained human synovial fibroblast (whole cell)
Fractal dimension	1.579	1.763
Percent fractal dimension (%)		

fractal dimensionality, and the proportion of lubricin-stained dimension vs. total cell dimension was computed (Table 4.1) and analyzed statistically using the MedCalc biostatistics software (medcalc.org).

To ensure quality of care, future clinical studies ought to be directed along the T3 paradigm and operate in the context of community-based participatory and action research through a research model that we defined as individual patient research and analysis (IPR&A) [21]. The IPR&A protocol is conceptualized as incorporating the utilization of the Cluster Randomized Stepped Wedge Blinded Controlled Trial design [24, 25] to test systematically and selectively clinically relevant variables for obtaining continuous quantification of the individual patient clinical outcomes.

In brief, following collection of baseline synovial samples from patients with TMD for measurements of IL6 and Substance P, repeated measures samples should be collected at regular intervals for each patient participant. Baseline measurements might best be processed as means ± standard deviation, a difference, deltas (Δ) obtained at each repeated measure time point, and the statistical analyses run on the Δ values. Thus, for each participating subject, individual patient data ought to be obtained and independently analyzed as repeated measures. The optimal clinical research design for individual patient data analysis approach might be the adaptive trial design where, for instance, all patients will first be in the placebo group and then sequentially rolled out into the treatment arm in a quasi-crossover paradigm. To be clear, the treatment arm must consist of the routine clinical intervention determined by the clinician's expertise and judgment, supplemented—as per the judicious determination of the clinician—with the best available evidence produced by comparative effectiveness research. Different clusters will cross over and switch treatments at different time points of the repeated measure analysis.

The first time point—placebo for all patients—will yield the individual baseline measurements. At subsequent time points, clusters switch over to the treatment group, following random ordering, and individual patient measurements are obtained and analyzed as Δ. Within each cluster, patients must be randomized, thus yielding a trial structure notorious for its stringency, power, and strength in preserving equipoise, as well as benefit and cost-effectiveness. Analysis of the data will be required by repeated measure ANOVA, with Newman-Keuls post hoc comparisons and Bonferroni corrections for comparative purposes, with either a frequentist (i.e., Fisher) or a Bayesian inference model. For predictive purposes integrating other patient characteristics in the model, analysis commonly entails hierarchical regression [26].

To illustrate the point, we might suggest the following specific example: We [20] confirmed and expanded the early reports by others [27] that proximally synovial fluid obtained from the TMJs with clinical signs and symptoms of internal derangement, as determined by examination and confirmed by CT imaging, contains elevated levels of IL6 and other inflammatory cytokines, in addition to certain pain neurotransmitters (e.g., substance P). These biomarkers were also elevated in whole saliva, confirming the possibility of integrating the measurement of these and related molecular markers in the diagnosis of TMD by means of noninvasive collection of salivary samples.

The use of individual patient data to test and verify the T1-T2-T3 transaction in translational healthcare is evidently not limited to clinical situations that involve TMD patients with internal derangement. We have showed that it has a wide range of clinical applicability, from Alzheimer's disease to psychoneuroimmuno-pathologies [28].

As critical as the choice of the design and statistical analysis, a timely and critical individual patient data analysis endeavor must rest on the sound selection of variables that are adequate and relevant to individual patient data outcomes research and analysis. Case in point, and returning to the focus of this writing on TMD patients with internal derangement, individual patient research outcomes, which must be repeated at every visit to constitute a body of individual patient data, and integrated in the IPR&A research paradigm and analysis, might include, in addition to the neuroendocrine-immune and molecular biomarkers (IL6, Th17 cytokines, substance P, lubricin, miRNA-155, etc.) in synovial fluid, saliva, serum, and other body fluids, as discussed above.

4.3 Proof of Concept Interpretation

Taken together, these preliminary experiments validate the in vitro model of human synovial fibroblasts to define and characterize the modulatory interactome of lubricin expression. Future studies need now to test specifically the most likely inflammatory immune factors that might be involved in the regulation of lubricin expression, based on the available clinical literature on osteoarthritic pathologies.

It is possible and even probable that pro-inflammatory cytokines produced by myeloid populations, including interleukin (IL)-1β, IL6, and tumor necrosis factor (TNF)-α, will be found to play an important role in this context. Expectations are also that cytokines of the TH17 and TH9 profile, which are produced by lymphoid subpopulations of activated mature naïve and memory T cells and which are known to be involved in sustained inflammation such as what occurs in osteoarthritic joints, may play an important role as well in the regulatory modulation of lubricin expression. The experimental model we have validated above can provide a useful protocol by which firstly a complete profile of cytokines produced by activated myeloid or lymphoid populations can be tested in vitro, secondarily the selective use of specific monoclonal antibodies can be tested for their capacity to abrogate the outcomes observed in the in vitro model, and thirdly the nature of the modulatory cytokine can be verified by means of its purified form added to the in vitro model under controlled conditions of concentration and time course.

Preclinical and clinical studies should follow this in vitro characterization of the model using adaptive Cluster Randomized Stepped Wedge Blinded Controlled Trial (CRSWBCT) designs, whose statistical power we have discussed previously in the context of testing novel clinical interventions for patients with osteoarthritic pathologies of the temporomandibular joint [24, 25]. Ultimately, these trials should test the hypothesis and corollary hypotheses proposed here to define and characterize novel therapies across a variety of patients with osteoarthritic pathologies.

Current trends in molecular medicine and clinical studies of interactome-based interventions point to genomic manipulations by means of the CRISPR/Cas protocol. In brief, the clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated proteins (Cas) system is currently the most promising genome engineering method that enables controlled modifications in selected genome sequences both for basic research purposes and for the development of new and improved therapeutic or biotechnological interventions. In fact, CRISPR/Cas systems show considerable diversity, which is conferred by the Cas protein itself. Two classes of CRISPR/Cas systems are distinguished based on whether the system has several Cas proteins (class I) or one Cas protein (class II). Both class I and class II CRISPR/Cas are further organized in subtypes [29, 30].

Mechanistically, CRISPR/Cas proceeds in a sequential manner, in which the bacterium responds to a foreign DNA during the acquisition phase. Secondarily, the foreign DNA is cleaved by Cas1 and Cas2 nucleases, and the resulting fragments inserted within a CRISPR locus in the bacterial genome, between palindromic repeats. Transcription of the CRISPR locus results in a precursor RNA (CRISPR-RNA, crRNA) that

hybridizes with the trans-activating crRNA (tracrRNA). tracrRNA is a small RNA whose sequence is complementary to the palindromic repeats and which allows Cas6 (aka, ribonuclease III) to cleave crRNA into mature fragments. Ultimately, the Cas/crRNA/tracrRNA complex (aka, crRNP) is formed, which scans the bacterial genome to identify and cleave the inserted viral DNA [29, 30].

In brief, CRISPR/Cas confers adaptive immunity to a bacterium via a mechanism that requires the Cas nuclease when it finds itself in association with the unusual genome structure consisting in palindromic repeats of about 30 base pairs separated by spacer segments of about 36 base pairs, referred to as CRISPR, into which viral DNA fragments have become interspersed. In fact, over time, the acquisition of several viral DNA fragments by the CRISPR locus via the Cas pathway provides the bacterium with resistance to multiple viral DNA's. From that viewpoint, it has become evident that CRISPR/Cas9 system efficiently serves to reprogram bacterial immunity, and the CRISPR/Cas9 system has now been established as a reliable and effective means of genome editing in eukaryotes [29–31].

CRISPR/Cas9 technology has revolutionized the field of genome editing in medicine. Novel molecular clinical interventions are being developed and tested that are based on the CRISPR/Cas9 system to add, delete, or modify genomic material in patient populations afflicted with certain interactomic conditions. Nonetheless, the applications of the CRISPR/Cas9 molecular technology to clinical therapeutic interventions are still cutting edge, and the caveat remains that a vector capable of efficiently, specifically, and safely conveying the CRISPR/Cas9 components to the target cell or tissue must be developed, tested, and validated in phase I and phase II clinical trials, before it can be safely tested on patients [30, 31].

Ongoing proof of concept experiments are generating new compelling evidence in support of the hypothesis that IL6 as well as IL17 and related TH17 inflammatory cytokines significantly depress the expression of lubricin by synoviocytes [32]. Phase I trials will therefore follow to test if injections of recombinant human lubricin in situ might alleviate joint pathology in TMD patients with internal derangement. Together, these will open new avenues of translational research on the molecular biology of TMD, including genomic engineering involving microRNA or the CRISPR/Cas9 genome editing technology.

4.4 Lubricin in the Context of Translational Healthcare for Temporomandibular Joint Disorders (TMD)

The term interactome refers to the set of molecular and cellular interactions, including gene interactions, gene product interactions, molecule-protein interactions, and the like, that characterize an organism or an organ within it. Interactomes are more than simply molecular or physiological networks: they display feedback properties that are essential for the organism's survival. Interactomics is a novel discipline at the intersection of bioinformatics and biology, which investigate the fundamental mechanistic principles of interactomic feedback and their consequences in health and disease. One important interactomic set of relationships is that which coordinates the intertwined cross-regulatory feedback between the psycho-neuroendocrine and immune systems, which we previously discussed in the context of patients with HIV/AIDS afflicted with the immune reconstitution inflammatory syndrome (IRIS) [33] or with Alzheimer's disease [28]. Taken together, these lines of investigations have led us to propose a new field of interactomic research, which we labeled psychoneuroendocrine-osteoimmunology [1], which directly pertains to the field of osteoarthritic pathologies [20, 21].

MicroRNAs (miRNAs) are endogenous noncoding RNA molecules of 20–24 nucleotides, which function to silence mRNA translation, and therefore blunt posttranscriptional regulation of gene expression. Most miRNAs are intracellular, but some miRNAs are released extracellularly

and can be detected in body fluids, including serum, saliva, and presumably synovial fluid. Case in point, miRNA-155, which has critical immune regulatory functions, is upregulated in the synovial membranes and in synovial fluid from patients with rheumatoid arthritis. In fact, miRNA-155 is crucial for the pro-inflammatory activation of human myeloid cells and antigen-driven inflammatory arthritis. Taken together, these lines of evidence suggest that miRNA-155 may be a strong candidate for therapeutic target in joint disease [34].

Clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) is a novel technology of genomic engineering that is used to functionally inactivate genes in human cell lines and cells with a high degree of fidelity and relatively simple construction. Studies are emerging that utilize CRISPR/Cas9 for better understanding the genomic underpinnings of potential drug targets [35] for a variety of bone and joint pathologies, including TMD (cf., Chap. 5). The miRNA-155 is a key pro-inflammatory regulator in clinical and experimental rheumatoid arthritis and putatively in TMD as well. In vitro experiments have shown that CRISPR/CAS9 genomic editing of miRNA-155 significantly blunts the production of inflammatory cytokines [36].

In brief and as introduced in Chap. 6 above, translational care proposes two rather well-defined facets of interrelated activities, as we and others have noted elsewhere. In the context of patients with TMD, for instance, translational research may involve obtaining synovial biopsies from each individual patient's TMJs and analyzing those samples for lubricin, or osteocalcin, in conjunction with the measurement of IL6 and cytokines of the TH17 family. These assessments, ideally, would be obtained at the patient's first visit to inform the clinician of certain aspects of the fundamental molecular pathology underlying each individual patient's case. Based on that information, the clinician may elect to supplement the orthotic intervention with, say, miRNA-155, monoclonal humanized neutralizing antibodies, such as romosozumab, or other such molecular-based interventions.

Translational research of this kind, however, is only valid if the molecular-based interventions are fully vetted for efficacy and effectiveness. The evidence in support of the use of miRNA-155 for a given patient who displays a certain molecular pathology of TMD, for example, must be carefully evaluated and systematically reviewed. The research must be cumulatively synthesized, and a consensus of the best available qualitative and quantitative evidence obtained. In brief, the process of establishing the rationale for the utilization of any given molecular-based intervention—that is to say, the predicate of the clinical decision-making that determines what molecular-based intervention is optimal for supplementing the orthotic intervention for a given patient based on his/her fundamental molecular pathology as determined by translational research—is itself obtained through a systematic process of research, which involves synthesizing the available research evidence (i.e., research synthesis) and determining its level, quality, acceptability, and overall consensus of effectiveness (i.e., comparative effectiveness research).

To be clear, translational healthcare rests on these two distinct modes of acquisition of knowledge about the needs of each individual patient: the characterization of the fundamental molecular pathology that defines and characterizes his/her clinical case (i.e., translational research, T1) and obtaining the best available evidence for treatment of his/her clinical case based on this molecular pathology profile (i.e., comparative effectiveness research, T2). From this perspective, it is self-evident that translational healthcare is patient-centered, focused on achieving optimal effectiveness, and grounded on the evidence-based paradigm.

It is also painfully manifest, however, that the translational healthcare paradigm suffers from one principal caveat. That is to say, it must integrate a component of evaluation by which hard data can be obtained to verify the efficiency of the translational treatment plan. In a following chapter (cf. Chap. 11), we will outline some principles of such patient-centered outcomes evaluation process and suggested, as

reiterated above (cf., this chapter, Sect. 4.1), the need for a third sine qua non-step for translational healthcare, T3.

The development, testing, and evaluation of novel patient-targeted therapies rest and require a patient-centered outcomes research and evaluation paradigm, as we explored in a following chapter (cf., Chap. 11). New and improved research protocols must be tailored to the needs and characteristics of individual patients, and patient-centered, effectiveness-focused, and evidence-based methodological standards and guidelines must be developed and tested.

In conclusion, the CRISPR/Cas9 system is a versatile molecular platform for introducing targeted genome modifications into mammalian cells. To ensure safe and efficient delivery into relevant cell types, adeno-associated virus (AAV) vectors are an efficient class of gene-delivery vehicles that safely infect dividing and nondividing eukaryotic cell types and serve as a highly effective donor template for homology-directed repair. Used together, CRISPR/Cas9 and AAV technologies can accelerate both basic research and clinical applications of genome engineering. Case in point, the AAV-mediated Atp6v1c1 knockdown gene therapy effectively treats bone erosion and inflammatory bone damage caused by periodontitis in a mouse model [31, 32, 37]. The broad array of rheumatic diseases ranges from rare monogenic auto-inflammatory diseases to complex polygenic autoimmune diseases. Correcting abnormalities in the genome using CRISPR/Cas9, in association with AAV vectors to enhance reliability and effectiveness, should undoubtedly improve not only our knowledge of molecular models of therapy but also benefit the patients [24]. A human chondroitin sulfate proteoglycan 4 (aka., lubricin) CRISPR/Cas9 guide RNA is being developed and tested [25]. To build on this paradigm to develop a CRISPR/Cas9—Atp6v1c1—guide RNA system for treating osteoarthritic inflammation and blunt its interactomic effect on lubricin must be the next step.

CRISPR/Cas9 technology will accelerate in vitro studies and in vivo investigations of lubricin as a key modulator of the psycho-neuroendocrine-osteoimmune interactomic modulator and of the regulation of synovial lubricin levels by immune products. This information will help develop new molecular-based patient-centered treatment interventions of osteoarthritic pathologies.

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Part II

Translational Effectiveness

5 Head and Neck Manifestations of Temporomandibular Joint Disorders

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Abbreviations

ACR	American College of Rheumatology
CNS	Central nervous system
FMS	Fibromyalgia syndrome
ID	Internal derangement
NIH	National Institutes of Health
OM	Otitis media
PGIC	Patient's global impression of change
PSQI	Pittsburgh Quality of Sleep Questionnaire Index
SB	Sleep-related bruxism
SSS	Symptom severity scale
TCC	Trigeminocervical complex
TMD	Temporomandibular joint disorder
TMJ	Temporomandibular joint
TTH	Tension-type headache
VAS	Visual analogue scale
WPI	Widespread pain index

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5.1 TMJ Anatomy

The temporomandibular joint (TMJ) is the articulation of the mandibular condyle to the temporal bone of the cranium. The articular surfaces are lined with fibrocartilage and are separated by the articular disc, which is made of dense fibrous connective tissue. Craniomandibular articulation is complex because it involves two separate synovial joints, which must function in unison to each other. The articular disc divides the TMJ into two compartments and creates two distinct joints known as a ginglymoarthrodial joint. The disc consists of dense collagenous tissue without any innervation or vascularization. The lower compartment of the TMJ is the relationship of the mandibular condyle to the articular disc creating a hinge-type movement, allowing the condyle a rotational movement against the disc. An upper compartment is formed by the articulation on the disc against the surface of the glenoid fossa creating a translation type movement of

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the disc. The disc has two posterior lamina attachments. The superior lamina attachment is to the tympanic plate, and inferiorly lamina is attached to the posterior head of the condyle. The anterior attachment of the disc is attached to the superior head of the lateral pterygoid muscles. The TMJ is a well-encapsulated and sterile environment. The fibrous capsule defines the anatomical and functional limitations of the joint. Both the medial and lateral collateral ligaments of the capsule ensure stabilization of the mandible during movement. The lateral capsule, which is reinforced by the lateral temporomandibular ligament, is much stronger than the medial capsule. The anterior and posterior capsule is loose, in order to allow the proper joint movement. The capsule consists of two layers, an outer fibrous and inner synovial layer. The synovial layers produce synovial fluid that assists in reducing friction between the articular surfaces serving as a lubricant, providing nutrition to the non-vascular tissue. Two accessory ligaments that protect the joint during wide excursions also support the TMJ: the stylomandibular ligament and the sphenomandibular ligament (Fig. 5.1).

5.2 Temporomandibular Joint Disorder

5.2.1 Pathophysiology of TMD

Temporomandibular disorders (TMD) are a multifactorial disease used to describe a number of related conditions that involve the TMJ and associated structures. In the 2000 to 2005 US National Health Interview Survey of 189,977 people, 4.6% (n = 8964) people experienced TMD [1]. Temporomandibular disorders are the most prevalent orofacial pain conditions for which patients seek treatment, the second most common chronic musculoskeletal condition (after chronic back pain) affecting 5–12% of the US population [2].

The pathophysiology of TMJ syndrome is not entirely understood. Earlier theories emphasized dental morphological factors of malocclusion, occlusal disharmony, and mandibular misalignment as being primarily responsible for the development of TMD symptoms. The Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) prospective cohort study identifying predictors of first-onset TMD from self-reported orofacial symptoms and

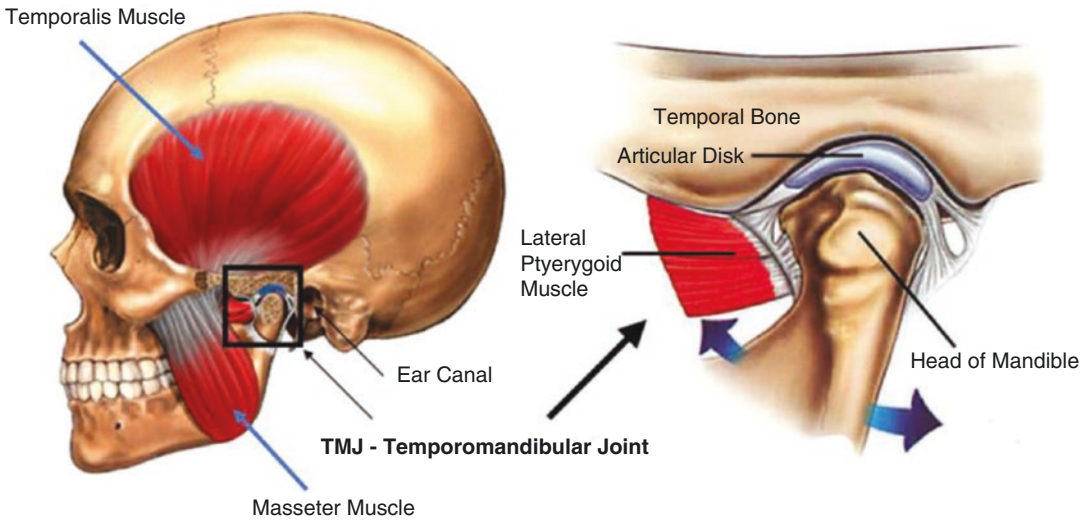

Fig. 5.1 TMJ anatomy. Figure modified from: healthinbalance.com

patient examination findings suggests a complex pattern of TMD etiology that is influenced by disorders locally, in masticatory tissues, and systemically, in pain regulatory systems [3]. Causes of TMD include acute trauma (direct assault), trauma from hyperextension (whiplash, oral intubation for general anesthesia, dental procedures, yawning, cervical trauma), parafunctional habits (bruxism, tooth clenching, lip or cheek biting), psychosocial factors such as stress, dentofacial deformities or associated disorders in growth and development (condylar hyperplasia or hypoplasia), instability of maxillomandibular relationships, laxity of the joint, and comorbidity with a number of psychosocial and systemic diseases (depression, rheumatoid arthritis and osteoarthritis, chronic fatigue syndrome, chronic headache, fibromyalgia, irritable bowel syndrome, sleep disturbances) [4, 5].

Researchers generally agree that the conditions fall into three main categories. Uyanik et al. identify the following three distinct causes of pain at the TMJ, which collectively fall under the broader term of TMJ syndrome: myofascial pain and dysfunction, internal derangement, and degenerative joint disease.

Myofascial pain-dysfunction (MPD) syndrome is believed to be a physical manifestation of psychological stress and depression. It comprises at least 50% of all TMD. TMJ pain is due to various causes of increased muscle tension and spasm, characterized by muscle hyperactivity with regional pain, tenderness in affected muscles, and episodic limited jaw opening. No primary disorder of the joint itself is present, and the pain is secondary to parafunctional habits such as nocturnal jaw clenching and teeth grinding. Treatment is focused on behavioral modification as opposed to joint repair.

Internal derangement (ID) of the joint involves a displaced disc, dislocated jaw, or injury to the condyle [6]. Patient manifests with intermittent locking of the jaw; a sudden onset of limited mouth opening, associated with cessation of joint sound; deflection of the mandible, with a midline correction on opening; and restricted lateral excursive movements away from the affected side.

Degenerative joint disease (DJD) is where arthritic changes result in degeneration of the articulating surfaces. Osteoarthrosis, a localized degenerative joint disease affecting the bone and articular cartilage, often idiopathic and non-painful, may involve predisposing factors such as advancing age, bruxism, abnormal joint posturing, or repeated surgical procedures. If pain is present, it is then referred to as osteoarthritis.

As pain-related TMD can affect an individual's daily activities, psychosocial functioning, and quality of life, it is important to accurately diagnose these complex musculoskeletal disorders to provide the best clinical care and explain the relationship of the TMD to the common TMJ symptoms.

5.2.2 Head and Neck Symptoms

TMD encompass a wide range of commonly occurring craniofacial conditions that compromise the comfort and health of the functioning hard and soft tissues of the masticatory system. The primary manifestations of TMD are described as pain that is persistent, recurrent, or chronic in nature. Limitations or alterations in range of mandibular motion are often accompanied by pain.

5.2.3 Dental Pain

Bruxism is a repetitive jaw-muscle activity characterized by clenching or grinding of the teeth. Bruxism has two distinct circadian manifestations: it can occur during sleep (indicated as sleep bruxism) or during wakefulness (indicated as awake bruxism) [7]. Bruxism has been associated with sleep disorders that have been reported to be aggravated by the consumption of alcohol and some types of medications. It has also been

observed in individuals with disturbances of the central nervous system. Children using CNS stimulants had a 2.5-fold higher number of worn teeth [8].

Involuntary clenching and grinding of teeth occurring mainly during non-rapid eye movement (REM) sleep is characterized as a movement disorder known as sleep bruxism (SB) [9]. Sleep bruxism has multiple and diverse effects that include tooth wear, mobility, erosion, abrasion, periodontal disease, muscle pain and spasm, disturbance of aesthetics, interference with oral comfort and temporomandibular joint pain and dysfunction, and head and neck pain [10, 11]. The estimated prevalence of sleep-related bruxism varies with age from 14% in childhood and 8% in adults to 3% in the elderly [9]. Although SB etiology and pathogenesis are thought to be multifactorial, it has been shown to be associated with stress and anxiety, arousal from sleep, altered dopaminergic and serotoninergic neurotransmission, and, to some extent, genetic predisposition [7].

The dentist often sees SB as signs and symptoms of dental attrition, temporomandibular joint dysfunction, hypertrophy of masticatory muscles, and craniofacial pain. A 66% prevalence of craniofacial pain has been reported in patients exhibiting bruxism, or bruxers [12]. It is mainly described as bilateral facial pain and headache (84.3%) or frontotemporal in location (67.1%) with a tightness/pressure quality and being worse in the morning [13].

Bruxism is primarily associated with TMD-type pain, and its occurrence in bruxers has been linked to higher levels of depression and somatization. In addition, a recent study reported a lack of correlations between TMD-type headache and the frequency of SB [13]. The high frequency of comorbidity between SB and tension-type headache (TTH), which favors the notion of a common pathogenetic link between the two conditions, remains controversial, given the considerable diagnostic and behavioral overlap between TMD and TTH [14, 15].

There is experimental evidence regarding the role of sustained tooth clenching as a trigger of headache in patients with TTH [16, 17]. Childhood SB has also been associated with migraine headaches due to the more frequent observation of SB in children with migraines than non-headache controls [18] SSRI's antidepressants induce bruxism.

Selective serotonin reuptake inhibitors (SSRI) inhibit the reabsorption of neurotransmitter serotonin back into the presynaptic cell, therefore increasing the level of serotonin in the synaptic cleft available to bind to the postsynaptic receptor. Since the introduction of SSRIs, reports have appeared indicating that they produce motor (extrapyramidal) side effects of dystonia and dyskinesia [19]. Nocturnal bruxism has been reported with venlafaxine, a serotonin/noradrenaline reuptake inhibitor, which responded to gabapentin [20]. Antidepressants have substantial effects on REM sleep. Many studies show that SSRIs prolong REM sleep latency and suppress REM sleep time [21]. REM sleep behavior disorder (RBD) is characterized by excessive motor activity during REM sleep with acting out of dreams [22].

Serotonergic antidepressants are associated with a statistically significant and persistent reduction in REM sleep atonia, even in individuals without overt clinical features of RBD [23]. Buspirone is an agonist of the 5-HT1A receptor that increases dopaminergic neuron firing in the ventral tegmental area and increases the synaptic release of dopamine in the prefrontal cortex, which effects the drug-induced bruxism [24]. Buspirone can also ameliorate extrapyramidal side effects, such as akathisia and tardive dyskinesia, and this property may be an additional explanation for the bruxism-related effects of the drug [25].

Attention deficit hyperactivity disorder (ADHD) is a common but controversial syndrome characterized by developmentally inappropriate hyperactivity, impulsivity, and inattention. There is substantial clinical evidence that shows associations between sleep problems and children with ADHD [8]. Selective serotonin reuptake inhibitors (SSRIs) are medications also used for the treatment of ADHD. They are prescribed as antidepressants that enhance serotonin neurotransmission. The use of SSRIs has been associated with the occurrence or worsening of several extrapyramidal reactions such as

dyskinesia, restless leg syndrome, dystonia, and bruxism [8]. Fitzgerald and Healy observed diurnal bruxism secondary to SSRI medication in five of six patients. Bruxism persisted in two of the patients after the drug was discontinued [26]. It was also found that there was a higher prevalence of day and night grinding among the ADHD children treated with medication when compared to the other two groups. When evaluating the number of worn dentition, it was found that the ADHD group receiving medications had significantly more signs of attrition. When comparing ADHD children using CNS stimulants to children using other medications, children using CNS stimulants had a 2.5-fold higher number of worn teeth [8].

Atomoxetine is the only FDA-approved non-stimulant to treat ADHD. Atomoxetine was related to exacerbation of nocturnal bruxism in a 12-year-old boy with ADHD, subsiding when the drug was discontinued, but re-worsening with retrial, and finally subsiding upon adding buspirone [27].

5.2.4 Neurologic

Neurologic pain can occur due to the posteriorization of the condyle and anteriorization of the disc where compression of the retrodiscal tissue occurs. The auriculotemporal (AT) nerve innervates the retrodiscal tissues where compression can cause pain when biting down in centric occlusion. The posteriorization of the condyle can occur from direct trauma or indirect trauma (bruxism, occlusal changes). Occlusal changes can occur due to orthodontics, excessive tooth wear, dental restorations, and extractions of posterior teeth (molars). As the bite slowly closes due to lack of posterior tooth support or loss of vertical dimension, the mandible starts to move posteriorly, compressing the retrodiscal tissue that is innervated by the AT nerve. This is evident in clinical TMJ cases where the patient reports that they have sharp shooting pain as in trigeminal neuralgia, when they speak or when eating. This posteriorization of the mandibular condyle causes afferent signals to be sent from the AT nerve, whether it is a mild from the disc movements or strong signals from the nerve being compressed. These signals travel from the periphery through the trigeminal nerve into the central nervous system (CNS) via the spinal trigeminal nucleus. These signals are being sent into the CSN every time the jaw moves while swallowing, eating, and talking. This compression/irritation of the AT nerve is further discussed in the chapters titled "Temporomandibular Joint Dysfunction, Trigeminal Nerve Inflammation, and Biomechanical Dental Treatments for the Suppression of Neurological and Neuropsychiatric Symptoms," showing a correlation of decompression of the AT nerve improves symptoms of neurological conditions such as cervical dystonia, Parkinson's disease, Tourette's, complex regional pain syndrome (CRPS), blepharospasm, cerebellar tremor, and certain gait/balance disorders.

5.2.5 Muscular

Muscle spasms and myofascial trigger points may occur from overuse of the muscles. A myofascial trigger point is defined as a hyperirritable spot in skeletal muscle that is associated with a hypersensitive palpable nodule in a taut band. The spot is painful on compression and can give rise to characteristic dysfunction and autonomic phenomena [28]. The muscles that have referral patterns to the jaw and face are the masseter, medial pterygoid, lateral pterygoid, digastric, sternocleidomastoid, trapezius, buccinator, orbicularis oculi, and zygomaticus major [28]. In orthopedic disorders, the muscle spasm is secondary and is the result of, not the cause of, pain: it causes no symptoms by itself. A spasm is evoked as a protective mechanism. It is useful in acute arthritis, preventing movement at the joint. As the spasm becomes chronic, then it becomes harmful causing unnecessary forces on the joint, causing chronic arthritic changes [29].

In patients who are primarily affected by TMJ, muscle symptoms may be secondarily masking the primary component. This is particularly important with orthopedic TMJ problems such as trauma, internal derangement, and hypermobility.

When a joint has an internal derangement, the disassociation of a joint causes a strain on the tendons and the muscles to spasm trying to stabilize the joint. Manfred Cohen discovered the arthrokinetic reflex while doing animal studies in 1956. The arthrokinetic reflex refers to how a joint movement can cause a reflex muscle activation or inhibition, and that joint mobilization can improve chronic pain [30].

5.2.6 Ligaments/Tendons

A tendon is a fibrous connective tissue made of collagen that connects the muscle to bony structures. Its function is to transmit the forces of the muscle onto the bone. Strains can occur at the tendon/periosteal junction and anywhere along the whole tendon. These strains can cause minor scarring resulting in pain at the affected area. When a muscle assumes the guarding of a strained ligament, it becomes tense and fatigues [29]. It is well documented and published by Dr. Edwin Ernest that ligament and tendon stenosis can cause pain such as temporal tendonitis and stylomandibular ligament strain (Ernest syndrome). Temporal tendonitis is the stenosis of the temporal tendon as it attaches the temporalis muscle to the coronoid process of the mandible. Temporal tendonitis can cause TMJ pain, ear pain, eye pain, temporal pain, pain in the maxillary posterior teeth, pain to opening the jaw wide, and pressure in the ear [31].

The stylomandibular ligament extends from the styloid process to the posterior aspect of the mandible above the gonial angle. The function to this ligament is to protect the joint from hyperextension. The pain referral area of Ernest syndrome can include pain at the gonial angle of the mandible, TMJ, ear, eye, temple, mandibular molars, and lateral neck [31].

5.3 Lower Face Symptomatology

A dysfunction of the TMJ is usually due to the disruption of the condylar-disc relationship causing joint sounds. The ligaments and the joint capsule maintain the integrity of the TMJ. As the joint functions against these ligaments over time, the length of the ligaments can be altered and lengthened thus leading to biomechanical changes of the joint known as internal derangement (ID). Displacement of the articular disk could result in traction and/or compression of nerve-rich regions of the TMJ. The capsular ligaments and retrodiscal tissues of the TMJ are highly innervated by substance P and CGRP-containing neurons.

5.3.1 Clicking

When the ligaments within the joint become stretched due to use or trauma, the tone of the superior lateral pterygoid muscle on the disc will cause the disc to assume a more anterior or medial position. This is due to the anatomy of the lateral pterygoid muscle, which extends from the infratemporal surface of the greater wing of the sphenoid bone to the disc. Generally, the disc is displaced in an anterior-medial direction but can also be displaced posteriorly, medially, or laterally.

A clicking sound may occur as the disc, which has displaced from the original position of being between the condyle and glenoid fossa in the closed mouth position (centric occlusion), returns (reduces) to its normal superior position above the condyle on the opening movement of the jaw. During the closing movement of the mandible, the disc slips back out of position. This process of the disc reducing is called disc displacement with reduction and is notably referred to as the first stage of disc displacement. Other causes of joint clicking are local soft tissue thickening on the articular surface, joint hypermobility, and loose intra-articular bodies.

5.3.2 Locking

Locking or disc dislocation without reduction occurs when the disc no longer reduces into the proper position upon opening and the disc becomes an obstruction to the movement of the condyle. This occurs due to the overstretching or tearing of the posterior ligaments. Clinically, in

an acute phase, there is a limited opening of the jaw (15–30 mm) where the joint only acts in a hinge-type movement without the translation or with minimal translation due to the obstruction. Additionally, a pronounced deflection of the mandible upon opening to the affected side is seen. There are two things causing the limited movement of the joint, one being a mechanical obstruction and the second a protective muscle spasm. This is beneficial when it prevents the ligaments from overstretching which results in a blocked movement [29]. In a chronic phase where the disc has been displaced over 6 months, the capsule and disc attachments progressively elongate pushing the disc gradually forward. At this time, minor deflection is noted upon opening to the affected side and greater jaw opening is achieved. The disc displacement with the muscle spasms can cause osteoarthritis.

5.3.3 Crepitus

Crepitus is a grating sound of the condyle against the glenoid fossa. This sound is usually heard during both opening and closing movements of the jaw and is associated with late findings of osteoarthrosis. This is due to the degenerative changes of the joint where the articular surfaces have become arthritic. Radiographic images will typically show osteoarthritis or degenerative changes of the mandibular condyle. Crepitus can also occur with rheumatoid arthritis and synovial chondromatosis.

5.3.4 Degenerative Arthritis

Chronic disc displacement eventually leads to arthritis in the joints. The condylar cartilage is a major growth site of the mandible, which makes it a crucial factor for treatment success in young orthodontics patients [32]. Changes in the lengths of the mandibular ramus and condylar process either reflect mandibular growth (1–4) or pathological processes in the TMJ [33]. The reported prevalence of TMJ involvement in patients with juvenile idiopathic arthritis varies from 17 to 87% [34]. Arthritis of the TMJ is a concern, particularly in patients who are actively growing, because the mandibular growth plate is located below the fibrocartilage and is therefore susceptible to damage from inflammation [35]. Damage to the mandibular growth plate leads to asymmetric growth, micrognathia, retrognathia, malocclusion, and a decrease in maximum incisal opening [36]. Stroustrup found in animal studies that the injection of intra-articular corticosteroid injections resulted in a more pronounced reduction of mandibular growth that caused by arthritis alone.

The condylar cartilage is a major growth site of the mandible and is crucial for a growing patient [32]. Changes in the lengths of the mandibular ramus and condylar process either reflect mandibular growth [37] or pathological processes in the TMJ [38].

TMJ arthritis leads to mandibular growth disturbances and masticatory dysfunction, which result in craniofacial dysmorphology and dental malocclusion [39].

The mandible becomes retrognathic having a posterior rotation. Unilateral TMJ arthritis occurs at a rate of 40–50% resulting in facial and dental asymmetries that increase with chronicity of the disease [40, 41].

Condylar growth is an important indicator for therapeutic success. It has recently been shown that not only inflammatory processes but also some treatment strategies, such as intra-articular corticosteroid injections, may potentially reduce or stop condylar growth [42]. Computed tomography (CT) is considered to be the gold standard for bony measurements but involves the highest radiation exposure, which should be avoided in growing individuals due to the increased risk of developing cancer [43, 44].

MRI imaging may depict joint abnormalities not seen with any other imaging method and thus is the best method to make a diagnostic assessment of the TMJ status. In patients with TMD referred for diagnostic imaging, the predominant TMJ finding is internal derangement related to disc displacement. This finding is significantly more frequent than in asymptomatic volunteers and occurs in up to 80% of patients consecutively referred for TMJ imaging [45]. Moreover, certain

types of disc displacement seem to occur almost exclusively in TMD patients, namely, complete disc displacements that do not reduce on mouth opening. Other intra-articular abnormalities may additionally be associated with the disc displacement, predominantly joint effusion (which means more fluid than seen in any asymptomatic volunteer) and mandibular condyle marrow abnormalities (which are not seen in volunteers) [45].

5.3.5 Inflammation

Synovitis is inflammation of the synovial lining within the joint causing pain upon movement of the joint. It is characterized by swelling due to fluid collection (effusion), which can be detected through an MRI. Capsulitis is inflammation of the joint capsule and is characterized by increasing pain, stiffness, and limitation of motion. Both conditions of the TMJ cause pain upon palpation of the TMJ and when there is loading of the joint during function. Osteoarthritis is the deterioration of the subchondral bone due to overloading of the joint where excessive forces are placed on the joint such as bruxism, trauma, infection, or systemic arthritis such as rheumatoid arthritis. When joint pain is present, it is called arthralgia. Symptoms of synovitis and capsulitis are inflammation due to increased blood flow, pain on palpation, and when the patient complains of a warm sensation at the TMJ or when they are unable to bite on the posterior teeth. The inflammatory cells release enzymes into the joint causing further pain and irritation. The chronicity of the inflammation causes the enzymes to have osteoclastic activity leading to degenerative changes within the joint.

5.4 Upper Face Symptomatology

5.4.1 Ear

The common symptomatology of otic and TMD symptoms are frequently observed. Otalgia has a high incidence rate with TMD patients. Multiple anatomical and neurological conditions start from muscular TMD that can generate otic conditions [46, 47]. Inflammation within the TMJ can be a cause of ear pain. The posteriorization of the mandibular condyle is the result of the disc becoming displaced anteriorly, thus cause the stimulation and impingement of the AT nerve creating pain. The trigeminal sensory nuclei have short neurons in the tegmentum connecting them with trigeminal motor nuclei and the vestibular nuclei in the brainstem [18].

The petrotympanic fissure is a reminder of the early evolutionary stages as it related to innervation of masticatory muscles and some middle ear and pharyngeal muscles [39]. The disc malleolar ligament extends from the anterior process of the malleus (inner ear) through the petrotympanic fissure and extends to the posterior capsule and disc of the TMJ. Also, as the disc becomes anteriorly displaced, it pulls on the mandibular malleolar ligament creating ear symptoms [48].

The middle ear has a common embryologic origin as the muscles of mastication and facial muscles [46]. The normal physiology of the tensor tympani muscles changes during abnormal activity of the mandible due to TMD and is associated with otic symptoms such as otalgia, otic fullness sensation, tinnitus, vertigo, and hyperacusis-hypoacusis. Due to the close proximity of the TMJ and the middle ear in adults and children, TMD may initiate otitis media (OM) due to the relationship of the tensor veli palatini muscle, which controls the function of the eustachian tube [49]. Tinnitus is more prevalent in TMD patients than in the general population [50]. Tinnitus frequency in patients with TMD varies from 33 to 76% [51–53]. There is 40–70% dizziness and 5–40% vertigo prevalence in patients suffering from TMD [54].

TMD produces contraction and tension of the masticatory muscles and reflex contraction in tensor veli palatini and tensor tympani muscles due to common motor innervation from the trigeminal mandibular branch (V3) [55–58]. These two muscles connect the tympanic cavity to the TMJ [59], and the dysfunction of these accessory muscles of mastication plays an important role in otic symptoms [60]. Reflex muscle contraction is present in tensor tympani and tensor veli palatini muscles [61, 62].

Shapiro suggested that the middle ear muscles such as the tensor tympani and tensor veli palatini may cause tonic spasms as a reflex due to the trigeminal nerve being peripherally irritated by TMD which can lead to hearing impairment [63]. Sustained contraction of these muscles may alter inner ear pressure through changes transmitted from the oval window toward the labyrinth and semicircular canals. This may lead to vestibular and cochlear impulse imbalance [52].

Vertigo and tinnitus are commonly reported symptoms among TMD sufferers [64, 65]. Kaplan made the correlation of neck muscles affecting ear and balance related issues to trigger points of the sternocleidomastoid (SCM). The SCM is the prime muscle source of proprioceptive input relative to orientation of the head and space. Any trigger points on the clavicular head of the SCM either due to shortening or hyperactivity have been stated to contribute to spatial disorientation, dizziness, and vertigo [4, 66]. In a study where a 1032 patients were surveyed, 338 had TMD and 694 two as control groups. Tinnitus and vertigo symptoms were significantly more prevalent in the TMD group than in either of the control groups [67].

A significant number of patients seeking treatment for ear pain have no findings in the ear but have referred pain from the TMJ and masseters [68]. Conservative treatment for TMJ disorders significantly reduces otalgia to the same levels of pain scores as the normal group [69]. Stabilization splints were used for 10 weeks in a randomized, controlled, double-blind study, using a VAS scale (from 0 to 100 mm) for measurements, and found a significant decrease (t2.12: p 0.006). The control group remained the same after 10 weeks. Therefore, concluding that stabilization splints are beneficial in treating secondary otalgia while treating TMD [70]. Many of the TMD symptoms fall within the scope of otolaryngology [50].

5.4.2 Eye

If there is an internal derangement, the muscles of mastication can become imbalanced and cause spasm. As the posterior attachment of the disc becomes stretched, the superior head of the lateral pterygoid becomes taut. The origin of the superior head of the lateral pterygoid is at the infratemporal surface of the greater wing of the sphenoid bone and inserts into the anterior surface of the TMJ disc. The origin of the inferior head of the lateral pterygoid is the lateral surface of the lateral pterygoid plate of the sphenoid bone and inserts into the head of the mandibular condyle. The contraction of this muscle is to aid in the translation of the mandibular condyle. The lateral pterygoid muscle is innervated by the mandibular branch of CN V. The stimulation of the AT nerve sends signals through the trigeminal sensory nuclei, through short neurons in the tegmentum, connecting to the trigeminal motor nucleus and ocular nucleus [18]. We propose that tension or spasm of the lateral pterygoid and medial muscles can create a pulling action of the sphenoid bone that makes up the retro-orbital wall. Also, the ocular nerve enters the orbit through the superior orbital fissure and innervates five extraocular muscles: the superior rectus, inferior rectus, medial rectus, inferior oblique, and levator palpebrae superioris muscles. All of these muscles have their origin at the back of the orbit from a fibrous ring called the annulus of Zinn. Signals from the oculomotor nucleus cause these muscles to spasm or contract resulting in retro-orbital pressure. Therefore, this explains why dental appliances have a positive effect on the pain and pressure behind the eyes.

There are several other conditions that cause the symptom of eye pain and should be considered as a diagnosis such as temporal tendonitis, Ernest syndrome, sphenomandibular tendonitis, Eagle's syndrome, lesser occipital neuralgia, sphenopalatine neuralgia, myofascial pain, and NICO (neuralgia-inducing cavitational osteonecrosis).

5.5 Neck and Shoulder Pain

5.5.1 Neck/Shoulders

The muscles of the neck and head perform important directives, including movement of the neck and head, chewing and swallowing, speech,

expressions of the face, and movement of the eyes. They produce the body's ability to close the mouth, bite, and chew food. The muscles of mastication move the mandible relative to the rest of the skull. These muscles, including the temporalis and the masseter, elevate the jaw during chewing and during speech.

The neck muscles, such as the sternocleidomastoid and the trapezius, are responsible for large motor movements in the muscular system of the head and neck. They move the head in every direction, pulling the skull and jaw toward the shoulders, spine, and scapula. The muscles are in pairs on the left and right sides of the body, and these muscles control the extension and flexion of the head and neck. On an individual basis, these muscles rotate the head or move the neck laterally to the left or right. Neck muscles are used to adjust the posture of the head throughout the course of a day.

The muscles of the neck run from the base of the cranium to the dorsal part of the body and work together to move the head and assist in breathing. The motion of the muscles of the neck is divided into the four categories of rotation, lateral flexion, flexion, and hyperextension. Rotation describes the action of turning the head from side to side, lateral motion brings the ear to the shoulder, flexion moves the chin to the chest as in looking down, and hyperextension hyperextends the neck upward to look up. The main function of the muscles of the neck is head movement, as well as contributing to the maintenance of blood flow to the brain and holding the head upright. The most common causes of neck pain are strain, tension, or trauma to the muscles of the neck.

The neck is the start of the spinal column and spinal cord. The spinal column extends from the base of the cranium to the pelvis. It protects and houses the spinal cord, the long bundle of nervous tissue that transmits neural signals to the brain and rest of the body connected to the brain.

The clinician must understand the importance of the neck and spine as it relates to the craniomandibular structures and the disorders that are associated with them. They must understand the mechanism involved in head and neck posture and how they influence mandibular positioning and movement [71]. The interruption of normal muscle function leads to spasm of the muscles, improper muscle tone, and with time degeneration of the muscle tissue [72]. A TMJ dysfunction usually coexists with this imbalance and symptoms of these somatic alterations.

Factors such as growth and development, environment, heredity, aging, declining health, and/or pathology can influence head and neck posture contributing to deterioration or a change in function and performance. Positioning of the head and neck are always in a dynamic state of equilibrium reacting to constant changes in the environment. Clinicians must recognize that the skeletal system is positioned and held together by these muscles and ligaments. Therefore, when an area is out of balance, the surrounding areas (even distant ones) assume a balancing distortion. A malocclusion of the teeth and/or an imbalance of the masticatory complex of muscles may be a factor in inframandibular neck and shoulder muscle imbalances [73]. This results in disturbed postural relationships of the head, neck, shoulders, spine column, and pelvis that may be stressful physiologically to any or all areas involved due to the maxillary-mandibular mal-relationship. Other structures that may also have complications with the disturbed imbalance are the chewing, the swallowing, the respiration, and the speech mechanisms.

In understanding the relationship between the head, neck, shoulders, and the TMJ, one must know the neuronal connections between them. Multiple studies have shown a relationship with damage caused to the neck and cervical tissues are a factor in symptoms of ataxia, vertigo, nystagmus, disorientation, and motor incoordination. It is believed that these symptoms were a result of an interruption of the afferent signals from the neck. Ataxia in people is associated with a broad-based staggering gait, hypotonia of the ipsilateral arm and leg, and a strong sensation of falling or tilting [74].

Neurons of the three divisions of the trigeminal nerve (CN V) and cranial nerve 7, 9, and 10 all interact within the subnucleus caudalis of the spinal nucleus of V within the brainstem. Also, interacting within this system are the

upper cervical neurons from the segments of C1, C2, and C3. This convergence of the trigeminal and cervical root fibers on the same sensory neuron at high levels in the cervical spinal cord is an anatomic and physiologic basis for the referral of pain from the cervical to the trigeminal systems and vice versa [75].

Most influential factors that affect head and neck positioning are trauma, whether it be micro- or macrotrauma. Aberrant nerve signals arising from these types of occurrences play an important part in the proprioception of the head and neck. Whiplash injuries are another type of macrotrauma that influence coordination and positioning. Microtrauma may arise from misalignment of teeth influencing the musculature of the head and neck as previously stated. Microtrauma usually does not elicit painful stimuli and dysfunction at the beginning but over time results in pain, whereas macrotrauma does develop painful stimuli and dysfunction rather quickly.

The hyoid bone within the cervical region is highly interrelated to the masticatory system. In conjunction with the mandible and the anterior portion of the shoulder and neck musculature, they form a series of suspensory levers and pulleys that control mandibular function and balance the head and jaws. In addition, the neck region houses the pharynx, larynx, and trachea, which provide a communication to the respiratory system. It is therefore justified to say that if there is an imbalance within the masticatory musculature, there will also be an imbalance or a dysfunction within the respiratory system affecting breathing, speech, and swallowing.

The most common altered head and neck position is the forward head posture (FHP). This may occur following macrotrauma and/or microtrauma. Other head postures such as spasmodic torticollis (ST) have been shown to occur from these types of traumas [76]. The resulting postures lead to a decreased physiological adaptive range for the patient. When this range is exceeded, cervical spinal symptoms begin to develop. A clinician must be able to determine upon evaluation whether cervical therapy is needed or a complete dental evaluation is needed as to ascertain the origin of the symptoms. Therapy must not only deal with the cervical spine dysfunction but also the maxillary-mandibular relationship and/or malalignment. In certain instances, "spinal curvature, which develops gradually over an extended period, begins to normalize when we adjust the 'jaw relationship' and provided we closely control the occlusal balance, we may get a reprieve from the symptoms (pain, etc.) and/or changes in the body systems" [77].

When Dibbets studied the symptoms of TMJ dysfunction, he found that most patients had an underdeveloped (retrognathic) mandible [78]. Craniofacial development and shape are extensions of this process such as elongation of facial structures with a small ramus height, large mandibular angles compared to cranial base, and smaller nasopharyngeal dimensions (airway). These factors result in retrusive development of the mandible [79]. The mandibles position helps to determine a patient's postural position by its movement and maintenance of one's airway. Therefore, one's upright positioning can be influenced by the mandible thus influencing the cervical spine and one's posture. The rest position of the mandible is the position where all noncontact and masticatory movements of the mandible start and end. This is determined by the vertical dimension of occlusion (VDO), which is also determined by the TMJ and how healthy it is.

The human neck makes essentially six movements. All movements of the neck are combinations and varying percentages of these six movements. These gently performed movements are (1) *flexion* (the movement in which the chin is lowered down toward the chest), (2) *extension* (the neck is extended, as in looking upward toward the ceiling), (3–4) *lateral rotation* to the left and to the right (these are simply direct lateral rotation to either side), and (5–6) *lateral flexion* (may be best described as trying to place the ear upon the shoulder through a sideways movement of the neck, directing the ear toward the shoulder tip on both sides). We will consider the main movements: extension and flexion. The others will be described with movement disorders of the head and neck.

When flexion occurs, the resultant dimension is a decrease in freeway space between the teeth and the mandible. During flexion, the mandible moves up and forward, and the posterior muscles of the neck become tightened. During extension, the mandible moves down and back, and the anterior muscles of the neck increase tension. The resultant dimension is an increase in the freeway space. Jaw muscle activity is increased in the temporalis, masseter, and anterior digastric muscles while flexion causes a decrease in these muscle groups. The vertical dimension of occlusion (VDO) is the distance from the nose to the chin when they are at maximum closure. This can be altered by any type of dental appliance that treats muscle imbalance and/or TMJ dysfunction that covers the occlusal surface. All appliances that change the VDO also change the relationship between the head and neck due the changes on the anterior muscles of the neck, thus either influencing flexion or extension [80, 81].

5.5.2 Neurological Aspect of the TMJ on the Head and Neck

A correlation has been established between the trigeminal nerve and the muscles of the neck [82]. There are many studies which link dysfunction of the TMJ/TMD or craniocervical mandibular disorders (CMD) to multiple symptoms including but not limited to tinnitus, Meniere's disease, decreased hearing, aural fullness, headaches, dizziness, difficulty balancing, difficulty swallowing, neck and shoulder soreness, crackling and clicking sounds in the jaw joints, limited mouth opening, visual disturbances, and in some cases neurological disorders [83, 84]. Many of these sources also cite cervical spine dysfunction (CSD) as being a contributing and correlating factor in TMD. The issue to be investigated is whether TMD is a result of CSD or vice versa? The TMJ is a connecting link between the cranium and the dentition. The mandible connects with the hyoid bone via suprahyoid musculature, and the hyoid bone connects with the clavicle via the infrahyoid musculature. The clavicle then connects with the sternum and rib cage. Additionally, the trigeminal nerve that innervates the jaw muscles and TMJ also co-mingles with the nerves of the neck. The entire trigeminocervical complex encompasses cranial nerves 5, 7, 9, 10, 11, and 12 along with cervical nerves 1–4. Therefore, dysfunction within cervical structures commonly leads to problems within the jaw and vice versa.

The principal sensory trigeminal nucleus receives input from the face and intraoral structures, along with the proprioceptive input from the TMJ. The spinal trigeminal nucleus processes mechanical, thermal, and nociceptive input from the TMJ, face, and skin of the occiput and cervical neck. The cutaneous innervation of the head is the trigeminal nerve. Additionally, the occipital nerves of the cervical spine (C1–C3) innervate the occiput, which includes the vertex of the head to portions of the submandibular region. Connection exists between the trigeminal, facial, glossopharyngeal, and vagus nerves along with the upper cervical spinal nerves (CI–C4). They interconnect within the subnucleus caudalis in the spinal cord. The spinal accessory nerve communicates with the superior ganglion of the vagus and anastomoses with the nerves of C2–C4 spinal segments and is part of the pharyngeal plexus and vagus. The spinal accessory nerve is a major stimulator for the sternocleidomastoid muscle along with nerves C2–C4. Other collaterals of the trigeminal have been traced to the spinal trigeminal nucleus from the upper cervical nerves both nociceptive and non-nociceptive afferents [85].

The trigeminal has four nuclei: (1) mesencephalic nucleus, (2) the principal nucleus, (3) the spinal trigeminal nucleus, and (4) the motor nucleus. The trigeminal nerve and its nuclei have extensive connections to other areas and to many other nuclei. In part, they are:

(a) To the spinal cord
(b) To the cerebellum
(c) To the hypothalamus
(d) To the reticular formation
(e) To the thalamus
(f) f) To the inferior olive
(g) To the hypoglossal nucleus

Neurons of the spinal trigeminal nucleus project caudally to mid and lower cervical motor neurons. These innervate the neck muscles. Rostrally, the spinal trigeminal nucleus projects to the thalamus, the superior colliculus, and the cerebellum via the inferior olive. This organization supports the trigeminal nuclei as a key structure in a large neural network modulating activity in motoneurons supplying muscles of the neck, face, and shoulders. Certain trigeminal reflexes and its intercommunications indicate complex pathways that project to the trigeminal spinal nucleus and neurons that travel to the reticular formation and terminate on motor nerve pathways of the facial, trigeminal, and/or cervical complexes [86].

Aberrant trigeminal impulses are present in those with blepharospasm and oromandibular, cranial, and cervical dystonia, where there is a loss of inhibition [87, 88]. "Trigeminal-mediated reflexes are deficient in craniocervical dystonia, indicating that the trigeminal sensory nuclear complex may play an important role, given its wide-ranging projections to motor regions of the brain. Abundant anatomical evidence indicates that motor control of the head and neck relies on normal function of the trigeminocervical reflex pathways, and therefore abnormal trigeminocervical function may impact this control" [89].

5.5.3 Cervical Spine and Analysis

Temporomandibular joint dysfunction and neck-shoulder pain is common even up to 70% of cases [90]. Facial pain also has a high incidence in patients with neck pain. The TMJ is a load-bearing joint, and inflammation may be exacerbated by bruxism. Head and neck posture influences the vertical and horizontal positions of the mandible at rest, which alters the path of closure in tooth-tooth contact. If the rest position is altered by a change in head position, the habitual path of closure of the mandible also must be altered by such change [91]. Both pathological and non-pathological symptoms may originate from disc disorder of the TMJ in addition to nerve root irritation, trauma (micro or macro), spinal cord compromise secondary to spinal stenosis, and myofascial pain.

The most common abnormality in the cervical spine with direct impact upon the craniofacial area is the forward head posture (FHP). A whiplash injury (hyperflexion/hyperextension) will cause reflex guarding of the levator scapulae and trapezius muscles, along with the suboccipital extensors, and the SCM's resulting in a FHP. A hyperflexion/hyperextension injury has the potential to damage the TMJ by (1) stretching and/or tearing of the retrodiscal ligaments, which result in disk displacement, (2) injury to the masseteric and deep temporal nerves, (3) compression injury to the posterior attachment and retrodiscal tissue secondary to the myotatic reflex, and (4) stretch/tear injury to the attendant muscles, ligaments, and tendons complicated by the myotatic reflex [92].

Mandibular-maxilla postural relationship and head posture are inversely proportional in a sagittal plane. Shifting the mandible backward results in a head shift forward, and alternately shifting the head forward causes mandibular retrusion. TMJ disorder patients typically have both a forward head posture and a mandibular backward posture.

Forward head posture can cause mandibular retrusion by increasing the tension on the muscles that are attached to the lower jaw (submandibular and infrahyoid muscles) to the chest and clavicles. When the head shifts forward (FHP), the mandible cannot shift as far anteriorly as the cranium, because it is still attached to the clavicles by the muscles and fascia within the submandibular region of the neck. Therefore, the upper dentition (fixed to the maxilla) shifts anteriorly farther forward than the lower teeth and the bite changes in a way which produces a perceived retrusion of the mandible compared to the maxilla (Class II malocclusion). Head and neck postures also influence the vertical and horizontal positions of the mandibular rest position, which subsequently alters the path of closure into teeth-teeth contact.

Conversely, retruded mandibular posture can cause FHP by eliciting adaptations to protect the airway. A hierarchy of neuromuscular reflexes

controls the muscles that maintain head and jaw posture and protect the airway. All head, neck, and face structures must grow around and maintain the airway. The muscles of the area enable resting postures that are necessary to hold the bones in whatever positions they need to maintain an adequate airway. Because the mandible supports the airway and the cervical spine borders it from behind, a retruded mandibular posture can constrict the airway against the cervical spine. If this happens, the muscles that surround the airway automatically respond by tipping the head backward (extension) in order to rotate the lower jaw forward to provide space for the airway. However, the head cannot just rotate backward, because the visual orientation reflex must keep the line of sight horizontal to the earth's plane and keep the head level. Therefore, the head tips backward and shifts forward, thereby resulting in a pulling upward and forward on the lower jaw while maintaining the patient's line of sight.

The literature is clear that cervical spine and neck tissues refer the pain to the head and neck areas and the neuroanatomical mechanism explains these pains. This happens through the trigeminocervical nucleus in the upper cervical spinal cord within the subnucleus caudalis of the trigeminal nerve. A complete examination of the TMJ, neck, and shoulders including the cervical spine is recommended as a routine diagnostic process for patients who show signs and symptoms accordingly.

5.6 Fibromyalgia

Fibromyalgia is a disorder characterized by chronic widespread musculoskeletal pain and the presence of multiple painful areas (tender points) especially at the axial skeleton. Its etiology is unknown; it occurs in varied ways, in different patients, which leads to characterize it as a syndrome instead of a disease—fibromyalgia syndrome (FMS). It is the most common musculoskeletal condition after osteoarthritis; however it is still often misdiagnosed and misunderstood.

The 1990 American College of Rheumatology (ACR) classification criteria for FMS included (1) widespread pain in the axial skeleton, at both hemibodies, above and below the waist in combination with (2) tenderness at 11 or more out of 18 specific tender points [93]. The ACR classification increased recognition of the disorder and furthered research on FMS and the overlapping signs and symptoms with other disorders. Chronic pain is used to be the defining feature of FMS; however patients demonstrated a wide range of other symptoms (sleep disturbances, depression, fatigue, TMD). The coexistence of a painful condition caused by FMS and TMD has been frequently raised for several studies [94].

Wolfe et al. revised the ACR classification eliminating reliance on tender point testing to simplify the diagnosis of FMS [95]. The revised criteria use a detailed interview of the patient to evaluate total body pain using a widespread pain index (WPI) and a measurement of the symptom severity scale (SS). In order to be diagnosed with FMS, the symptoms must have been present for at least 3 months; no other diagnosable disorder otherwise could explain the pain [93].

Although the signs and symptoms of TMD are not part of FM diagnosis criteria, several studies have associated FMS with TMD. Eriksson et al. [96] first described the relationship of mandibular dysfunction in primary fibromyalgia syndrome. Using the Helkimo anamnestic dysfunction index, it was demonstrated that 75% of FMS patients presented clinical history of TMD [96]. The incidence of pain in the muscles of mastication in patients with FM was reported to be high in a study by Pennacchio et al. [97]. Ninety-seven percent of patients with FM were also diagnosed with TMD and that only 30% from the control group presented with TMD [97].

Plesh et al. using the RDC and ACR criteria for the diagnosis of TMD and FM, respectively, showed that 18.4% of TMD patients also had FM, but most of those with FM (75%) satisfied criteria for muscular (myofascial) type of TMD. Comparing both groups, the patients with FM had lower pain thresholds, more severe manifestations of all disease measures (pain, fatigue, sleep, etc.), and more painful body regions.

Patients with FM also differed significantly from those with TMD in self-reported work ability and health assessment. The features that best differentiate FM from TMD are functional disability, reports of work difficulty, and general dissatisfaction with health [1].

Another comparative study by Cimino et al. investigated common symptoms and divergent features in women with FM against women with masticatory myofascial pain (MFP). Both groups of patients showed common evidences of TMD, such as pain during mandibular function, articular sounds, and also cephalalgia. They presented similarities regarding the presence and intensity of pain in the palpation of masticatory muscles [98].

Similarly, Hedenberg-Magnusson et al. found 94% of the patients diagnosed with FM reported local pain from the temporomandibular system with a mean duration of 12 years. General body pain had a significantly longer duration than TMD, indicating that FM starts in other parts of the body and later extends to the temporomandibular region. The authors agreed that a set of FMS symptoms may lead to the onset of TMD symptoms, while there is a TMD subgroup of patients that could present widespread pain but do not meet the criteria for FMS [99]. Review of literature by Gui et al. demonstrated a high prevalence of TMD in patients with FMS ranging between 59.37 and 93.7%. FMS patients were 31 times more likely to have a diagnosis of facial muscle pain than patients without the condition. Salvetti et al. [100] reported 79.6% of fibromyalgia patients present at least one TMD diagnostic factor; the most found factor was inflammatory and degenerative disorders (71%), followed by muscular disorders (40.9%). Leblebici et al. studied a group of 31 people diagnosed with FMS and a group of 21 people diagnosed with TMD. Both groups completed a questionnaire with information about prior head and neck trauma, parafunctional habits, muscle fatigue, crepitus of the TMJ, restricted mandibular movement, jaw pain, and prior TMD treatment. Clinical examination of both groups included bilateral manual palpation of the masticatory muscles. Results revealed 80% of patients with FMS had masticatory myofascial pain and TMD. The studies demonstrated greater involvement of the stomatognathic system in fibromyalgia, and myogenic disorders of masticatory system are most commonly found in those patients. Furthermore, the prevalence of TMD signs and symptoms in FM patients is higher than the other way around. The authors concluded that FM appears to have a series of characteristics that constitute predisposing and triggering factors for TMD [101].

Fibromyalgia is linked to a multifactorial etiology. Suspected causes of FMS include abnormalities in pain pathways, as well as genetic and environmental factors. Although FM and TMD are distinct clinical entities, they can simultaneously occur, as well as share common signs and symptoms, especially those related to pain [102]. Data rather suggest an overlap in pathophysiology with FMS, e.g., a disturbance of central pain processing, in a subgroup of TMD patients. Recent investigations on FM etiology reported that the clinical condition occurs due to an alteration in the hypothalamic-pituitary axis, the main path of the neuroendocrine response to stress, altering the levels of cortisol, growth hormone, and serotonin. The same conditions have been found in subjects suffering chronic pain, including orofacial chronic pains and TMD [103, 104]. Both TMD and FMS are found to have similar pathophysiological changes and psychological features indicating that FMS may be the predominant problem predisposing to TMD. The pain in FMS may be leading to psychological distress and increased healthcare visits, leading to aggravation of the TMD [105].

Besides the reduction of pain threshold, FM and TMD share other signs and symptoms, such as cephalalgia, sleep, and attention disorders as well as articular sounds and movement limitations. Oral manifestations prevalent in FMS patients include limited mouth opening, pain upon opening, and masticatory pain. Muscle and joint pain during opening and closing is prevalent with FMS. The prevalence of limited mouth opening has been reported to be ten times higher in people with FMS than controls with the average maximum voluntary mouth opening for FMS

patients at 41 mm, compared to 44 mm in the control group. The exact cause is unknown, but it is likely that muscle pain during jaw movements contributes to lower range of motion during mouth opening. FMS and widespread pain should receive important consideration when evaluating and developing a treatment plan for patients with TMD [106].

Studies have suggested that tactile stimulation in the form of massage has had a positive effect on clinical signs and subjective symptoms of TMD, as well as widespread pain in FMS patients who were unaffected by routine TMD treatment. The use of occlusal splints and stabilization splints has significantly reduced the pain intensity in patients suffering from myogenous TMD. Occlusal splints and stabilization splints, in this case, have a positive effect as a treatment option for patients with TMD [107]. Occlusal splints often recommended for patients suffering from TMD have not yet been proven to be beneficial for treating myofascial pain in people with widespread pain. There is not enough evidence to show that the use of occlusal splints is beneficial for treating myofascial pain in patients with widespread pain and FMS.

Recently, Molina-Torres et al. designed a single-blinded, randomized clinical trial to investigate the therapeutic effects of laser therapy and of an occlusal stabilization splint for reducing pain and dysfunction and improving the quality of sleep in patients with TMD and FMS. Participants in the study were 58 women and men who had been diagnosed with FMS and TMD, randomly assigned to the occlusal-splint or the laser group. Pain intensity, widespread pain, quality of sleep, and joint sounds were assessed in both groups at baseline and after a 12-week treatment. The measurements used were (1) a visual analogue scale (VAS), (2) the widespread pain index (WPI), (3) the symptom severity scale (SSS), (4) the patient's global impression of change (PGIC), (5) the Pittsburgh Quality of Sleep Questionnaire Index (PSQI), (6) an assessment of the number of tender points, (7) a measurement of the active mouth opening, (8) a measurement of the vertical overlap of the incisors, and (9) the measurement of joint sounds during mouth opening and closing. Overall, the study found an average improvement in symptoms from baseline of 21%, $P < 0.001$, based on the PGIC. In their conclusion, laser therapy or an occlusal stabilization splint can be an alternative treatment for reducing pain symptoms and the clicking sound for TMDs in patients with FMS [108].

5.7 Headaches

Headaches are a major comorbid condition of TMD. We are going to discuss how the different headaches are related to the TMD. TMJ pain-dysfunction syndrome appears to be an unappreciated cause of headache distinct from other headache entities [109]. Temple headaches are typically due to overuse of the temporalis muscle. As in the case of TMJ internal derangement, the muscles of mastication may start to become taut and spasm due to an unstable joint relationship. The temporalis muscle is innervated by the anterior and posterior deep temporal nerves, which are a part of the mandibular branch of the trigeminal nerve (V3). Also, in an internal derangement, as explained previously, as the AT nerve is innervated at subthreshold levels, aberrant signals are sent to the central nervous system (CNS) via the trigeminal system or trigeminocervical complex (TCC), and the signals return through the trigeminal motor nucleus to the muscles of mastication which can cause tightness, spasms, and bruxism.

A headache was precipitated by jaw activity more often in subjects with more frequent temple headaches [110]. The literature is increasing in showing that while treating TMD for its common symptoms, there is a significant decrease in headaches. Also, that 66% of headache patients have TMD and 40% have TMJ internal derangement and myofascial pain [111, 112].

It is widely accepted that the pathophysiology of migraines involves activation of the trigeminovascular system and the nuclei within the brainstem [55, 113]. Occipital, parietal, frontal headaches and migraines can occur due to the trigeminocervical complex [33]. Animal models

have demonstrated central afferent projection to the trigeminal nucleus (VC) by stimulation of the dura mater, and the VC extends to C2 and C3 regions of the cervical spinal cord describing the TCC [114–116]. Just like the muscles of mastication being affected by the trigeminal stimulation via the AT nerve, so are the muscle of the neck who are being innervated by the nerves of the cervical spine via the TCC. These nerves can stimulate the muscles in the back of the head and neck to spasm creating trigger points. Simon and Travell have published demonstrating trigger points in the occipital and cervical muscles causing referral patterns to different parts of the head. Occipital and parietal headaches can be caused by the contraction of the occipital muscles constricting the occipital nerves. Frontal headaches can be caused by the aponeurosis, which extends from the occipital muscles to the frontal muscles. This pulling from the occipital muscles can cause the frontal headaches.

5.8 Control of Movement/ Treatment

Many healthcare practitioners have different philosophies on how to treat the TMJ [117, 118] and are adopting a multidisciplinary approach to the pathology and symptomatology of the TMJ. TMD treatment revolves around two major factors, orthopedic and neurological. If there is a structural issue, the orthopedic component must be addressed in order to affect the neurological issue.

Given the wide array of diagnostics and controversy regarding the TMJ, there are two forms of therapy that have evolved: reversible and irreversible.

Reversible treatment means that there should not be any permanent changes to the teeth and jaw. Such treatments are splint therapy, pharmacotherapy, physical therapy, massage, and acupuncture. According to the National Institutes of Health (NIH), American Dental Association, and the National Institute of Dental and Craniofacial Research (NIDCR), TMJ treatments should be reversible whenever possible [119].

Irreversible treatment should be avoided if possible and be based on the evaluation of the patient's response to the reversible therapies. Irreversible treatments are occlusal equilibration of the teeth; mandibular repositioning splints which move the jaw, ligaments, and muscles into a new position; full mouth reconstruction such as crown and bridgework; orthodontics; and surgical procedures. The surgical therapy can range from arthrocentesis and arthroscopy to the more complex open joint surgical procedures such as disc replacement and total joint replacement [119].

Conclusion

With respect to the above discussion, there is a close relationship between the anatomy and physiology, of the TMJ and many neurological disorders.

The proper craniomandibular relationship can affect the trigeminal system. When signals are produced in the trigeminal network and enter the brainstem via the spinal trigeminal nucleus, it crosses over fibers in the brainstem through the reticular formation, thus causing improvements in movement disorder patients. It has been shown that by treating the TMD and making changes in the craniomandibular relationship with oral appliances, we are not only effecting and treating the symptoms of pain and discomfort, but we also resolve symptoms of neurological disorders, neuromuscular dysfunctions, and dystonia. Clinically, this is accomplished simply by removing the aberrant signal or compression of the AT nerve, which innervates the posterior and lateral ligaments of the disc [76, 120].

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6 Temporomandibular Joint Dysfunction, Trigeminal Nerve Inflammation, and Biomechanical Dental Treatments for the Suppression of Neurological and Neuropsychiatric Symptoms

Anthony B. Sims and G. Gary Demerjian

Abbreviations

AT	Auriculotemporal
TMJD	Temporomandibular joint disorders

6.1 Temporomandibular Joint

The right and left temporomandibular joints articulate the mandible (lower jaw) with the maxilla (upper jaw). Temporomandibular joint disorders (TMJD) refer to clinical dysfunctions in either one or two of the bilateral temporomandibular joints. TMJD may arise from acute to chronic inflammation, trauma, myofascial causes, developmental anomalies, or neoplasia. TMJD manifest as signs and symptoms that involve the surrounding muscles, ligaments, bones, capsule, connective tissue, teeth, and innervations to the temporomandibular joint. TMJD induce proximal and distal, chronic and acute, dull or intense pain and discomfort, muscle spasms, clicking/popping/grating sounds upon opening and closing of the mouth, as well as chewing and speaking difficulties [1]. The trigeminal nerve (fifth cranial nerve) and its branches provide primary sensory innervation to the TMJ. The auriculotemporal (AT) nerve, a branch of the mandibular nerve and the largest of the three divisions of the trigeminal nerve, plays an important role in the sequela of TMJD. The AT nerve provides sensory innervation to the TMJ capsule posteriorly, medially, and laterally [2].

It has been estimated that over 20% of human adults currently have, or have had, internal derangement of the temporomandibular joint [3]. In recent years, oral appliances have been fabricated that provided improvement of certain dystonias [4]. These neurological actions of the oral orthotics were regarded as sensory tricks or *geste antagoniste* [4]. In addition to sensory tricks, specially constructed oral orthotics might also suppress movement disorders by relieving pressure on entrapped trigeminal nerve endings in the TMJ, thereby reducing aberrant afferent signals to the brainstem, which may be triggering movement disorders [5, 6].

The authors have analyzed the reported literature and texts on neuroanatomy to better understand the possible causal relationship between these disorders. Internal derangement of the TMJ

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occurs when the cartilaginous disc that lies on the superior surface of the condyle becomes displaced from its normal location. Such internal derangement of the articular disc causes retrodiscal tissues, which normally lie posterior to the condyle, to move forward into the compression zone produced by the condyle articulating against the temporal bone of the skull. Retrodiscal tissues contain sensory fibers of the auriculotemporal (AT) nerve, a branch of the mandibular nerve. Compression of AT fibers may result in focal neuroinflammation. This neuroinflammation might spread from the site of nerve entrapment to the trigeminal ganglion and then onto the spinal trigeminal nucleus, as well as into the reticular formation of the brainstem [5, 6]. Neuroinflammation in brainstem centers could act as physiological drivers for aberrant reflexive behaviors, as well as supra-brainstem changes within the nervous system [6].

The trigeminal nerve is a tonic regulator of the reticular formation and thus has strong influence on sensorimotor circuits in the brainstem [7]. The specific network for postural control in humans and the locomotor region signals are transmitted from the midbrain to the spinal cord via the ponto-medullary reticular formation and integrated through multisensory input at different levels [8]. Teeth clenching in humans, for instance, modifies cortical, subcortical, and spinal circuit activity. Teeth clenching also modifies deep tendon reflexes in the extremities [9–11]. These studies provide evidence that mechanosensory signals from the jaws, which are transmitted via the trigeminal nerve, can modify muscular tone in many locations of the body [12–14].

Patients may not always recognize trauma to their temporomandibular joints or suspect that the position of their jaws may be linked to their sensorimotor symptoms. In this paper, the authors present clinical work that suggests there may be pathological interrelationships between TMJ dysfunction, inflammation in the trigeminal nerve, neuroinflammation in the trigeminal spinal nucleus, and functional neurological and neuropsychiatric disorders. The authors discuss a set of cases of patients with TMJD, who also suffer from a variety of movement, sensory, and cognitive disorders. In each case, clinical benefits are discussed resulting from jaw realignment. Then utilizing clinical-anatomical analysis of neural pathways to discuss how TMJ injury, as well as subsequent inflammation initiated in the trigeminal nerve, might drive changes in the brainstem and brain, leading to the symptoms observed in patients.

6.2 Tourette's Syndrome

6.2.1 Case Presentations

6.2.1.1 Case 1: Tourette's Syndrome by Dr. Anthony Sims

Patient History

A 25-year-old male presented to our office with a history and diagnosis of Tourette's syndrome for the past 14 years. His symptoms were tics that consisted of neck flexion to the right in which his head and right ear would contact his shoulder intermittently and with constant frequency (Video 6.1). Also, present was a consistent eye rolling tic, a constant cough, loud vocal tics (barking), shallow breathing with difficulty, head jerks, shoulder shrugging, abdominal contractions, right arm atrophy, freezing right thumb such that he could not hold a pen, facial grimacing, and jaw clicking. The patient also presented with signs of obsessive-compulsive disorder. For instance, in response to urges, he would constantly adjust his clothing.

Prior to his dental examination, the patient had been examined by 33 neurologists. His previous medications were Motrin for neck pain, Klonopin, and Haldol, which he discontinued because it diminished his mental capacity or "slowed him down". He stated that the medication. Tenex was not helpful, and Orap caused sedation for him. Previous MRI showed degenerative joint disease and stenosis at C5–6/C6–7. He had no history of any previous accidents or trauma to the face or jaw. He was given a psychological evaluation by his physician and his cognitive abilities were found to be within normal limits.

Clinical Presentation and Treatment

In addition to the previous signs and symptoms, the patient reported that he was right-handed in

sports and that his right hand felt as if he had pins and needles in it. The patient had suffered a prior neuropathy in his upper right arm, owing to a repetitive motion injury. His shoulder-shrugging tic resulted in frequent dislocation of the upper humerus from its socket. The patient commented that these shoulder dislocations had resulted in nerve injury in his right arm. The patient also reported that his tics increased with stress. In response, he would open his mouth to help "soothe" his problems. He had a constant clearing of the throat, slight suboccipital pain, and a high mandibular jaw angle in addition to multiple posterior missing and/or carious teeth.

The vertical dimensions of the patient's occlusion were increased by having the patient bite down on a stack of eight tongue depressors. Tongue depressors (also known as tongue blades) are individually approximately 1.5 mm in thickness. When patient's jaws are vertically distracted by biting on a stack of tongue depressors, there is an estimated 3:1 ratio for anterior opening versus posterior distraction of the temporomandibular joint (TMJ). In this patient, his TM joints were opened approximately 4 mm. The articular disc within a given TMJ is 3 mm in thickness. In a healthy individual, the articular disc should be located at the 11–12 o'clock position within the TM joint [15].

Results

After producing this vertical distraction, the patient was instructed to advance his mandible forward until his anterior teeth were aligned edge to edge as much as possible. At that point, the signs and symptoms of his Tourette's tic disorder discontinued. An oral orthotic was designed to the vertical dimension that was determined to distract his jaws. It was then sent to a commercial laboratory for construction. The patient was then followed for 3, 6, 12, and 24 months and 6 years, and there was no return of symptoms as long as the patient wore the orthotic. Without the orthotic the symptoms would return within 1 h. The patient was given an option to have orthopedic surgery and orthodontic treatment in order not to wear the orthotic. He decided not to pursue this option.

Discussion of Case 1

In many cases of Tourette's syndrome, one of the first clinical signs is repetitive and uncontrollable eye blinking [16, 17]. If the pathway for the blink reflex is examined, CN V transmits tactile sensation from the cornea, which is perceived as irritation that evokes bilateral eyelid closure (an eye blink). Trigeminal ophthalmic primary afferents (V1) send signals, which end in the spinal trigeminal nucleus (subnucleus caudalis). From here, interneurons transmit signals to the reticular formation. Within the reticular formation, interneurons send signals to the facial nucleus, cranial nerve VII. Facial nerve efferent neurons from the facial nucleus send their signal to the orbicularis oculi, which closes the eyelid; blinking occurs. This is the simplified summary of the corneal blink reflex neural circuit [18].

The primary incoming afferent signals can come from other sensory branches of the trigeminal nerve itself. Sustained low-frequency nociceptive impulses can be transmitted by the auriculotemporal nerve, a branch of the mandibular nerve (V3). Transmission of these impulses may be facilitated through neuronal glia activation and interaction within the Gasserian ganglion. This facilitation may arise from neuroinflammation in these regions, as well as sites where the ophthalmic nerve division (V1) and the maxillary nerve division (V2) terminate in the subnucleus caudalis [19–22]. Motor efferent nerves from this nucleus may stimulate other muscles of facial expression such as frontalis, orbicularis oris, platysma, zygomaticus major, and zygomaticus minor. These are some muscle groups that are involved in facial motor tics. It is the afferent sensory fibers in the mandibular division of CN V that are triggering the oromandibular dyskinesia via a potentiated activation of motor neurons in the brainstem, whose efferent drive is carried by CN VII.

Another frequent finding in Tourette's syndrome is throat clearing and sniffing. Examining the anatomy of the trigeminal nerve, within the spinal tract of V, which ends in the subnucleus caudalis, there are connections within the subnucleus caudalis to the glossopharyngeal nerve, CN IX, which contains general sensory fibers and provides sensation from the posterior 1/3 of the

tongue, the tonsil, the skin of the external ear, the internal surface of the tympanic membrane, and the pharynx. In experimental animals, the cough/gag reflex is triggered when this nerve is chronically stimulated [23]. Neuroinflammation within the trigeminal subnucleus caudalis (where CN IX and CN V primary neurons interact and terminate), the cough/gag reflex could also be stimulated in response to afferent drive from CN V. This pathway might account for the chronic coughing and gagging, which a subset of Tourette's syndrome patients' experience.

A well-documented symptom of many Tourette's syndrome patients is echolalia (the spontaneous utterance of sounds). The vagus nerve (CN X) interact within the spinal trigeminal nucleus, as does CN V. CN X is a general sensory afferent nerve providing sensation from the posterior meninges, concha, and skin at the back of the ear and in the external acoustic meatus, part of the external surface of the tympanic membrane, the pharynx, and the larynx (the vocal cords). As a result of its irritation, the voice feels hoarse and a clearing of the throat results. If the primary irritant is not in CN X, but itself originates from CN V and its primary terminals within the subnucleus caudalis, the vocal expressions of echolalia (throat clearing, grunting, and barking sounds) would occur.

Another documented clinical sign with those who have Tourette's syndrome is shoulder shrugging. It is known that the muscles of the neck (sternocleidomastoid) and shoulder (trapezius) are innervated by the spinal accessory nerve, CN XI. This nerve originates at the level of C1 through C5 as rootlets from the anterolateral portion of the anterior horn of the spinal cord. The myelinated fibers of the spinal tract of V and the large spinal nucleus of V also extend to the level of C2. The ventral horn of cranial nerve XI gives rise to the motor portion of the nerve, and it goes to the level of C2 [24].

The ventral pontine medial reticular formation, when stimulated, mediates posture and orients head and neck movements and turns them to the ipsilateral side of the stimulation [7]. These reticular cell groups are called premotor networks, and they control the activity of large groups of muscles such as in the neck, trapezius, sternocleidomastoid, and axial muscles. This brainstem nucleus, when stimulated by CN V, might initiate the shoulder shrugging and head turning that is commonly observed in individuals with Tourette's syndrome [25, 26].

Respiratory centers are also within the pontine reticular formation of the brainstem. The trigeminal nerve projects primary afferent nerves to the reticular formation raphe nuclei, which stimulate the medial and lateral nucleus portions of the reticular formation. These areas project both rostrally and caudally throughout the brainstem's tegmentum and influence both the autonomic and voluntary muscle reflexes. A series of paired and functionally related autonomic nuclei are located bilaterally in the reticular formation of the brainstem; this control center consists of the medullary rhythmicity area, the dorsal respiratory group (DRG), the ventral respiratory group (VRG), and the pontine respiratory center; these collections of neurons regulate the rate and depth of breathing as an involuntary unconscious activity in response to the needs of the body for O_2 and CO_2. When the trigeminal nerve's normal firing frequency is altered, the breathing rate and depth may be altered [7]. This might account for the patient's shallow breathing, which rapidly normalized upon using an oral orthotic.

Aberrant afferent drive to the brainstem is likely to rapidly diminish, when irritated endings of the auriculotemporal nerve are decompressed within a TMJ, via a vertical distraction of the jaws. Decompression of the auriculotemporal nerves, bilaterally in this Tourette's syndrome patient, resulted in the rapid suppression of his tics, including vocalizations, head turning, abdominal contractions, and shoulder shrugging.

6.3 Cervical Dystonia

Cervical dystonia (CD), also known as spasmodic torticollis, is the abnormal posturing or movement of the neck and head muscles. It is the most common form of focal dystonia and affects women

twice as often as men [27]. CD spasms can result in various head postures depending upon the muscles that are affected. There may be side bending or rotational twisting of the head/neck (laterocollis), or backward rotation (retrocollis), or frontal rotation (anterocollis), or a combination of these. Pain or head tremor is often associated with those that have a sustained contraction. There is often an associated dystonia in the upper muscles of the same side (segmental dystonia). Presentations of torticollis or cervical dystonia are often defined using terms such as acute or chronic torticollis, congenital or acquired torticollis, and idiopathic or secondary torticollis. Some more common causes include congenital problems, trauma, inflammation, and infections [28, 29].

1. The pathophysiology for CD is presented as congenital or acquired. Congenital muscular torticollis is rare (<2%) [30]. This disorder may be caused by soft tissue trauma to the neck just before or during delivery [31]. The explanation is believed to involve birth trauma to the sternocleidomastoid (SCM) muscle, resulting in incorrect intrauterine positioning or fibrosis, which leads to unilateral shortening of the SCM [32]. There may be resultant hematoma formation followed by muscular contracture. These children often have undergone breech or difficult forceps delivery [33, 34].
2. Acquired CD, on the other hand, depends on an underlying disease process, such as injury or inflammation to the cervical muscles, or pathology to cranial nerves [35]. Idiopathic spasmodic torticollis is a chronic, neurodegenerative form of torticollis classified as a focal dystonia. The etiology is unclear, although it is thought that changes within the basal ganglia's inhibition system influences the motor movements within the cerebral cortex, brainstem, and spinal. It is characterized by having an acquired, non-traumatic origin consisting of episodic tonic and/or clonic contractions of neck muscles. Symptoms last more than 6 months and may result in somatic incapability and psychological distress.
3. Why would the symptoms of the CD respond positively to the oral orthotic?
4. Research has shown that when the auriculotemporal nerve in the TMJ is stimulated, there is motor activity in the sternocleidomastoid and splenius muscles of the neck [36, 37]. This stimulus travels via primary afferents in the auriculotemporal nerve to the brainstem and activates an area called the reticular formation [38, 39]. Within certain areas of the reticular formation are nerves that, when stimulated, cause the head and neck muscles to turn toward the same side as the stimulation [25, 26]. The etiology for spasmodic torticollis may be that these reticular formation nerves are being constantly bombarded by noxious stimuli originating in over stimulated nerves within the TMJ. With a constant stimulation of the auriculotemporal nerve, possibly caused by some type of peripheral trauma or injury (i.e. an internal derangement of the Temporomandibular Joint), the aberrant signal may be a factor in causing the head and neck to turn to the ipsilateral side of the stimulation.
5. When the stimulus is relieved in the TMJ, the stimulus in the reticular formation is also relieved, which then relieves the turning of the head to that side [40]. With regard to sensory tricks, which are common in patients with typical dystonia, the trigeminal nerve's general sensory fibers convey information regarding pain, temperature, touch, and conscious and unconscious proprioception and senses the head in relation to the rest of the body in space. When a patient touches their face, chin, or head they are activating the proprioceptive function of the trigeminal nerve which projects to the subnucleus caudalis, then to the reticular formation, which communicates with the vestibular system's medial longitudinal fasciculus [41, 42]. The medial longitudinal fasciculus carries the descending tectospinal tract into the cervical spine, which is involved in guiding the head to its proper position and innervating some muscles of the upper limbs and neck. This proprioceptive touching then allows the head to orientate itself into the proper upright position [43, 44].

6.3.1 Case 2: Cervical Dystonia (Torticollis) by Dr. Gary Demerjian

6.3.1.1 Patient History

A 32-year-old female presented in April 2012 with pronounced cervical dystonia (Fig. 6.1). Additional symptoms were neck pain, shoulder pain, back pain, fatigue, migraine headaches, headaches, muscle twitching, dizziness, throat pain, sinus congestion, and visual disturbances. Currently she suffers from moderate bilateral parietal and occipital headaches that last for weeks, moderate bilateral temporal daily headaches that last a few hours, pain behind the ears, upper back pain, middle back pain, lower back pain, limited movement of her neck, shoulder pain, shoulder stiffness, and tingling in the hands. She has sensitivity to lights, to sound, and to touch on top of her head. The patient reports being diagnosed with cervical dystonia (retrocollis and laterocollis) in 2001. She has received Botox injections into her neck and shoulder muscles since then, but the effects are diminishing over the years. As a child, she hit her head on the bottom of a swimming pool many times while diving in the shallow end. She has also had numerous falls, repeatedly injuring her coccyx.

The patient has been diagnosed with cervical dystonia, fibromyalgia, Bell's palsy, and C2–3 radiculopathy. She developed stomach pain and cramping in January 2012. The patient was diagnosed with gall bladder problems. The gall bladder was removed with surgery, and her abdominal pains subsided.

In addition to her dystonia, the patient reports a history of low blood sugar, muscle spasms or cramps, muscle aches, muscle shaking, sinus problems, chronic fatigue, cold hands and feet, depression, dizziness, frequent stressful situations, tired muscle, and difficulty concentrating. Her current medications are docusate sodium, fentanyl transdermal system, gabapentin, oxycodone, Savella, tizanidine HCL, norgestimate-ethinyl estradiol tablets, and Lunesta.

6.3.1.2 Clinical Examination and Treatment

Dental examination revealed a mid-opening click of the left TMJ while opening the jaws. Mandibular range of motion measurements revealed a maximum inter-incisal opening of

Fig. 6.1 Posture photos. A patient with pronounced laterocollis (cervical dystonia), during her initial dental consultation

40 mm, maximum protrusive of 8 mm, and 7 mm right and 5 mm left lateral excursion. Posture screening revealed right shoulder higher than left shoulder, forward head posture, and facial right-left asymmetry.

Intraoral examination of the teeth revealed occlusal wear facets and extracted third molars. The molar relationship is class I with a 2 mm overbite and 4 mm overjet. Severe tenderness was elicited upon palpation of bilateral temporalis, masseters, lateral capsule, posterior joint space, sternocleidomastoid, anterior digastric, anterior scalene, middle scalene, posterior scalene, occipital, splenius capitis, and trapezius.

Diagnostic tests included electromyographic studies, as well as photographic, videographic, and thermographic documentation (Figs. 6.2 and 6.3). The patient was seated at rest, while the EMGs were placed on her bilateral temporalis, masseter, anterior digastric, and sternocleidomastoid muscles. Before the orthotic was placed, her right SCM was contracting, and upon delivery of the orthotic, her muscle activity balanced on the EMGs. Photographs were taken demonstrating her cervical dystonia. The videographic documentation demonstrated her history and progress of care. Thermographic images demonstrate the changes in surface temperature at a screening at normal resting position and with tongue depressors between her teeth. The CT scan of the maxillofacial examination revealed posterior displacement of both condyles, flattening of the posterior portion of both condyles, and pharyngeal airway impingement. MRI study shows both TMJ articular discs displaced in the closed mouth position (Fig. 6.4). The articular discs had normal translation and position in the open mouth position (data not shown).

The patient was diagnosed with allodynia of the scalp, hyperalgesia on her neck and shoulders, articular disc displacement with reduction, limited mouth opening, muscle spasm, myalgia, cervicalgia, and nocturnal bruxism. During the examination, one to four tongue depressors were placed at an angle across the mouth where she bit down on her molars on the left and bicuspids on the right. An immediate improvement of her cervical dystonia symptoms occurred (Figs. 6.2 and

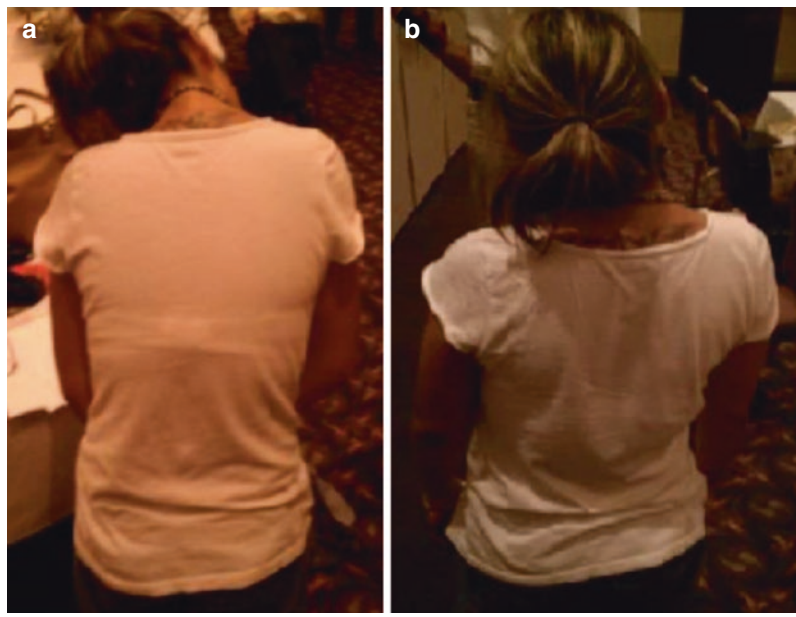

Fig. 6.2 Before and after photos of patient with cervical dystonia; biting unilaterally on a stack of tongue depressors. (**a**). Baseline photo shows effects of muscle spasms in the cervical and superior thoracic regions. The head is twisted to right and torso hunched forward. (**b**) After the patient's jaw is realigned by biting on a stack of tongue depressors. Spasms are noticeably relieved as evidenced by reduced head twist and improved posture (**b**). Back images are supplied by Mr. Kenneth Price. The patient's skin temperature was also imaged at the same time (see Fig. 6.3)

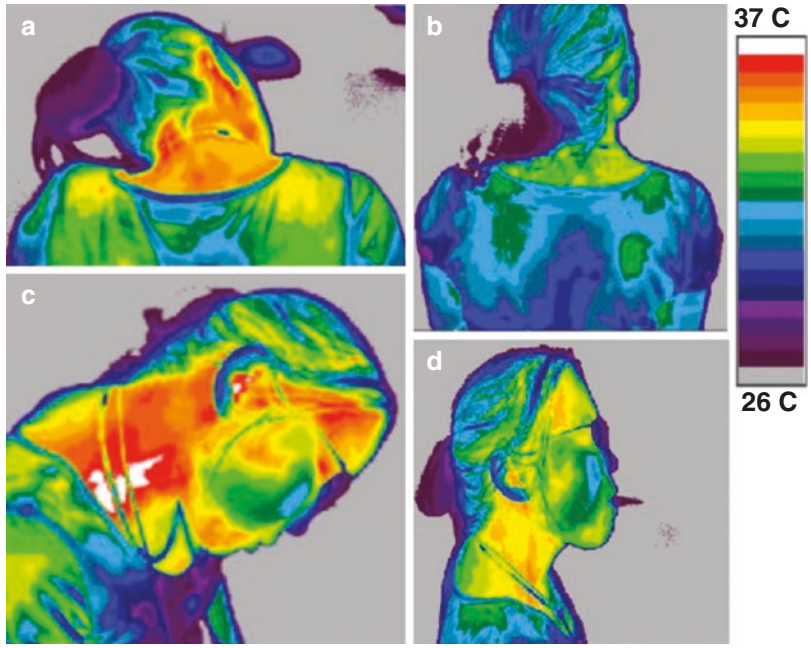

Fig. 6.3 Normalization of surface temperatures after cervical dystonia is suppressed with jaw realignment. Thermographic views before (**a**, **c**) and after (**b**, **d**) application of a tongue depressor TMJ splint. Initial thermographs (**a**, **c**) demonstrate a higher than normal heat signature in the cervical and superior thoracic area. Temperatures in the mantle area (head, neck, and shoulders) decrease bilaterally by about 4 °C, within 5 min after the patient bites unilaterally on a stack of five tongue depressors. This temperature shift was coincident with a suppression of the patient's cervical dystonia. Note the upright posture in panels **b** and **d**, following jaw realignment. Thermographic images were taken by Mr. Richard C. Price, P. A., using a ICI Prodigy 640 infrared camera (Beaumont, TX). Temperature bar represents half-degree increments

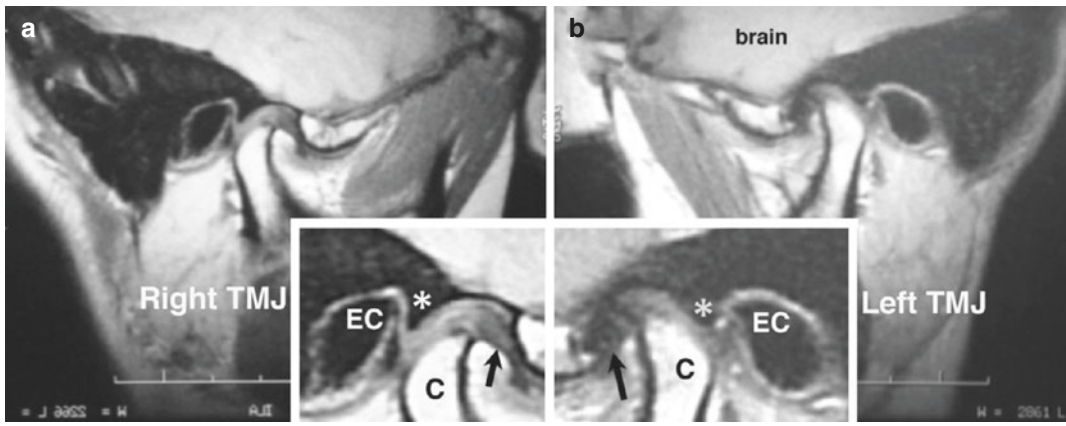

Fig. 6.4 Pathologies in the TMJs of the cervical dystonia patient (Case 2) are detected using MRI. In the closed position, the articular disc in each of the right and left TM joints has been displaced anteriorly. The clinical diagnosis for this TMJ condition is known as an internal derangement, with reduction. This finding is consistent with the audible popping in the patient's TMJs, when she opens and closes her jaws. Arrows: articular disc. Asterisks: post-glenoid process. *C* condyle; *EC* ear canal

6.3). An oral orthotic was fabricated to stabilize this vertical position of jaws (Fig. 6.5).

6.3.1.3 Results

On follow-up visits, the patient reported that her dizziness, visual problems, and migraines had resolved. Thermographic images were taken while doing a screening test to decompress the TMJ. The following charts show the thermal response of the patient to repositioning of the patient's TMJ using a stack of tongue depressors inserted between upper and lower molars. Thermal images were taken with an infrared camera, first in the dystonic state (muscles in spasm causing abnormal posture) and then minutes later in a more relaxed state following TMJ repositioning. Two posterior photographs of the patient are shown in Fig. 6.3. Each color bar in the figure's temperature scale is about one-half degree Celsius temperature difference. At 3 months after treatment, her headaches, neck pain, and shoulder pain have largely diminished. However, she still experienced a mild lateral and anterior pulling of her head. At 15 weeks, the patient became symptomatic as her orthotic had worn down due to the bruxing of the appliance. The vertical height of the orthotic was increased, by rebuilding the orthotic to its original height. By decompressing the retrodiscal tissues, her cervical dystonia was once again suppressed. CT scans were taken documenting the proper position of the condylar eminence relationship. Documentation was done over 2 years of follow-up visits where the patients were stable using her orthotics. She has decreased the use of her medications and Botox dosage injections. The orthotics need to be adjusted every 3–6 months as needed (Fig. 6.6).

6.3.2 Case 3: Cervical Dystonia (Torticollis) by Dr. Anthony Sims

A 59-year-old female patient presented to the clinic with a diagnosis from her neurologist of spasmodic torticollis (right laterocollis) for the past 14 years. Her symptoms were back pain, dizziness, fatigue, muscle twitching, neck and shoulder pain, and difficulty with downward gaze. Medications

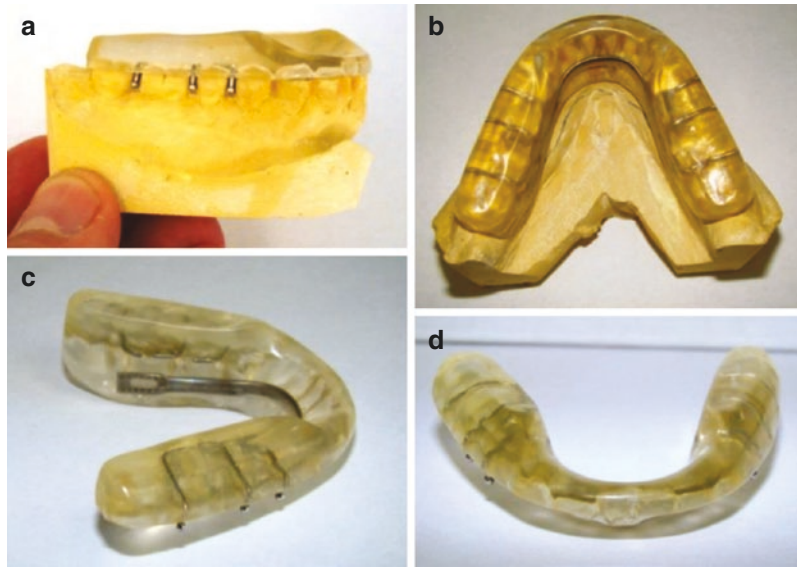

Fig. 6.5 Oral orthotic used to correct internal TMJ derangement and suppress cervical dystonia, in a TMJ patient (Case 2). (**a**) Side view of orthotic, showing its anchoring clasps to lower molars and bicuspids in a plaster cast of the mandible. (**b**) Upper view of orthotic situated in a plaster cast of the mandible. (**c**) Side view shows longitudinal indentations in the posterior platforms of the orthotic. These platforms interact with the occlusal surface of the upper molars. The vertical dimension of the platforms results in a vertical distraction of the jaws. (**d**) Front view of orthotic. Elevated platforms above the lower molars are evident

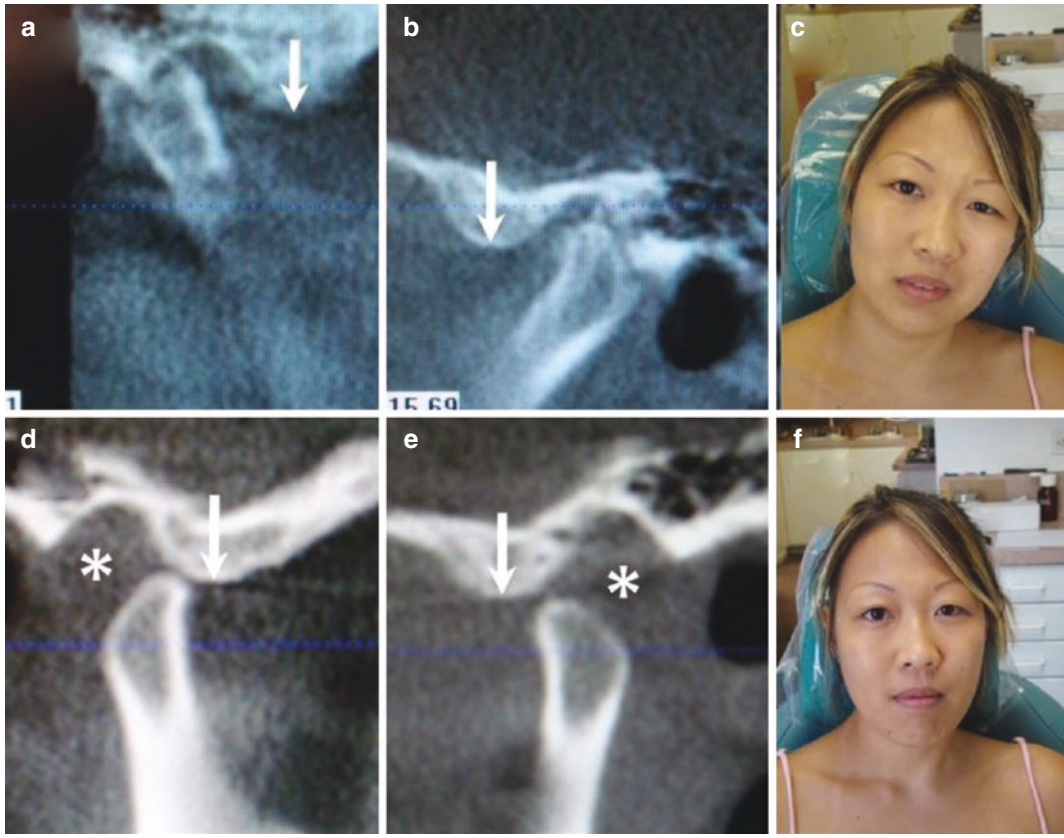

Fig. 6.6 Relapse of a TMJ patient's cervical dystonia (Case 2) correlates with a recurrence of TMJ internal derangement. CT images in A and B were taken at week 0. CT and photographic images in D and E were obtained 15 weeks after the initial delivery of an oral orthotic (at week 0). The vertical dimension of the acrylic orthotic platforms had been worn down by dental activation. The vertical dimension of the orthotic was rebuilt with acrylic paste, to again provide mechanical support for the TMJs. Wearing the orthotic generates a vertical distraction of the jaws and a repositioning of the condyles. The restored oral orthotic was able to suppress the patient's movement disorder symptoms. CT scans confirm that the orthotic moved the patient's right and left condyles beyond the normal locations to suppress her cervical dystonia, i.e., closer to the apex of the right and left articular eminences, respectively. Arrows: position of the right and left articular eminences. Asterisks: locations of decompressed retrodiscal tissues. (**a**) Right TMJ without oral orthotic. (**b**) Left TMJ without oral orthotic. (**c**) Without an oral orthotic, the patient's head tilts to the left. Her left eyelid is drooping. (**d**) Right TMJ after jaw realignment with a restored oral orthotic. (**e**) Left TMJ after jaw realignment with a restored oral orthotic. (**f**) The patient's head position is normalized following jaw realignment

were Lexapro, Klonopin, Botox injections, muscle relaxants, and antibiotics. She was also being treated for high blood pressure, sinus problems, and swollen painful joints. Upon evaluation, she had loss of equilibrium, vertigo, constant grinding of teeth, left temporomandibular joint pain, left masseter pain, constant sinus drainage, and complaints of jaw locking open. Her maximum maxillary-mandibular opening was 42 mm (normal is 50 mm) with a deviation to the left.

An MRI revealed evidence of a lateral articular disc internal derangement of the right and left TMJs. Both condyles were displaced posteriorly and superiorly. A temporary oral orthotic was fabricated that opened the vertical dimension of occlusion approximately 9 mm anteriorly (six tongue depressors), and with a 3:1 ratio, the TM joint space was opened 3 mm. Upon opening, the patient's laterocollis began to diminish over a time period of 10 min. Upon removal of the tongue depressors, dystonic contractions returned, and the patient's head returned to the laterocollis position.

An oral orthotic was ordered and delivered at the predetermined vertical dimension the patient's

symptoms ceased. Follow-up care was at 3, 6, and 12 months. At those appointments, the dystonic spasms in her neck and shoulder symptoms had not returned since the use of the orthotic.

6.4 Blepharospasm

Blepharospasm is a focal dystonia typically present at rest and a neurological movement disorder involving involuntary and sustained contractions of the orbicularis oculi muscles of the eyes. Also, blepharospasm is the most common ophthalmic manifestation in Tourette's syndrome. New studies into the pathophysiology of blepharospasm indicate increased trigeminal sensitization. Previous studies have shown that the inverse Marcus-Gunn syndrome will cause the eyelid(s) to close upon jaw movement [45]. Inverse Marcus-Gunn is when eyelid closure occurs upon movement of the lateral pterygoid muscle of the mandible moves to the opposite side. When the mouth is closed the eye(s) show a ptosis. Studies have shown that there is a trenchant co-innervation of the muscles of mastication by the trigeminal nerve and the extraocular muscles (levator palpebrae superioris) by the oculomotor nerve [46]. Blepharospasm usually starts when a patient observes that their blinking becomes excessive and prolonged. Signs for blepharospasm are dry eyes, sensitivity to sunlight or bright indoor light (photophobia), and/or eye irritation, pain, or other trigeminal sensory stimulants [47]. Blepharospasm affects approximately 1:20,000 people in the United States, and there are about 2000 new cases presented each year. The median onset is between 56 and 60 years of age. It is commonly associated with another dystonia called Meige's syndrome which is an orofacial dystonia or hemifacial spasm which involves blinking, chin thrusting, pursing of the lips, tongue movements, and sometimes shoulder movements [48]. Blepharospasm is twice as common in women compared to men. At the present time, there are three major types of medical treatments for blepharospasm: pharmacological intervention, surgery, or botulinum injections.

In normal blinking, eyelid closure is the result of activity and co-inhibition of two groups of muscles, the protractors of the eyelids (i.e., orbicularis oculi, corrugator superciliaris, and procerus muscles) and the voluntary retractors of the eyelids (i.e., levator palpebrae superioris and frontalis muscles). Primary sensory afferents from the cornea and eyelid terminate densely in the medullary spinal trigeminal nucleus. The subnucleus caudalis of the spinal trigeminal tract sends excitatory projections to the orbicularis oculi motoneurons, ipsilaterally. The principal trigeminal nucleus sends excitatory projections to the orbicularis oculi motoneurons and inhibitory projections to the levator palpebrae motoneurons, bilaterally. This is the appropriate circuitry for the trigeminal blink reflex, which occurs with the orbicularis oculi contraction and the levator inhibition. In patients with blepharospasm, this inhibition between the protractors and retractors is lost.

The initial symptom in patients with blepharospasm is photophobia, which has been thought of as an irritation of the rich innervations of the eye, which is supplied by the first division of the trigeminal nerve that leads to excessive blinking. Eckhardt and colleagues (1943) showed that direct irritation to the trigeminal afferents of the eye surface (cornea and iris) can produce photophobia [49, 50]. They concluded that surface sensitivity must be present for the disorder to occur. Moreover, direct irritation to a monocular portion of the ophthalmic branch of the trigeminal nerve can also induce photophobia [51].

Activation of a particular branch can be caused by several factors: peripheral tissue injury, compression of the nerve processes resulting in neuroinflammation, or tissue inflammation mediated by the release of pro-inflammatory molecules at site of injury initiating a neurogenic inflammatory response [52]. Following activation, trigeminal nerves release neuropeptides and other inflammatory molecules from peripheral terminals that initiate and maintain neurogenic inflammation [22]. From Thalokoti et al. (2007) study, it was shown that activation of a few sensory neurons in the V3 region of the trigeminal ganglion resulted in intracellular changes in neighboring neuronal and glial cells within that same region but also in the V2 and V1 region. These fibers also end in the subnucleus caudalis which have motor efferent nerves from the nucleus that stimulate muscles of facial expression such as frontalis, orbicularis

oris, platysma, and zygomaticus major and zygomaticus minor [53]. Nardone described 14 patients with a reflex characterized by spontaneous and involuntary anterior or anterolateral movement of the jaw associated with eye blinks. This is known as the palpebromandibular reflex. The mandible moves simultaneously with the closure of the eye because of contraction of the ipsilateral external pterygoid [54].

Examining the anatomical structures presented by the aging population, many have either had their posterior teeth extracted or have lost their youthful vertical dimension (maxilla-mandibular vertical interrelationship) that once existed through wearing and grinding of tooth structure. This loss of posterior occlusal vertical support relocates the mandibular condyle into a more superior or posterosuperior position within the glenoid fossa. With the passage of time, malocclusion displaces the condylar disc anteriorly or medioanteriorly and increases pressure or excess stimuli upon the retrodiscal tissues, which contain a complex of blood vessels and nerve endings, particularly those of the auriculotemporal nerve. Compression of the auriculotemporal nerve fibers may lead to sensitization of nociceptive afferents and increased firing in these portions of the auriculotemporal nerve. These impulses stimulate the reticular formation (nucleus raphe and the medial reticular nuclei) and begin to initiate an inhibitory effect on the reticular formation, thereby decreasing voluntary control by the cortex. In blepharospasm, there is a synaptic interneuronal connection from the trigeminal to the facial nerve, which allows the blink reflex to be elicited. Decreased inhibition within this pathway to the reticular formation may result in constant blinking and/or closing of the eyelids [55]. By removing the aberrant stimulus using vertical distraction of the lower jaw, the impulse to blink is diminished, allowing voluntary control of the eyelids to return.

6.4.1 Case 4: Blepharospasm (Video 6.4) Dr. Anthony Sims

A 56-year-old female presented in February 2008 on an emergency basis for a fractured lower left first molar. The oral exam showed that patient would grind her teeth, and molar morphology was missing on both right and left posterior teeth. Patient wore corrective lens. She squinted and blinked with abnormal frequency (Fig. 6.7a). Patient had a collapsed vertical dimension of her occlusion, due to lifelong bruxism. She stated that the blepharospasm appeared after she had been in a car accident in 1994.

Before the accident, the patient stated she was an avid reader of 100 books per year. Since the accident, the patient states that her eyelids have become heavier each year, but her vision had not changed until recently. The ophthalmologist diagnosed her with cracked vitreous humor, as well as blepharospasm. The patient also has had to have physical therapy to restore arm strength in her right arm. She could only elevate her arm up to shoulder length before pain would begin.

Written consent was given by the patient to be videotaped concerning the dental procedures. The patient's inter-incisor vertical dimension was then increased incrementally at 1.5 mm intervals by tongue depressors. At each interval, a 1-min pause was taken to see if any changes occurred. When the fourth 2 mm interval (6 mm) of vertical distraction was reached, the patient's eyelids began to open wider enabling more of the sclera of the eye to be visible (Fig. 6.7b).

The patient stated that her eyes were not as "heavy." The orthotic enabled the patient to open her eyes freely. In addition, the patient was asked to raise both arms above her shoulders and above her head, and without hesitation the patient was able to raise both arms without pain in either arm. When the stack of tongue depressors was removed from patient's mouth, the patient states that her eyelids became heavy again. The white sclera of the eyes became visually diminished, and her right arm began to develop pain. Replacing the tongue depressors caused the symptoms to subside once again. The patient returned for orthotic delivery and 1-month follow-up and her symptoms did not return. The patient was lost to follow up due to moving out of state.

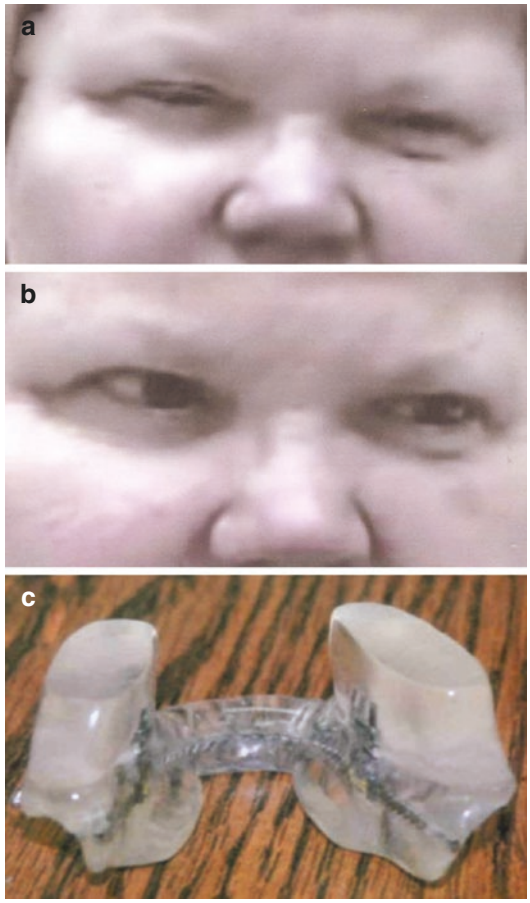

Fig. 6.7 Case 4: The blepharospasm symptoms were (**a**) suppressed within minutes after the neurocranial vertical distractor (NCVD) oral orthotic was inserted and positioned in the oral cavity (**b**). (**c**) A posterior view of the NVD. The orthotic, which sits on the lower teeth and presses on the upper molars, physically separates (i.e., distracts) the upper jaw (maxilla) from the lower jaw (mandible) (by 0.2–1.0 cm depending on the individual), thus altering pressure and tension in, and around, the temporomandibular joint (TMJ). The NVD as shown here is typically reduced in size and optimized in vertical dimension for each patient

6.4.2 Case 5: Blepharospasm by Dr. Gary Demerjian

6.4.2.1 Patient History

A 53-year-old female presented to the clinic in June 2012. Her chief complaints were eyelids do not stay open, headaches, migraine headaches, facial pain, jaw pain, neck pain, throat pain, sinus congestion, shoulder pain, back pain, and fatigue. She also complained of joint pain in her fingers, hands, and elbows for years.

The patient has been diagnosed with Hashimoto's disease and blepharospasm. She has been getting Botox injections every 8 weeks for blepharospasm. She has had an allergic reaction to penicillin and sulfa drugs. Current medications are clonazepam and imipramine. She suffers from muscle aches, shortness of breath, poor circulation, bruising easily, nervousness, as well as swollen and stiff joints.

6.4.2.2 Clinical Presentation and Treatment

The patient suffered from severe bilateral temporal headaches every day that have lasted for weeks, moderate frontal and occipital headaches weekly, jaw pain on the right side while at rest, teeth clenching, bruxism, dry mouth, pressure behind the eyes, blurred vision, photophobia, pain in front of the ear, ear pain, lower back pain, neck pain, shoulder pain, and stiffness.

Clinical examination, as well as computerized (joint vibration analysis) examination, revealed left TMJ middle opening and middle closing click. Mandibular range of motion measurements revealed a maximum inter-incisal opening of 50 mm, maximum protrusive of 6 mm, and 12 mm right and left lateral excursion. Cervical range of motion measurements indicated right and left side rotation of 60°.

Intraoral examination of the teeth revealed narrow dental arches, maxillary and mandibular tori, existing veneers on the maxillary and mandibular anterior teeth, and missing teeth #1, 16, 17, and 32. There is a molar class I dental relationship with 2 mm overbite and overjet.

Severe tenderness was elicited upon palpation of the bilateral temporalis, lateral TMJ capsule, posterior joint space, masseters, sternocleidomastoid, anterior scalenes, middle scalenes, posterior scalene, occipital, splenius capitis, and trapezius. Radiographic evaluation revealed the left condyle is posteriorly and superiorly positioned. The MRI correlates with the CT showing the thinning of the left disc (Figs. 6.8 and 6.9). The diagnosis was left articular disc had displacement with reduction, bilateral capsulitis,

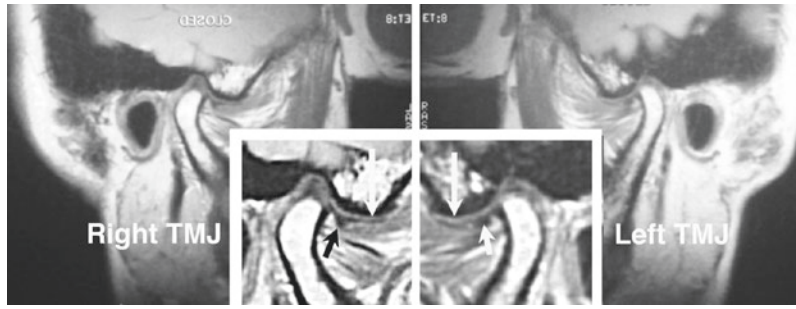

Fig. 6.8 MRI of blepharospasm patient (Case 5) reveals internal derangement of the articular disc in each TMJ. Long white arrows: apex of articular eminence in right and left TMJs. Dark arrow: points to an anteriorly displaced articular disc fragment in right TMJ. Small white: points to an anteriorly displaced articular disc fragment in left TMJ. Both condyles are resting on the posterior band area of the disc. The space between the left condyle and the articular eminence is narrow demonstrated by the thinning of the disc

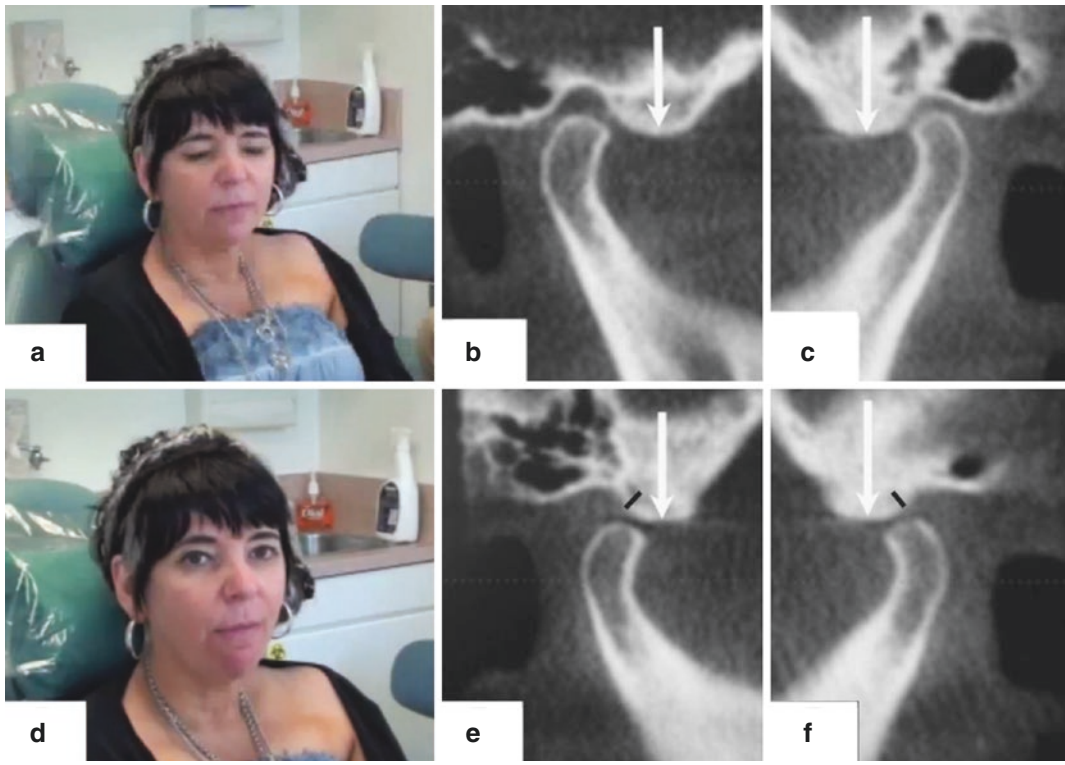

Fig. 6.9 A blepharospasm patient (Case 5) before (**a**) and (**d**) after insertion of an orthotic into her oral cavity. CT scan images of the right and left (**b**, **c**) temporomandibular joints in the patient before treatment. At the time of examination, demonstrating the mandibular condyle and articular eminence relationship, with the patient engaging her normal bite. There is flattening of the anterior surface of both condyles indicating the early stage of osteoarthritic changes (**a**, **b**). Note the narrow joint space on the left TMJ (**b**). The malrelationship is evident in the left joint, the left condyle being positioned posteriorly and superiorly in the infratemporal fossa. This causes compression of the retrodiscal tissue where the AT nerve is situated. The condyles are repositioned with the temporomandibular joints by the mechanical action of an intraoral orthotic that maintains a more anterior-inferior position of 3 mm vertical distraction (i.e., displacement) between the upper and lower jaws. CT scans at the time of orthotic delivery show the heads of the condyles more inferiorly and anteriorly with the oral orthotics (see **c**, **f** vs. **b**, **d**). For anatomical reference, arrows indicate the inferior limit of the articular eminence (also known as the articular tubercle) of the temporal bone in the TMJ. Dark line segments demarcate the preferred locations to place condylar heads in TMJ practice. It is important to emphasize that in this patient, the condylar heads were advanced beyond these usual locations, in order to suppress her blepharospasm symptoms

chronic tension-type headache, muscle spasm, crepitus, and bruxism.

6.4.2.3 Results

During the dental examination, one to four tongue depressors were placed at an angle across the mouth where she bit down on her molars on the left and bicuspids on the right. An immediate improvement of her blepharospasm symptoms was noticed. A dental appliance was fabricated to maintain the jaws in this resting position (Fig. 6.9a, d). At the 2-day follow-up visit, the patient reported that her headaches, neck, and shoulders were starting to relax. The joint pain in her hands, fingers, and elbows had subsided. At the 2-month follow-up visit, the patient reported reduction of migraine headaches from every day to once every 2 weeks and absence of wrist or joint pain, her eyes are more open, and she has not had Botox for 12 weeks. Before utilizing the oral orthotic, the patient typically received Botox injections every 8 weeks.

At her 2-month follow-up visit, the patient reported that her symptoms of the blepharospasm had improved and that everyone had noticed. Also, the patient reported that her headaches diminished in frequency. Her neck and shoulders continued to stay relaxed, and her joint pains in her elbows and hands stayed subsided. The oral orthotic was realigned by adding 2 mm of new material. This improved her symptoms further. The patient was last seen at an 18-month follow-up visit, complaining of waking with headaches every day and facial pain. Her orthotics were adjusted and relined due to new dental work of veneers and crowns. Jaw and neck stretches were recommended daily.

6.5 Strabismus

Strabismus is a disorder in which the two eyes do not line up in the same direction, and therefore do not look at the same object at the same time. The condition is more commonly known as "crossed eyes." It typically involves a lack of coordination between the extraocular muscles, which prevents bringing the gaze of each eye to the same point in space and preventing proper binocular vision, which may adversely affect depth perception. One eye may look straight ahead, while the other eye turns inward, outward, upward, or downward. Adult strabismus may have resulted from childhood, or they may acquire strabismus in adulthood possibly from a stroke, tumor, or trauma of the brain [56].

Within the brainstem is the medial longitudinal fasciculus (MLF), which connects cranial nerve 3 and cranial nerve 6 nuclei [57]. They terminate with the paramedian pontine reticular formation (PPRF). These areas control and integrate the extraocular eye muscle movement. The PPRF is located in the pons and is important for horizontal gaze and saccades. The PPRF receives input from the vestibular nuclei, cerebral cortex, cerebellum, superior colliculus, and the spinal cord. Neurons from the left vestibular nuclei send axons ipsilaterally through the MLF to excite the neurons of the left oculomotor nucleus and at the same time send axons contralaterally through the MLF to inhibit the neurons of the right abducens Nucleus [57].

Disturbances of these reflexes may therefore impart effects on the motoneurons of the eyes. The trigeminal nerve has input into both the cerebellum and the reticular formation. The inhibitory region of the reticular formation is of significant importance. When this region of the reticular formation loses its excitatory input from the cerebral cortex, the result is reduced inhibition of the descending excitatory connections to the spinal cord, thus producing increased motor neuron firing [58]. This increased firing may cause a change in extraocular muscles, which result in a disturbance of the equilibrium between these muscles, culminating with the presentation of strabismus. Removing the excitatory input into the RF and the cerebellum may allow normal coordination to recur, thus discontinuing the strabismus. The oral orthotic suppressed strabismus by decompressing irritated afferent fibers of the auriculotemporal nerve in the patient's TMJ, thus reducing aberrant excitatory input to the RF and cerebellum.

6.5.1 Case 6: Strabismus by Dr. Gary Demerjian

A 52-year-old female presented clinically with the following symptoms: unable to bite on her

back teeth, generalized tooth pain, jaw pain, facial pain, neck pain, shoulder pain, back pain, jaw locking, limited jaw opening, pain to chewing, fatigue, eye shaking and bouncing, and tingling hands. Her symptoms first appeared in 2000, while she was having dental work (crowns) on her molars. After several visits, when her bite did not feel normal with the new dental crown, she saw a bite specialist who adjusted her bite by an occlusal adjustment to her. Since then, she has seen numerous dentists who have further adjusted her bite and have given her dental splints. Her symptoms became worse after each new splint and/or adjustments of her teeth. She has seen several healthcare providers including neurologist and neuro-ophthalmologist for light sensitivity of the eyes, fatigue, eyes shaking and bouncing, difficulty with depth perception, coordination and balance issues, and difficulty breathing.

6.5.1.1 Clinical Examination and Treatment

Dental examination revealed bilateral crepitus on opening and closing and right TMJ middle opening click. Mandibular range of motion measurements revealed a maximum inter-incisal opening of 42 mm, maximum protrusive of 10 mm, 14 mm left lateral excursion, and 11 mm right lateral excursion. Her posture screening revealed a forward head posture, facial asymmetry, and right shoulder higher than the left. Intraoral examination revealed the tongue also retracts into the airway upon opening and upon closing, and there is bilateral posterior open bite. Periodontal examination revealed gingival recessions. Examination of the teeth revealed cervical erosion/abfractions and facets. There is a molar class I dental relationship with an overbite of 2 mm and overjet of 2 mm. Severe tenderness was elicited upon palpation of the bilateral middle temporalis, left posterior temporalis, right posterior joint space, left stylomandibular ligament, bilateral trapezius, left temporal tendon, bilateral medial pterygoids, and bilateral masseter origins. The CT scan of the maxillofacial examination revealed flattening of the anterior portion of both condyles, both condyle displaced posterior and superior (Fig. 6.10), and pharyngeal airway impingement. Her diagnosis was osteoarthritis, capsulitis, myalgia, and bruxism.

During the examination, three tongue depressors were placed at an angle touching the molars on the right and the bicuspids on the left. We noticed an immediate correction of the strabismus. A dental oral orthotic was fabricated to stabilize this position.

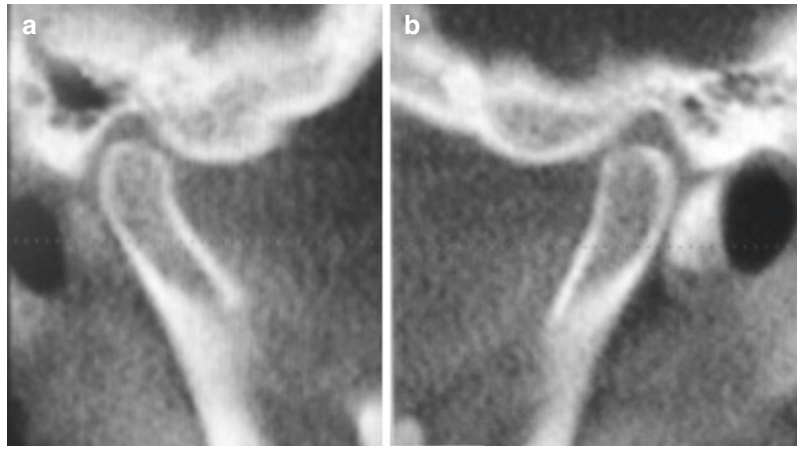

Fig. 6.10 CT scan of the right (**a**) and left (**b**) TMJs in a strabismus patient (Case 6) demonstrates a posterior relationship of the mandibular condyle to the infratemporal fossa. The right condyle flattening is seen on the anterior surface indicating the beginning of osteoarthritic changes (**a**). Note the narrowing of space between anterior surface of the left condyle and the articular eminence indicating thinning of the articular disc. The patient's strabismus improved with the insertion of the oral orthotic

6.5.1.2 Results

During the follow-up visit, 3 days later, the patient reported resolution of her symptoms of back pain, face pain, fatigue, inability to open her mouth, jaw clicking and popping, jaw lock, jaw pain, muscle twitching, neck pain, pain to chewing, shoulder pain, visual disturbance, and balance. Her mouth opening had improved from 42 mm to 57 mm. Right and left lateral movements had increased to 14 mm and protrusive to 12 mm.

She stated that she was able to walk and exercise better. She also reported being "fully connected," and being able to appreciate normal exteroceptive sensations again (e.g., hearing, smell, and taste). The numbness in her hands had resolved. The patient also reported that she has stopped "constant eating to wake up her brain." Three days after receiving her oral orthotic, her eyes were tracking together normally (Video 6.8). The patient reported more peaceful and restful sleep. After a few visits, the patient no longer returned for follow-up monitoring.

6.6 Gait Disorder

A state of equilibrium or equipoise is the definition of balance whether it is an upright posture (static balance) or in locomotion (dynamic balance or gait). An individual's surroundings depend on various systems such as vision, vestibular, and proprioception to maintain this balance. In addition, the dental (stomatognathic) system may also contribute to balance and balance disorders [59–62].

The central nervous system (CNS) organizes motor systems in the cerebral cortex, brainstem, spinal cord, cerebellum, and basal ganglia. The brainstem and spinal cord motor muscles receive input from the cerebral cortex. Descending motor pathways within the brainstem modulate the motor activity within the spinal cord. It processes and coordinates the neural signals received from the cortex and cranial nerves such as the vestibular and trigeminal nerves. The spinal cord is involved in automatic and stereotypic motor reactions to peripheral stimuli known as reflexes. The maintenance of the body posture in a human being relies on these myotatic reflexes to maintain balance. The basal ganglia receive input from all cortical levels, process the information, and then send output to the premotor and motor areas of the cerebral cortex to initiate and stop movements. The cerebellum helps regulate fine movements and posture including eye movements and balance. Another area that is not relatively thought of in balance is the reticular formation, which integrates various kinds of information including actions on skeletal muscles. The reticular formation thus has important inhibitory and excitatory input when it comes to disturbances of postural reflexes. This increased firing then results as a change of muscle tension in postural muscles usually manifested as a disturbance of the equilibrium [7].

Selective control of reflex arcs has been exhibited by trigeminal afferent neurons, particularly from the spinal tract of V directly to the nucleus raphe of the reticular formation (1). Without this reticulospinal activity, voluntary activity occurring over the corticospinal tract is unable to initiate motor movement (2). If the trigeminal nerve gives excessive abnormal physiological neuronal stimulus, this may cause interference with the normal conduction of impulses from the cerebral cortex via the reticular formation and therefore producing enough neuronal stimuli to initiate the involuntary movements that cause balance disorders [63].

The cerebellum has afferent connections from the vestibular nuclei, the cortex, the spinal cord, and the reticular formation [7]. Information from proprioceptive sensory receptors can also reach the cerebellum from the trigeminal nuclei via the trigeminal cerebellar tract. The cerebellum influences movements by acting on neuronal pathways (the pyramidal tracts, the reticulospinal tracts, and the vestibulospinal tracts). These pathways control the activity of the spinal and cranial nerve motor neurons [7]. Damage to or a lesion within any of these pathways primarily produces a change of muscle tone or postural reflexes.

Displacement of the mandibular condyle into the glenoid fossa causes excess stimuli upon the retrodiscal tissues with its complex of blood

vessels and the auriculotemporal nerve fibers where sensitization occurs [64]. Impulses travel along the mandibular division of the trigeminal nerve and enter the spinal nucleus of V, which stimulates the reticular formation (nucleus raphe and the medial reticular nuclei), which begins to initiate an inhibitory effect on cerebral cortex, thus decreasing its voluntary control. Multiple studies concerning the maxillary-mandibular relationship show that there are positive and negative influences on a patient's posture when the proper vertical dimension is altered [59–62]. Therefore, when the proper vertical dimension was restored, the inhibitory effects on the cortex was discontinued. Normal voluntary control appeared to be reestablished, as the patient's are able to sustain a normal gait pattern without loss of balance.

6.6.1 Case 7: Gait Disorder by Dr. Anthony Sims

A 76-year-old female retired patient presented to the clinic with multiple diagnoses of vertigo with spatial disorientation, congestive heart failure, shortness of breath difficulties, diabetes, right rotator cuff that would not allow hand to be raised above the shoulder, right eye blurriness, tearing, and diplopia with photophobia and was given a diagnosis of multiple sclerosis by her neurologist. The patient had difficulty standing and would fall down continuously. She had shoulder pain, neck pain and tingling that extended to fingertips, tremors of hands, and hip problems that required her to use a hand walker or wheelchair. The patient was in a motor vehicle accident in 2004 and fractured five ribs and dislocated three vertebrae. Multiple tests were given including MRI of brain, CT scans, blood tests, EEG, EKG, and a visual potential study. No abnormalities in the brain or brainstem were found. The CT scan was normal, EEG was within limits, EKG was normal, and vision was 20/20 with corrective lens. Blood work-up determined that diabetes was present, along with high blood pressure. The patient's medications were Lipitor, Lasix, prednisone, Cozaar, Toprol XL, Bayer aspirin, Aranesp injections, Novolin, Zetia, potassium, clonidine, and Motrin. The patient underwent nerve blocks for spine pain and rotator cuff and eye surgery. Physical therapy was given and ongoing for arms, hands, and gait disorder. However, after physical therapy, the patient's arm range of motion, weakness, and gait disorder persisted.

Clinical evaluation revealed right and left retro-orbital pressure/pain, tinnitus in left ear, left preauricular pressure, the inability to open mouth with the required 50 mm (normal opening), difficulty chewing food with a constant throat clearing, and pain on the right and left side of the neck with limited mobility. The patient has been edentulous for 10 years. The vertical dimension of occlusion was collapsed, and the patient did not wear her lower dentures. There were 42 points of face and neck muscle palpation that provoked pain. The patient had the following disabilities: decreased ambulatory ability (full-time walker), positive Romberg test in less than 5 seconds, could not walk up- or downstairs without falling, unable to turn 90 degrees without loss of balance, and unable to walk backward without loss of balance.

A temporary oral appliance was fabricated for upper and lower edentulous ridges, and proper vertical dimension of occlusion was then established. Once the correct dimension was provided, the patient was able to raise hands above her head, and the tingling in the hands stopped. The face and neck pain discontinued. The Romberg test was negative, and the patient was unable to turn 180° without falling. Patient was then given an ambulatory test without her walker, and she was able to show a steady gait around the office. The oral orthotic was then removed, and patient showed loss of balance upon turning and walking. The oral orthotic was then returned to the patient, and she was asked to walk backward and then up a flight of stairs, which she did without hesitation and/or falling.

6.7 Parkinson's Disease

Balance control is accomplished by an autoregulating reflex reaction with inputs from the sensory systems of the eyes, ears, muscles, and

joints. Additionally, organismic balance relies on the brain and the brainstem's ability to process this information. If balance control is abnormal, the human nervous system must exert conscious effort to control balance. This leads to compensatory symptoms. Determining the cause of a balance disorder and what treatment options are appropriate may be diagnostically difficult, because of the existence of underlying medical conditions. Ear infections, blood pressure changes, vision problems, and medications contribute to balance disorders [65]. Medical conditions such as multiple sclerosis, stroke, and Parkinson's disease can contribute to balance disorders. There are motor systems in the central nervous system (CNS), which are organized in the cerebral cortex, brainstem, spinal cord, cerebellum, and basal ganglia. The cerebral cortex contains the motor areas from which commands originate that go to the brainstem and spinal cord and activate voluntary muscle movement. The brainstem contains descending motor pathways that modulate the motor activity within the spinal cord. It processes and coordinates the neural signals received from the cortex, the cranial nerves (vestibular, trigeminal, etc.), and sensory neurons [7].

Disturbances of postural reflexes are due in part to the effects on the motoneurons distributed by the vestibulospinal and the reticulospinal tracts. The inhibitory region of the reticular formation is of significant importance. When this region of the reticular formation loses its excitatory input from the cerebral cortex, the result is reduced inhibition of the descending excitatory connections to the spinal cord, thus producing increased motor neuron firing [63]. This increased firing then results as a change of muscle tension in postural muscles usually manifested as a disturbance of the equilibrium.

The midline raphe nuclei are regarded as a major portion of the brainstem's reticular formation. The reticular formation has been divided into multiple subsets (medial reticular nuclei, reticularis gigantocellularis, reticularis pontis, reticularis caudalis, and others), and portions of these subsets have always been regarded as playing a role in pain-producing stimuli [66, 67]. Efferent functions of the reticular formation produce postural reflexes and righting reactions and play a critical role in phasic movement and in maintenance of muscle tone. Trigeminal afferent neurons project directly to the nucleus raphe of the reticular formation and exhibit selective control of the responses (reflex arcs) to their input [68]. The trigeminal cerebellar tract arises for the spinal nucleus of V and the chief sensory nucleus of the trigeminal nerve and then terminates in the cerebellum via the inferior cerebellar peduncle. The cerebellum does not initiate movement, but it contributes to coordination, precision, and accurate timing. Because of this fine-tuning function, damage to the cerebellum does not cause paralysis but instead produces disorders in fine movement, equilibrium, posture, and motor learning [13, 69].

Damage or pathology to the cerebellum does not only involve structural alterations (e.g., tumors, strokes, or physical trauma) but also involves changes in the electrical postsynaptic potential (PSP)**.** The medial zone of the anterior and posterior lobes constitutes the spinocerebellum, also known as paleocerebellum. This sector of the cerebellum functions mainly to fine-tune body and limb movements. It receives proprioception input from the dorsal columns of the spinal cord (including the spinocerebellar tract) and from the trigeminal nerve. It sends fibers to deep cerebellar nuclei that, in turn, project to both the cerebral cortex and the brainstem, thus providing modulation of descending motor systems [70]. Changes in the PSP of the reticular formation and the trigeminal nerve also change the PSPs that regulate theta rhythms in Purkinje cells [71]. When these changes occur, it may be possible that the coordination of the cerebellum's equilibrium, posture, and motor movement controls is disrupted.

A constant neuropathy or neuroinflammation in the trigeminal nerve has the potential to alter normal functions of the cerebellum and to induce balance and motor symptoms. The two Parkinson's disease patients presented here had definite TMJ pathologies. It was concluded from the diagnosis of their neurologists that these patients also probably have a definite degenera-

tion of their substantia nigra. It is remarkable that their motor dysfunctions improved so rapidly upon utilizing oral orthotics to reposition their jaws. Aberrant afferent drive from the trigeminal nerve into the brainstem may interfere significantly with proprioception in patients with Parkinson's disease. Removal of aberrant afferent drive may relieve dysfunctions that are generated by the abnormal proprioception processing, which is taking place in the basal ganglia of Parkinson's disease patients.

6.7.1 Case Study 8: Parkinson's Disease by Dr. Gary Demerjian

6.7.1.1 Patient History

A 70-year-old male presented for evaluation of daily sinus congestion, visual disturbance, and fatigue. He complained of frequent occipital, frontal, and temporal headaches, shoulder pain, frequent heavy snoring, significant daytime drowsiness, and breathing abnormalities. Patient reported having symptoms of migraines in the mornings, which started 40 years ago. The fatigue is due to the diagnosis of sleep apnea from a polysomnogram in 2003. Continuous positive airway pressure therapy was attempted, but the patient was unable to tolerate it. He had a sleep pattern of resting 4–5 hours a night and awakening three to four times per night. Patient was also diagnosed with diplopia and treated for an allergic sinus condition that was evaluated by an ENT. The patient was diagnosed with Parkinson's in 1997. In 2005, deep brain stimulation (DBS) surgery was attempted in this patient but was discontinued due to hemorrhaging. The patient stated that after the attempted surgery, he began to drool constantly. He has developed heartburn, dizziness, tingling, tremors in the hands and feet, and a balance disorder. The patient has had deep vein thrombosis in his left calf, carpal tunnel surgery, and cataract surgery. The patient's daily medications are Sinemet 10/100, Sinemet 25/100 CR, Requip 0.5 mg, Lorazepam 0.5 mg, Omeprazole 20 mg, and Fluticasone 50 mg spray.

6.7.1.2 Clinical Examination and Treatment

Dental examination revealed right TMJ middle opening and closing click, and his mandibular range of motion measurements showed a maximum inter-incisal opening of 50 mm, maximum protrusive of 1 mm, left lateral excursion 5 mm, and right lateral excursion of 7 mm. The patient exhibited a forward head posture and facial asymmetry.

Intraoral examination revealed scalloped lateral borders and fissures on the tongue that also retracts into the airway upon opening. He presents with Mallampati airway scale of class three, elongated uvula, and loss of tone of the soft palate. Examination of the patient's dentition revealed wear facets due to bruxism, gingival recessions, and a cross bite of the lower left lateral teeth. There is a molar class I dental relationship. Severe tenderness was elicited upon palpation of the bilateral temporalis, lateral TMJ capsule, posterior joint space, masseters, stylomandibular ligament, temporal tendon, medial pterygoid, and posterior digastric muscles. The CT scan of the maxillofacial examination revealed flattening of the anterior portion of both condyles, both condyles displaced posterior and superior (Fig. 6.11), pharyngeal airway impingement, and mandibular antegonial notching. The patient was diagnosed with arthralgia and osteoarthrosis of the TMJ, myalgia, and disc displacement.

During the patient's evaluation, four tongue depressors were placed bilaterally across the occlusal surfaces of the anterior bicuspids. An immediate improvement of his Parkinson's symptoms was noticed. A dental oral orthotic was then fabricated to stabilize this position of the jaws, and a dental sleep appliance was fabricated for his diagnosed obstructive sleep apnea.

6.7.1.3 Results

On follow-up visits, the patient reported that his symptoms of headaches had resolved, fatigue had improved by 50%, and sinus congestion improved 30–50%. There was no change in his vision; however, his balance and gait had improved greatly. His wife stated that he is more energetic

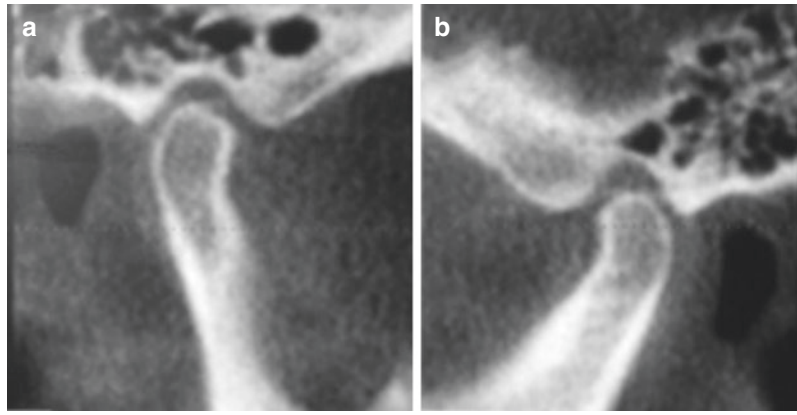

Fig. 6.11 CT scan of the right (**a**) and left (**b**) TMJs in a Parkinson's disease patient (Case 8) demonstrates a posterior-superior relationship of the mandibular condyles to the infratemporal fossa. Note the flattening on the superior surface of the right condyle, which indicates an early stage of osteoarthritis. This patient's tremors and gait disorder were suppressed by an oral orthotic (Videos 6.10 and 6.11)

and is able to walk 2 miles without assistance. She was able to be away from the house, because of his mobility improvements. Documented follow-up visits of 3 years showed that his Parkinson's disease did not progress and/or was minimal.

6.7.2 Case Study 9: Parkinson's Disease by Dr. Gary Demerjian

6.7.2.1 Patient History

A 46-year-old female presented with complaints of a limited mouth opening, ear congestion, headaches, neck pain, shoulder pain, stiffness, lower back pain, and fatigue for years. She reported that the stiffness in her neck and back has been causing pain in shoulders and occipital headache for the past year and a half on a weekly basis. The patient has been diagnosed with Parkinson's disease since 1996. Her Parkinson's symptoms are right side tremors, lack of coordination, lack of balance, shortness of breath, stiffness, rigidity, slowness of movements, slowness to communicate, numbness of legs, right leg foot drop, and the feeling of brain fog. During the past 5 years, she has experienced a loss of hearing and now wears hearing aids. She reports decreased sleep and tiredness during the day. The patient's current medications are Sinemet 25/100 QID, Amantadine 100 mg BID, and Celexa 40 mg once a day.

6.7.2.2 Clinical Examination and Treatment

Clinical examination revealed left TMJ problems, including early opening and early closing click, as well as a deviation of the mandible to the left upon opening. Mandibular range of motion measurements revealed maximum inter-incisal opening of 40 mm, maximum protrusive of 6 mm, a 10 mm left lateral excursion, and a 9 mm right lateral excursion. The patient has facial asymmetry and forward head posture, and her right shoulder is significantly higher than left shoulder.

Examination of the patient's dentition revealed wear facets, cervical erosion, and gingival recession. There is a molar class I dental relationship with seven extracted teeth including her four wisdom teeth. Tenderness was elicited upon palpation of the right TMJ, sternocleidomastoid and temporal tendon, left temporalis, middle scalene bilaterally, right and left masseter, right and left posterior digastric, and occipital muscles. A CT scan of the maxillofacial examination revealed flattening of the anterior and superior portion of left condyle, posterior flattening of the right

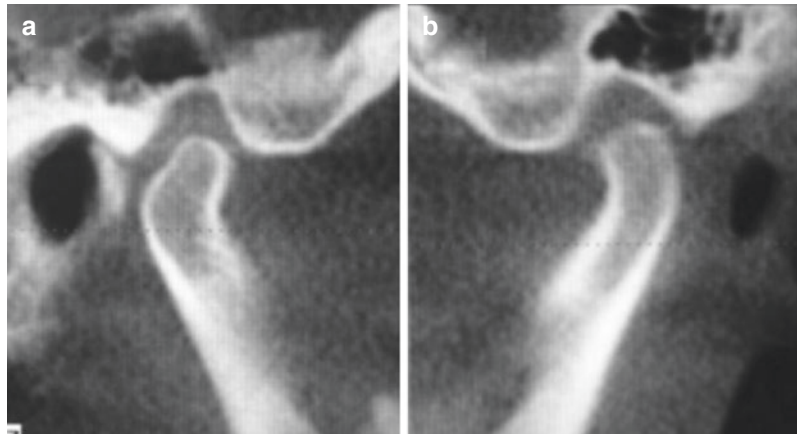

Fig. 6.12 A computer tomography (CT) scan of the right (**a**) and left (**b**) condyle in a second Parkinson's disease patient (Case 9). The right condyle has flattening of the posterior surface (**a**). The left condyle (**b**) has flattening of the anterior surface and is displaced posteriorly. The osteological abnormalities are different from the Parkinson's patient of Case 8 (see Fig. 6.11). However, a pathological constriction of retrodiscal tissues, caused by a malposition of condylar heads, is seen in both patients

condyle, bilateral condylar displacement posteriorly (Fig. 6.12), antegonial notching, bone deposition at the gonial angle, and pharyngeal airway impingement. During the patient's initial evaluation, four tongue depressors were placed as in the previous case, and video documentation of her gait was taken. The patient was diagnosed with disc displacement with reduction, myalgia, and limited opening. Her oral orthotic was fabricated to that new position.

6.7.2.3 Results

At delivery of the oral orthotic, an increase in upper body strength was noticed, along with improvement in gait, coordination, and balance. She began taking deeper breaths and stated that her shoulder pain level decreased by 50% within 5 min.

A clinical test was performed to evaluate strength in the patient's shoulders. The patient was asked to extend her arms horizontally and to resist downward pressure applied to her arm. Light-to-moderate pressure was applied to the wrists of the patient. Before the orthotic, she was unable to resist this downward pressure. The custom-made oral orthotic was then inserted into the patient's mouth. Pressure was reapplied. The patient was now able to resist moderate-to-strong pressure applied to her wrists. Thus, the paresis in the patient's arms appeared to be a functional weakness. This functional weakness was eliminated when using the oral orthotic.

Follow-up visits revealed the patient's symptoms of headaches, neck pain, shoulder pain, and ear congestion had resolved, fatigue improved by an estimated 90%, with balance and gait improved. Her mouth opening range of motion increased to 56 mm. After 6 months of wearing the TMJ appliance, it was determined to slowly tapered the use of the oral orthotic to nighttime use only. Her improvements have remained the same. She was advised to use the appliance during the day as needed.

At the 3-year and 10-month post-delivery appointment, she still reports sustained benefit from the oral orthotic. She reported absence of pain and having sustained clarity of thought. Her balance, coordination, and gait remained improved.

6.8 Chronic Obstructive Pulmonary Disease

The response of the next patient is particularly surprising because COPD, or chronic obstructive pulmonary disease, has been long considered to be a progressive, irreversible, respiratory disease. COPD can cause coughing that produces large amounts of mucus, wheezing, shortness of breath,

chest tightness, and other symptoms. Most people who have COPD smoke or have a history of smoking. COPD is a major cause of disability, and it is the third leading cause of death in the United States. Most cases of COPD occur as a result of long-term exposure to lung irritants that damage the lungs and the airways. The signs and symptoms of COPD include (a) an ongoing cough that produces large amounts of mucus (often called "smoker's cough"); (b) shortness of breath, especially with physical activity; (c) wheezing; and (d) chest tightness [72, 73].

In COPD, obstruction due to airway inflammation and excess mucus occurs in the airways of the lung (called bronchi and bronchioles), leading to decreased airflow. This ultimately results in decreased amounts of oxygen delivered to the body's tissues. In emphysema, there is also destruction of the alveoli (tiny sacs where oxygen and carbon dioxide exchange takes place). Emphysema and chronic bronchitis may both be present in an individual at the same time. COPD is one of the leading causes of death in developed nations and affects both men and women.

Studies have shown that neurons with respiratory movement-related activity are found in several regions of the reticular formation and are concentrated in the ventrolateral medullary RF, which is called the ventral respiratory group (VRG) [7]. The VRG contains both inspiratory and expiratory neurons and is responsible for motor control of these muscle groups during activity [74]. The network that participates in respiratory control involve (1) several clusters of cells dispersed in the pontine RF known as the pontine respiratory group (PRG) consisting of the parabrachialis medialis and Kolliker-Fuse nuclei, (2) the accessory respiratory motor nuclei (hypoglossal, vagal, facial, and trigeminal), and (3) the central respiratory rhythm pattern generator so-called the pre-Botzinger complex [7]. The VRG receives signals from the thoracic cage and the lungs about the degree of expansion and from chemoreceptors about blood pH and CO_2 content [75]. This information modulates the activity of the rhythm generator, without being necessary for the maintenance of breathing [76].

The autonomic nervous system controls ventilation, and the pattern of motor stimuli during breathing is divided into inspiratory and expiratory phases. Within the medulla, the VRG controls voluntary forced exhalation and acts to increase the force of inspiration, while the dorsal respiratory group controls mostly inspiratory movements and timing. Within the pons the pneumotaxic center coordinates the transition between inhalation and exhalation and sends inhibitory impulses to the inspiratory area. It is involved in the respiration rate. The apneustic center of the pons sends stimulatory impulses to the area and prolongs inhalation. This center is overridden by pneumotaxic area to end inspiration [77]. Blood levels of carbon dioxide and oxygen determine the hypoxia and the metabolic rate. These levels are sensed by chemoreceptors in the medulla for pH, the carotid, and the aorta. The effects are mediated by reticulospinal fibers acting on preganglionic sympathetic neurons and fibers to the brainstem and preganglionic parasympathetic neurons from the glossopharyngeal and vagus nerves [78]. In addition, the nasopulmonary and nasothoracic reflexes regulate the mechanism of breathing through deepening the inhalation process. Triggered by the flow of the air, the pressure of the air in the nose, and the quality of the air, impulses from the nasal mucosa are transmitted by the trigeminal nerve to the breathing centers in the brainstem, and the generated response is transmitted to the bronchi, the intercostal muscles, and the diaphragm [79]. Respiratory-modulated trigeminal and hypoglossal discharges are dependent upon reticular mechanisms [78]. Afferent influence of the trigeminal nerves moderately inhibits activity of the respiratory center in quiet breathing. Blockade (or lesion) of the trigeminal nerves entails an increase by 20–30% of lung ventilation, owing to a cessation of the tonic influence and of the impulses induced by stimulation of the nose cavity receptors with air stream [79]. This results in shortened or decreased ventilation.

When this patient's mandible was realigned inferiorly and anteriorly by an oral orthotic, multiple physiological factors were addressed.

First, the pharyngeal airway was mechanically opened, thereby allowing a greater influx of air to enter into the lungs. A loss of vertical dimension of occlusion resulted due to the lack of posterior support as a consequence of multiple molar extractions. Because of this, the force vectors placed on the patient's mandible by contraction of the temporalis and masseter muscles were posterior and superior, thus a decreasing closure of the airway. It is well-known that restricted ventilation alters the O_2/CO_2 pH ratio within the blood and signals chemoreceptors in the medulla, carotid, and aorta [7]. Secondly, jaw realignment removes compression of the auriculotemporal nerve, which projects into the reticular formation. When aberrant signals from the AT nerve are discontinued, a normalization of the central pattern generator for inspiration and exhalation is renormalized in the VRG of the reticular formation. Clinically, it is observed that patients often initiate a large inspiration, soon after they clench on a properly designed oral orthotic. In this case, the patient remarked that she could breathe better after using the orthotic for a few minutes.

6.8.1 Case 10: Chronic Obstructive Pulmonary Disease by Dr. Anthony Sims

6.8.1.1 Patient History

A 63-year-old female presented to the clinic with a diagnosis chronic obstructive pulmonary disease (COPD) with shortness of breath and coughing with wheezing and had been a long-term tobacco user but no longer smoked. She also presented with chronic hypertension, migraines 2× per week, gastroesophageal reflux disease, and chest tightness. Her chief complaint over the past 5 years was joint pain in her left knee, pain, tingling, and slight swelling in her right hand. She has had a previous rotator cuff surgery. Her current medications are Imitrex, Celebrex, Symbicort, Actonel, Lisinopril, and vitamin D. She was told to obtain long-term insurance because the pulmonologist believed her symptoms would deteriorate further.

6.8.1.2 Clinical Presentation and Treatment

The office evaluation showed symptoms of cephalgia, right retro-orbital pain, photophobia, vertigo and loss of equilibrium, right ear stuffiness with preauricular pressure and pain, right and left cheek bone pain, right and left popping noises in the temporomandibular joint upon protrusion, maxillary and mandibular odontalgia, and right side neck and shoulder pain. She had an 8 mm overbite and a 9 mm overjet with a 3 mm mandibular deviation to left of 3 mm. The MRI report stated bilateral degenerative changes of the condyle and meniscus with anterior displacement without recapture on the right and recapture on the left only in the open mouth view (Fig. 6.13). Patient had partial dentures made by previous dentist to the dentition she had approximately 7 years prior. A lateral skull X-ray was taken which showed a smaller than normal pharyngeal airway in conjunction with the odontalgia. Treatment goals were to normalize the maxillary-mandibular relationship by increasing the vertical dimension and placing the mandible in a more anterior-inferior position, and thus reducing the neuropathy within the TMJ. A new oral orthotic was built to these new dimensions.

6.8.1.3 Results

After jaw realignment with the oral orthotic, the patient's hand and knee pain, swelling, and tingling symptoms discontinued. At 3 months after treatment, the frequency of her migraines diminished to less than 1/month. She was able to raise her arms and hands above her head without pain. Patient's airway was expanded, and her breathing improved. Within less than 1 year, her pulmonologist stated that her COPD was not present any longer and that she only needed an inhaler for emergencies (Video 6.15).

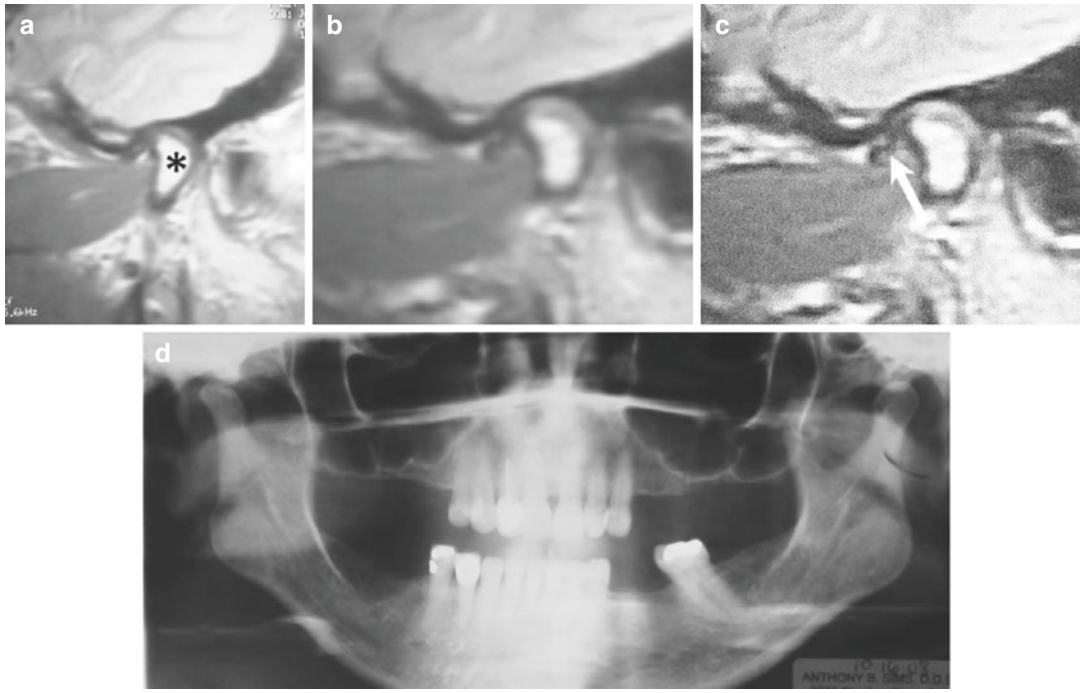

Fig. 6.13 Chronic obstructive pulmonary disease (COPD) patient (Case 10). The MRIs (**a**–**c**) and panoramic X-rays (**d**) of the Case 10 patient show bilateral anterior displacement of the menisci (dark sinusoidal tissue marked with white arrow in panel **c**) of the temporomandibular joints, as well as distal displacement and erosion of the condyles (condylar head in A marked with an asterisk). Image quality in Panel **c** has been enhanced using unmask sharp image processing. The dark line between the condylar head and the convolutions of the brain is the temporal bone of the skull. Retrodiscal tissues have been displaced to the superior surface of the condylar head. During articulation of the jaws, a compression of auriculotemporal nerve endings in the retrodiscal tissues is likely to induce an excitation of the trigeminal nerve, which has projections to brainstem regions of the reticular formation. These centers include the ventrolateral medullary area, which is called the ventral respiratory group [7]. This group of neurons of the reticular formation influences the inspiratory and expiratory motoneurons that innervate intercostal muscles

Conclusions

The trigeminal nerve is the largest of the cranial nerves and has three major branches: the ophthalmic nerve (V1), the maxillary nerve (V2), and the mandibular nerve (V3). There are separate pathways for touch/position sensation and pain/temperature sensation. When there is a disturbance, such as trauma to the nerve, signal transmission becomes abnormal within its afferent pathways. Aberrant sensitization of these afferent pathways creates different neurological and neuropsychiatric disorders. The trigeminal (CN V) interacts with many portions of the CNS. It connects not only with the four nuclei in the reticular formation but also the cerebellum, which is possibly the cause of certain ataxias. CN V connects with the trigeminal subnucleus caudalis, which is possibly a center for the different manifestations of Tourette's syndrome and for blepharospasm. Through its connection with the reticular formation, inflammation of CN V may be involved in the symptoms for many sensory and motor disorders. All divisions of CN V must be considered when analyzing the pathologies of patients. V1 and V2 may be sources of CN V neuropathies as well. Following a peripheral neuropathy, a patient's symptoms may be generated by afferent signals processed in a brainstem that

may have focal sites of neuroinflammation [40, 52]. The dental treatment protocol using oral orthotics involves a vertical distraction of a dysfunctional temporomandibular joints. This therapeutic approach offers a non-invasive means of treating a variety of movement and neuropsychiatric disorders, which may be linked directly, or indirectly, to TMJ dysfunction.

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Dr. Anthony B. Sims also receives financial remuneration from patients for the construction and fitting of the oral orthotics.

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7 The Relationship of Temporomandibular Joint, Orofacial Pain, and Sleep Apnea

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Abbreviations

AHI	Apnea hypopnea index
BMI	Body mass index
CH	Cluster headache
HH	Hypnic headache
ICSD	International Classification of Sleep Disorders
OSA	Obstructive sleep apnea
OSAS	Obstructive sleep apnea syndrome
PH	Paroxysmal hemicrania
PSG	Polysomnography
RDC	Research diagnostic criteria
REM	Rapid eye movement
RLS	Restless legs syndrome
SB	Sleep-related bruxism
SRBD	Sleep-related breathing disorders
TMD	Temporomandibular joint disorder
TMJ	Temporomandibular joint
TTH	Tension-type headaches

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7.1 Diagnosis of Sleep Disorders

The *International Classification of Sleep Disorders* (ICSD) is a primary diagnostic, epidemiological, and coding resource for clinicians and researchers in the field of sleep and sleep medicine. The recently released third edition of the ICSD is a fully revised version of the American Academy of Sleep Medicine's manual of sleep disorders nosology, published in cooperation with international sleep societies. It is the key reference work for the diagnosis of sleep disorders. The ICSD-3 is built on the same basic outline as the previous editions, identifying seven major categories that include insomnia disorders, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, sleep-related movement disorders, parasomnias, and other sleep disorders [1].

7.2 Sleep-Related Breathing Disorder

Sleep-related breathing disorders (SRBD) consist of conditions like OSAS, central sleep apnea syndrome, central alveolar hypoventilation syndrome, and primary snoring. OSAS is the most prevalent of these disorders both in children and adults. Risk factors for SRBD included waist circumference and nasal abnormalities (e.g., chronic sinusitis/rhinitis, deviated septum, large termi-

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nates). A strong linear relationship between waist circumference and body mass index (BMI) across all degrees of severity is observed as well [2]. The AHI is equal to the average number of episodes of apnea and hypopnea per hour and must be based on a minimum of 2 h of sleep recorded by polysomnography using actual recorded hours of sleep (i.e., the AHI may not be extrapolated or projected). Two hours of recorded sleep is consistent with current practice. Apnea is defined as a cessation of airflow for at least 10 s. Hypopnea is defined as an abnormal respiratory event lasting at least 10 s with at least a 30% reduction in thoracoabdominal movement or airflow as compared to baseline and with at least a 4% oxygen desaturation. OSA severity is defined as mild for AHI ≥ 5 and < 15, moderate for AHI ≥ 15 and ≤ 30, and severe for AHI >30/h. In the general adult population, the SRBD prevalence (AHI > 5) is estimated as high as 9 and 24% among women and men aged 30–50 years, respectively. Investigators found that 2% of women and 4% of men meet the minimum diagnostic criteria for OSAS (an AHI > 5 and daytime hypersomnolence). Male sex and obesity are strongly associated with the presence of SRBD. Habitual snorers, both men and women, tend to have a higher prevalence of AHI > 15. Thus, a detailed history and clinical examination have a key role in the diagnosis and assessment of OSAS. In a practice diagnosing and managing orofacial pain, a sleep history is vital in your decision-making process and when necessary testing.

The mechanisms underlying OSAS are complex. During sleep in general, upper airway dilator muscles are relaxed (loss of tone) which may lead to airway collapse and obstruction in at-risk patients for OSAS. In addition, narrowed upper airways, due to either local fat deposition or abnormal bony morphology (craniofacial underdevelopment), are common among OSAS patients. An equal decrease in both tonic and phasic contraction of the dilating muscles of the upper airways during sleep has also been observed in OSAS patients, compared to healthy controls. Upper airway diseases, nasal obstruction, and hypertrophy of tonsils are thought to contribute to OSAS. A variety of defective respiratory control mechanisms, including impaired chemical drive, defective inspiratory load responses, and abnormal upper airway protective reflexes, may also play a role. Arousal (change in brain wave pattern for 3 s) is key for the termination of each apnea. Several classic neurotransmitters and a growing list of neuromodulators have now been identified that contribute to neurochemical regulation of pharyngeal motor neuron activity and airway patency. Several risk factors have been recognized, among which the most important are obesity, male sex, middle age (40–60 years), cigarette smoking, alcohol intake, narcotics (chronic pain management), and benzodiazepines before bedtime [3].

The pathophysiology underlying OSAS in children may differ from that of adults. Commonly, it is secondary to adenotonsillar hypertrophy and can be cured by tonsillectomy in the absence of other coexisting causative factors. Additionally, one should consider obesity and sleep habits along with anatomical and neuromuscular parameters as key factors associated with OSAS in children [4].

7.3 Pain and Sleep

Pain in the head and neck region can have many contributing factors, but we want to focus on TMJ pain, acute and chronic. Acute pain is when the pain lasts for 3–6 months in duration. Acute TMD pain can be attributed to a recent event or trauma that occurred, which causes the pain. Causes of acute trauma can occur from a blunt force trauma to the jaw, any dental or surgical procedures that could have stretched the ligament of the temporomandibular joint (TMJ) and the tendons of the associated muscles. This can cause inflammation of the area, muscle spasms and if the posterior attachment of the TMJ is injured where it causes clicking or popping as the mouth opens and closes. As the joint functions where the disc is recapturing, there may be pain involved as the auriculotemporal nerve is getting pinched between the mandibular condyle and the articular fossa. Acute TMD pain is typically localized and sharp in nature.

Chronic TMD pain is when the pain and condition lasts more than 12 weeks. This pain is typically spread out over several areas of the head and neck as the muscles adapt and compensate to the changes of the joint. This pain is typically described as a dull, nagging, or an aching type of pain.

Research in this area, is complicated by the use of many different noxious stimuli making comparisons difficult [5–10]. The physiological responses to these stimuli ranged from minor to quick awakening to a full conscious, vigilant state. Brain response to stimuli is based on the type and intensity and the stage of sleep involved. An important point to clarify is that pain is associated with the conscious processing of a potential harmful experience during wakefulness and during sleep occurs at a subconscious level.

Lack of continued sleep is defined as sleep fragmentation. Cyclic alternating pattern is often seen during sleep fragmentation as a reaction of the brain and autonomic nervous system to preserve sleep quality and allostasis [11].

7.3.1 Sleep Breathing Disorders

Sleep breathing disorders and particularly OSAS are one of the most overlooked factors causing headaches. Some OSAS patients experience headaches, typically upon waking up and only rarely during sleep. Headaches in OSAS have mainly features of tension-type headaches (TTH) or vascular-type headaches such as migraine and CH. Chronic migraine, TTH, and CH have all been associated with sleep fragmentation. Globally, the percentage of the adult population with an active headache disorder is 47% for headache in general, 10% for migraine, 38% for tension-type headache, and less than 1% for cluster headache [12]. This comorbidity is believed to be based on common neurophysiological mechanisms and neurotransmitter systems, involving the hypothalamus, serotonin and melatonin neurotransmission [13]. OSAS, which causes sleep fragmentation, is the same as having insomnia, which has been associated with increased pain levels. The intermittent hypoxia due to sleep apnea is also linked to elevated inflammatory markers, including proinflammatory cytokines known to sensitize nociceptors and contribute to hyperalgesia [14]. Sleep disturbance directly affects central sensitization and pain amplification [15]. A well-controlled study found REM sleep deprivation increased thermal pain sensitivity [16]. Also, in two investigations, Onen and Kundermann found evidence of sleep deprivation inducing hyperalgesia [17, 18].

7.3.2 OSAS and Tension-Type Headache

TTH is by far the most prevalent primary headache in the general population, but its relationship with OSAS has been little investigated and thus poorly understood. Furthermore, it is not known whether TTH is more frequent in OSAS patients than the general population. Evidence from polysomnography studies among headache patients indicates that the largest part of TTH patients with OSAS is suffering from chronic TTH or mixed headache [19].

Vendrame M, performed a polysomnographic study in children and found no association between OSAS and TTH but revealed an association of OSAS with bruxism [20]. On the other hand, Carotenuto M and his group observed that chronic TTH might trigger OSAS in children [21].

7.3.3 OSAS and Migraine

In a few polysomnographic studies, migraine headaches were more frequently reported by OSAS patients, and particularly women, but there are no available data on the comorbidity of migraine and OSAS in larger samples of the general population [22]. Vendrame M did a polysomnography study in children revealing an association between the two conditions. Almost 60% of migraineur children ($n = 60$) were found to have sleep-disordered breathing and disruption in sleep architecture; reduced REM and slow-wave sleep were more frequent in children with

severe and chronic migraines. Dysfunction of arousal systems has been documented in migraineurs with sleep-related migraines indicating dysfunction in neuronal structures involved in both REM sleep regulation and migraine pathophysiology.

7.3.4 OSAS and Cluster Headache

For this primary headache disorder, several studies support a strong and possibly causative relationship with OSAS. Kudrow and colleagues in their original paper in the early 1980s reported that episodic but not chronic CH is associated with OSAS and that attacks are triggered by oxyhemoglobin desaturation during REM sleep [23]. These findings have been confirmed by several subsequent studies [24, 25], indicate that CH is strongly associated with OSAS, and estimate their comorbidity between 31 and 80%. CH attacks are thought to be triggered by oxygen desaturation during REM sleep. Furthermore, CH patients have an eightfold higher risk of exhibiting OSAS than normal individuals [26]. This risk increases up to 24-fold in patients with a body mass index (BMI) > 25 kg/m^2 and 13-fold for CH patients older than 40 years of age.

Thus, there is no doubt that OSAS not only complicates CH but also triggers CH attacks. Although chronic CH was not originally found to associate with OSAS, 76 others have reported a relationship between chronic CH and OSAS [19].

7.3.5 OSAS and Paroxysmal Hemicrania

Paroxysmal hemicrania (PH) and particularly its chronic form may also exhibit an association with OSAS [21]. PH is a rare disorder and reports of PH comorbid with OSAS are scarce. Like CH, PH attacks appear to be closely associated with REM sleep, which supports the notion of a biological clock impairment being involved in the pathogenesis of both OSAS and PH. However, in the case of suspected PH, sleep evaluation is warranted.

7.3.6 OSAS and Hypnic Headache

There is no better proof for an inherent relationship between sleep and headache than the example of the hypnic headaches (HH). HH attacks occur exclusively during sleep, even during daytime sleep, and respond to lithium, like CH often does. HH typically affects the elderly in whom nocturnal sleep is severely decreased. Altered hypothalamic modulation may be involved in its pathogenesis given that cell numbers in certain hypothalamic nuclei decrease dramatically with age. On the other hand, OSAS also typically occurs in the elderly increasing the risk of co-occurrence with HH [27].

7.4 Insomnia

Insomnia or sleep loss occurring in the context of chronic pain occurs secondarily to the sleep interrupting effects of pain, we and others have demonstrated that insomnias associated with chronic pain are often phenotypically similar to primary insomnia [28].

Insomnia is characterized by difficulty in falling asleep, staying asleep, frequent awakenings, or non-refreshing sleep and leads to impairment of functioning and psychological distress.

Almost one-third of the general population complains of insomnia [29]. In most cases insomnia is secondary to another condition, usually depression or anxiety and only rarely is it idiopathic. Idiopathic insomnia is thought to result from an abnormal activation of the hypothalamic-pituitary system [30] and may be cytokine or melatonin modulated and adenosine and/or calcium channel dependent [31]. At a theoretical basis these structures, channels, and neuropeptides are also involved in cephalic pain processing and signaling, thus providing a common pathophysiological substrate between the two conditions. Everyday clinical observations confirm this association, which is in line with large-scale epidemiological evidence. Strine study looked at 28,828 US citizens who were evaluated for severe headaches and sleep disturbances. Approximately 15.1% of adults aged

18 years or older reported severe headaches in the past 3 months. Those reporting severe headaches were significantly likely to have insomnia, excessive sleepiness, recurrent pain, and depression or anxiety symptoms during the preceding 12 months. Approximately 88% of those with severe headaches also had at least one comorbid medical condition, compared to 67% of those without severe headaches [32]. Data indicate that depression and/or anxiety is almost invariably present in comorbid chronic headache and insomnia patients. These findings are applicable to adolescents and children as well [33].

7.4.1 Insomnia and Tension-Type Headache (TTH)

Insomnia has been identified as a potential risk factor for TTH, although the pathogenesis of sleep disturbance in this population is unclear. In a small size sample study, a significantly greater proportion of TTH sufferers reported sleep problems and stress as headache triggers and going to sleep as a coping strategy, compared to controls. The TTH group also more frequently reported pain interfering with sleep. Going to sleep was the most commonly used (81%) and the most effective self-management strategy employed by headache sufferers suggesting a causative bidirectional relationship between sleep disturbance and TTH. Another large-scale longitudinal study showed that insomnia increases the risk of developing headache over a 1-year period and chronic TTH over a 12-year follow-up period. Poor outcome of TTH was also associated among other factors, with insomnia [34]. Several lines of evidence advocate a causative role for depression and/or anxiety as a common denominator in symptomatic insomnia and chronic TTH [27].

Except for depression and anxiety, insomnia is a recognized independent factor potentially responsible for transforming episodic headache into chronic. Gray matter decrease in regions involved in pain processing has been observed using magnetic resonance imaging (MRI) in patients suffering specifically from chronic TTH [35]. These gray matter areas are also involved in sleep modulation indicating that the pathophysiological impairment responsible for insomnia might also be the cause of comorbid chronic TTH. Conversely, chronic pain even of low intensity may also cause insomnia, as seen in patients suffering from chronic pain due to peripheral neuropathy or cancer.

7.4.2 Insomnia and Migraine

Insomnia frequently exhibits as a comorbidity with migraine. This has been repeatedly confirmed by several epidemiological studies in children, adolescents, adults, and the elderly, across the world. In the PAMINA study, approximately 500 migraineurs were screened with the Pittsburgh Sleep Quality Index together with other anxiety and depression tools. Data suggested that lower sleep quality in migraineurs is a consequence of migraine itself and cannot be explained exclusively on the basis of comorbidity with depression or anxiety [36].

In a family survey, adults with migraine reported having significantly more lifetime sleep problems and more current sleep difficulties (inadequate sleep, difficulty falling asleep, and persistent nightmares of childhood onset) than those without migraine [37]. Unrefreshing sleep is considered responsible for converting episodic migraine into chronic among other factors. Moreover, sleep repair transforms chronic migraine back into episodic, indicating that sleep and migraine interact in a bidirectional manner [38].

Questions yet not fully understood are how migraine affects sleep and vice versa, but several hypotheses have been postulated. The hypothalamus is the principal structure involved in modulating pain processing and adjusting circadian rhythms and sleep. Other structures include the locus coeruleus and the dorsal raphe nuclei. Melatonin and serotonin have therapeutic effects in migraine, insomnia, and even depression. The role of nitric oxide supersensitivity has also been proposed [39]. Evidence also demonstrates that ponto-geniculo-occipital spikes seen during REM sleep may trigger cortical spreading

depression, thus providing a link between sleep disorders and migraine [14]. Independent of the physiological basis of this comorbidity, the clinical management of migraineurs, and especially those with chronic migraine, necessitates careful assessment and treatment of comorbid sleep disorders.

7.5 Restless Leg Syndrome

The term restless leg syndrome (RLS), coined by Ekbom in 1945, describes a common condition typically characterized by deep unpleasant crawling or formication-like sensations in the legs causing motor restlessness, occurring at rest and especially at bedtime and relieved by voluntary movement [40]. RLS greatly disrupts sleep and has a major impact on quality of life. The idiopathic form of the disease exhibits a familial predisposition in 40–60% of the cases (Allen RP, et al.), and twin studies have revealed high concordance rates suggestive of a strong genetic influence [41]. Symptomatic RLS is associated with a number of conditions including pregnancy, iron deficiency, uremia, rheumatoid arthritis, peripheral polyneuropathy, diabetes mellitus, spinal disorders, celiac disease, and some medications [42, 43]. The prevalence of RLS varies from 5 to 10% in Europe and North America [44, 45] and from 0.6 to 3.9%, and there is a slight female preponderance.

7.5.1 RLS and Headache

Epidemiological observations indicate a greater occurrence of RLS with migraine. The prevalence of RLS is increased in patients with migraines compared to the general population [46, 47] but also compared to patients with other primary headache disorders. Concurrence of RLS with migraine was estimated at 11.4–17.3% in patients [46, 48]. Interestingly, comorbidity of RLS with migraine has also been shown to correlate with the number of migrainous symptoms and to worsen sleep quality [48]. Comorbidity of RLS with migraine implies that the two conditions may share common pathogenetic mechanisms.

7.5.2 RLS and Migraine

Although the pathogenetic mechanisms underlying the two conditions have not been fully elucidated, several explanations for the correlation between migraine and RLS have been suggested.

1. *Dopaminergic Dysfunction:* A large body of evidence supports the dopaminergic dysfunction hypothesis for the pathogenesis of RLS. Levodopa and dopamine agonists are effective treatments for RLS [49]. PET study demonstrated increased D2 receptor availability, suggestive of dopaminergic hypoactivity, in different regions of the thalamus and the anterior cingulate cortex, regions thought to play a role in the regulation of affective and motivational aspects of sensory processing to demonstrate the dopaminergic dysfunction role [50]. Evidence from a rat model of RLS, induced by lesioning the A11 hypothalamic dopaminergic nucleus that projects to the spinal cord, suggest that A11 may be involved in the pathophysiology of RLS [51]. Interestingly, A11 appears to also have a role in regulating trigeminovascular nociception thus providing a possible link in the pathogenesis of RLS and migraine [52].
2. *Abnormalities of Iron Metabolism:* Iron deficiency is an established cause of secondary RLS, which is corrected with iron supplementation [10]. Iron is an important element of dopaminergic neurotransmission as it is a cofactor for tyrosine hydroxylase, the rate-limiting enzyme of dopamine synthesis. Moreover, novel data indicate that iron metabolism abnormalities may also underlie the pathophysiology of migraine as MRI studies have shown increased accumulation of iron in the periaqueductal gray matter, putamen, caudate, and red nucleus, compared to age-

matched controls that correlated with longer migraine history and frequency of attacks [53]. Further work is required into the putative role of iron metabolism abnormalities as a link between RLS and migraine.

3. *Endogenous Opioid System:* Several lines of evidence relate RLS to the endogenous opioid system and may indirectly link it to migraines. Opioid receptor agonists are effective in treating RLS, and the opiate receptor blocker naloxone causes RLS symptoms to recur in opioid-treated patients [54]. On the other hand, opioid mu receptors are among the receptors in the dorsal nucleus caudalis that promote c-fos expression and modulate activation of the trigeminovascular system in animal models of migraine [55]. Nevertheless, direct evidence of a pathogenetic link between RLS and migraines involving the endogenous opioid system is still missing.

7.6 Sleep Bruxism

Sleep-related bruxism (SB) is a movement disorder characterized by involuntary teeth clenching and/or grinding occurring mainly during nonREM sleep [56]. The estimated prevalence of sleep-related bruxism varies with age from 14% in childhood and 8% in adults to 3% in the elderly [56]. Although SB etiology and pathogenesis are thought to be multifactorial, it has been shown to be associated with stress and anxiety, arousals from sleep, altered dopaminergic and serotoninergic neurotransmission, and to some extent genetic predisposition [20, 57].

Dental professionals may see SB as signs and symptoms of dental attrition, temporomandibular joint dysfunction, hypertrophy of masticatory muscles, and craniofacial pain. A 66% prevalence of craniofacial pain has been reported in bruxers. It is mainly described as bilateral facial pain and headache (84.3%) or frontotemporal in location (67.1%) with a tightness/pressure quality and being worse in the morning [58].

Bruxism is primarily associated with temporomandibular disorder-type (TMD) pain, and its occurrence in bruxers has been linked to higher levels of depression and somatization. In addition, a recent study reported a lack of correlation between TMD-type headache and the frequency of SB [58]. The high frequency of comorbidity between SB and TTH (Aaron LA, et al.), which favors the notion of a common pathogenetic link between the two conditions, remains controversial, given the considerable diagnostic and behavioral overlap between TMD and TTH [59].

Contrasting experimental evidence regarding the role of sustained tooth clenching as a trigger of headache in patients with TTH supports this contention [60, 61]. Childhood SB has been associated with migraine headaches due to the more frequent observation of SB in children with migraines than non-headache controls [62]. Questions aiming to explore the possibility of comorbid bruxism and or TMD should be used when interviewing migraine and TTH sufferers.

7.7 TMD and Poor Sleep Quality

Patients with TMD report poor sleep quality because of their pain [55]. Poor sleep has been shown to be a risk factor for first onset TMD, and painful disorders interfere with sleep [63]. Poor sleep quality is a strong predictor of chronic pain than chronic pain is for poor sleep quality.

There are several studies that have found that majority of TMD patients report poor sleep quality, and subjective ratings of poor sleep are associated with an increase in clinical pain severity [64].

Cunali's study shows that the presence of TMD and the impact of TMD pain were high among OSA patients that were referred for appliance therapy. Their findings regarding TMD grade scale in OSA patients were consistent with some TMD studies examining the general population [65–67].

Patients with TMD pain report a poor quality of sleep, while patients who do not sleep well are more susceptible to TMD [64, 68, 69].

7.8 Associations Between Sleep-Disordered Breathing and TMD

Disturbed sleep may interfere with the daily functioning of the patients, and poor sleep may be a contributing factor, to the extent that it increases one's sensitivity to pain [63, 70]. It has been suggested that sleep disturbance in chronic pain patients may increase pain sensitivity and create a self-perpetuating cycle of sleep disruption, increased pain, and depression.

Smith et al. showed in his study that the overwhelming majority of their sample of TMD patients, who were unselected for sleep disorders, were diagnosed with at least one sleep disorder, most commonly, ICSD self-reported sleep bruxism (75%); 17% met Research Diagnostic Criteria and polysomnography criteria for active sleep bruxism. More striking, they found that 43% of the sample was diagnosed with two or more sleep disorders. Insomnia disorder (36%) and obstructive sleep apnea (28.4%) demonstrated the highest frequencies [15]. They concluded that high rates of primary insomnia and sleep apnea highlight the need to refer TMD patients complaining of sleep disturbance for polysomnographic evaluation. The association of primary insomnia and hyperalgesia at a non-orofacial site suggests that primary insomnia may be linked with central sensitivity and could play an etiologic role in idiopathic pain disorders. The association between sleep-disordered breathing and hyperalgesia requires further study and may provide novel insight into the complex interactions between sleep and pain-regulatory processes.

Lei et al. studied 510 patients who visited the Center for TMD & Orofacial Pain, Peking University School & Hospital of Stomatology. In this Chinese population of TMD patients with myofascial pain patients were found to have significantly more frequent symptoms of sleep disturbance, depression, anxiety, and stress than other subtypes of TMD such as disc displacement, arthralgia, and joint degenerative diseases. They concluded that the Chinese TMD patients with myofascial pain have a high prevalence of sleep disturbance and psychological distress symptoms. Sleep disturbance and psychologic distress symptoms such as anxiety are possible risk indicators for myofascial pain.

Cunali P.A et al. examined Patients diagnosed with mild to moderate OSAS referred for oral appliance therapy were evaluated at the Sleep Clinic. As a result, the population in the current study consisted of 32 patients diagnosed with TMD by the RDC who also had an indication for oral appliance therapy. In the present study, 52% of the OSAS patients presented TMD. The prevalence of pain associated with TMD and the impact of this dysfunctional pain were high in OSAS patients [65].

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8 Immunologic and Physiologic Effects of Dental Sleep Appliance Therapy

G. Gary Demerjian and Pooja Goel

Abbreviations

AASM	American Academy of Dental Sleep Medicine
AHI	Apnea-hypopnea index
BMI	Body mass index
CGRP	Calcitonin gene-related peptide
CKD	Chronic kidney disease
CPAP	Continuous positive airway pressure
CPH	Craniofacial Pain Handbook
CT	Computerized tomography scan
GERD	Gastroesophageal reflux disorder
GPT-9	Glossary of Prosthodontic Terms Ninth Edition
HTR	Hormone replacement therapy
IBS	Irritable bowel syndrome
ICSD-3	International Classification of Sleep Disorders Third Edition
LES	Lower esophageal sphincter
MA	Microarousals
MRI	Magnetic resonance imaging
OAT	Oral appliance therapy
ODI	Oxygen desaturation index
ODS	Obsessive daytime sleepiness
OFPG-4	Orofacial Pain: Guidelines for Assessment, Diagnosis, and Management, Fourth Edition
OSA	Obstructive sleep apnea
PAP	Positive airway pressure
PAS	Posterior airway space
PGP 9.5	Protein gene product 9.5
PM	Portable monitors
PSG	Polysomnogram
RAAS	Renin angiotensin-aldosterone system
RDI	Respiratory distress index
REM	Rapid eye movement
RME	Rapid maxillary expansion
RMMA	Rhythmic masticatory muscle activity
RPS	Retropharyngeal space
SB	Sleep-related bruxism
SP	Substance P
TAD	Temporary anchorage device
TCR	Trigemino-cardiac reflex
TMD	Temporomandibular joint disorder
TST	Total sleep time
TTH	Tension-type headache
VDO	Vertical dimension of occlusion

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8.1 Introduction

Obstructive sleep apnea (OSA) is characterized by episodes of oropharyngeal obstruction due to repetitive collapse of the oropharyngeal tissues

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during sleep [1]. The oropharyngeal collapse is due to several factors. It is associated with sleep fragmentation, hypoxemia, hypercapnia, marked swings in intrathoracic pressure, increased sympathetic activity, and cardiovascular complications [2]. The prevalence of OSA in the adult population is estimated to be between 2 and 4% [3, 4], with the major factors being age [5, 6], sex [7], and weight [8]. The Wisconsin Sleep Cohort Study reported the prevalence of AHI greater than 5 per hour among 30–60-year-old men is 24% and women is 9% [4].

There are multiple forces that contribute to oropharyngeal collapse, including the elongation of the soft palate and uvula from the pulling forces that have been put on it from snoring; loss of vertical dimension resulting in a shortening of the lower 1/3rd of the face (can be due to bruxism resulting in attrition of teeth, clenching or extraction of teeth causing a loss in jaw support) [9]; increase in tongue size due to fat deposition in the tongue [10], which is due to weight gain [11]; and constriction of dental arches [12] due to extraction of first bicuspids when in braces and headgear and negative transmural pressure gradient and tissue weight.

8.2 Causes of OSA

Oropharyngeal patency depends on the balance between collapsing and dilating forces. The contraction of dilator muscles cause a stiffening of the oropharyngeal tissues resulting in dilation. However, an increase in oropharyngeal dilator muscle activity can still occur in patients with OSA during an obstructive event [13, 14]. In vitro studies show that dilator muscle activity and tension produced are higher due to OSA [15].

It has been shown that uvular stiffness is higher in subjects with OSA compared with non-OSA subjects who snore [16]. Recurrent OSA can lead to the development of an inflammatory process causing histologic alterations of oropharyngeal tissues, which can alter the integrity of the extracellular matrix and also interfere with the mechanical properties of soft tissues [1]. There are a few studies that have examined the inflammation of the oropharyngeal tissues in OSA [17] and the inflammation of the mucosa of the uvula [18]. The treatment with CPAP has become the standard of care for moderate to severe OSA. The primary aim of this chapter is to show the correlation and improvements on immunologic and physiologic effects of dental sleep appliance therapy based on the improvements seen with CPAP therapy.

Obstructive sleep apnea (OSA) is the most common forms of sleep apnea. There are various forms of sleep apnea, which are obstructive, central, and complex sleep apnea. OSA is a chronic clinical syndrome characterized by snoring, periodic apnea (episodes of oropharyngeal collapse during sleep), hypoxemia during sleep, and daytime hypersomnolence [19, 20]. OSA is prevalent among 4% of men and 2% of women [21]. The disorder is characterized by repetitive collapse (apnea) or partial collapse (hypopnea) of the pharyngeal airway during sleep [22]. OSA is classified as cessation of breath for ≥10 s. In 2007, there were some changes made by the task force in the respiratory scoring rules. Apnea in adults is scored when there is a drop in airflow by ≥90% from normal airflow for ≥10 s. A hypopnea in adults is when there is a drop in airflow by ≥30% for more than ≥10 s in association with either ≥3% arterial oxygen desaturation or an arousal. The numbers of both event types such as apnea and hypopneas are ultimately combined to compute an apnea-hypopnea index [23]. OSA is defined as apnea-hypopnea index (AHI) or respiratory distress index (RDI) greater than five events an hour and associated with symptoms such as excessive daytime sleepiness, impaired cognition, mood disorders, insomnia, hypertension, ischemic heart diseases, or history of stroke. The presence of respiratory efforts during these events suggested that they are predominantly obstructive [24].

There are multiple risk factors for patients who may be diagnosed with OSA. Some are genetic factors, while others are social factors. Roughly 84% of all apnea sufferers are diagnosed with OSA [25]. Patients with OSA have a small pharyngeal airway which is commonly due to being overweight in adults and enlarged tonsils in

children. While a subject is sleeping, the muscles are relaxed and therefore causing the pharyngeal airway to narrow and the upper airway to collapse for intervals [26].

8.3 Risk Factors

8.3.1 Obesity

Obesity is the most common risk factor of obstructive sleep apnea. Those who are overweight have a higher chance of developing symptoms for OSA. Obesity relates to OSA due to the excess fatty tissue, thickening of the walls, and decreased lung volume [27]. If a subject is overweight, the thickness of the lateral walls compromises the air to pass through which may cause the subject to choke during sleep or have fragmented sleep. The thickness of the lateral walls can be seen in a computerized tomography (CT) scan or magnetic resonance imaging (MRI) scan. With weight increase, excess fat starts to develop on muscular tissue which, in return, narrows the airway. Obesity also contributes indirectly to upper airway narrowing, especially in the hypotonic airway present during sleep, because lung volumes are markedly reduced by a combination of increased abdominal fat mass and the recumbent posture [28].

8.3.2 Narrow Airways

Narrow airways hinder the subject from breathing normally during sleep, which leads to increased hypopnea and apneas. The primary factor, which can predispose to a narrow airway and development of OSA, can be a result of restriction in the size of the bony compartment because of the deficient craniofacial skeleton. The maxillary and mandibular micrognathism of the jaw size results in a narrow airway [27]. A narrowed airway causes snoring, a common symptom of OSA. An airway can be narrowed by increase of soft tissue. Enlargement of soft tissue structures both within and surrounding the airway contributes significantly to pharyngeal airway narrowing in most cases of OSA [28]. A narrowed airway can also be caused if the subject is aging. An aging subject tends to have sagging muscles which may increase pharyngeal compliance and in turn cause their airway to be narrowed. Additionally, a narrow airway may be caused by hormonal factors such as the presence of testosterone or the absence of progesterone [27].

8.3.3 High Blood Pressure

Hypertension is another risk factor of OSA [29]. Many patients with OSA also have high blood pressure. Researchers have found that adults with severe apnea were more than twice as likely to have hypertension, while moderate OSA patients also had increased risk for high blood pressure [25]. OSA episodes produce surges in systolic and diastolic pressure that keep mean blood pressure levels elevated at night [30]. If OSA is able to be controlled, then blood pressure levels may also be lowered. Patients with pulmonary hypertension and OSA tend to have more profound nocturnal hypoxemia but may also have daytime hypoxemia as well [31].

8.3.4 Chronic Nasal Congestion

Nasal congestion causes the upper airway to narrow, which increases the risk of both snoring and OSA. Breathing through the nasal airway is important and idealistic for improved sleep. If the nasal airway is congested, then the subject is forced to breathe through their mouth [32]. Nasal congestion is a risk factor due to allergic rhinitis or an acute upper airway infection. Nasal congestion is commonly related to anatomical abnormalities such as septums, conchal hypertrophy, or nasal polyps [33]. Nasal breathing is better for the patient as the lungs will absorb more nitric oxides, due to the back pressure from the resistance air flowing out of the sinuses, compared to no resistance when breathing through the mouth [34].

8.3.5 Smoking

Smoking puts a subject at higher risk of being diagnosed with OSA and has greater changes in the upper airway. The airway becomes inflamed which makes it difficult to breath. Nicotine, an ingredient in cigarettes, is a stimulant. Smoking can refrain a subject from getting a restful sleep and may deter a subject from falling asleep as well. According to a 2011 study, people who currently smoke are 2.5 times more likely to also suffer from OSA, the most common type of sleep apnea caused by the collapse of muscles in the back of the throat during sleep. Smokers experience this repeated cessation of breathing more often because the smoke they inhale irritates the tissues in the nose and throat, causing swelling that further restricts airflow [35].

8.3.6 Diabetes

Diabetes and OSA are common disorders that often coexist. In one study of middle-aged men, the prevalence of sleep-disordered breathing (AHI > 20) was 36% in patients with diabetes compared with 15% in normoglycemic subjects [36]. Diabetes is a risk factor of OSA due to insulin resistance in subjects. There is a growing body of evidence from numerous human and animal studies that suggests an association between OSA and insulin resistance, glucose intolerance, and type 2 diabetes mellitus (DM2) [31]. Subjects who suffer from OSA have a higher chance of also suffering from insulin resistance. Most studies have demonstrated impaired glucose tolerance, higher fasting glucose, and insulin resistance in patients with OSA compared with patients without OSA irrespective of weight, presence of visceral fat, and age [31].

Whether a subject is male or female may also be a risk factor. In the general population, sleep-disordered breathing is estimated to occur in 9% of middle-aged women and 24% of middle-aged men. Only 2% of women and 4% of men also complain of daytime sleepiness and therefore may be at risk for OSA [36]. Generally, being a male is a risk factor for OSA itself [37]. Men are 2–3 more likely to have OSA. However, after menopause, women start to get OSA more than men due to their hormones. OSA will be more prevalent especially in women who are not getting hormone replacement therapy [19]. The male population tends to have an increased amount of fat around the upper airway as they age or it may also be due to obesity. In fact, the upper airway in men is frequently greater in length than women, which affects the airway collapsibility. Since the upper airway is longer in men, they are more susceptible to having their airway collapse. Additionally, hormones play a role in being associated with OSA as well. For instance, the presence of testosterone (higher in males) is a factor leading to the collapse of the upper airway [27].

8.3.7 Genetics

Genetics are a prominent risk factor for OSA. Upper airway anatomy, neuromuscular activity, and ventilatory control stability are determined based on genetics. OSA is more prevalent in specific ethnic groups due to their genetics. Craniofacial abnormalities are most common in Asians who have OSA, and an enlarged soft palate is more common in African Americans [27]. As mentioned previously, obesity is a risk factor of OSA. Interestingly, studies have shown that there are specific genes which increase the probability of obesity and OSA [19].

8.3.8 Asthma

Asthma has accumulating evidence suggesting a bidirectional relationship between asthma and OSA, where each disorder has a harmful influence on the other [38]. Alkhalil showed in cross-sectional studies that the prevalence of sleepiness, snoring, and OSA was significantly higher in participants with asthma [39]. Similarly, in clinical studies, OSA symptoms were frequently reported by patients with asthma than by the general population [40]. Furthermore, in a polysomnographic-based study, asthma was reported difficult to

control in almost 90% of OSA patients [41, 42]. Nighttime oropharyngeal narrowing in asthma patients is often associated with episodes of nocturnal and early morning awakening, difficulty in maintaining sleep, and daytime sleepiness [43]. A polysomnographic study showed no statistical differences between the two groups of OSA and non-OSA, except for changes in the percent of time spent in stages I and IV. Asthmatic patients with OSA had a higher percent of time in stage I and a lower percent of time spent in stage IV compared to patients without asthma. Therefore, sleep is superficial and poorer in quality for asthmatics with OSA. Whether CPAP can treat asthmatic nighttime symptoms and improve the pulmonary function test is questionable. A study conducted by Ciftci TU, on patients with asthma, concluded that after 2 months of continuous usage of nCPAP, there was no significant difference in the pulmonary function test. However, there was a significant improvement in the asthma nighttime symptom scores, which are quite evident in asthmatic patients with OSA [43].

8.4 Signs and Symptoms of OSA

8.4.1 Excessive Daytime Sleepiness

In patients with OSA, frequent arousals during the night lead to sleep fragmentation, depletion of slow-wave sleep (N3), and rapid eye movement (REM), which leads to excessive daytime sleepiness [44]. Excessive daytime sleepiness occurs if a subject is feeling tired or groggy in the morning or if the subject requires multiple naps throughout the day and is unable to perform regular day-to-day tasks. This may occur if a patient is unable to stay asleep during the night and wakes up multiple times. It may also occur if the patient is not getting enough sleep or restful sleep. Excessive daytime sleepiness can also occur if the subject is using drugs and alcohol, lacks physical activity, and/or is leading an unhealthy lifestyle. If the subject is unable to perform regular duties during the day due to excessive daytime sleepiness, this can lead to an impact on their lifestyle and work performance. OSA can be an underlying cause of excessive daytime sleepiness. In severe cases, patients fall asleep during stimulating activities, such as driving, or during conversation or meals. More frequently, they fall asleep during passive activities, such as watching TV or reading [36]. The Epworth Sleepiness Scale is a good tool to assess daytime sleepiness. Subjects are asked to fill out a questionnaire with eight questions and rate their activities. The higher the score, the higher the subjects sleep propensity in daily life [33].

8.4.2 Loud Snoring

Snoring is a symptom of OSA that often occurs with men who are overweight, but that isn't always the case. Up to 95% of patients with OSA snore. Normally, patients are unaware of their snoring and only realize they snore when their bed partner or someone else tells them. Snoring occurs when the flow of air through the mouth and nose is physically obstructed. Furthermore, airflow can be obstructed due to nasal airways, poor muscle tone, throat tissue, and/or a long soft palate [27, 45]. Loud snoring is a common complaint and symptom by patients suffering from sleep apnea [46].

8.4.3 Nighttime Sweating

Nocturnal sweating has been associated with cardiovascular disease, hypertension, and sleepiness, which are all symptoms of OSA. Based on a study conducted in 2013, inclusive of both OSA patients and the general population, it was noted that those diagnosed with OSA were much more likely to excessively sweat at night. Nocturnal sweating occurred more than three times per week in patients with OSA. Statistically, 30.6% of males and 33.3% of females with OSA suffered from nighttime sweating versus 9.3% of males and 12.4% of females in the general population. When the OSA patients were treated with PAP therapy, nocturnal sweating decreased from 33.3 to 11.5%, which was the general population [47]. Thermoregulation regulates the body

temperature by heat conduction. An increase in heat conduction will maintain thermoregulation, thus leading to a decrease in the core body temperature and further leading to a deeper level of sleep; an increase in the core body temperature can lead to increased nocturnal awakenings and lighter stages of sleep. Thermoregulation has a different pattern of mechanism between various sleep stages. For instance, thermoregulation is less prevalent during REM sleep vs. non-REM sleep. This is why the nighttime sweating is decreased during REM sleep as compared to non-REM sleep. There has been enlightening literature on the sleep-related perspiration as a consequence of OSA. In a study conducted in 2009, patients with untreated, moderate to severe OSA were evaluated for parameters such as temperature and electrodermal activity (EDA) to evaluate the perspiration in patients. All of the patients were medically managed with continuous positive airway pressure (CPAP) for a period of 3 months, and surprisingly, the electrodermal activity levels, along with systolic and diastolic blood pressure, decreased significantly after CPAP therapy. Not only this, there was a significant increase in REM sleep patterns in these patients. There is a future scope of research the hypothesis that high blood pressure found in OSA patients has a correlation with nocturnal sweating [47].

8.4.4 Decreased Libido

Sleep apnea does not only interfere with sleep, but after continuous research, it is becoming prevalent that sleep apnea is also leading to decreased libido in females and erectile dysfunction with males. There is a speculation by scientists that a decreased sex drive may be due to a decrease in testosterone. Testosterone increases when a subject gets enough sleep and the opposite happens if sleep is lacking. If an OSA patient has multiple arousals at night, they are unable to have a deep sleep. Based on a study conducted in 2011 with females who have untreated OSA, it was indicated that their libido was negatively affected when compared to the general population [48]. Budweiser mentions in a study with 401 male patients that sleep apnea independently decreases libido and causes erectile dysfunction [49]. In a randomized trial done on 40 patients with severe apnea, patients were made to wear a CPAP for a period of 1 month. Pleasantly, after the medical management of severe OSA over the period of a month, the International Index of Erectile Function improved from 15.71 ± 5.12 to 19.06 ± 3.94, which lead to a remarkable improvement in the sexual performance of the patients. According to the study done by Perimenis et al., the medical management of OSA with erectile dysfunction, one group was made to try CPAP solely, and another group tried CPAP along with pharmacological management of erectile dysfunction using sildenafil. The results were better with the latter group who tried CPAP and sildenafil vs. CPAP alone [50].

8.5 OSA Correlation to Medical Conditions

8.5.1 Diabetes

OSA is highly associated with insulin resistance. Evidence suggests that OSA is involved in the development of glucose metabolism alterations [51]. Several studies have shown that subjects with OSA have increased glucose levels and increased insulin resistance, which makes them genetically predisposed to developing type 2 diabetes [52]. Evidence suggests that OSA causes sleep loss and hypoxia, which elevates sympathetic activity. The inflammation caused by OSA, in combination with elevated sympathetic activity and weight gain, leads to insulin resistance and diabetes [53].

Bialasiewicz and collegues found in a study that continuous monitoring of interstitial glucose during a polysomnography (PSG) showed an increase in interstitial glucose concentrations and there was no effect during NREM sleep [54], whereas Grimaldi's findings support OSA in rapid eye movement (REM) sleep has a strong and clinically significant association with glucose levels in subjects with type 2 diabetes. Since

REM sleep is dominant during the second part of the night, REM-related OSA often remains untreated with 4 h of CPAP use. He recommends that in order to achieve significant improvement in glucose level in patients with type 2 diabetes, CPAP should be used over 6 h per night [55]. The level of hemoglobin A1C is correlated with the severity of hypoxemia in OSA and decreased with the use of CPAP for 3–5 months [56].

8.5.2 Blood Pressure

There is a very strong association demonstrated to date between OSA and hypertension, but a direct etiologic link between the two disorders has not been established definitively [57]. In his animal study, Brooks demonstrated that obsessive daytime sleepiness (ODS) produced sustained daytime hypertension and recurrent arousals from only sleep and cannot account for daytime hypertension observed in OSA. Early studies have shown conflicting results in the association between OSA and hypertension [8, 13].

OSA episodes cause surges in systolic and diastolic pressure, which maintains the mean blood pressure levels elevated at night. The blood pressure remains elevated during the daytime, when breathing is normal in many patients. Contributors to daytime hypertension include overactivity of the sympathetic nervous system, alterations in vascular function and structure caused by inflammation, and oxidative stress [30]. In the Wisconsin Sleep Cohort Study by Peppard, it showed the correlation between incidences of hypertension with severity of OSA in middle-aged patients. In contrast, the Sleep Heart Health Study, by O'Connor GT and his group, failed to show an association between OSA and the risk of incidence in hypertension [58].

The presence of OSA was associated with increased risk of incident for hypertension; however treatment with CPAP therapy was associated with lowering the risk of hypertension. Observational findings suggest that OSA appears to be a modifiable risk factor for new-onset hypertension [59]. In a study, Litvin and his group showed that effective CPAP use for 3 weeks resulted in a significant decrease in blood pressure and improvement in arterial stiffness in a group of hypertensive patients with OSA [60]. CPAP treatment in patients with difficult-to-control hypertension and OSA showed a significant reduction in diurnal and nocturnal systolic blood pressure, with no significant variations in diastolic blood pressure. This led to more patients who recovered to their normal nocturnal dipper pressure pattern [61].

8.5.3 Gastroesophageal Reflux Disorder

There is no causal link between gastroesophageal reflux disorder (GERD) and OSA, but they share common risk factors. Morse suggests that reflux medications may have a role in helping a selected population sleep better [62]. This effect likely is caused by controlling arousals secondary to gastroesophageal reflux [63].

Several investigators have concluded that there is a greater prevalence of GERD in patients with OSA based on reported symptoms of GERD and based on measurements of esophageal pH [64, 65]. Several studies have shown that the CPAP use for the treatment of OSA has reduced the occurrence of GERD [66–69]. The correlation between OSA and GERD remains unclear and controversial [62].

Several factors may increase GERD in patients with OSA, such as alterations in the function of the lower esophageal sphincter (LES), transdiaphragmatic pressure gradient increase, and decrease in the defenses against gastroesophageal reflux, due to reduction of esophageal clearance. The phrenoesophageal ligament may pull on the LES, creating an opening during an apnea event caused by an increase in diaphragmatic activity [70].

The transdiaphragmatic pressure may also increase due to abdominal pressure caused by obesity or when turning in bed during an OSA arousal [68]. In a study where acid reflux was simulated, the group with OSA had an impaired swallow reflex almost twice as long, when compared to the normal group [71]. Impaired clearance of gastric juices increases the contact time, causing an

irritation of the mucosa resulting in inflammation, further aggravating the obstruction and worsening the OSA [72–74]. Furthermore, the gastric acid also causes destruction of the dentition, wearing away enamel and dentin, known as attrition.

Science has yet been determined the amount of contribution that repetitive acid reflux has on OSA. Several studies using a PSG and a 24-h monitoring of esophageal pH were unable to show a bidirectional causal relationship between gastroesophageal reflux and OSA [66, 75, 76]. Several studies have shown that treatment with CPAP reduced the frequency of acid reflux events and nocturnal awakenings due to heartburn [63, 66–68]. When proton-pump inhibitor (PPI) therapy was initiated, AHI was reduced by 31%, and treatment with a histamine type 2 receptor antagonist (H_2RA) decreased arousals, but did not affect OSA [63, 66]. CPAP and OAT treat OSA by opening the oropharyngeal airway, stopping paradoxical breathing, and allowing the LES to function normally, thereby controlling the acid reflux while sleeping.

8.5.4 Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is characterized by recurring abdominal pain in conjunction with irregular bowel movements. The prevalence of IBS is about 8–20% among adults, and it is one of the most common diagnoses used by gastroenterologist [9]. The study conducted by Kumar D supports the hypothesis that IBS may be a disorder of inappropriate brain-gastrointestinal interaction which can lead to the motor abnormality of the small bowel only during the waking state. The cause and effect relationship between sleep disturbance and IBS is not definitive [77]. The studies conducted in the past confirm the finding that IBS patients are considered to have poor sleep functioning. The study done by Rotem AY with the aid of a sleep questionnaire, actigraphy, and the polysomnography findings supports the hypothesis that IBS patients have more difficulty in falling asleep and have lots of movements while asleep. The polysomnography findings show a significant shorter total sleep time (TST), indicating compromised sleep efficiency. Patients were found to have more than 70% decreased proportion of slow-wave sleep stage, and as a result, stage II sleep was significantly longer. The arousal index was found to be twice as greater in patients with IBS versus the control group. Similarly, subjects with IBS witnessed more events of shifting to lighter sleep when compared to the control group. Please refer to Fig. 8.1. Findings also

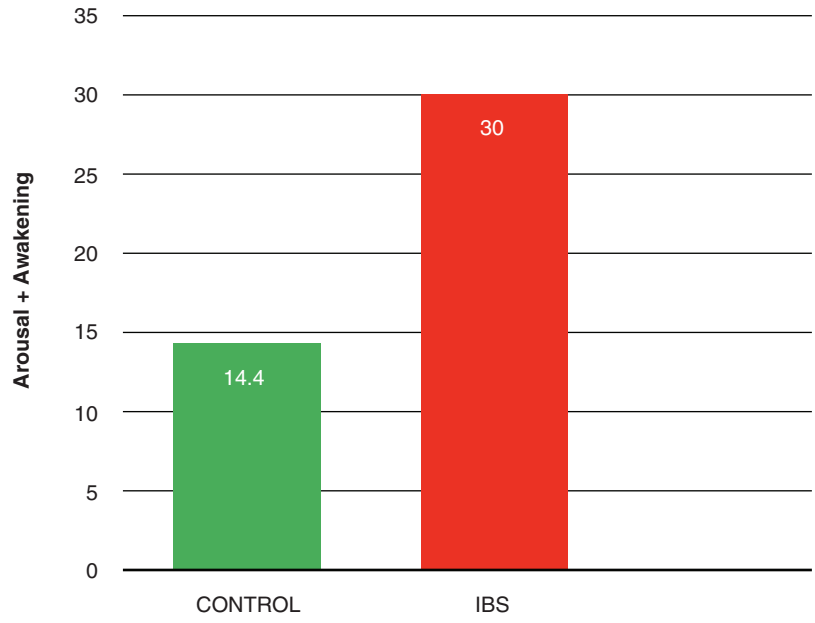

Fig. 8.1 Sleep Fragmentation in IBS Patients. Sleep fragmentation is doubled in subjects with IBS, as arousals and awakening was measured per hour [9]. Figure created by Mr. Haig Demerjian

suggested the increased proportion of REM sleep and longer wake period after sleep onset. A sleep questionnaire leads to the conclusion of greater excessive daytime sleepiness and higher Epworth Sleepiness Scale, thus leading to poor quality of life. All of these can lead to exacerbation of gastrointestinal abnormalities such as IBS [9]. Whether CPAP can aid in the treatment of IBS is a matter of debate, perhaps due to the limited number of studies. There is lack of evidence indicating that patients with IBS have poor quality of life; they were reluctant in trying CPAP therapy for the control of IBS symptoms. However, if patients were educated on how sleep disorders can be a risk factor for IBS and vice versa, then they may be willing to consider CPAP as an effective treatment to relieve symptoms and feel better. There is a lack of evidence supporting a direct cause and effect relationship between sleep disorders and IBS. Hence, we cannot conclude that CPAP can effectively treat patients with IBS. A future scope of study is required [78].

8.5.5 Cardiovascular System

Obstructive sleep apnea affects the cardiovascular system in multiple ways. OSA causes central hemodynamic effects. Episodes of OSA produce arterial oxygen desaturation, elevated carbon dioxide levels or hypercapnia, intrathoracic pressure oscillations, and possibly disrupted sleep [28]. Several studies have shown an independent association between OSA and increased cardiovascular morbidity [4, 59, 79].

In cases where the OSA is severe (AHI over 30), there is a higher predictability of mortality [80]. OSA treatment with CPAP improves quality of life, but there is no published study that has adequately showed a mortality benefit [81]. In echocardiographic studies, systolic and diastolic dysfunction occurred when AHI was increased [82, 83]. Possible mechanisms include the effects of hypoxia and the repetitive intrathoracic pressure changes that accompany obstructive apneas [84]. Studies have shown that negative intrathoracic pressure causes an increase in left ventricular afterload and impairs left ventricular relaxation [85, 86]. Cardiac contractility is also reduced, and left ventricular volumes rise, both at end-systole and end-diastole [87]. Hypoxia and arousals may induce tachycardia and peripheral vasoconstriction, further increasing ventricular afterload, caused by sympathetic nervous system activation [88].

CPAP use reduces the need for intubation during acute exacerbations in heart failure patients while providing symptomatic relief [89, 90]. In trials, it has been demonstrated that CPAP therapy has an improvement in exercise capacity, quality of life, and ventricular afterload [90–92]. Left ventricular ejection fraction had improved when on CPAP therapy but worsened when the CPAP was removed [93]. Furthermore, CPAP therapy has improved pulmonary hypertension and arrhythmias [94, 95].

8.5.6 Chronic Renal Failure

Renal failure also known as kidney failure is an important issue with patients who suffer from OSA. Patients who already have chronic kidney disease (CKD) are likely to also have OSA. OSA is also associated with proteinuria or protein in urine and hypertension. Proteinuria is a symptom of renal disease. If OSA is corrected with therapy, then renal outcomes may also be cured or improved [37]. As reported by one study from 2015, OSA can lead to decrease of kidney functionality. Furthermore, if moderate to severe OSA is treated, then the treatment also improves kidney filtration by minimizing glomerular hyperfiltration as sustained OSA is also associated with glomerular hyperfiltration [96]. The prevalence of OSA in patients with end-stage renal disease ranges from 40 to 60% [97]. The complete pathophysiology and background of disease mechanism are beyond the scope of this article. However, a brief introduction may be helpful. OSA mediates the renal damage via several mechanisms. In fact, the relationship between OSA and chronic renal failure is a complex system as illustrated in Fig. 8.2. The OSA patients are associated with hypoxia and sleep fragmentation which can contribute to the origin

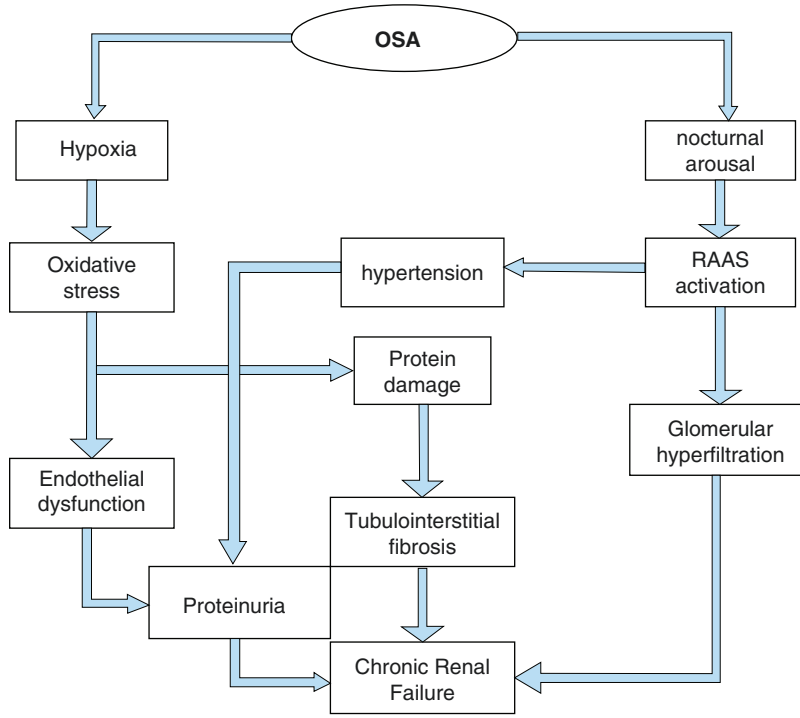

Fig. 8.2 Relation of OSA and chronic renal failure. Provided by "Dr. Pooja Goel". Pathophysiologic links between OSA and CKD. The figure is depicting the link between OSA and CKD. The flow is indicating how the elevated blood pressure during repetitive cessation of breathing during OSA can contribute to sympathetic nerve discharge to the renal vascular bed. Once the renal vascular bed is affected, renal failure occurs through different mechanisms

of chronic renal disease by activating renin-angiotensin-aldosterone system (RAAS) and elevation in the blood pressure as a result of activated sympathetic nervous system and via glomerular hyperfiltration. The following predictors of chronic renal failure can be improved with CPAP therapy: endothelial function, levels of circulating apoptotic endothelial cells, attenuates free radical production from neutrophils, inflammatory mediators, vasodilator levels, and mediates a decline in vasoconstrictor levels in patients with sleep apnea. A further study is required to support the hypothesis that chronic renal failure can be reversed back with CPAP therapy [37].

8.5.7 Stroke

Stroke is the fifth leading cause of death in the USA, with one person dying every 4 min as a result. Strokes occur due to problems with the blood supply to the brain; either the blood supply is blocked or a blood vessel within the brain ruptures, causing brain tissue to die. Stroke is a condition of acute injury to central nervous system tissue arising either from ischemia or hemorrhage [31]. The three main types of stroke are ischemic, hemorrhagic, or transient ischemic attacks (also known as mini-strokes). The narrowing or blocking of arteries to the brain causes ischemic strokes. Hemorrhagic strokes are caused by blood vessels in and around the brain bursting or leaking [98]. OSA has an independent correlation with cardiovascular disease, with stroke being one of them [37]. Since snoring is a symptom OSA, both have been known to increase incidence of stroke. Additionally, as the severity of sleep apnea increases, so does the risk of developing a stroke incident [31]. Whether or not CPAP can definitively decrease the chance of stroke is still a matter of debate. The current literature suggests that the medical management of OSA in a timely manner with CPAP can alter the severity of stroke by not leading to brain damage. In a recent editorial, there is a widespread belief that medical management of moderate to severe OSA associated with cardiovascular mortality by the use of CPAP can lead to a better prognosis but lacks the strong supportive evidence. However, CPAP treatment will prevent subjects from

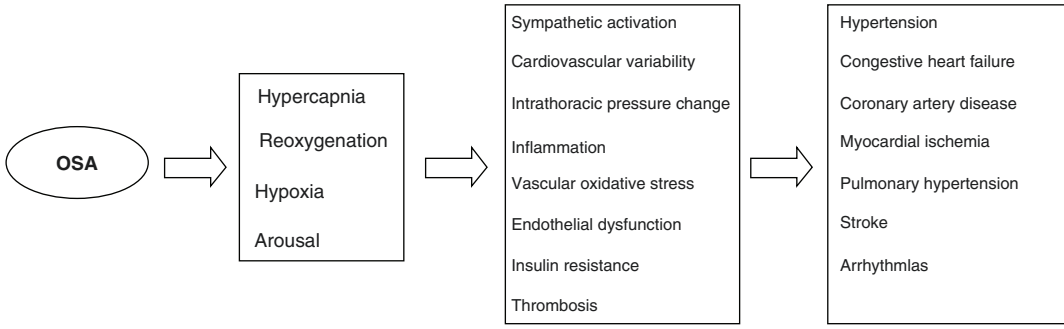

Fig. 8.3 OSA and cardiovascular consequences. Adapted from Vrints H et al.

getting hypoxia and cerebral flow fluctuation and thus in turn can prevent stroke occurrence [99]. According to a randomized trial, some enlightening considerations surfaced that there was correlation between CPAP therapy and a substantial reduction in cardiovascular morbidity. Thus, we can conclude that CPAP adherence in patients with OSA can reduce the severity of cardiovascular morbidity and cerebrovascular accidents but has not been found to be effective in recovering the patients from pre-existing stroke conditions [100] (Fig. 8.3).

8.5.8 Metabolic Syndrome

Metabolic syndrome, also known as syndrome X or the insulin resistance syndrome, is a condition where multiple factors lead to an increase for the risk of heart disease such as stroke and/or diabetes [36]. There are five conditions, which indicate that a subject may be diagnosed with the metabolic syndrome. If a subject has at least three out of the five conditions, then he or she may be diagnosed for the syndrome. The conditions are abdominal obesity, triglycerides, high-density lipoprotein cholesterol, blood pressure, and fasting glucose [31]. The interaction of the metabolic syndrome and OSA is known as syndrome Z [26]. In a study conducted in 2004, patients were examined to see the correlation between metabolic syndrome and OSA. Sixty-one male subjects were studied, and the findings were that people with OSA had the characteristics of the metabolic syndrome. The similar characteristics found among the subjects with OSA were that they were obese, had higher blood pressure, were resistant to insulin, had a lower HDL cholesterol level, and, finally, had an increased chance of diagnosis of the metabolic syndrome. Subjects, who have OSA, were 9.1 times more likely to also be detected with the metabolic syndrome [101]. Similarly, in another study it was concluded that patients with metabolic syndrome have a high chance of also having OSA and therefore should be tested with a PSG [102]. There is an independent association between sleep apnea and insulin resistance [103]. Metabolic syndrome may be treated with CPAP therapy as concluded in a study conducted in 2011. Subjects with metabolic syndrome were tested with CPAP therapy for 2 months. Before and after tests were conducted for several components, which are highly predictive of metabolic syndrome such as blood pressure, blood glucose (while fasting), insulin resistance, blood lipid profile, and visceral fat. It was concluded that patients with OSA, who were treated for 3 months with CPAP, had lower blood pressure and metabolic factors were also normalized [104]. As OSA leads to lack of sleep, treatment with CPAP will help patients to recover from sleep loss and thus may result in bringing the metabolic parameters to the normal levels, including glucose levels, blood pressure, blood lipid profile, and visceral fat [26].

Leptin, called a satiety hormone, is released by fat cells. It provides information about status of energy to the hypothalamus [105, 106]. Lepton level becomes elevated at night, partly as a

response to food ingestion during the day and to sleeping [107, 108], but decrease during the day when energy and calories are dimensioning [109]. When sleeping during the daytime, leptin levels stay elevated in subjects receiving continuous nutrition, which indicates leptin regulation is affected by sleep [110]. Leptin crosses the blood-brain barrier via saturation transport [111]. Leptin resistance is a common finding among subjects who are obese and have metabolic syndrome [112]. Based on many studies, leptin levels increase in subjects with OSA, and effective CPAP therapy decreases leptin levels in the long run [113].

Ghrelin, known as the hunger hormone, is necessary for body functions having to do with energy and appetite. In a study conducted in 2003, OSA patients were tested for ghrelin levels, both before and while using the CPAP machine. It was noted that OSA patients have higher levels of ghrelin as a baseline after fasting. After going through with CPAP therapy for 2 days, the levels of ghrelin had reduced significantly and remained only slightly higher in OSA subjects [114]. Another study conducted in 2010 on 55 OSA patients concluded that there is a positive relationship between the apnea-hypopnea index (AHI), Epworth Sleepiness Scale, and ghrelin levels [115].

8.5.9 Headaches

Previously there were not enough studies to establish a clear connection between OSA and headaches, perhaps due to the lack of evidence [116]. Recently, however, there are numerous studies which have mixed conclusions about OSA and headaches being directly related. There are two major findings for sleep-related headaches distinguished by the International Classification of Headache Disorders, one is "sleep apnea headache" and the other is "hypnic headache." Another type of primary headache which is known to be perpetuated with sleep-related headaches is tension-type headache (TTH) [117]. The most commonly described sleep apnea headaches are the recurrent morning headaches found to be three times more prevalent upon awakening in heavy snorers and OSA patients [118]. Although repetitive episodes of sleep apnea result in hypoxemic events, sleep fragmentation and nocturnal awakenings may be potential causes of recurrent morning headaches; however hypoxia is not an independent risk factor [51]. Additional studies support the established relationship between sleep apnea and other neurological and neurodegenerative disorders such as stroke, epilepsy, and headaches. Furthermore, OSA is known to exacerbate Alzheimer's disease and may be a sole cause of Parkinson's disease [119]. Sleep apnea, due to sleep loss and poor quality of sleep can lead to stimulation of nociceptive receptor system through different mechanisms and lead to an increase in various inflammatory markers such as proinflammatory cytokines, IL-6, and PGE_2 and exacerbates chronic pain conditions such as fibromyalgia, myofascial pain, temporomandibular joint disorder (TMD), and headaches [27]. There is evidence of dysfunction of serum serotonin levels in patients with OSA. In a study conducted in 2015, 4759 patients who were diagnosed with OSA were tested for TTH. TTH were noticed in 10.2% of patients with OSA and 7.7% of patients without OSA. The study concludes that patients who have OSA also have higher chances of getting tension-type headaches [117]. There is no definitive study on confirming the cause and effect relation between cluster headache and sleep apnea, but sleep apnea has been suggested to be a stimulus for cluster headache [120]. The oxygen desaturations caused by sleep apnea can lead to inappropriate functioning of carotid body activity perpetuated because of the dysfunction of the hypothalamus vasomotor system; and if it can lead to cluster headaches, it is not definitive. We need further research to see the cause and effect relationship [121]. CPAP treatment and other treatment modalities such as a dental oral appliance to treat sleep apnea have led to resolution and improvement in headaches from time to time. Treating OSA might not only improve headaches but also leads to decreased comorbidity [122].

8.5.10 Effects of Hormones

Hormone levels have always been a probable culprit in the propensity of OSA. It has been an intriguing matter of discussion that what leads to more prevalence of OSA in women after menopause. How do levels of progesterone, estrogen, testosterone, and hormones like calcitonin gene-related peptide (CGRP) affect the physiology of airway? As discussed previously, the collapse of the upper airway is a key issue in patients with OSA. A recent study concluded that a progressive lesion in the nervous system can be caused by the mechanical trauma due to snoring, leading to a collapse of the upper airway. This trauma is caused by the constant and repetitive low-frequency vibration of tissues from snoring. As a result of the trauma, there will be a sprouting effect leading to an increase in the number of varicose nerves and number of afferent nerve fibers. Eventually because of constant trauma, the sprouting effects fail to compensate and lead to the development of a degenerative neurogenic lesion. Such nerves contain specific hormones known as protein gene product 9.5 (PGP 9.5) and possibly substance P (SP) and CGRP. Whether the upper airway is unobstructed is dependent on both anatomical and neuromuscular factors, such as the negative intrapharyngeal pressure created during inspiration. Both afferent and efferent nerves mediate the reflex mechanism by stimulation of the mechanoreceptors located in the mucosa and submucosa of the pharynx, which causes the dilator muscles to react through the hypoglossal motor neurons. Oxygen desaturation index (ODI) is the number of time when the oxygen level in the blood drop below baseline measured in an average hour of sleep. Patients with severe OSA and significant increased ODI seemed to have a lower number of varicose nerves. Because of the degenerated nerves and significant depletion in the CGRP-immunoreactive small unmyelinated nerve fibers (C fibers), there are depleted levels of neuropeptides such as SP and CGRP, and the progressive degenerative neurogenic lesion can lead to injury of efferent nerve fibers and will lead to collapse of airway [123]. There is no linear relationship between the hormone levels and their repercussions on the central and neural respiratory mechanism, but the current literature is suggestive of the fact that increased level of progesterone/estrogen and lower levels of testosterone play a protective role against the development of OSA in women and men. The supporting fact for the suggestion mentioned can be that postmenopausal women without hormone replacement therapy (HRT) tend to have fourfold risk of development of OSA, as compared to the ones with HRT [124]. OSA per se is not directly related to the low levels of testosterone, but inadequate or exorbitant amounts of testosterone can alter sleep. The supporting fact is that people who are deficient in testosterone levels of hormones (hypogonadal) with poor sleep quality get benefited with HRT; however excessive doses of testosterone replacement therapy can lead to abnormal sleep quality and architecture as well [125].

8.5.11 Sleep Homeostasis

Sleep has many benefits. Sleep is a necessity for energy conservation, restoration, brain temperature regulation, modulation of neurochemistry, hormonal regulation, memory consolidation, and other neurocognitive functions. Sleep is not a well-defined entity, which is controlled independently or has a definite purpose. Sleep represents the process of meta-regulation which internal/external factors following the history and current hemostatic needs. Although sleep is a common practice and is a major component in the maintenance of the body functionality, it is intricate to comprehend easily and simply the effect of sleep deprivation as it's a multifactorial entity. Whether the regain of sleep loss will lead to an efficient functioning of specific physiological variables in the same way is a matter of debate. Homeostatic regulation is a crucial function of sleep physiology. An increase in the number of hours awake is equivalent to an increase in the homeostatic drive. This process will increase the metabolic demands and will lead to an increased intracellular adenosine. Adenosine inhibits wakefulness maintaining

neurons and promotes sleep. An increased level of adenosine will bring the homeostatic drive down and patient will. Hence, the main concept remains that the longer one stays awake, the deeper/longer they will require to maintain the integrity of the tissues and regulation of brain metabolism and synaptic plasticity. A common enlightening thought is that prolonged wakefulness can result into detrimental effects such as molecular, cellular, network, physiological, psychological, and behavioral levels [126]. During a 24-hour day, there is a bidirectional flow between catabolism and anabolism; one end is driven by the wakefulness which enhances the more intracellular breakdown of tissues and cells and thus is depicted as catabolism, while the other end, which offsets the catabolism, is known as anabolism and is represented by sleep. The sleep keeps the balance between catabolism and anabolism by decreasing the secretion of cortisol, catecholamines, releasing more growth hormones which in turn will lead to more production of protein and will metabolize the free fatty acids to provide energy and will eventually lead to the more synthesis of bone and increased number of red blood cells production. In a nutshell, this balance between catabolism and anabolism helps to get better sleep and relieve patients of sleep debt. In the latest practice, modern hypnotic drugs prevent the sleepiness and thus help in attaining better sleep and relieve the patient's anxiety and help in the restoration and normalization of the tissues [127].

8.5.12 Trigeminal Cardiac Reflex

The trigeminal nerve (V) is the fifth cranial nerve. It exits to pons and enters Meckel's cave, forming the gasserian ganglion. The gasserian ganglion divides into the three major divisions that contain sensory impulses eyes, face, and cranium. The ophthalmic division is purely sensory, which supplies sensation to the eyes and forehead. The maxillary branch is purely sensory also. It supplies the midface, including the nose, nasopharynx, upper lip, maxilla, maxillary teeth, palate, soft palate, and tonsils. The mandibular division consists of a large sensory root and a minor motor root. The sensory root supplies the lower face, including the tongue, mandible, mandibular teeth, lower lip, lateral surface of the ears, temples, and TMJ. The motor root supplies the muscles of mastication, which consists of masseters, temporalis, lateral pterygoids, medial pterygoids, anterior digastric, tensor-veli tympani, and tensor-veli palatini.

As sensory impulses are transmitted via the trigeminal nerve, they enter the trigeminal spinal nucleus, within the pons. The trigeminal spinal nucleus has numerous collateral and longitudinal connections to other cranial nerve nuclei and to the reticular formation. The rostral trigeminal sensory nucleus has neurons that convey information to the thalamus [128].

The trigemino-cardiac reflex (TCR) is a powerful autonomic reflex that helps the body to autoregulate by conserving oxygen and reducing the heart rate under challenging situations [129, 130]. Any stimulation of the trigeminal nerve anywhere along the nerve will result in sympathetic withdrawal and parasympathetic over activation via the vagus nerve, thus resulting in apnea, bradycardia, bradypnea, and hypotension. TCR has various manifestations, which include central TCR, peripheral TCR, the diving reflex, and naso-cardiac reflex [131–133]. TCR is linked to sleep-related bruxism (SB) as a probable cause [134] and has been hypothesized to play a role in sudden infant death syndrome (SIDS) [135]. It is reported that sudden microarousals (MA) occurring in the brain due to airway obstruction during sleep cause tachycardia, which stimulates rhythmic masticatory muscle activity (RMMA) and SB, that activate the TCR resulting in bradycardia [128, 134, 136]. When breathing is normal during waking or sleep, the heart rate remains stable. When breathing becomes labored due to airway obstruction such as a hypopnea or apnea, the oxygen level drops in the blood causing the body to put extra effort in obtaining oxygen [128]. This will lead to MA of the brain. MA episodes are characterized by an increase in brain activity, heart rate, and muscle tone during sleep [137]. Sleeping in the supine position causes oropharyngeal obstruction, due to the gravita-

tional pull on the tongue, soft palate, and mandible. Therefore, the frequency of SB increases an effort to get more oxygen [138].

Before SB occurs, activation of the TCR causes a sequence of physiological changes starting with an increase in respiratory rate, followed by an increase in EEG activity and then an increase in heart rate [139]. Brunelli demonstrated that when using a spring device that keeps the teeth apart and performing partial jaw movements, it caused prolonged reduction of blood pressure and heart rate [140]. Chase identified the specific neurons in the medullary reticular formation that are responsible for the inhibition of the postsynaptic trigeminal motor neurons during active REM sleep, which caused masseter muscle atonia [141]. In a study using transcranial magnetic stimulation, Gastaldo found data suggesting that the trigeminal motor system has a group of interneurons that modulate. The alteration in excitability of these interneurons can increase the firing of the trigeminal motor neurons during sleep arousals, causing excessive masseter muscle contractions, seen in SB [142].

8.6 OSA Correlation to Dental Conditions

8.6.1 Sleep Bruxism

Bruxism is of great interest to researchers and clinicians in the dental, neurology, and sleep medicine communities. Common clinical symptoms associated with bruxism are craniofacial pain, tooth wear, tooth sensitivity or pain, and failing dental restorative treatments [143].

There are four definitions of bruxism based on the perspective from organizations defining the term. The definition of bruxism formulated in the *Glossary of Prosthodontic Terms Ninth Edition (GPT-9)*; in the Craniofacial Pain Handbook (CPH) published by the American Academy of Craniofacial Pain; in the *Orofacial Pain Guideline for Assessment, Diagnosis, and Management, Fourth Edition (OFPG-4)*, published by the American Academy of Orofacial Pain; and in the *International Classification of Sleep Disorders Third Edition (ICSD-3)*. These four definitions have been critically scrutinized by these organizations, after which a new definition of bruxism was proposed.

The *Glossary of Prosthodontic Terms Ninth Edition (GPT-9)* has two definitions for bruxism: "(1) the parafunctional grinding of teeth; (2) an oral habit consisting of involuntary rhythmic or spasmodic nonfunctional gnashing, grinding, or clenching of teeth, in other than chewing movements of the mandible, which may lead to occlusal trauma; nocturnal bruxism, occlusal neurosis, tooth grinding" [144].

The *Craniofacial Pain Handbook (CPH)* defines bruxism as "Grinding or gnashing of the teeth when not masticating or swallowing. Gnashing and grinding of teeth. An unconscious habit usually limited to the sleeping period but sometimes occurs under the strain of mental or physical concentration. Diurnal or nocturnal parafunctional activity including clenching, bracing, gnashing and grinding of the teeth. In the absence of subjective awareness, can be diagnosed from presence of clear wear facets that are not generated by masticatory function. Diurnal or nocturnal parafunctional activity including clenching, bracing, gnashing and grinding of the teeth. In the absence of subjective awareness, past bruxism can be inferred from presence of clear facets that are not interpreted to be the result of masticatory function, and contemporary bruxism can be observed through sleep laboratory recordings. (1) The parafunctional grinding of teeth. (2) An oral habit consisting of involuntary rhythmic or spasmodic nonfunctional gnashing, grinding or clenching of teeth, in other than chewing movements of the mandible, which may lead to occlusal trauma- called also tooth grinding, occlusal neurosis" [145].

The *Orofacial Pain Guidelines for Assessment, Diagnosis, and Management, Fourth Edition (OFPG-4)* defined bruxism as: "Diurnal or nocturnal parafunctional activity including clenching, bracing, gnashing, and grinding of teeth; in the absence of subjective awareness, past bruxism can be inferred from the presence of clear wear facets that are not interpreted to be the result of masticatory function, and contemporary bruxism can be observed through sleep laboratory recordings" [146].

The International Classification of Sleep Disorders Third Edition (ICSD-3), defines bruxism "as a repetitive jaw-muscle activity characterized by clenching or grinding of the teeth and/or bracing or thrusting of the mandible. Bruxism has been divided into its two circadian manifestations known as sleep bruxism and awake bruxism" (ICSD-3).

ICSD-3 classifies sleep bruxism among the sleep-related movement disorders which was previously among the parasomnias. The *International Classification of Sleep Disorders Third Edition* defines bruxism as "an oral activity characterized by grinding or clenching of the teeth during sleep, usually associated with sleep arousals" [147].

When sleeping, frequently repeated jaw muscle contractions occur and are referred to as rhythmic masticatory muscle activity (RMMA). When looking at electromyographic tracings, RMMA has two forms, phasic and tonic contractions. Phasic contractions are repetitive jaw muscle activity, and tonic contractions are an isolated sustained jaw clenching. The tooth grinding sounds are referred as sleep-related bruxism [147].

This can lead to abnormal tooth wear, tooth pain, jaw muscle pain, and headaches. Sleep bruxism may also result in sleep disruption in association with sleep arousal. The sounds made by friction of the teeth can be quite loud and disturb the bed partner or others nearby [147] (Fig. 8.4).

8.6.2 Malocclusion

Malocclusion is the misalignment of teeth and the jaw. In obese patients, hyperplastic soft tissue is one of the predisposing factors causing OSA. Whether the same holds true for nonobese patients is questionable. There is no substantial literature supporting the statement that malocclusion is an independent risk factor of OSA. The editorial study conducted in 2008 on 97 male patients with the help of diagnostic tools such as cephalometric and dental analysis concluded that increased overjet and overbite are related to the propensity of OSA severity in nonobese patients. Malocclusion is such an irregularity that tends to make a subject breathe through their mouth more prominently as compared to nasal breathing. Furthermore, evidence is increasing which demonstrates that OSA patients have dentofacial/skeletal characteristics associated with a narrow upper airway [148]. In turn, that leads to the downward and backward rotation of the mandible, tongue, and occlusion into the retropalatal (velopharynx) and retroglossal (oropharynx) [148–152]. Please refer to Fig. 8.5. If a person has an increase in overjet and overbite, then they will tend to breathe through their mouth and that in turn leads to retro-inclination of maxillary and mandibular incisors and hence increases the severity of malocclusion. Please refer to Fig. 8.5. We can conclude that overjet in nonobese subjects may possibly occur due to mandibular hypoplasia or

Dental clinical signs of bruxism

Worn dentition	Due to the forces placed on the teeth
Fractured restorations	Due to the forces placed on the teeth
Abfractions	Due to concavity of the tooth structure at the gum line caused by lateral forces placed on the teeth
Tori	Overgrowth of bone typically seen in the lingual aspect of the teeth, either at the middle of the palate or on the premolar section of the mandible
Buccal exostosis	Overgrowth of bone on the cheek side of the teeth
Loosening of teeth	Caused by trauma from bruxism
Tooth sensitivity	Due to the trauma caused by bruxism
Gingival recessions	Caused by a response to the forces placed on the periodontium
Muscle pain	Caused by overworked muscles
TMJ-related symptoms	Internal derangement, clicking, popping, crepitus, capsulitis, arthralgia, ear pain or fullness, dizziness, myalgia, cephalgia, pain or tenderness of the neck and shoulder, pain or pressure behind the eyes, pain or sensitivity of the dentition

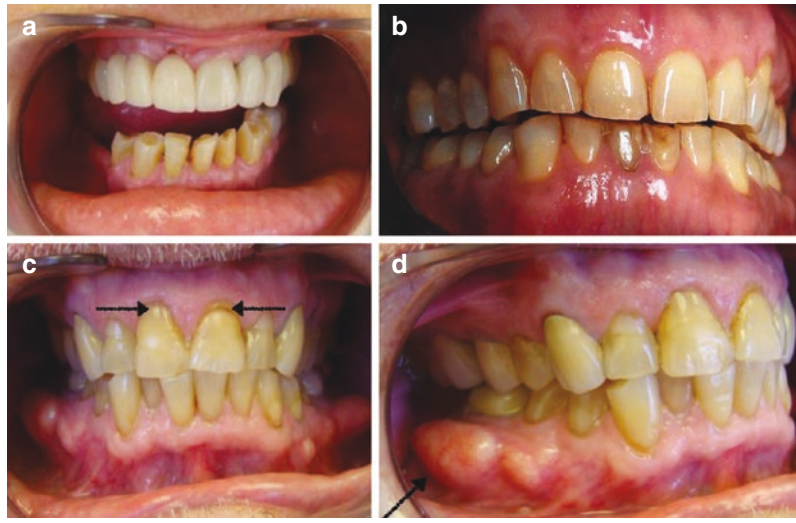

Fig. 8.4 (**a**) Attrition associated with sleep bruxism. Notice the wear of the lower teeth. Image provided by "Dr. G. Gary Demerjian". (**b**) Severe attrition seen in sleep bruxism. Notice the flat edges of the upper and lower teeth. Image provided by "Dr. Pooja Goel". (**c**) Severe recession and abfraction. Abfractions are indentations of the teeth at the gum line, as seen in this photo where tooth-colored fillings have been placed. Image provided by "Dr. G. Gary Demerjian". (**d**) Buccal exostosis. Overgrowth of bone indicated by the arrow. Image provided by "Dr. G. Gary Demerjian"

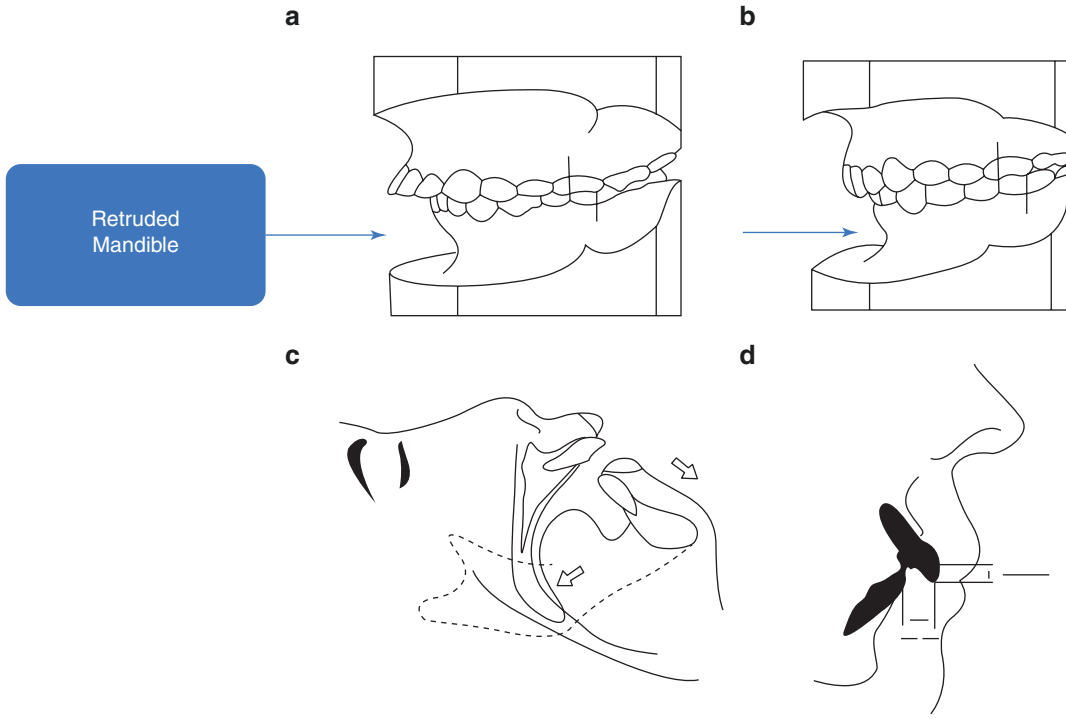

Fig. 8.5 Maxillary and mandibular relationship. Adapted from Miyao E et al. (**a**) Maxillary protrusion/mandibular retrusion, (**b**) deep overbite, (**c**) upper airway and protrusion of maxillary anterior teeth during sleep in a patient with mouth breathing, (**d**) measurement of overbite and overjet

a retrognathic placed mandible and can lead to OSA. Also, the Sella-Nasion to B point angle (SNB) is smaller, less than 80°, in nonobese patients according to this study and is a bony irregularity which can lead to the propensity of OSA. The lateral cephalometric steiner analysis depicts a recessive mandible. Please refer to Fig. 8.6 [150, 153]. The hypothesis is that maxillofacial anomaly, also known as malocclusion, may play a critical role in increased propensity of OSA. The supportive fact for the hypothesis is that the inability of the lip closure around an increased overjet/overbite in subjects can eventually lead to increased tension in the orbicularis oris muscle, which will lead to the imbalance of pressure in the ring of muscles of orbicularis oris, buccinator, and constrictor superior muscles. The ring of muscles mentioned above plays a crucial role in the physiology of breathing in human beings. Any unwanted increase in the tension of these muscles can lead to a narrowing of the airway and decrease the posterior airway space and contribute to OSA in patients [154]. The effects of oral appliances on OSA and the upper airway, involving alterations in the dentofacial morphology, have been investigated extensively by the dental field of orthodontics [155–158].

Class I

Class I is known as normal occlusion. When the jaw and the molars are in normal alignment, however the teeth may be crowded/rotated or missing. Normal position of the tongue rests against palate posing a balancing force on the teeth between the tongue and cheek muscles.

Class II

Class II is known as retrognathia of the mandible. An overbite occurs when the mandible is deficient, and therefore the maxilla protrudes over the mandible.

It has been accepted for decades that dental arches in mouth breathers can be influenced by an imbalanced muscular function [159]. Nasal breathing due to obstruction can impact the facial growth was acknowledged, by Schendel described as a long face [160]. The dental relationship is mostly determined by genetics [161] and adaptation to breathe; therefore mouth breathing is a secondary etiological factor to class II development.

Several observational studies found that a class II malocclusion seen in permanent dentition had an underlying skeletal imbalance which can be detected as a distal step in the primary or deciduous dentition [162–164]. Baccetti et al.

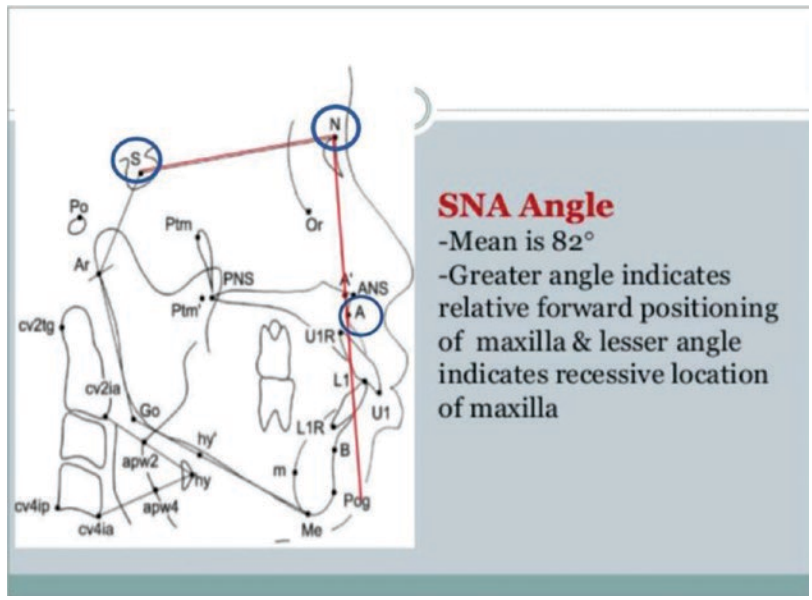

Fig. 8.6 SNA angle. Adapted from Nabil et al. SNA landmarks from the lateral cephalometric analysis are circled

concluded that in the primary dentition, when looking at the dental relationships in the sagittal plane, the mandibular teeth will have a distal step, the canine will be in a class II relationship, and an excessive overjet will be seen. A transverse interarch discrepancy is due to a narrower maxillary arch which is a common feature of early class II malocclusion. Skeletal findings of class II malocclusion in children is clinically seen as mandibular retrusion and shorter total mandibular length [162]. When looking at the transition during mixed dentition, class II occlusal characteristics are either maintained or even worsen. Treatment to correct the class II malocclusion should be initiated in all three planes of space by expanding the maxilla and using mandibular repositioning to aid in the skeletal development.

As the mouth stays open to breathe, the tongue does not rest against the palate to resist the forces of the facial muscles; thus the maxillary arch can become narrow, and the mandible rotates back and down, causing an anterior open bite and a posterior crossbite. Environmental factors such as sucking habits (fingers or pacifier) and mouth breathing work as a secondary cause in creating an anterior open bite [74, 165]. Mocellin et al. found palatal constriction in 63% of mouth breathers and 5% of nasal breathers. This demonstrated the correlation of posterior crossbite to be significant factor for mouth breathers in relation to the general population [97]. Souki BQ and colleagues concluded in their study that children in primary dentition with nasal obstruction have a higher prevalence of posterior crossbite than the general population. Subjects in mixed and permanent dentitions, who present as mouth breathers, were more likely to present with an anterior open bite and class II malocclusion. There is also a sample of mouth breathers with the presence of rhinitis, adenoid, and tonsillar hyperplasia where there is no association with the prevalence of class II malocclusion, anterior open bite, and posterior crossbite [97].

According to a study by Banabilh conducted on 120 adults, the class II malocclusion patients are significantly more prevalent in the OSA category. The subjects with OSA, when compared to the control group, had a larger number of candidates with a convex profile, class II malocclusion, and the V-shaped palate [166]. Similarly, another study conducted in 2008 supports the hypothesis that malocclusion and OSA are linked in nonobese subjects. Specifically, those with an overjet bite had increased chances of OSA [150].

Class III

Class III is when the mandible is larger than the maxilla that causes the anterior teeth to be edge to edge or an underbite [70]. Most cases of skeletal discrepancy are due to insufficient growth of the maxilla or an overgrowth on the mandible. The tongue position in class III subject is resting at the lower dental arch. If the tongue is not filling the palate to balance the buccal forces of the facial muscles, that can cause a narrowing the maxillary arch. This author believes that due to the tongue position and the need to breathe, the patient will subconsciously protrude the jaw, thus causing a dental and skeletal class III.

Iwasaki et al. compared the cephalometric of class I to class III regarding the position of the maxilla, the mandible, and the oropharyngeal airway. The class III group had mandibles more anterior than the class I group. There was no difference in the nasopharynx, but the oropharyngeal airway was significantly larger in the class III group, indicating a low tongue position [167]. Also, the difference of the oropharyngeal width was wider in the class III, indicating hyperplasia of the palatine tonsil. In class III children, the hypertrophy of the palatine tonsils and the lower position of the tongue affect both occlusal relationships and upper airway space [70, 168–170]. With the use of CBCT, children with class I malocclusion had a square oropharyngeal airway 84% of the time, and children with class III malocclusion had a relatively flat rectangular shape 70% of the time, either in the lateral direction (55% wide) or anteroposterior direction (15% long) [167].

Cross-sectional area of the oropharynx tends to be wider in proportion to the severity of the class III malocclusion, thus indicating the class III children have less occurrence of OSA. Several

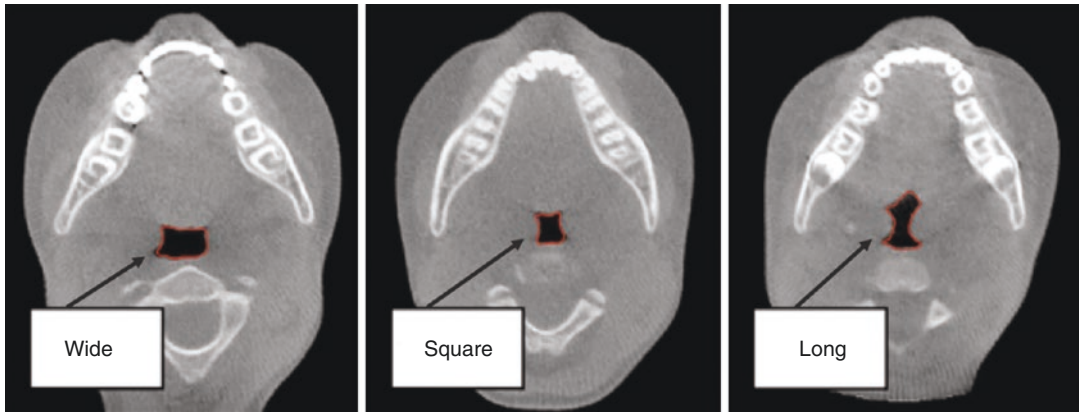

Fig. 8.7 Oropharyngeal airway shapes. Adapted from Iwasaki T et al. The arrows are pointing to the oropharyngeal airway

studies found that the base of the tongue is 3.0 mm inferior in patients with severe OSA than in those with mild to moderate OSA [171] (Fig. 8.7).

Breastfeeding and Non-Nutritive Sucking Habits

There is considerable body of literature indicating the link between breastfeeding and non-nutritive sucking patterns such as thumb-sucking and pacifier into the proper development of dental arches. There is concrete evidence suggesting that non-nutritive sucking habits can lead to an increased propensity of malocclusion such as anterior open bite in the primary dentition. In the study conducted by Romero, it was concluded that consistent breastfeeding for 12 months decreased the chances of an anterior open bite by 3.7 times. Comparatively, consistent yearly non-nutritive sucking habits increased chances of malocclusion development by 2.38 times. Interestingly enough, there was another finding having to do with the length of duration of breastfeeding. If an infant was breastfed for less than 6 months, their chances of developing an improper dental arch was increased by 5.35 as compared to infants who were breastfed for more than 12 months. The anterior open bite and development of malocclusion lead to dental skeletal alterations which caused improper swallowing pattern, improper speech, and improper posture of tongue in the position [172]. Certain congenital conditions such as ankyloglossia (tongue-tie) can pose difficulty occasionally in breastfeeding neonates and infants. Approximately 4.2–10.7% newborns are affected with tongue-tie. Tongue-tie is a condition where mobility of the tongue is limited due to an exceptionally short lingual frenum. The research conducted by Rowan-Legg on 36 neonates with ankyloglossia showed that there is evident incidence of latching difficulty ranging from 19% when compared to a control group where there was 0% difficulty. Furthermore, breastfeeding was overall proven to be difficult with neonates suffering from ankyloglossia by 25% when compared to the control group who had 0% difficulty. A procedure known as frenotomy can be performed if there are major breastfeeding issues caused by tongue-tie to relieve in neonates [172]. When there is a tight maxillary frenum, the newborn will have improper latching of the breast, creating a difficulty with breastfeeding [173].

If the newborn cannot breastfeed, the tongue will not function properly and be trained for proper swallow patterns. During suckling, the tongue places forces on the breast to extract the milk and to move it from the front of the mouth to the posterior of the mouth to swallow. The mandible also moves forward and back with the tongue to move the bolus of milk. This movement of the tongue will develop the palate, and the mandibular movement will develop mandibular growth. Therefore, releasing the maxillary and

lingual frenum requires an early diagnosis and treatment. This can potentially prevent developmental problems [173].

However, according to Sum there is research suggesting certain parafunctional habits; nonnutritive sucking habits such as digit sucking and pacifier have detrimental effect on dental occlusion and dental arches. According to this 2015 study conducted on 851 children, between the ages of 2 and 5, these habits can lead to the development of anterior open bite, decreased overbite, increased overjet, posterior cross bite, and constricted arches. Narrow maxillary arches are quite frequently associated with digit sucking. Breastfeeding more than 6 months can lead to a proper development of dental relationship by developing the arches into anterior sagittal and transverse dimensions. Constant breastfeeding in children for more than 6 months leads to a lower frequency of development of class II incisal relationship, less increased overjet, and a wider intercanine and intermolar widths. Hence, we can conclude that proper development of arches will lead to proper swallowing function, speech function, and proper posture of the tongue and the correct balance of forces between orofacial musculature [174]. In conclusion, getting rid of parafunctional habits and following proper breastfeeding way of nutrition for neonates will lead to less craniofacial development abnormalities and help the children to develop a normal airway leading in proper breathing.

Bi-Extractions and Narrow Dental Arches

There is controversy regarding the effects of four premolar (bicuspid) extractions on the oropharyngeal airway. In orthodontic premolar extraction cases, the treating dentist or orthodontist is looking at trying to correct issues of crowding or bimaxillary dentoalveolar protrusion. In a study of adolescents, orthodontic treatment was done in combination with extraction of four premolars, resulting in no influence on oropharyngeal airway volume [175]. Germec-Cakan reported a narrowing of the oropharyngeal airway in orthodontic cases following four bicuspid extractions, where maximum anchorage was used in retraction of the anterior teeth. Conversely, when the anterior teeth were not distalized and the molars were medialized, the airway dimension was increased [176]. In a study, 14 children were chosen who had a malocclusion and OSA confirmed with a PSG. Ten of the subjects completed rapid maxillary expansion (RME) over a 12-month period. Two of the children had a fail result. Of the other eight subjects, the apnea-hypopnea index (AHI) decreased by the end of the treatment period, and the symptoms had resolved. Two years after the end of RME, there were no significant changes in the AHI [177]. Any changes in the position of incisors and soft tissue can potentially affect tongue position and oropharyngeal airway [175]. In bimaxillary protrusive patients, extraction of four premolars and retraction of the incisors affected velopharyngeal, glossopharyngeal, hypopharyngeal, and hyoid position [178]. In a systematic review, Hu Z concluded that based on the current evidence, more trials are needed with reliable evidence. In cases of extractions, followed by retraction of the anterior teeth (reducing the inclination of the incisor) causes upper airway narrowing by reducing the tongue space and causing retraction of the tongue. Mesial movement of the molars increased the posterior tongue space enlarging the oropharynx dimensions [148].

If we treat OSA cases in the early developmental phase, we can potentially help develop patients skeletally in the dentofacial region when they are in mixed dentition, to possibly avoid extraction of permanent teeth and widen the dental arches to create more room to the tongue in the long term. When looking at skeletal discrepancy cases, such as class II or class III, there is usually underdevelopment of mandible or maxilla [166]. If there is any underdevelopment, we believe that when teeth are extracted in order to close that space, the anterior teeth have to be retracted, thus resulting in reduction of space for the tongue. Furthermore, as the subject grows into adults, all of the hard and soft tissues continue to grow and develop except the size and shape of the teeth. We need long-term studies showing the relationship between dentofacial airway development, respiratory function, and oropharyngeal collapsibility (Fig. 8.8).

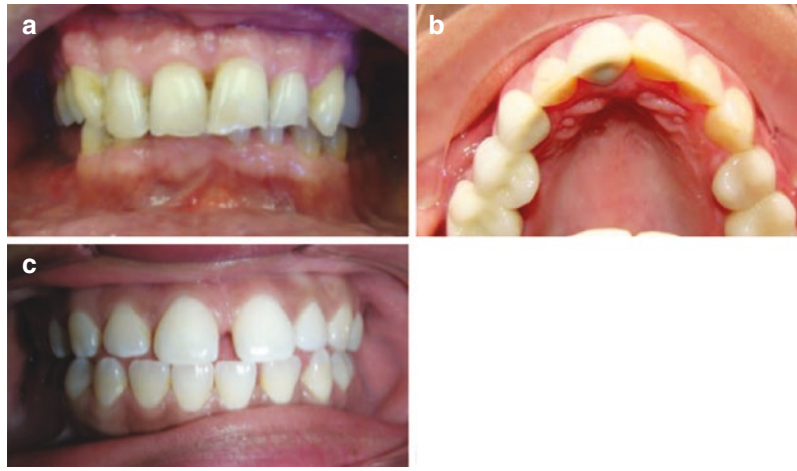

Fig. 8.8 (**a**) Deep bite malocclusion. A deep bite occurs when the upper anterior teeth cover most of lower front teeth. Image provided by "Dr. G. Gary Demerjian". (**b**) Missing first premolars. Extraction of bicuspids causes a shortening and narrowing of the Dental arch resulting in less room for the tongue. Image provided by "Dr. G. Gary Demerjian". (**c**) Interproximal spacing. Notice the spacing between the teeth. Four premolars were extracted on this person, and tongue is pushing when swallowing due to the limited tongue space. Image provided by "Dr. Chetan Parikh"

Tori

There is insufficient of evidence directly associating maxillary and mandibular and tori to OSA. The concept of bone remodeling or growth as it adapts to mechanical forces is called Wolff's law. However, this is not always true and is comprised of various processes [179]. According to Drs. Prehn and Simmons, parafunctional habits such as clenching and grinding can be secondary to offset the restricted or reduced airway caliber to prevent its collapse. Patients with sleep bruxism as a result of sleep-disordered breathing such as OSA are prone to lead to formation of buccal exostoses and the mandibular tori [180]. Mandibular tori are more frequently found bilaterally on the premolar area onto the lingual aspect of the mandible. Overgrowth of bone in the oral cavity can lead to narrowing of the oral cavity volume and will leave minimal space for the tongue to rest in the floor of mouth. Hence, the tongue will have a tendency to fall back into the upper airway due to gravity. Eventually, the oropharyngeal region will crowd and cause upper airway obstruction. Upper airway narrowing can lead to OSA. There is no cause and effect relation with tori and OSA. The surgical removal of tori has led to improvement of OSA in many cases. Once the tori are removed, the oral volume is increased which then allows the tongue to have more room and open airway. Although there is not a direct relation between tori and OSA, there is an indirect link [181]. In another 2016 recent study, it was concluded that if the tori are larger than 2 centimeters, then the possibility of OSA in a patient may be present [182]. If a patient has these kinds of malformations of bone morphology and has associated sleep-related issues, he/she should be asked to get a sleep study done by the sleep physician to rule out the possibility of sleep apnea. In children if parents do bring out the concern of habitual snoring, clenching, and grinding and evident wear and tear on the primary dentition noticed by the dentist, they should be given a referral for the sleep physician or the ear, nose, and throat specialist to rule out the OSA. Tori and nocturnal bruxism are not the telltale symptoms for the diagnosis of sleep apnea but can be a valuable diagnostic tool in the armamentarium of dentist to rule out the classic triad of TMD, sleep-disordered breathing, and malocclusions [180] (Fig. 8.9).

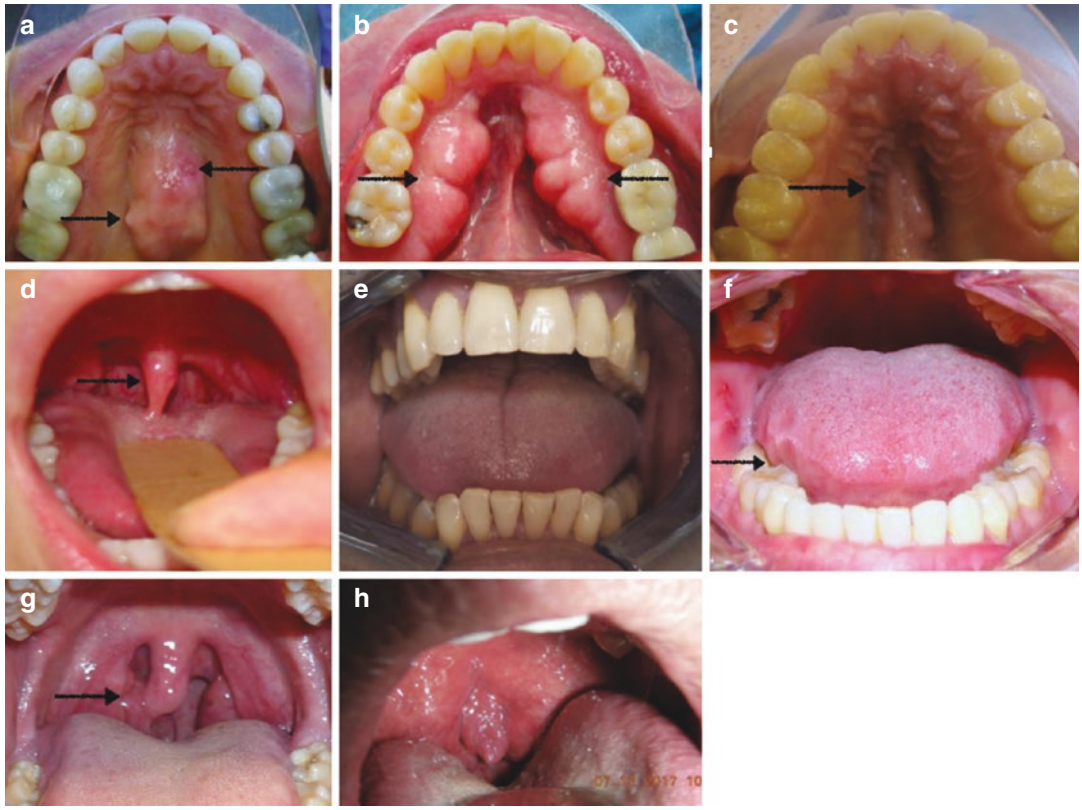

Fig. 8.9 (**a**) Maxillary tori. Notice the overgrowth of bone at the center of the palate. Maxillary tori are due to the stimulation and flexion of the maxillary sure caused by bruxism. At the right arrow is a sore spot which is healing due to abrasion from eating hard food. Image provided by "Dr. G. Gary Demerjian". (**b**) Bilateral lingual mandibular tori. Mandibular lingual tori are the overgrowth of bone cells (osteoblasts) due to stimulation from bruxism. Image provided by "Dr. G. Gary Demerjian". (**c**) Narrow maxillary arch and high-vaulted palate. Clinical symptoms seen in patient with snoring and sleep apnea. Image provided by "Dr. G. Gary Demerjian". (**d**) Elongated uvula. Due to the pulling of the uvula during snoring. Image provided by "Dr. G. Gary Demerjian". (**e**) Enlarged tongue. Large tongue placed above the occlusal plane of teeth. Image provided by "Dr. Pooja Goel". (**f**) Scalloped tongue. The side of the tongue is scalloped taking the shape of the teeth, indicated by the arrow. Image provided by "Dr. G. Gary Demerjian". (**g**) Enlarged tonsils. Notice the uvula touching the tonsil on the left and the tonsil on the right is half way between the pharyngeal wall and the uvula. Image provided by "Dr. Mayoor Patel". (**h**) Elongated and edematous uvula and soft palate. Image provided by "Dr. Chetan Parikh"

8.7 Dentofacial Changes Via Orthodontic/Orthopedic Treatments

8.7.1 Maxillary Expansion

The term maxillary constriction refers to a narrow maxilla, in the lateral dimension relative to the mandible. Maxillary arch width was significantly smaller in the groups of OSA and snoring children than in the control group [12]. Based on clinical observations, many clinicians suggest that maxillary constriction may also play a role in the pathophysiology of OSA. The maxillary arch width is measured by the distance between the first molars [183]; this can be seen clinically in OSA patients [184]. It is known that subjects with narrow maxilla have increased nasal resistance causing one to mouth breathe [185] and causing the tongue to acquire a low posture [186, 187]. A low tongue posture can result in retroglossia, causing oropharyngeal narrowing and possibly affecting OSA

[188, 189]. In cases of Marfan's syndrome, which is characterized as having a high palatal arch with maxillary constriction, they are known to have a high prevalence of OSA, where the degree of sleep apnea is correlated with the measurements of the maxilla [190].

Several studies have investigated the radiographic changes after maxillary expansion of the nasal cavity using a posterior-anterior cephalometric radiograph [185, 191]. Acoustic rhinometry was used before and after expansion, which revealed an increase in the nasal volume and minimum cross section and a decrease in nasal resistance [71, 192, 193]. Due to the variations in the individual response to the expansion, the degree of reduction of nasal resistance cannot be predicted [194, 195], but over 50% of patients with maxillary expansion subjectively reported an improvement of breathing [194].

Maxillary expansion has been studied for years and recently with the use of mini-implants (MI), also known as temporary anchorage device (TAD). Maxillary expansion separates the mid-palatal suture and cause less tipping of the teeth, depending on the type of expander being used [196]. The use of TADs has expanded to include various clinical applications: correction of deep bite and occlusal cants; closure of extraction spaces; dental midline alignment; intrusion, extrusion, and uprighting of teeth; retraction of anterior teeth; medialization and distalization of posterior teeth; and correction of sagittal discrepancies and vertical skeletal discrepancies which traditionally require orthognathic surgery [197–202]. Several investigations have evaluated the failure rates and success rates of MIs and risk factors associated with their use as temporary anchorage devices (TADs) for orthodontic purposes. According to these studies, the success rates of MIs have significantly increased to between 75.2 and 90.7%. Researchers believe that MIs have already become efficient anchorage devices for orthodontic purposes and suggest them as the conventional anchorage devices of future everyday clinical practice [199–201].

8.7.2 Hyoid Bone

The connection of the hyoid bone to the surrounding musculature has been implicated in maintaining oropharyngeal patency. Various studies have demonstrated that changes in mandibular position can result in changes to the hyoid position [203]. Several studies reported that patients with mandibular retrognathia had a posterior position of the hyoid bone and an association with narrowing of the oropharyngeal airway [204, 205]. In a cephalometric study of skeletal class I compared with class III subjects, Adamidis and Spyropoulos found a significant difference in the position of the hyoid bone [206]. The contraction of the hyoid muscles caused a reduction of airway resistance as a response to chemical, vagal, and negative-pressure stimuli [76]. There is also a correlation between the length of the hyoid bone muscles, head position, and upper airway volume [207]. In an orthodontic study, Parisella V found in cephalometric analysis that the hyoid position was modified by maxillary arch expansion, reconditioning tongue posture and function. Orthodontic treatment resulted in the skeletal improvement of class II malocclusion of the skeletal class I [208]. In surgical studies, surgical advancement or setback of the mandible influences the hyoid position. The hyoid bone is typically described as being inferiorly positioned in OSA patients [154, 209]. The oropharyngeal airway was shown that mandibular advancement resulted in a forward displacement of the hyoid with minimal widening of the pharyngeal airway [210], whereas in surgical mandibular setback cases, the opposite was true [203, 210]. The mechanics of an oral appliance for the treatment of OSA is mandibular advancement to cause tension of the pharyngeal muscles in order to keep the airway patent. Therefore, when advancing the mandible with an oral appliance, the hyoid position can be a determining factor of airway patency.

8.8 Dental Orthopedic Jaw Position: Loss of Vertical Dimension/Bite Collapse

Pharyngeal narrowing can occur at the oropharynx, at the level of the tongue and soft palate or hypopharynx. Several structural changes in craniofacial morphology have been associated with

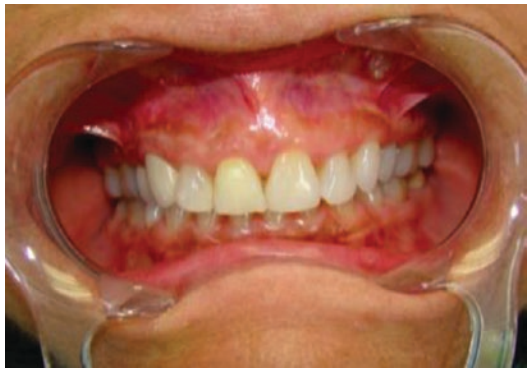

Fig. 8.10 Deep overbite. Image provided by "Dr. G. Gary Demerjian"

OSA pathogenesis, such as retrognathia of the mandible, posterior placed pharyngeal walls, macroglossia, and soft palate collapsibility [211]. Loss of vertical dimension due to loss or absence of teeth produces prominent anatomical changes that influence oropharyngeal size and function, therefore resulting in reduction of the lower face height and mandibular rotation [212]. In several studies, Bucca and his colleagues show a worsening of OSA with the extraction of teeth where the subject slept without their dentures. They observed the retropharyngeal space (RPS) and posterior airway space (PAS) to be reduced. Anatomical changes were caused by the decrease in vertical dimension of occlusion (VDO) resulting in the collapse of orofacial structures [213]. In same edentulous subjects, after wearing complete dentures and having an acceptable VDO, the RPS and PAS were found to increase, resulting in an improvement of the OSA, due to restoration of the VDO [214]. This also applies to patients with deep overbite, where the tongue has no room but to retract into the oropharyngeal airway (Fig. 8.10).

8.8.1 American Academy of Dental Sleep Medicine (AASM)

8.8.1.1 Recommendation on Dental Sleep Appliance Therapy

Whether or not the oral appliance is an effective treatment modality for the treatment of OSA used to be a matter of debate, perhaps owing to fewer number of studies. There is a wealth of literature on the efficacy of oral appliances in the treatment of OSA in the past few years. A task force of seven members, three physicians board certified in sleep medicine, two dentists, and two AASM research staff members were put together to develop the guidelines stated below [215].

8.8.1.2 Suggested Recommendations

1. Sleep physicians should prescribe oral appliance therapy, rather than no treatment, for adult patients who do not have OSA and want treatment for primary snoring. (*Standard*)

   When we weigh the benefits over risk, certainly the benefits are lot more in controlling the health consequences of snoring by providing the treatment for it. If the primary snorers have tried the other treatment modalities such as weight loss and positional therapy and want another treatment, then they should be prescribed for an oral appliance by the sleep physician, to be fitted by a qualified dentist [215].
2. When sleep physicians prescribe oral appliance therapy (OAT) for adults with OSA, qualified dentists should fabricate custom, titratable appliances over prefabricated appliances. (*Guideline*)

   An evidence-based systematic review clearly shows that the custom titratable oral appliances are effective in improving the sleep physiologic sleep parameters such as decreasing the AHI index, decreasing the arousal index, increasing the oxygen saturation, and possibly also improving the daily function and quality of life. Therefore, OAT should be considered as treatment of choice for the patients who are suffering from OSA and cannot tolerate CPAP or prefer alternate therapy [215].
3. Sleep physicians should consider prescribing OAT, for patients diagnosed with OSA who are CPAP intolerant or prefer alternative treatments, rather than no treatment. (*Standard*)

   Although some of the sleep physiologic parameters such as AHI, arousal index, ODI, and oxygen saturation levels are better improved by CPAP as compared to OA, the adherence is better with OA. Hence an oral appliance outweighs the efficacious nature of CPAP and should be offered to adult patients

who are intolerant to CPAP and prefer alternative therapy [215].

4. Qualified dentists should regularly monitor OAT outcomes for OSA patients to minimize the occurrence of undesirable side effects. (*Guideline*)

   The side effects caused by the use of OAT are not permanent or major in nature. All the therapies have pros and cons, and having said that OAT for the treatment for OSA is no different. With the proper supervision and constant follow-up by the dentist, the impact of undesirable side effect can be superseded [216].

5. Sleep physicians should perform follow-up sleep testing to confirm or improve OAT efficacy. (*Guideline*)

   In many instances, after the subjective relief of symptoms, patients might have residual OSA and high AHI. The follow-up sleep testing with sleep physicians can allow the dentist to redesign or further titrate the appliance to achieve better efficacy and success with the oral appliance [216].

6. Sleep physicians and qualified dentist should instruct adult OSA, who are being treated with OAT, to return for periodic follow-up visits. (*Guideline*)

   For a chronic condition like OSA, even after the successful treatment, the recommendation is to do 6-month follow-up for the first year followed by yearly follow-up visits. This proposal is made to make sure that dentist can oversee the condition of oral appliance such as excessive wear and tear, cracks, discoloration, and lack of retention. Also, if the patient's symptoms have come back, then further sleep testing can be done by sleep physician, and depending on the results, either a new appliance can be made or the old appliance can be titrated further [216]. All of this is possible only if the protocol is followed for the periodic visits after rendering the treatment.

8.9 Medical Intervention

8.9.1 Diagnosis

Whether a patient has OSA or is at risk of developing the complications of OSA is a complex, multifold method. The most important step in the diagnosis of OSA is to start with a complete sleep-oriented history and a physical examination carried out by a sleep physician. Following the initial exam, if a patient falls into a high pretest probability of suffering with sleep-disordered breathing, then they should be referred for further objective testing conducted by an acceptable method in order to have an established diagnosis of OSA. The two commonly used methods for objective testing are an in-laboratory PSG and with portable monitors (PM). The two out of many major AASM practice parameters to be diagnosed with OSA with PSG and PM are as such: PSG is routinely indicated for the diagnosis of sleep-related breathing disorders (Standard). PMs may be used to diagnose OSA when utilized as a part of comprehensive sleep evaluation in patients with a high pretest likelihood of moderate to severe OSA (Consensus). PM testing is not indicated in patients with major comorbid conditions including, but not limited to, moderate to severe pulmonary disease, neuromuscular disease, or congestive heart failure or those suspected of having a comorbid sleep disorder (Consensus) [1].

8.9.2 Treatment Options

A long-term, multidisciplinary course of medical intervention should be considered for a chronic disease like OSA. There are behavioral/medical/surgical options along with some very effective adjunctive therapies such as weight loss, positional therapy, myofunctional therapy, or pharmacological intervention which are used along with the major primary treatment rendered for the treatment of OSA for better success and improvement of results. The patient should be completely engaged in the discussion of the commonly offered treatment options, including their associated modalities, risks, and benefits. OSA management is evaluated by looking at several factors such as decrease in daytime sleepiness, improvement in the oxygen saturation, improved quality of life measures, patient and spousal satisfaction, adherence to the therapy, and long-term management of sleep apnea. While fractional improvement may be of

significant benefit, achievement of the threshold level of apnea severity at which there is no significant morbidity or mortality would appear to be the desired goal [1].

8.9.3 CPAP

The gold standard of care for the treatment of OSA is with positive airway pressure (PAP) therapy. PAP is a treatment modality which leads to the pneumatic splinting of the upper airway. PAP can be of various kinds such as CPAP (continuous positive airway pressure), bi-levels of pressure in PAP, auto-PAP, or servo ventilation PAP. Depending upon the severity of OSA, the initiation management and follow-up of PAP therapy should be approached by a multidisciplinary team. The patient should be well taught about the functionality, adherence, and maintenance of their equipment to make it a success by their disease management team. After the initial PAP setup, active follow-up by the appropriate trained health providers is indicated yearly and as needed to troubleshoot PAP mask, machine, or usage problems [1].

8.9.4 Oral Appliance

Over the past decade, oral appliances have emerged as a well-proven alternative in the treatment of OSA. Oral appliance therapy (OAT) works by modifying the position of the mandible, the tongue, and the pharyngeal structures. A proper diagnosis of OSA should be made by a sleep physician followed by a prescription of oral appliance before the initiation of OAT. A complete dental examination, including the condition of teeth, periodontal tissues, and TMJ, is crucial prior to therapy. The AASM guideline is that custom-made titration appliance should be considered over non-custom appliance for better efficacy [215]. The meaningful definition of response must include outcomes such as improved sleep, improved oxygen saturation, decreased AHI, improved sleep architecture, improved EDS (excessive daytime sleepiness), and improved quality of life [217]. Additional cardiovascular and neurobehavioral outcomes should also be improved. A regular follow-up is required to make sure adherence is there and no recurrence symptoms and also to evaluate no breakage or wear/tear of appliance [216].

8.9.5 Surgical Treatment

Patients who cannot tolerate or failed PAP and OAT or patients with established diagnosis of OSA who have severe obstructive anatomy that is surgically correctable (e.g., tonsillectomy) or maxillary and mandibular deficiency and have a preference for surgery should be given an option of upper airway surgery [218]. Upper airway can be an important treatment option in patients and can help to resolve the concern of patient compliance to treatment modalities such as PAP and OAT therapy [219]. In order to be successful, upper airway surgeries require the proper patient selection, proper procedure selection, proper procedure execution, and proper skill set of the surgeon, recognizing the primary site of correctable probability, which is causing the OSA [218]. There are three main subdivisions for surgery alternatives. The first one is to reconstruct the upper airway including procedures such as nasal operations, uvulopalatopharyngoplasty (UPPP), expansion sphincter pharyngoplasty (ESP), palatal implants, tonsillectomy, tongue volume reduction, genioglossal advancement, and maxillomandibular advancement (MMA). The second surgical alternative is the use of a hypoglossal nerve stimulator. The stimulator is implanted in the chest and acts like a pacemaker, and the lead wire is implanted under the tongue at the hypoglossal nerve. The hypoglossal nerve innervates the tongue muscles (genioglossus, hyoglossus, and styloglossus). It sends signals to the tongue muscles causing a contraction of the tongue muscles, thereby keeping the oropharynx open. The third surgical alternative is to bypass the upper airway by doing the surgery such as tracheostomy [217]. With all the recent advancements in the technology and new surgical approaches, there is a data suggesting a satisfactory success rate of about 70 to 99% with combined surgical procedures [218].

8.9.6 Adjunctive Therapy

Adjunctive therapies include weight loss, bariatric surgery, positional therapy, myofunctional therapy, and pharmacological intervention. These therapies can be an immensely effective tool in your armamentarium, along with the primary treatment of OSA to improve the results drastically.

8.9.7 Bariatric Surgery

Bariatric surgery is indicated in patients with a body mass index (BMI) greater than or equal to 40 kg/m^2 or with BMI greater or equal to 35 kg/m^2 with potential comorbidities. Bariatric surgery can lead to reduction in the 75% of RDI [220]. When speaking of BMI, 35 kg/m^2 is equivalent to at least a height of 58 inches with a weight of 167 pounds. 40 kg/m^2 is equivalent to at least a height of 58 in. with a weight of 191 pounds ("body mass index"). A close and active follow-up with these patients is absolutely critical. According to a study conducted on 600 subjects, it concluded that a 10% weight gain predicted in a 32% increase in AHI and a 10% loss of weight predicted a 26% decrease in AHI [221]. According to the study conducted by Maree when a proper 16-week diet and exercise program was tailored for patients with mild to moderate OSA, the results showed significant improvement in variables such as neurobehavioral and cardiometabolic outcomes but no significant changes in sleep-disordered breathing [222].

8.9.8 Pharmacological Management

The exacerbation of existing OSA can be prevented by the avoidance of sedatives and alcohol. AHI and apnea length increased significantly resulting in greater hypoxemia in subjects with severe OSA [223]. There is insufficient literature supporting the role of drug therapy in OSA. Drug therapy is not much of clinical value [217]. Certain medications such as SSRI, strychnine, nicotine, progesterone, protriptyline, and acetazolamide have been used in the past to increase the upper airway tone but are no longer used [44]. Supplemental oxygen has limited role in treatment of OSA. Some of these medications that have been shown to have beneficial effects on the treatment of OSA have been constrained because of their side effects. In patients with residual sleepiness after CPAP, FDA-approved drug such as modafinil, which is a wake-promoting agent, can be of beneficial use [224]. Thyroxine can be beneficial in patients suffering with OSA with hypothyroidism [44].

8.9.9 Myofunctional Therapy

There is evident literature supporting the role of myofunctional therapy as a very effective adjunctive tool in healthcare provider's armamentarium to treat OSA. The severity of OSA can be reduced by 50% reduction of AHI in adults and 62% in children according to the study conducted by Camacho M [225]. Upper airway patency is a result of complex interplay of the balancing forces between negative inspiratory intraluminal suction as a result of diaphragm constriction and dilating forces of the pharyngeal muscles [219]. There have been unsuccessful attempts in improving the neuromuscular control of the abnormal pharyngeal dilator muscles with the aid of medications and nerve stimulators [219]. The myofunctional therapy is comprised of isotonic and isometric exercises that train the oropharyngeal structures such as soft palate, tongue, and facial muscles and the dilator muscles. The goal behind the myofunctional therapy is to increase the tonicity of the abovementioned muscles of oropharyngeal tissues and is to train the tongue to be positioned in the oral cavity at the right place, which is to place the tip of the tongue at the incisive papilla as the rest of the tongue is resting on the palate to encourage the nasal breathing as compared to mouth breathing. The results according to the study done by Camacho M were impressive. The results were as such; myofunctional

therapy reduced the snoring both subjectively and objectively. There was improved reduction in Epworth Sleepiness Score (ESS). Regardless of heterogeneity in the muscles of oral cavity and the nature of oropharyngeal exercises, there was a consistent improvement in the AHI and the subjective sleepiness scales [225].

8.9.10 Positional Therapy

There is wealth of data supporting the fact that the severity of OSA and the frequency of AHI events are far less in the lateral and non-supine positions as compared to supine position in OSA patients. What exactly happens in the lateral position that leads to increased activity of dilator muscle activity and opens up the airway is questionable. According to the study conducted by Matsuzawa Y, the constriction of the oropharyngeal was more severe in the supine posture [226]. The hypothesis was supported by the fact that gravity plays an evident role in it and the tongue will fall backward leading to stenosis of the oropharyngeal airway. According to the research study Tsuiki S, the velopharynx is the main contributing culprit site of obstruction and is the narrowest anatomical site in the pharynx and does keep changing with the different sleep positions [227]. The positional therapy thus can play a very important role as an adjunct therapy in addition to the primary treatment for OSA. By avoiding the supine posture, one can improve the subjective sleepiness and reduce the severity of AHI events in patients who have more events in the supine-related OSA [228]. Approximately 30–50% of patients with OSA can be treated with positional therapy alone [229]. A very interesting finding is that supine-dependent apnea is more prevalent in young, lean, and lower BMI patients. The same study suggested that non-positional obese patients became supine dependent after losing weight [228]. The various positional therapy methods are such as the use of the sleep position trainer [86], positional pillows such as cervical pillows, various bumper belts such as slumber belt and Rematee belts, and lastly the elevation of the head by 30°.

Conclusion

It has been an intriguing matter of debate which treatment option is better than the other. Our primary aim of this chapter was to show the correlation and improvements on immunologic and physiologic effects of dental sleep appliance therapy based on the improvements seen with CPAP therapy, and according to a randomized control study conducted by Phillips, it concluded that CPAP is more efficacious in reducing the objective variables such as AHI, arousal index, oxygen desaturation index, and respiratory distress index (RDI), but the adherence and compliance was better with OAT. The 24-h mean arterial pressure response was similar with both OAT and CPAP. However, neither one of the treatment options overall were able to improve the blood pressure. Similarly, other variables such as subjective sleepiness, driving simulator performance, and analysis of improved quality of life responded in a similar manner with both the treatment options. OAT was noted to be efficient in improving four general quality-of-life domains [230]. In a long-term study ranging 2.5–4.5 years, OAT remained effective in improving RDI, fatigue, sleepiness, sleep quality, blood pressure, cardiac rhythm, and quality of life [231]. We can conclude from the study that even though CPAP and OAT both work hand in hand in the treatment of OSA, the adherence and better compliance with OAT offsets the efficacy of CPAP because of inferior compliance eventually resulting in the similar effectiveness. Therefore, considering the comorbidities associated with OSA and being improved with CPAP, the treatment with OAT should also improve these OSA-related comorbid conditions.

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AIRWAY-kening® Orthodontic/ Orthopedic Development: A Correlation of Facial Balance, TMD, and Airway for All Ages

9

William M. Hang

Abbreviations

MAD	Mandibular advancement device
OSA	Obstructive sleep apnea
PSG	Polysomnograph
REM	Rapid eye movement
TADs	Temporary anchorage devices
TMJ	Temporomandibular joints
UARS	Upper airway resistance syndrome
UPPP	Uvulopalatopharyngoplasty

9.1 Why Do We Have a Problem?

The apparent epidemic of OSA which is occurring in all industrialized countries should not come as a surprise. Many in the sleep community routinely cite the increase in obesity rates over the last 3–4 decades as the cause of this epidemic [1–7]. There is no question that obesity is a factor. However, focusing on obesity causes us to ignore a more obvious issue that is a real problem. Our change in lifestyle since the advent of agriculture and, particularly, since the industrial revolution has resulted in changes to the human face. Faces no longer grow *forward* the way they did prior to our adoption of a Western diet. Mew describes a hypothetical Paleolithic profile and compares it with two commonly used cephalometric norms (Steiner and McNamara) [8]. Both these norms have both the upper and lower jaws substantially recessed from the Paleolithic norm. The Steiner norm is perhaps 6–8 mm. recessed in the maxilla alone. The point is that our faces are substantially further back from where they were a few thousand years ago. With the maxilla back, the soft palate which attaches to it is also recessed. With the mandible back, the tongue which attaches to it is also back. The airway in the region of the soft palate and tongue is the most prone to collapse and closure.

Remmers states that "…a structural narrowing of the pharynx plays a critical role in most, if not all, cases of OSA" [9]. Essentially he is saying that OSA would not exist if both jaws were forward in the face. The narrower the airway, the faster the air has to flow to get the same volume of air into the lungs. This rapid airflow goes over the curved surface of the tongue and/or soft palate producing a negative pressure (Bernoulli principle). The smaller the airway, the easier it is for this negative pressure to cause the tongue and/or soft palate to close and completely occlude the airway when the muscles are relaxed during certain sleep stages. The size of the airway is not diagnostic of OSA, but the incidence of OSA is much greater with diminished airway size [10].

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9.2 Facial Changes from Lifestyle Changes of Agriculture and Industrialization

Weston Price toured the world in the 1930s and noted a dramatic change in dentofacial structures in populations in the space of one generation [11]. He noted the dramatic increase in dental caries but also reported on the production of malocclusions in children of parents with normal faces, no malocclusions, and low caries rates. The one common factor in all the societies he studied was adoption of a Western diet with refined flour, sugar, and pasteurized milk.

Catlin [12] had observed essentially the same phenomenon as he described differences between Caucasians vs. Native Americans in the 1830s. He described the open-mouth posture of the Caucasians vs. the lip-together oral posture of the Native Americans and made a passionate plea for people to keep their lips together and breathe through their noses in his book first published in 1860. His illustrations clearly show the facial changes of both jaws falling back in people whose mouths are constantly open at rest. He further observed big differences in childhood mortality and overall disease rates between Caucasians in the Eastern USA to the Native Americans in the Western USA. He described the Native Americans as overall much healthier than the Caucasians.

Pottenger [13] experimented with two groups of cats and fed each group the exact same food. The first group was fed raw meat and unpasteurized milk. The second group was fed cooked meat and pasteurized milk. The cats in the second group were smaller skeletally, and within three generations many could not reproduce.

Corruccini [14] has spent his career investigating the differences in skeletal structures of humans based on differences in their diets. Studying genetically similar populations in India, he noted the more rural groups had better teeth and better developed faces than their urban relatives. He felt the differences were likely diet related with the rural group eating more raw food which required more chewing.

Lieberman's [15] book, *The Evolution of the Human Head*, outlines how faces in modern society have fallen back dramatically relative to our ancestors. He speculates the reason is our eating softer, more processed foods relative to our ancestors.

Harvold's [16] monkey studies showed how facial growth is caused to be more vertical (less forward) with alteration in the airway. He plugged the noses of normally growing, nasal breathing monkeys making them obligate mouth breathers. He noted vertical growth changes with longer faces and more recessed jaws. It is hard not to draw parallels between what happened to Harvold's monkeys and what occurs in growing children living today in industrialized countries.

The changes these investigators have noted clearly result in many people today having faces which have not grown as far forward as those of our ancestors. Therefore, airways are smaller as a result, and the OSA epidemic is not surprising.

9.3 Example of Face Falling Back with Growth

The patient in Fig. 9.1a–c illustrates how the lower face falls back with altered rest oral posture. The cheeks appear flatter as the maxilla drops back in the face and the mandible also drops back. The soft palate is attached to the maxilla and can be expected to fall back along with the maxilla. The tongue is attached to the mandible and will fall back as the mandible fails to grow forward properly. With minor exceptions one can expect that the airway will be reduced as a result of the maxilla and mandible failing to achieve its genetic potential for forward growth.

The facial changes illustrated by this example are not unique, but have actually become the norm to one degree or another. The changes occur slowly as growth proceeds so that most parents are unaware anything negative is happening. By the time children graduate from high school, many have noses which appear large because the maxilla has fallen back and mandibles are recessed massively from where they should have been had growth proceeded according to the genetic plan.

The impact that such falling back of the face has on the size of the airway has not made it into the mainstream growth and development literature. Orthodontists consider themselves the stewards of growth and development, and yet many articles are published in the journals without showing lateral head X-rays or any concern for the airway. Gelb [17] has brought attention to the importance of the airway and has coined the term "Airway Centric®" to bring attention to the importance of airway in diagnosis for all dental patients.

9.4 What Is Commonly Recommended for OSA in the Orthodontic Literature?

Low-rest tongue posture results in the maxilla narrowing [8]. Orthodontists often notice posterior crossbites and/or crowding of the teeth as reasons to expand the maxilla to correct these problems. More recently an awareness of OSA and a possible role for orthodontics in its treatment has emerged. The most common reaction in the orthodontic community is to expand the maxilla (laterally) as a solution for OSA [18–20]. Indeed this can help by creating more space for the tongue to be properly positioned upward in the palate at rest. Expansion of the maxilla laterally can be successful, but results are, by no means, a panacea.

Outcomes of such expansion can be dramatically improved if expansion is followed by myofunctional therapy to train the tongue to be firmly against the palate at rest. Combining expansion and myofunctional therapy can be helpful in eliminating OSA [21, 22].

An example of the need for myofunctional therapy is illustrated with the following case. Figure 9.2a–c shows the case of male who underwent traditional orthodontics to widen the maxilla as well as maxillomandibular advancement surgery in his mid-teens to open his airway, normalize facial balance, and eliminate his snoring problem. The surgery was a total success. He was told to wear his retainers full time for a year and nighttime forever. He was also instructed in the importance of adopting proper rest oral posture. Proper rest oral posture means having teeth together lightly, tongue firmly to the palate with the tip at the incisive papilla, and lips together without strain breathing through the nose. This patient did not adopt proper rest oral posture and stopped wearing his retainers 5 years prior to the last picture. The teeth crowded again as the width of the maxilla collapsed dramatically due to his low-rest tongue posture. Such a collapse of the maxilla also narrows the nasal airway increasing resistance to airflow affecting his ability to breathe.

Lateral expansion of the maxilla even if retained is relatively limited in its ability to solve airway problems since it ignores the fact that both the soft palate and tongue are distalized in

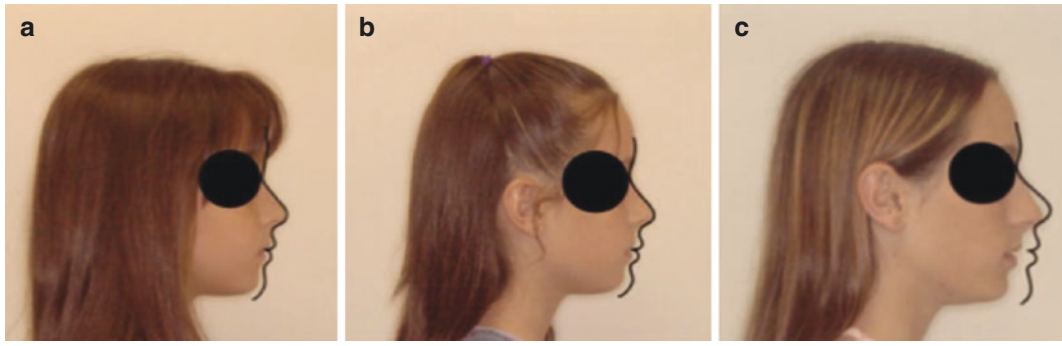

Fig. 9.1 (**a**–**c**) shows the results of poor rest oral posture with the maxilla and mandible both falling back relative to the Bolton norm superimposed on glabella and soft tissue nasion. Growth patterns like this are, unfortunately, completely normal in all industrialized countries

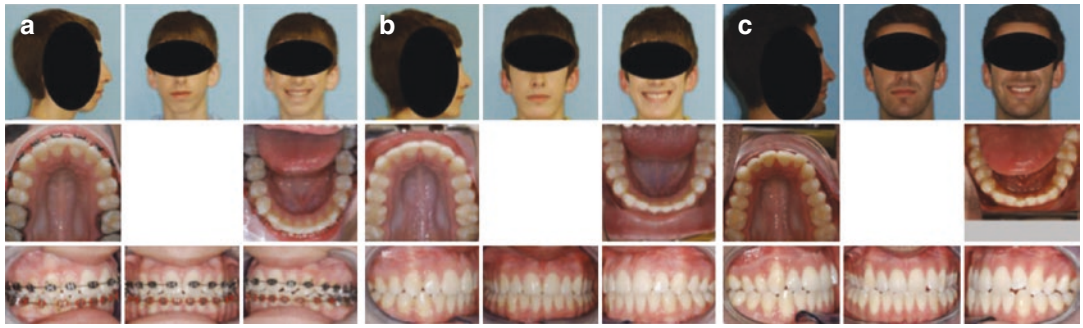

Fig. 9.2 (**a**) Patient with teeth aligned ready for orthognathic surgery. (**b**) Patient post-ortho and orthognathic surgery. (**c**) Patient after 5 years with no retainer with maxilla and mandible narrowed and incisors beginning to crowd due to low rest tongue posture

the face. Increases in the airway are limited as long as the anteroposterior plane of space is ignored. Lateral expansion should be viewed as a nice start in trying to address the OSA problem.

9.5 What Should Be the Focus of Orthodontics in Treating the Airway?

Some resolution of sleep apnea may be realized with lateral expansion, but our experience is that much bigger improvements can be achieved working in the anteroposterior plane of space. Remmers [8] comments focus on the anteroposterior plane of space. Mew indicates that the very first thing to change in every malocclusion is that the upper anterior teeth fall back from their ideal positions upward and forward [8]. Combining lateral expansion with forward development of the upper and lower jaws appears to give the patient the greatest chance of success in avoiding OSA or eliminating existing OSA.

9.6 Orthodontics Traditional Focus on the Anteroposterior Plane of Space

Angle's classification of malocclusion is focused entirely on the anteroposterior plane of space. One might, therefore, assume that Angle classification might be very useful in diagnosis and treatment of OSA problems. Nothing could be further from the truth. Reliance on an Angle classification is to be strongly discouraged. Angle Class I occlusions are supposedly "normal" jaw relationships. Normal, in this case, can often mean "normal" relative to each other, but not to the face. The teeth can, and often do, fit together nicely with each other, but the teeth exist in a face with both jaws massively recessed to the point that the patient has OSA.

The patient illustrated in Fig. 9.3a–c had a perfect Class I occlusion and a very compromised airway. Her chin was forward only because she had a chin implant. Her airway was dramatically reduced with an OSA diagnosis resulting. Her BP (with medication) was 179/121 prior to her undergoing maxillomandibular advancement surgery to resolve a severe case of OSA. Her BP 7 weeks after surgery (without medication) was 128/89. She had a Class I occlusion before the surgery and after the surgery. The difference after the surgery was that both jaws were forward where they were meant to be.

Angle Class II relationships were studied by McNamara in 1981 [23]. The lay public, and most of the dental profession, will view anyone with a Class II malocclusion as having "buck teeth" which essentially implies that the upper teeth protrude in the face. McNamara actually found that the upper teeth in Class II patients were more likely too far back, rather than too far forward. Indeed, he found that maxillary protrusion was relatively rare in Class II patients and that mandibular retrusion was the most common characteristic. Mew's [8] assessment, which looks at the lower face in relationship to

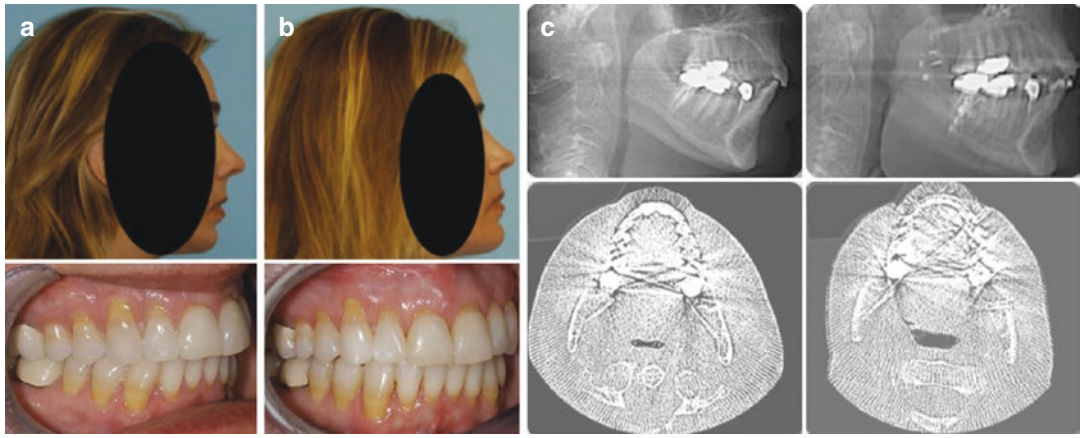

Fig. 9.3 (**a**) Patient with perfect Class I occlusion (with genioplasty) prior to orthognathic surgery for OSA. (**b**) Post-orthognathic surgery for OSA (**c**) Airway in lateral and cross-sectional view pre- and post-orthodontic and orthognathic surgery for OSA. BP 179/121 (with meds) prior to surgery and BP128/89 (no meds) 7 weeks postsurgery

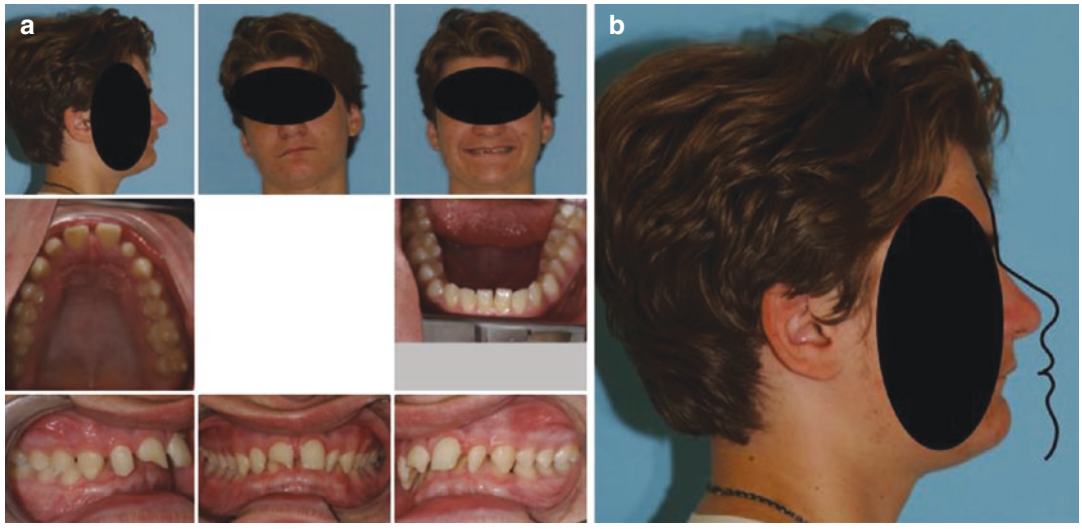

Fig. 9.4 (**a**) Adolescent male with Class II deep-bite malocclusion and large overjet with both jaws massively recessed from ideal position in face. (**b**) Bolton norm superimposed on glabella and soft tissue nasion shows maxilla and mandible severely recessed in face. Patients with this degree of lack of forward growth of both jaws are not uncommon in all industrialized societies

the nose and/or forehead, actually finds that the maxilla in Class II patients is virtually always too far back. Figure 9.4a, b shows an adolescent male with a Class II Division 1 malocclusion, a very large overjet, and overbite to the palate. The Bolton norm superimposed on glabella and soft tissue nasion shows both jaws massively recessed from proper positions in his face. With the maxilla and mandible both recessed in Class II patients, it follows that the airway behind both the soft palate and the tongue is reduced in size.

Figure 9.5a–c shows a 55-year-old female who had previously undergone surgery to advance only her mandible to correct her Class II malocclusion. Her lateral head X-ray shows an airway with a minimal x-section of 40.8 mm^2. A polysomnograph (PSG) confirmed her moderate

OSA. The Bolton norm superimposed on glabella and soft tissue nasion shows both jaws still substantially recessed from a more ideal position where her airway might naturally be much larger. The point is that her Class II occlusion was treated to a Class I occlusion, but she still suffers from OSA because her mandible was brought forward to meet her recessed maxilla. Had her maxilla and mandible both been advanced, her airway would have opened massively increasing the probability of eliminating her OSA. Virtually every Class II patient who undergoes surgery should have *both* the maxilla and mandible advanced.

Angle Class III patients are defined as having the lower molars forward of where they would fit with the upper molars with the focus being on the teeth themselves (without reference to the face). Most in dentistry, and even many orthodontists, assume that Class III malocclusions are associated with overgrowth of the mandible. In fact, such is rarely the case. The maxilla is almost always recessed in Class III cases [24]. In addition, even though the mandibular teeth are in front of the maxillary teeth, the mandible is almost always recessed in Class III patients. The airway reduction in such patients can be dramatic. Figure 9.6 shows a 19-year-old male with a Class III malocclusion with both jaws recessed from an ideal location.

Figure 9.7 shows a 56-year-old male who had surgery for a Class III malocclusion approximately 30 years earlier. The surgery performed was a one jaw procedure to set the mandible back. Such

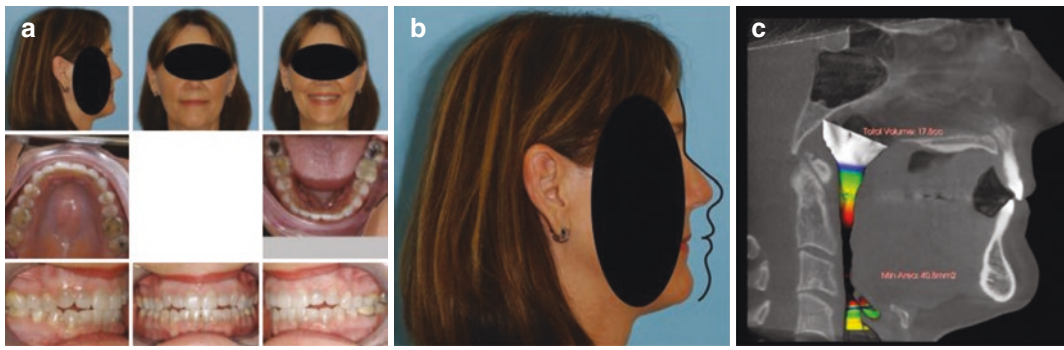

Fig. 9.5 (**a**) Patient had previously undergone surgery to advance mandible to correct Class II occlusion. This surgery did not include advancement of the maxilla so the mandible was advanced to a pre-existing recessed maxilla. (**b**) Patient with Bolton norm superimposed on glabella and soft tissue nasion shows both maxilla and mandible still severely recessed from ideal positions. (**c**) Airway is completely inadequate (minimal x-section of 40.8 mm^2) and patient still suffers from OSA

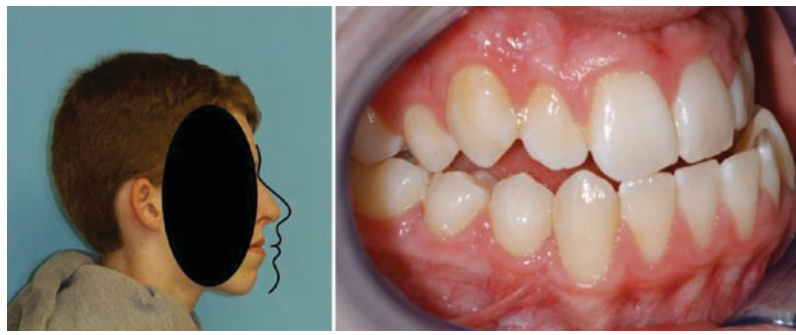

Fig. 9.6 Patient with severe Class III malocclusion and both maxilla and mandible massively recessed from Bolton norm superimposed on glabella and soft tissue nasion. Class III patients rarely have mandibles which protrude in the face. Most Class III patients have both jaws recessed from ideal positions

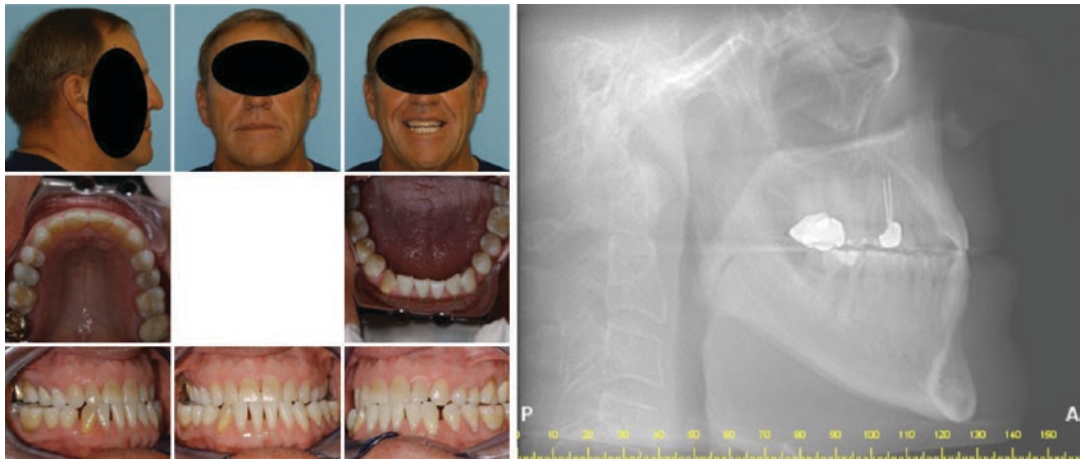

Fig. 9.7 Patient underwent surgery for Class III malocclusion to set mandible back 30+ years prior. Lateral head X-ray shows reduced airway as a result of mandibular setback which contributed to OSA

treatment was accepted at the time when tongue space and airway were not considered. He came to us because he suffered from OSA. His lateral head X-ray shows his reduced airway which had been made smaller by the previous surgery. He underwent successful double jaw surgery to advance both jaws to eliminate his OSA.

These examples show that reliance on the angle classification of malocclusion is absolutely meaningless and provides us no clue as to what is really happening with either the airway or facial balance. OSA can be present in all Angle classes, and the classification is useless in helping us decide on a treatment regimen to deal with the OSA. Good facial balance is not dependent on any Angle classification. Treatment must be focused on optimizing both facial balance and the airway no matter the classification. The teeth become secondary in treatment planning.

9.7 Tools to Evaluate Jaw Position to Optimize Facial Balance/Airway

Traditional cephalometric analyses have been used in orthodontic diagnosis since the advent of the lateral head x-ray. Virtually all measurements in these analyses focus on hard tissue landmarks

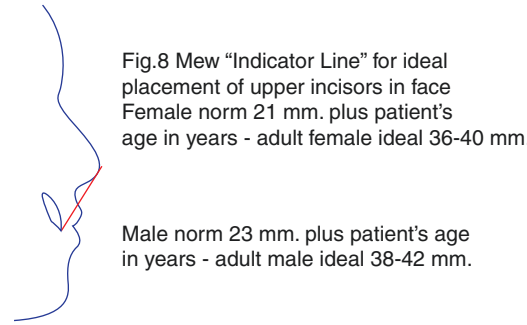

Fig. 9.8 Mew "Indicator Line" for ideal placement of upper incisors in face: Female norm 21 mm. plus patient's age in years—adult female ideal 36–40 mm. Male norm 23 mm. plus patient's age in years—adult male ideal 38–42 mm

of the bony structures and are made on averages of large populations of patients. As such, they are merely describing an average position of jaw structures in patients whose faces have all been adversely affected by growing up in an industrial society as noted above [11–15]. They are absolutely useless in analyzing faces to optimize facial balance since few in our society have optimal facial balance.

There are three simple tools to analyze faces in treatment planning which are useful in achieving better looking faces with larger airways. The first is the indicator line as proposed by Mew [8]. Figure 9.8 shows how this is measured. It is a

clinical measurement from the tip of the nose to the incisal edge of the upper central incisor. In a growing female, it should ideally be 21 mm. plus the patient's age in years. In a growing male, it should be 23 mm. plus the patient's age in years. In adult patients the ideal range is 36–40 mm. for a female and 38–42 mm. for a male.

Figure 9.9 shows a female with an ideal indicator line and a 20 mm. airway created by orthognathic surgery. Few people have faces as forward as this patient and 20 mm. airways are equally rare.

Mew [8] notes that the very first thing to change in all malocclusions is that the maxillary anterior teeth fall back increasing the indicator line measurement. The larger the deviation from the ideal indicator line, the less balanced the face and usually the smaller the airway. This is irrespective of classification of malocclusion as noted above. This single measurement can be extremely helpful in screening for possible OSA.

The second measurement is the nasolabial angle illustrated in Fig. 9.10. The range for this number is 90–110° with the ideal being 100°. It is another way to determine the proper position of the maxilla. Faces with nasolabial angles larger than 110° become progressively less attractive as the number gets larger. Retractive orthodontics, with or without extractions, can make this number dramatically larger with obvious negative effects on the airway as the number gets larger. Patients with Class II malocclusions and large overjets almost always have nasolabial angles on the high side of this range as illustrated by the patient in Fig. 9.11. This is just further evidence that the maxilla in Class II patients is recessed from an ideal position.

The third measurement tool used in helping us optimize facial balance and airway is the facial contour angle illustrated in Fig. 9.12. The norm is −11° from a straight line. The larger this negative number, the more the mandible is recessed. In

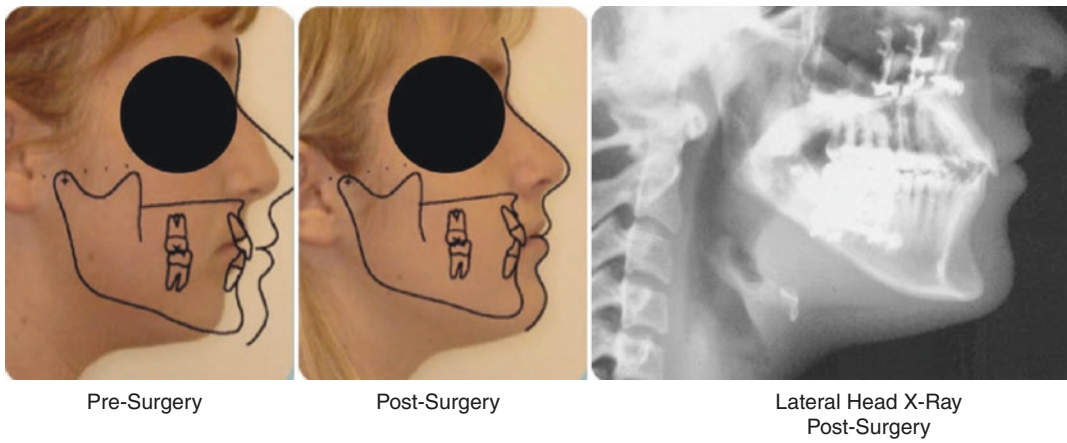

Fig. 9.9 Patient underwent surgery to advance maxilla and mandible. Indicator line measurement ideal for adult female and Bolton norm superimposed on face shows ideal placement of both jaws. Airway is a massive 20 mm

Fig. 10 Nasolabial Angle, ideal range 90-110˚ with 100˚ ideal. Numbers larger than this range indicate recessed maxillas.

Fig. 9.10 Nasolabial angle, ideal range 90–110° with 100° ideal. Numbers larger than this range indicate recessed maxillas

general, one can expect that the airway will get progressively smaller as this number gets larger. Figure 9.13 shows a patient with a facial contour angle of −28°, a small airway, and severe breathing problems.

Using the above three guidelines in evaluating faces provides the practitioner easy-to-use tools to evaluate and plan treatment for optimizing facial balance and airway health. In summary, anything which results in the maxilla and mandible being more forward in the face can be expected to bring both the soft palate (connected to the maxilla) and the tongue (connected to the mandible) forward, thereby, increasing the airway volume and decreasing the probability of collapse during sleep.

9.8 Retraction Reducing the Airway

Extraction of teeth with subsequent retraction has been shown to decrease the size of the airway [25–27]. It is critical for dentists to understand the

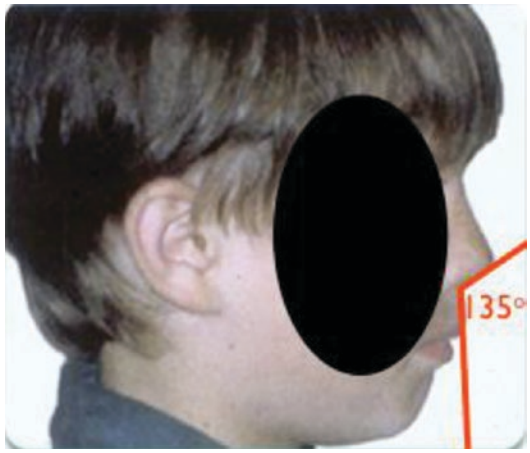

Fig. 9.11 Patient with Class II Division 1 malocclusion, 10 mm overjet, and 135° nasolabial angle showing maxilla severely recessed

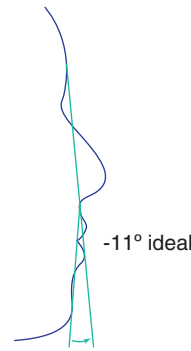

Fig.12 Facial Contour Angle shows the position of the mandible in the face. The norm is -11° with a standard deviation of +-4°.

Fig. 9.12 Facial contour angle shows the position of the mandible in the face. The norm is −11° with a standard deviation of ±4°

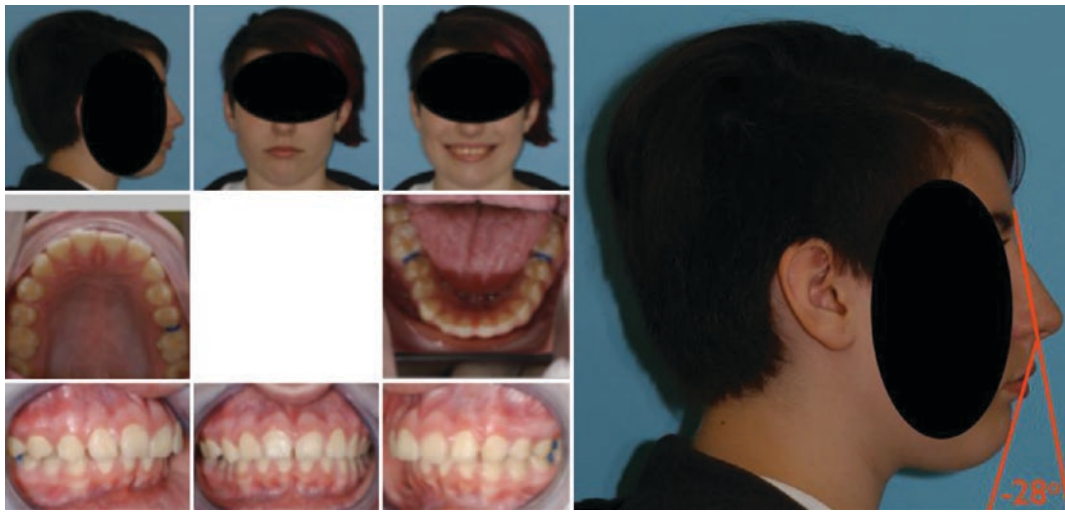

Fig. 9.13 Patient has Class II malocclusion with moderate overjet. Facial contour angle of −28° indicates severely recessed mandible

possible effects of *any* form of retraction. The first question we must ask is "Is it possible to retract enough to produce OSA?" If we accept that it is possible to retract teeth enough to produce OSA, logic dictates that we ask the next question which is "How far can one retract before producing an airway reduction large enough to result in OSA?" I know of no one who has been able to answer that question. The final question is obvious. "If you do not know where safe retraction becomes unsafe retraction, how can you retract at all?" If one accepts the logic of this argument, it would seem that traditional orthodontic approaches which retract must be stopped.

9.9 Practical Application of Treatment to Optimize Facial Balance and Airway Size in Varying Ages and Situations

It is not the purpose of this article to dictate treatment plans but to outline treatments which have been helpful in optimizing facial balance and airways. An obvious general rule is that treating at the earliest possible time has the best possibility of optimizing facial balance and airway health.

It is also important to remember that nothing which retracts the upper front teeth or restricts the forward growth of the lower face is appropriate at any time. This would include the use of headgear which has a goal of restricting maxillary growth. It would also include anything with a headgear effect. All so-called functional appliances and early treatment preformed appliances can have a headgear effect [28–30]. Class II elastics are routinely used in traditional orthodontics to reduce an overjet in a Class II patient and produce a Class I occlusion. Unfortunately, Class II elastics retract the maxillary anterior teeth and cannot be a part of any treatment concerned with facial balance and airway.

Even closing generalized spacing between the teeth can retract the teeth and reduce the airway. Such space closure must be accomplished in such a way that there is no retraction or reduction in the airway. Figure 9.14 shows an adolescent where generalized spacing was closed in the anterior, but no retraction was done. The generalized spacing was consolidated distal to the second bicuspids where it is not obvious. Such spaces can be left alone or can be closed by overcontouring the adjacent teeth with composite resin.

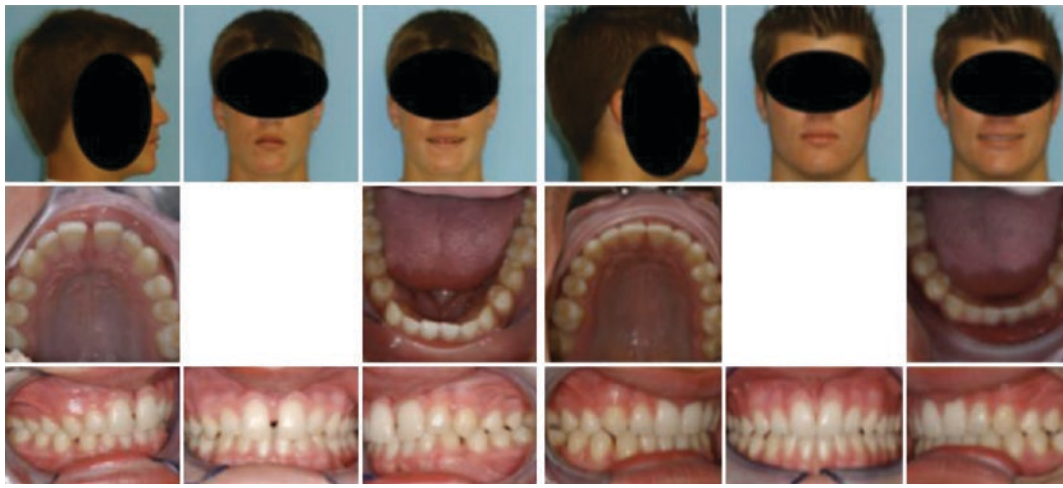

Fig. 9.14 Patient with generalized spacing in upper and lower arches has spacing closed in the anterior without retraction. Spaces have been consolidated between second bicuspid and first molar teeth in all four quadrants. Spaces are large enough to be easily cleaned and are not food traps

9.10 Treatment in the Primary Dentition

Gozal [31] indicates that 2–3% of children have OSA, and this number is growing. Harper [32] shows that brain damage can result from even one night of OSA in a young child. Cooper [33] describes the relationship between airway/breathing/OSA issues in African-American children and its impact on many who simply cannot read due to the damage their brains have already endured by the time they enter first grade. Given these facts, it is imperative to eliminate the OSA problem as soon as possible. This includes treating patients who have primary teeth. The patient illustrated in Fig. 9.15 was 5 years old and referred to us by a pediatric sleep specialist. The child was diagnosed with Pierre-Robin sequence, OSA, and failure to thrive. We did not promise a result, but outlined Orthotropics® treatment developed by Mew as an effective method of developing both the maxilla and mandible forward.

The maxilla was expanded laterally and anteriorly using a removable appliance (Hang Expancer™). The anterior development was augmented by a reverse-pull face mask. The maxillary anterior teeth (as noted by the indicator line measurement) were brought forward 7 mm. in approximately 5 months. The mandible was brought forward after the development of the maxilla using a Stage III Biobloc according to the protocol outlined by Mew [8]. Many so-called "functional" appliances posture the mandible forward. They also produce a headgear effect which retracts the maxilla because there is nothing to prevent the patient from allowing their mandible to fall back and pull the maxilla back. The Stage III and IV Biobloc appliances used in Orthotropics® as defined by Mew have acrylic extensions to the floor of the mouth which will engage the mandible and make it uncomfortable for the patient to allow the mandible to fall back. Figure 9.16 shows a Mew Stage III Biobloc appliance. These extensions are adjusted to keep the patient held tightly in an ideal bite position at

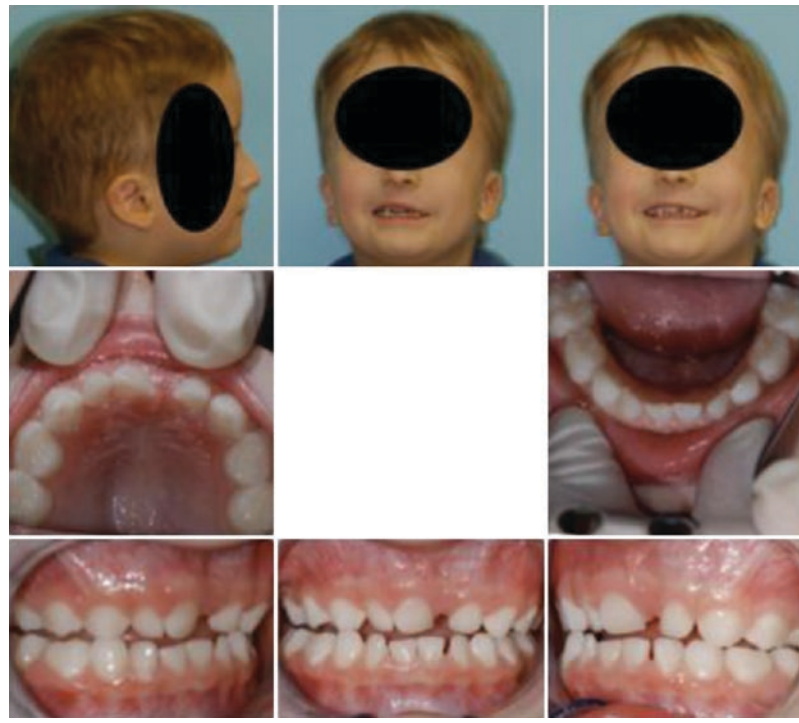

Fig. 9.15 Patient presents with pediatric OSA, Pierre-Robin sequence, and failure to thrive

rest and prevent the patient from putting pressure on the maxilla. By eliminating the headgear effect forward, development of both jaws is allowed to occur. Over time the mandible assumes this more forward position and will not fall back. A sleep test done for the patientwas done after the mandible was developed forward and showed complete elimination of the OSA problem. The improvement in the airway size is noted in Fig. 9.17.

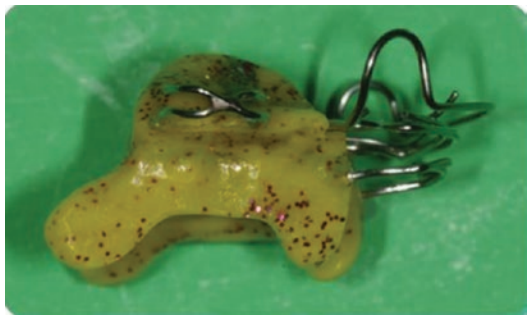

Fig. 9.16 Mew Stage III Biobloc "postural" appliance with extensions to floor of the mouth. Extensions are adjusted with plastic material to engage the floor of the mouth, prevent the mandible from falling back, and eliminate the "headgear" effect of "functional" appliances

The results of a study [34] of consecutively treated Orthotropics® patients which have confirmed excellent airway improvements are achievable with both lateral and anteroposterior forward development of both arches. Indeed, a 31% airway increase was noted at the level of the palate, a 23% increase at the base of the tongue, and a 9% increase in the area of the laryngopharynx.

Treatment in the primary dentition has not been commonly done because historically the focus of orthodontics has been on straightening teeth. The focus on teeth must be changed to a focus on optimizing facial balance and airway development. The teeth must be viewed as a convenient handle to the cranial bones which make up the face. The earlier we treat the better—even in the primary dentition.

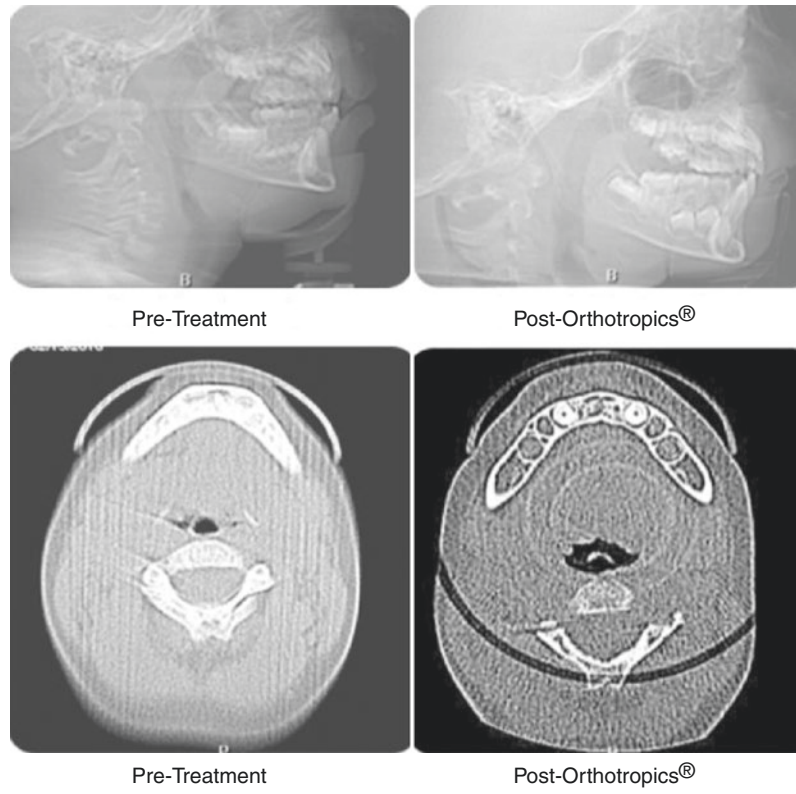

Fig. 9.17 Pre- and post-treatment airways for patient in Fig. 9.15. Pre-treatment OSA was eliminated post-Orthotropics® treatment

9.11 Treatment in the Early Mixed Dentition

The patient in Fig. 9.18a–c began treatment at age 8 years when the four permanent maxillary anterior teeth were erupted into the mouth (standard time for Orthotropics®). Her maxillary anterior teeth were advanced 8 mm., while the width of her maxillary arch was dramatically increased to over 40 mm. (at the first molars) from a number in the low 30s. Her mandible was then brought forward with an ADAPT-LGR® (similar to a Stage IV Biobloc) which has extensions to the floor of the mouth and no headgear effect. By first advancing the maxilla and then advancing the mandible, the entire lower face can be brought forward. This enhances both facial balance and optimizes airway development as the soft palate and tongue move forward with the maxilla and mandible. The airway improvement in this case is dramatic as shown in Fig. 9.19. This child's mother reported that she has more energy, is more outgoing, and is now two grades ahead of her classmates in most subjects. Her mother attributes a good portion of this change to the dramatically improved airway and better sleeping pattern.

9.12 Treatment in the Permanent Dentition

The traditional time for wearing braces is generally in the very early teenage years when all the permanent teeth have erupted and can be aligned easily. Unfortunately, the grand

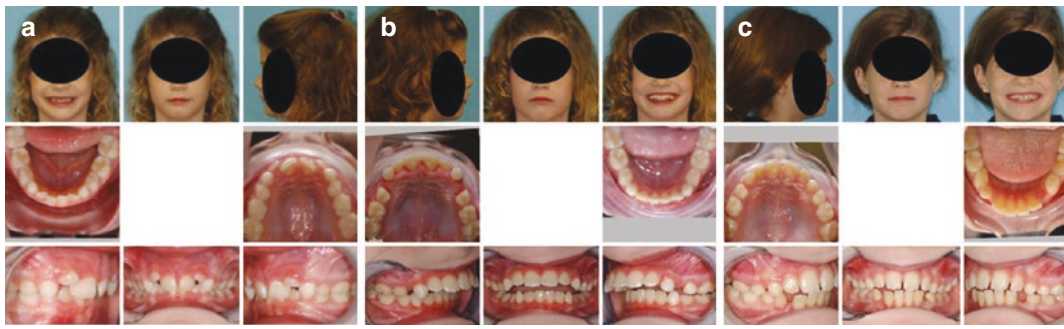

Fig. 9.18 (**a**) An 8-year 3-month-old patient with deep-bite and end-to-end Class II occlusion, maxillary anterior teeth 8 mm too far down and back in face. (**b**) An 8-year 7-month-old patient in the middle of Orthotropics® treatment with massive lateral expansion of maxilla, 8 mm. upward and forward advancement of six maxillary anteriors, and lower arch leveled to a near-flat occlusal plane as per Orthotropics® protocol. (**c**) A 10-year 3-month-old patient after Orthotropics® treatment with ADAPT-LGR® appliance to develop mandible forward and correct poor rest oral posture

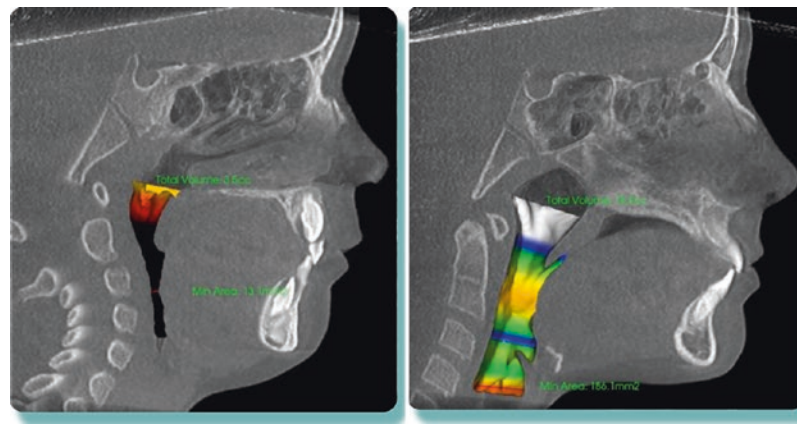

Fig. 9.19 Note dramatic profile and airway improvements for patient in Fig. 9.18a–c. 13.1 mm^2 minimal x-section (high risk for OSA) becomes 186.1 mm^2 minimal x-section (low risk for OSA) after Orthotropics®

majority of facial growth has already occurred, and trying to get both the maxilla and mandible to develop further forward is nearly impossible. Johnston [35] compared traditional orthodontics with headgear and braces with "functional" appliances which purported to "grow the mandible" in the 1980s and concluded that both groups had a "moderate mid-facial dentoalveolar retrusion".

No mention was made in this article that the resulting lack of forward growth of the lower face might impact health through reduced airway increasing the chances of OSA, upper airway resistance syndrome (UARS), or any other airway-related problem. Current evidence suggests that there is cause for concern.

Many efforts have been made to develop the mandible forward in children who are still growing and are of the traditional age to wear braces. The Herbst appliance was developed in Germany in the early 1900s and enjoyed a surge of interest in the USA in the early 1980s. The literature is pretty clear that there is very little forward development of the mandible and a pronounced headgear effect [30]. The bottom line is that there is very little forward development to be expected because there can be a headgear effect. Many other approaches have been proposed such as the MARA appliance, Forsus, Twin Force Bite Corrector, Jasper Jumper, etc. All can be effective in correcting a Class II malocclusion to a Class I occlusion. However, there does not appear to be dramatic improvement in achieving forward growth of the maxilla and mandible resulting in airway increases.

In a Class II situation, the treating doctor who wants to optimize facial balance must consider a surgical approach to advance both jaws to more ideal positions in the face. When the discrepancy is severe and OSA is already present, this may well be the only effective approach. For many reasons most orthodontists will try to do anything to avoid subjecting the patient to surgery. The traditional orthodontic approach to avoid surgery is to remove the maxillary right and left first bicuspid teeth and retract the anterior teeth to produce Class I cuspids and ideal incisal guidance. Unfortunately, this treatment approach can have negative consequences on both facial balance and the airway.

There may be an alternative treatment approach for the Class II patient who is not severely retrognathic. The overjet can be reduced by advancing the lower anterior teeth and creating space between the bicuspid teeth (or elsewhere in the lower arch) using a removable appliance. Once the lower anterior teeth are advanced, the posterior teeth can be brought forward and the space closed by using temporary anchorage devices (TADs) as anchorage. The case in Fig. 9.20a–d illustrates this treatment. This patient started treatment at 12:10 with a sagittal appliance to advance the lower anterior teeth. After approximately 7 months of appliance wear, the lower anterior teeth were sufficiently anteriorized to reduce the overjet and open the bite. Braces were placed on the teeth for alignment. TADs were placed after approximately 2 years of treatment. Elastic chains from the TADs to the molars brought the molars forward. Another 14 months of treatment were required to completely close the spaces. Effectively this treatment brought the entire lower dentition forward on the mandible without changing the position of the mandible itself. The airway improvement resulting from this treatment as well as substantial bone on the labial aspect of the teeth is shown in Fig. 9.21.

Advancing lower anterior teeth in this fashion is not considered the standard of care in the community and is generally thought to risk recession and possible loss of lower anterior teeth. This general feeling still is pervasive in the orthodontic community despite a complete absence of published reports of such treatment ever causing problems. It also ignores the refereed literature which confirms that it is NOT a problem to substantially advance lower anterior teeth [36–42]. This treatment approach should be considered as an excellent way to resolve an overjet without retracting the upper anterior teeth when treatment to develop the entire lower face forward with Orthotropics® is too late or not to be considered because of expected poor patient compliance. It should not be done for patients who have significantly recessed chins.

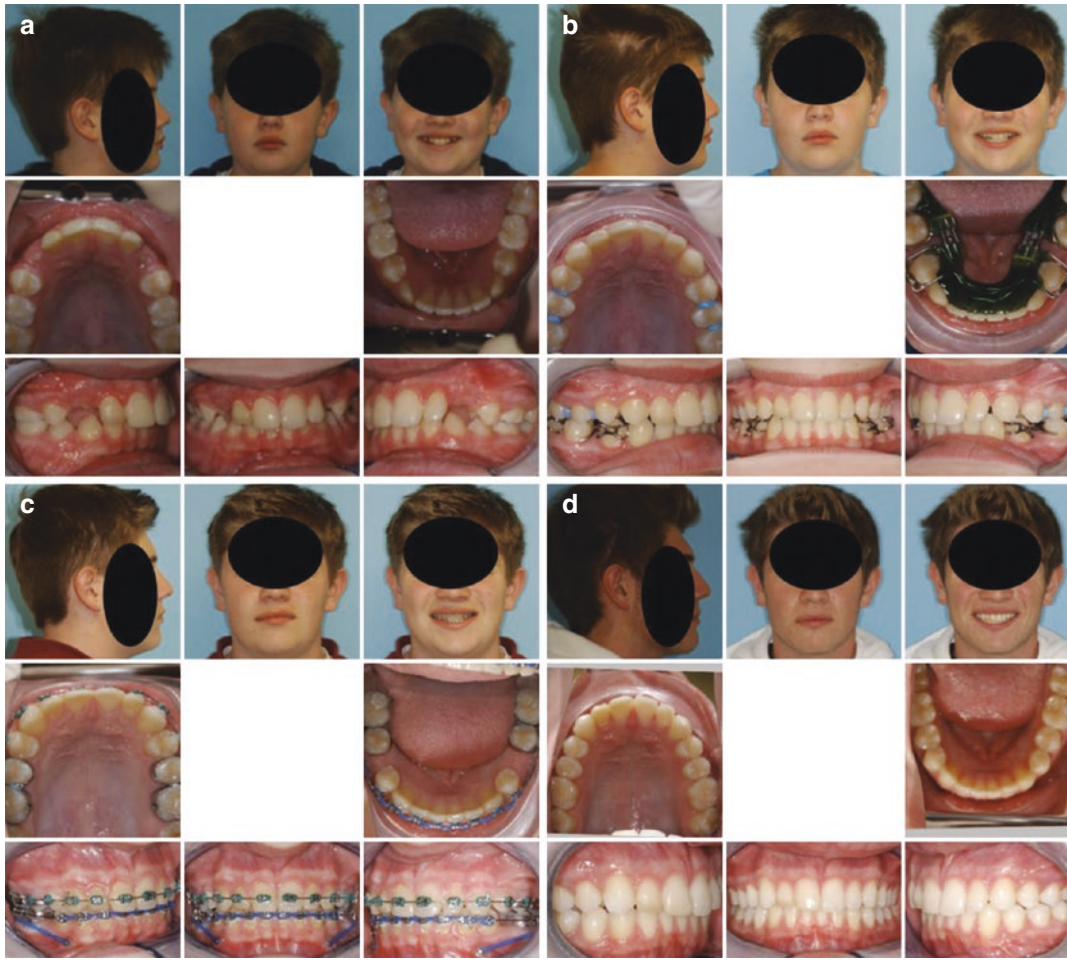

Fig. 9.20 (**a**) Male patient (10 years and 9 months) with end-to-end Class II deep-bite malocclusion. (**b**) Male patient (13 years and 5 months) in the midst of treatment with lower sagittal appliance opening spaces between permanent bicuspid teeth to advance lower anterior teeth. (**c**) Male patient (14 years and 10 months) in full braces with TADs placed between lower cuspids and first bicuspid teeth. Elastic chains from TADs to first molars bring molars forward to close the spaces created by the sagittal appliance. (**d**) Male patient (17 years and 8 months) more than a year post-treatment. Entire lower dentition has been moved forward to eliminate overjet. Note no gingival recession

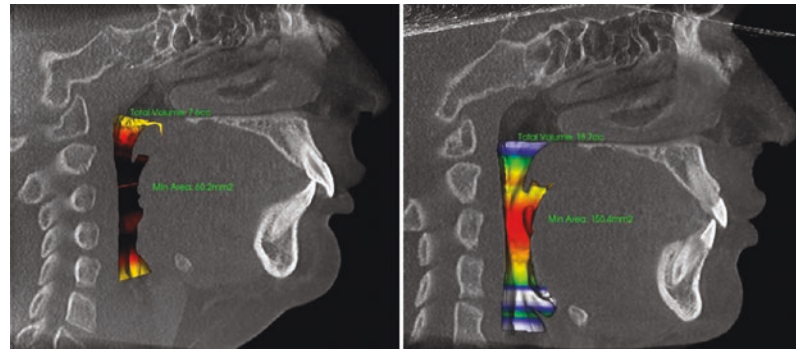

Fig. 9.21 Patient in Fig. 9.20a–d had 60.2 mm^2 minimal x-section (moderate risk for OSA) which became 150.4 mm^2 minimal x-section (low risk for OSA) post-treatment. Note substantial bone on labial aspect of lower incisors post-treatment. Incisor advancement did not cause bone loss or recession as orthodontists are taught

9.13 Missing Lateral Incisor Teeth in Adolescents

Congenital absence of lateral incisor teeth is certainly not uncommon. Its treatment has been the subject of much controversy for many years. Prior to the advent of implants, the focus was largely on closing the missing lateral incisor spaces to avoid preparing virgin teeth for a bridge. Implants changed that discussion when the adjacent teeth no longer needed to be prepared for bridges. There is still a lot of controversy in treating this problem with many still happy to remove the other lateral incisor which often is a peg lateral and close both spaces. The intimation is that the "cuspid teeth will be brought forward in the face". Anchorage considerations of the roots of all the teeth involved render that statement almost preposterous. The result of such space closure is almost always significant retraction of the two central incisor teeth with a very unaesthetic increase in the nasolabial angle. The patient in Fig. 9.22 (shown here as an adult) was missing an upper lateral incisor and had a peg lateral incisor on the contralateral side as an adolescent. The peg lateral incisor was removed as well as the lower second bicuspid teeth, and all spaces were closed with retraction. Her nasolabial angle is approximately 140° when a number of 100 is considered ideal. It has been shown that such retraction can also change the direction of growth of the lower face in a formerly forward growing face [43].

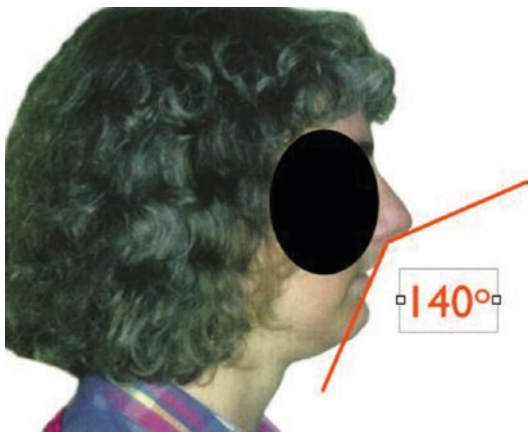

Fig. 9.22 This patient exhibits severe flattening of the entire maxilla and a very recessed mandible. The nasolabial angle is 140° (100° ideal)

It is particularly tempting for orthodontists to close missing lateral incisor spaces when the patient is Class II. A very common treatment approach for Class II patients with all their teeth is to remove the upper first bicuspids and retract the six anterior teeth to produce Class I cuspids. It is an easy transition from this thinking process to close the missing lateral incisor spaces and retract the centrals. The goal for the orthodontist is to reduce the overjet. Almost always this will be done at the expense of the face and the airway. Figure 9.23 shows the face of a 55-year-old male whose missing lateral incisor spaces were closed by "canine substitution" when he was an adolescent. The retraction of his teeth resulted in a severe lack of forward development of his entire lower face. The Bolton norm superimposed on his face in Fig. 9.24 illustrates just how far back both jaws are from the norm. He unconsciously tips his forehead back which positions his lower face forward to open his airway. He has OSA and suffered a stroke in his early 50s. Since 65–80% of all stroke patients suffer from OSA [9], it seems likely that the retraction of his face which occurred with the space closure contributed to his OSA and his stroke.

The following case illustrates an alternative to closing the spaces. This 10-year 9-month-old male in Fig. 9.25a, b had a missing upper left lateral and a peg right lateral. He had received another orthodontic opinion to have the peg lateral removed, and both lateral spaces closed orthodontically. His Class II bite relationship would have been perfect for that treatment plan if the face and airway were not considerations. One might suggest that the only way to correct the Class II relationship without retracting the upper teeth in some fashion would be surgery to advance the mandible. Certainly that would have

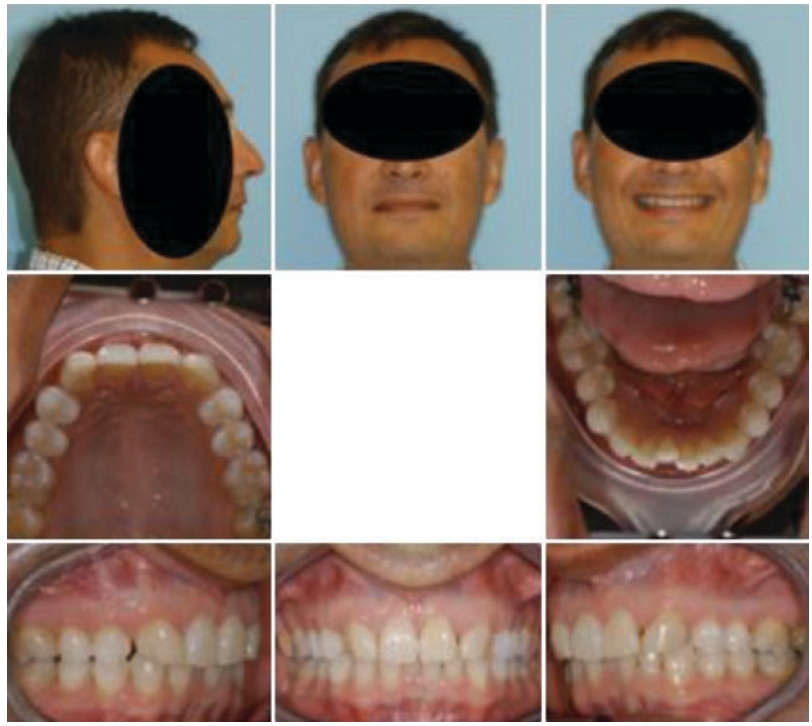

Fig. 9.23 A 55-year 2-month-old male treated as child for missing lateral incisors with "canine substitution"

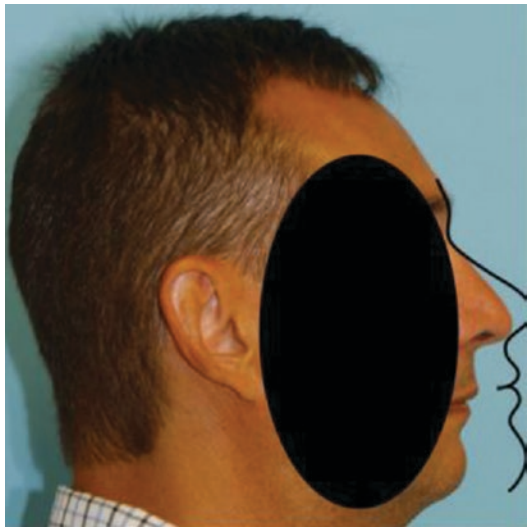

Fig. 9.24 Patient in Fig. 9.23 with Bolton norm superimposed on glabella and soft tissue nasion. Maxilla and mandible are severely recessed. 35° backward tilt of forehead from vertical (should be vertical) keeps chin forward and maintains airway

been an option, but his chin prominence made this seem very unnecessary. Instead, we advanced his lower anterior teeth dramatically to reduce the overjet using a removable appliance. We opened space between the lower first permanent molar and the second bicuspid teeth bilaterally. This space is large enough for an implant. We could have placed TADs and brought the molars forward, but it would have added significant treatment time in a case where the patient had very poor oral hygiene. The goal of the treatment was to reduce the overjet by advancing the lower anterior teeth forward rather than by retracting the upper anteriors. The prevailing wisdom in the orthodontic profession is that such an advancement of the teeth would cause recession and possible tooth loss of the lower anterior teeth. We have been advancing lower anterior teeth in this fashion for over 30 years and have not experienced this problem even once. The refereed literature clearly supports such treatment with

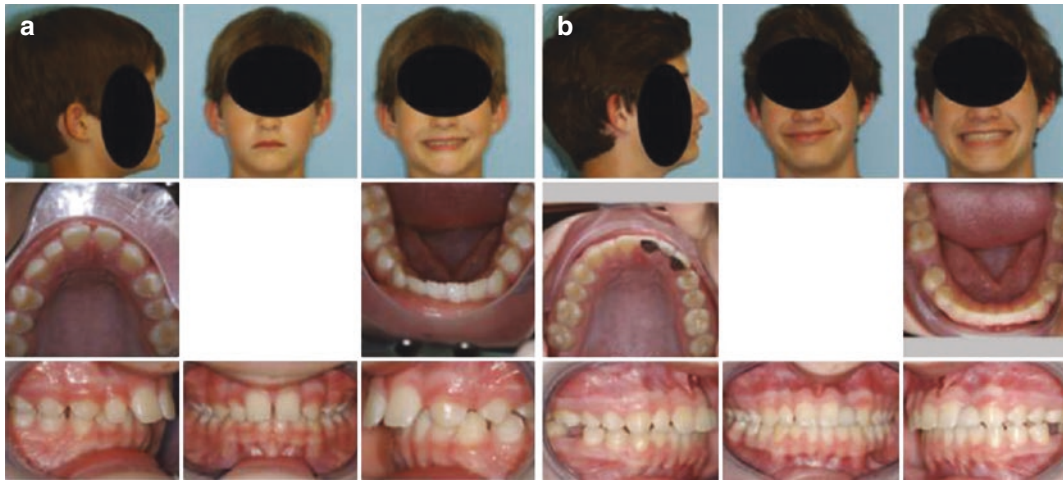

Fig. 9.25 (**a**) A 10-year 9-month-old male with missing upper left lateral incisor, undersized maxillary right lateral incisor, and Class II malocclusion with moderate to large overjet. Patient received orthodontic opinion to have maxillary right lateral incisor removed, and both lateral incisor spaces closed by retraction of the central incisors ("canine substitution"). (**b**) Orthodontic treatment opened space for the missing upper left lateral incisor to be and spaced the right lateral incisor for veneering. A temporary bonded bridge replaces the missing lateral incisor until growth is complete and implant placement is accomplished. Massive advancement of ten lower anterior teeth reduced the overjet. Spaces large enough for an extra bicuspid were created between second bicuspids and first molars. Note absolutely no recession on lower anterior teeth despite what orthodontists are taught

confirmation that such advancement is not a threat to periodontal health [36–42].

The retraction of the central incisors in missing lateral incisor cases cannot be justified for facial aesthetic reasons or for the possible airway reduction which may accompany this treatment. Instead, space must be opened whenever there is a missing lateral incisor so that a suitable replacement can be placed.

9.14 Adult Class II Nonsurgical Correction

Figure 9.26a–c shows a 38-year-old male who had undergone 4 years of retractive orthodontics in which minor lower anterior spacing had been closed and spacing had been left in the maxilla for replacement of missing teeth. The restorative dentist was unhappy with the way the teeth fit and referred the patient for further treatment. At this point, the patient was a snorer and suffered from OSA. A surgical approach to advance both jaws was considered but rejected by the patient. A compromise treatment to advance the entire lower anterior segment of teeth was selected. First, ideal spacing of the upper anterior teeth for implants created an overjet. The overjet was corrected by advancing the lower anterior teeth with a sagittal appliance. Within a few weeks of wearing the sagittal appliance, the patient's wife reported his snoring had ceased completely. The final advancement of the lower anterior teeth resulted in enough space for an extra bicuspid tooth on each side of the lower arch.

Despite the generally held warning in the orthodontic profession that such advancement of lower anterior teeth might cause recession and ultimate tooth loss, there is no hint of loss of attachment of the tissue as noted in Fig. 9.26c.

9.15 Adding Extra Bicuspid Teeth

Adding teeth where none are missing may seem a radical thing to do. The patient shown in Fig. 9.27a–e suffered several migraines per week and reportedly lost 2–3 weekends a month being incapacitated with migraines. Nothing she had done to address this nearly 20-year problem had

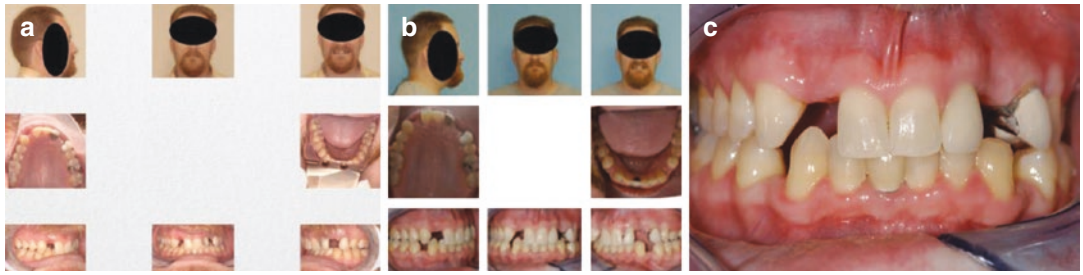

Fig. 9.26 (**a**) A 38-year-old male underwent orthodontics which closed lower anterior spacing in preparation for replacing missing maxillary teeth. He snored and suffered from OSA. (**b**) Revisionary orthodontic treatment reopened lower incisor spacing. Maxillary spaces were better idealized for restorative. Spaces for "extra" bicuspid teeth implants were created between lower cuspids and first bicuspids reducing the Class II overjet. Snoring and apparent OSA eliminated. (**c**) There is no recession despite massive advancement of lower anterior teeth

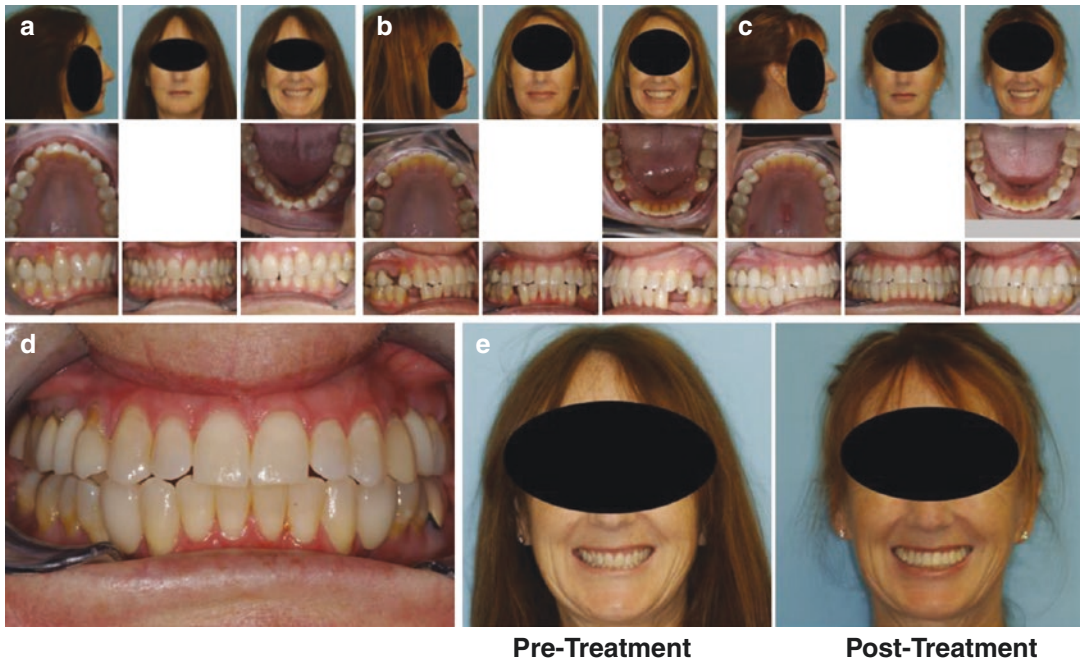

Fig. 9.27 (**a**) Migraine-suffering patient who never had orthodontic treatment. (**b**) Patient after orthodontic treatment to open space for "extra" bicuspid teeth between upper bicuspids and between lower cuspids and first bicuspids. Substantial lateral expansion of both arches was also accomplished. Migraine pattern was completely eliminated. (**c**) Patient after restoration of "extra" bicuspid teeth in each quadrant. (**d**) No recession in lower anterior despite massive advancement of anterior teeth. (**e**) Pre- and post-treatment smiles

been successful. We noted her tender temporomandibular joints (TMJs), tender facial and cervical muscles, etc. and also recognized that her upper and lower teeth appeared tipped back in her face. Without promising her resolution of any symptoms, we suggested that we open spaces in both arches to give her more tongue space. As the treatment progressed, she became happier and happier with the cessation of symptoms and the aesthetic appearance of a fuller profile. Her migraine pattern was entirely eliminated and has not returned. We created enough space so that an extra bicuspid tooth in each quadrant was added. Implants were placed in the sites and ultimately

restored with porcelain crowns. She states that she sleeps well and awakes well rested since the treatment. Her headache pattern was completely eliminated as her tongue space/airway was increased. Her broader smile with no excessive gum tissue was a nice side benefit of the elimination of her pain pattern.

9.16 Reopening Extraction Spaces

The patient shown in Fig. 9.28a, b suffered from severe TMJ/pain and had undergone arthroscopic surgery to the TMJs more than a decade before we examined her. The pain pattern was not a current problem, but she suffered from moderate OSA and typically slept about 2 hours a night. Tomograms confirmed both TMJs were undergoing severe degenerative changes but were asymptomatic at the time. Since both jaws were massively recessed, orthognathic surgery was the obvious treatment of choice.

She had a history of previous orthodontic treatment as an adolescent with four bicuspid teeth having been removed as part of the treatment. We are strong advocates of reopening extraction spaces as part of the treatment so that the patient has a better chance of having their tongue properly positioned to the palate at rest. Without promising her that even one symptom would be relieved, we started her on a protocol we have developed to reopen the extraction spaces in the maxilla, but not in the mandible. She agreed that orthognathic surgery should be part of the treatment plan from the beginning. By not opening bicuspid spaces in the mandibular arch, we kept the lower incisors more retruded which would allow for a larger surgical advancement of the mandible. A larger mandibular advancement would produce a greater increase in the posterior airway space (distance between the back of the tongue and back of the throat). She agreed to the treatment approach.

During the treatment, she obtained several surgical opinions since all the surgeons she saw diagnosed her with severe degenerative joint disease and recommended total joint replacement. She didn't want to undergo surgery but continued the treatment plan hoping for some miracle. In the midst of our reopening the extraction spaces only in the maxillary arch, she started to sleep better. Without consulting us, she decided to have another sleep test done and found that she was completely free of OSA. A portion of the sleep report signed by the M.D. sleep physician follows:

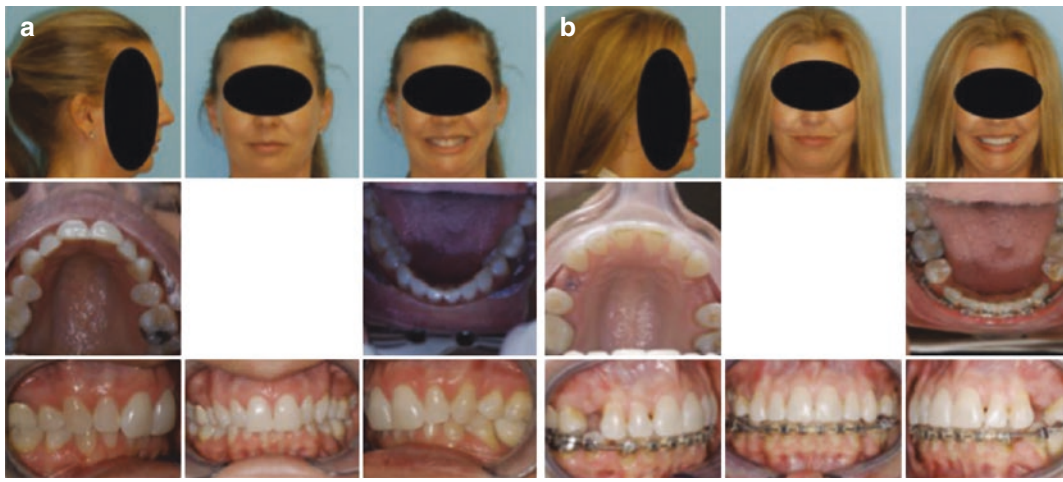

Fig. 9.28 (**a**, **b**) A 44-year-old female patient suffering from moderate OSA subsequent to adolescent retractive orthodontic treatment with removal of four bicuspid teeth. Bicuspid spaces reopened completely in maxilla and partially in mandible completely eliminating OSA

(Patient name) had mild obstructive sleep apnea-hypopnea syndrome with a rapid eye movement (REM) dominant component. Her sleep apnea has completely resolved with orthodontic therapy—despite the 10+ pounds of interim body weight gain. It is quite remarkable how much improvement she has had in her apnea severity despite the presence of a large tongue and crowded oropharynx.

Having completely eliminated her OSA problem, the patient wanted to terminate the treatment even though she had a poor bite relationship. We were able to convince her to allow us to open some space in the lower arch to reduce her overjet. After a very short time, she terminated the treatment. The door was left open for her to do orthognathic surgery in the future if she changed her mind.

The significance of this case is that by merely opening a 7 mm. space in each upper buccal segment for placement of an implant, her tongue gained enough space to be positioned upward and forward so that she was declared free of OSA by her sleep physician. She had undergone no myofunctional therapy which might have had an additional benefit in helping her have proper rest position of the tongue to the palate. Her tongue had spontaneously found enough space in the palate to move upward and forward to eliminate her OSA. It is clear that we simply do not know where the threshold exists for OSA.

9.17 Class II Camouflage Treatment

Camouflage treatment of Class II cases has long been a part of traditional orthodontic treatment. Such treatment involves retracting the upper anterior teeth after the removal of the upper first bicuspid teeth. More recently temporary anchorage devices (TADs) have been used to retract the maxillary anterior teeth, and extraction of the first bicuspid teeth is avoided. This approach takes an already deficient maxilla and makes it more deficient. It damages the face and decreases the airway. In no way can it still be justified.

Figure 9.29a–c is the case of a 40-year-old female who merely wanted her teeth straightened. She sought the services of a local orthodontist in her area who recognized that she had a Class II malocclusion with little or no lower crowding. He did not offer her the option of surgery to advance the mandible. Instead, he offered her the camouflage treatment of removing her upper right and left first bicuspid teeth to allow him to retract her six anterior teeth and reduce the overjet. The goal was no overjet with proper cuspid and incisal guidance long advocated by the profession.

During the original orthodontic treatment, she began to experience severe symptoms. She had trouble breathing and sleeping. She developed a severe pain pattern in the muscles of her face and

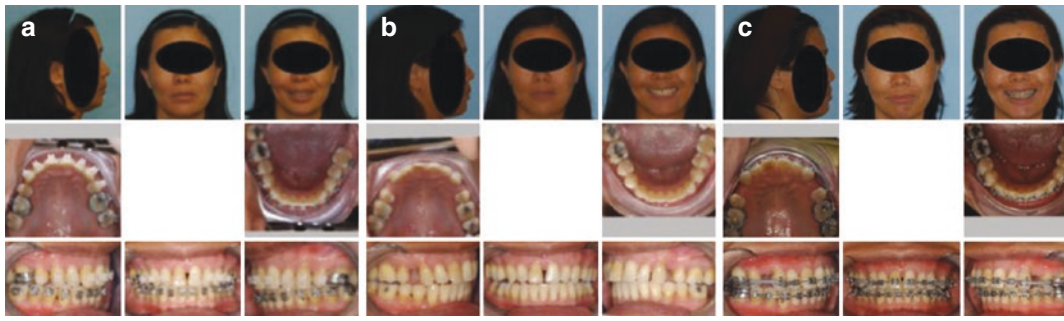

Fig. 9.29 (**a**–**c**) A 40-year-old female patient had maxillary right and left first bicuspid teeth extracted and her overjet completely eliminated by retraction when she presented for a second opinion. She had developed severe pain in the TMJs, an inability to breathe, and OSA. Patient reported, "I thought I was going to die". (**b**) Shows result of approximately 3 months of upper sagittal appliance wear to readvance the six maxillary anterior teeth and produce a slight overjet. The pain, breathing, and OSA problems were eliminated. (**c**) Shows her ready to have braces removed having received approval from an implant surgeon and restorative dentist

around her TMJs. She would awaken in the night in a sweat with panic attacks thinking that she was going to die. She brought this problem to the attention of her orthodontist, but he said the problem was unrelated to what he was doing, and she would get used to it. She consulted with pain specialists in a large city near her home and was told there was no physical problem that could be identified. Deep inside she suspected that the retraction of her front teeth was causing the sleep and pain problem. She convinced her orthodontist to remove the upper arch wire which was continuing to retract her teeth. He reluctantly did so because she insisted. Within 2 hours she found her pain pattern subsiding, but the sleep problem persisted.

She presented to us in a panic mode thinking that she was going to die. We found all the muscles of her face and neck to be extremely tender to palpation. There was no clicking in her joints, but her maxillary anterior teeth had been retracted so much that they were hitting traumatically with the lower incisors and causing distal pressure into the TMJs. Her clenching pattern was an unconscious effort to push the anterior teeth forward and free her mandible from being trapped by the maxillary anterior teeth. We did not promise reduction or elimination of even one symptom, but did promise to do our best. A maxillary sagittal appliance was used to reopen her extraction spaces. She wore it and activated it as instructed. The spaces opened as predicted. She returned to our office in 4 months with the extraction spaces more than halfway reopened. Her symptom pattern had been completely eliminated. The pain was gone, and she was sleeping like she did before her retractive treatment. The final gallery shows treatment complete but with braces still in place.

Some may argue that this is a single example of one case and does not occur all that often. The fact is that it is not an uncommon occurrence with this treatment approach. Unfortunately, both the orthodontic profession and the public are largely unaware of a connection between retraction and symptom patterns. With the internet many more patients are realizing the connection and that treatment to resolve the problem may be available. Some orthodontists are beginning to understand this connection and no longer feel comfortable doing this retractive treatment. Ideally this process would happen much faster so fewer will suffer.

9.18 Surgical Correction of OSA with Double Jaw Advancement Surgery

When more conservative measures are ineffective, the ultimate correction for OSA is surgery. When the word “surgery” is used in most sleep clinic settings, it refers to uvulopalatopharyngoplasty (UPPP) [44, 45], which does not enjoy a great track record of success and isn’t without serious negative consequences. Other surgical procedures to the nasal or pharyngeal airway itself can be considered, but none have a great chance of success. Such procedures as straightening a deviated septum, reducing turbinates, removing nasal polyps, etc. can improve the nasal airway. Whereas they may benefit the nasal airway, they do nothing to open the airway in the soft palate or base of the tongue areas where occlusion of the airway in OSA is often the critical issue.

The greatest chance of success in eliminating OSA surgically comes from surgery to advance both the maxilla and the mandible. It must be done with careful preparation for the outcome to be ideal. Orthodontic preparation of the arches is of paramount importance. Orthodontics should be part of the treatment in every case. The lower arch must be developed laterally in all cases so that the maxillary arch can be expanded to maximum dimension. Mew [8] indicates that an intermolar width of 42 mm. between the maxillary molars is necessary for the tongue to be permanently postured to the palate at rest. Getting the patient to adopt such proper rest oral posture is critical for optimizing success in treating OSA. Figure 9.30 shows a 55-year-old male who had undergone double jaw advancement surgery without orthodontics in an effort to resolve his OSA. His intermolar width was about 30 mm. A PSG done months after the surgery showed that

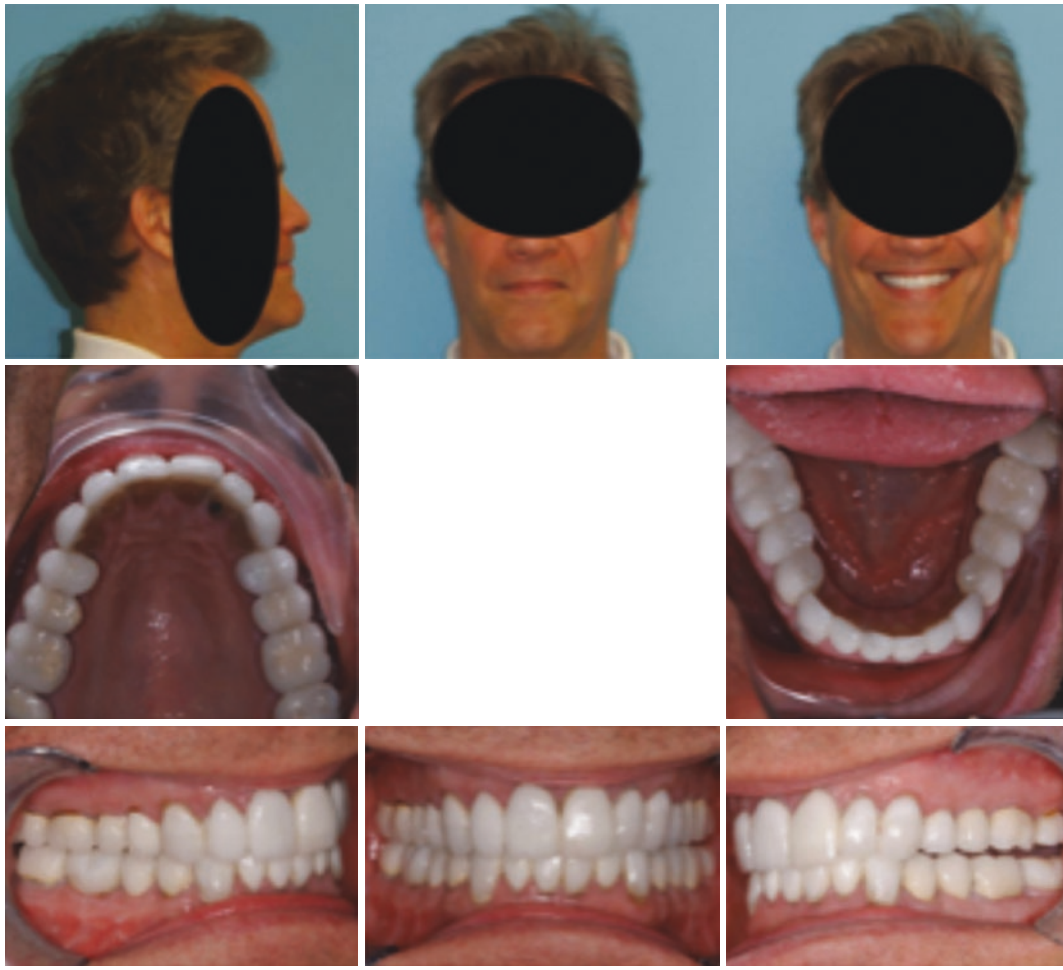

Fig. 9.30 Patient had undergone double-jaw surgery to advance maxilla and mandible to eliminate OSA without any orthodontic preparation. OSA persisted. Had orthodontics been done pre-surgically to expand the mandibular arch, the maxilla could have been expanded surgically improving the likelihood of eliminating OSA

he still suffered from OSA. Had the patient undergone orthodontics to widen the mandibular arch and ultimately have the maxillary arch surgically expanded to the expanded lower arch, the OSA might well have been eliminated.

Surgery to advance the mandible almost always needs to be done with a counterclockwise rotation of the occlusal plane. Such a rotation brings the mandible forward maximally with the projection of the bony chin optimized. Because the genioglossus muscle is attached to the lingual aspect of the mandible at the bony chin, the tongue advancement is optimized when surgery is done in this fashion. Most surgeons doing mandibular advancement surgery today are not doing this. Figure 9.31a, b shows a 62-year-old male who had presurgical orthodontics to broaden the lower arch and underwent surgery to expand the maxilla to the widened mandibular arch and advance both jaws with a counterclockwise rotation. After years of suffering fatigue from untreated OSA, having both jaws advanced surgically has allowed him to go on to lead a normal life with renewed interest in skiing and other outdoor sports. The airway improvement produced with proper advancement of both jaws is dramatic. His sleep physician performed a PSG to confirm that he no longer suffers from OSA and

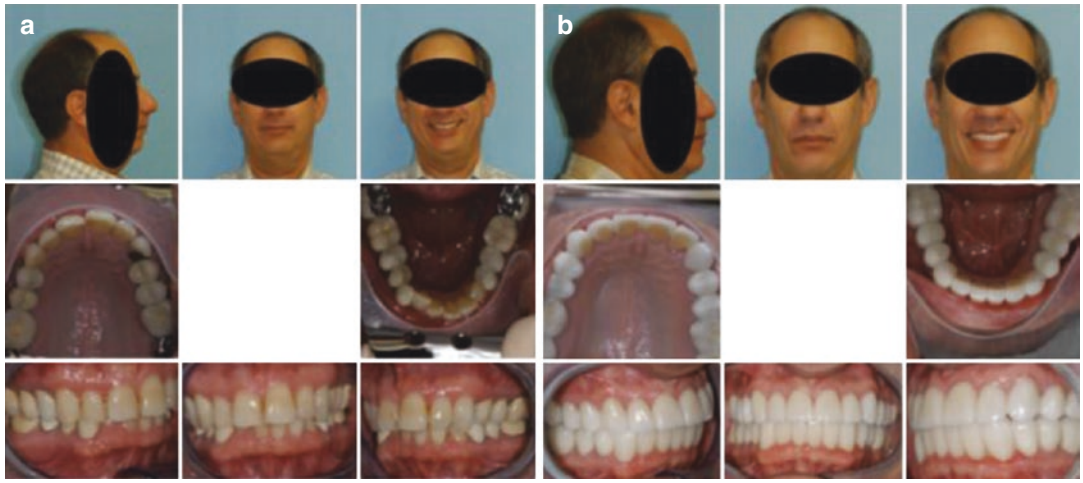

Fig. 9.31 (**a**, **b**) A 62-year-old male patient presented with severe fatigue and OSA. Pre-surgical orthodontics broadened the lower arch allowing the maxilla to be expanded at the time of surgery. Both jaws were advanced massively with a counterclockwise rotation of the occlusal plane to maximally advance the genioglossus muscle. The improvement in the airway eliminated his OSA and caused the sleep physician to remark, "You have an airway like a wind tunnel!"

commented that "You have an airway like a wind tunnel".

Orthognathic surgery to advance both jaws can be a very successful approach to treating OSA sufferers if it is planned properly, prepared for properly orthodontically, and executed properly by a surgeon who understands how to advance the jaws for optimal esthetics and airway. Patients who finally are free of OSA often awake in recovery and say, "I can breathe!" like they had never taken a breath before in their life. Many also indicate dramatically improved brain function when they are finally sleeping normally.

9.19 Palliative Solutions

Managing patients' airway problems with oral appliances can be very helpful and is now becoming a focus of many dentists. Unfortunately, such treatment is more of a "Band-Aid" solution. It is not a permanent "fix" of the problem. Mandibular advancement devices (MADs) which posture the mandible forward can open the airway enough to reduce the AHI in many mild or moderate OSA sufferers. Unfortunately, over time, all have a headgear effect of retracting the maxilla and ultimately will become less effective. Figure 9.32 shows an OSA sufferer who had a normal occlusion before wearing a MAD for many years. The headgear effect of that appliance produced the end-to-end incisor relationship and open-bite. Patients need to be warned of such bite changes and reduced effectiveness over time.

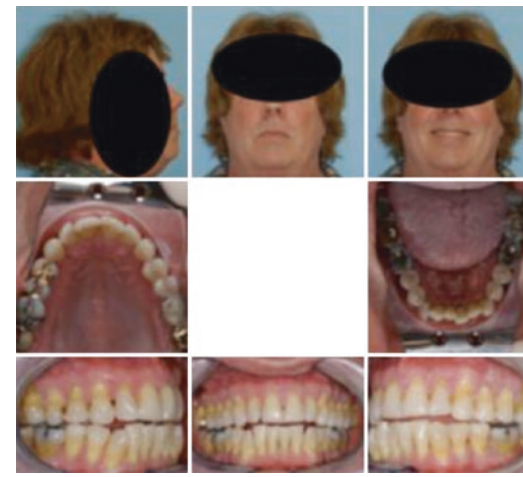

Fig. 9.32 This patient wore a MAD (mandibular advancement device) for OSA for several years causing the maxilla to be retracted with a "headgear effect" and producing an open-bite. The appliance became less effective in reducing the OSA

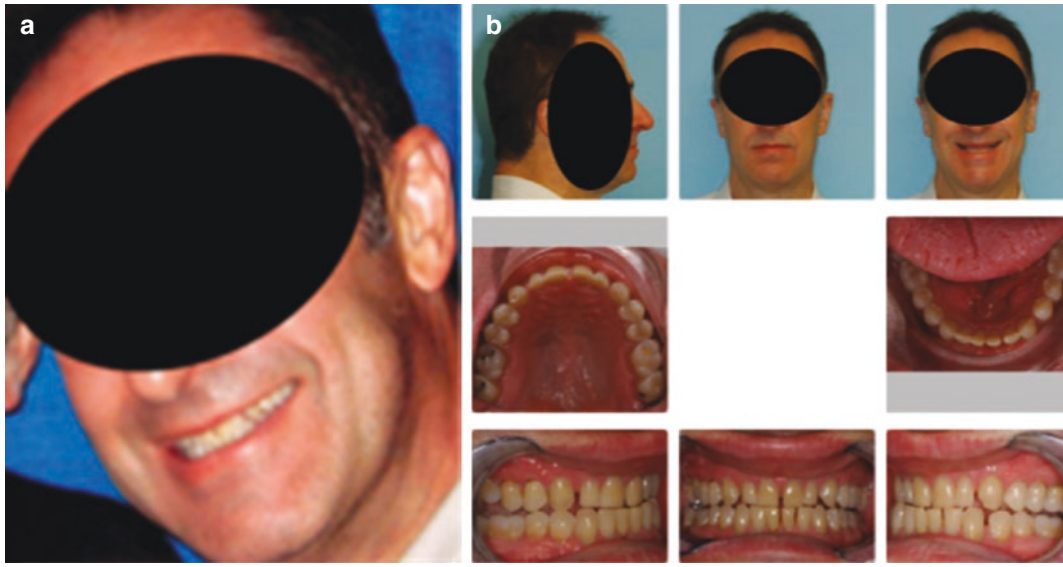

Fig. 9.33 (**a**) A 47-year-old male with normal bite relationship prior to CPAP treatment. (**b**) After approximately 10 years of CPAP therapy, an anterior crossbite was produced and CPAP was no longer effective. Maxillomandibular advancement surgery was recommended to treat his OSA

CPAP is the gold standard of OSA treatment. CPAP is the treatment of choice in cases of mild to severe OSA when a MAD is not effective. Sadly, CPAP does not enjoy a high rate of compliance long term. It can also have a headgear effect of driving the maxilla distally. Figure 9.33a shows a male prior to his wearing a CPAP for about 10 years. He began with a perfect Class I occlusion, but the headgear effect retracted the maxilla to the illustrated bite relationship in Fig. 9.33b. The CPAP became largely ineffective after this occurred. Maxillomandibular advancement surgery was the only solution to his problem.

9.20 Alternatives to Palliative Treatment

There will always be a place for palliative treatment of OSA. Many healthcare issues do not have "solutions," and the best option is some form of palliative treatment. However, the prevention of the problem is the option that really makes sense. Myofunctional therapy to teach children to have their tongue to the palate, teeth touching lightly, and lips together breathing through the nose would ideally become the standard and would eliminate many of the orthodontic and breathing issues children present with today. Optimizing forward facial development as early as possible in growing children has been shown to improve the airway short term [34]. Surely optimizing the forward facial development and keeping that development will have long-term benefits. This is a great subject for future research.

9.21 Dentistry: The Gateway to the Airway

Dentists have been given a gift and responsibility to manage the airway. Most are completely unaware that the decisions made regarding treatment for malocclusions can have a positive or negative effect on the airway. We need to become aware of this critical role we have been given and shoulder the responsibility of addressing these problems in a way that reflects the life and death importance of optimizing airways.

As with any problem, it is obvious that the earlier the treatment is done, the easier it is and the better the outcome. Nevertheless, the profession needs to be ready to effectively help patients of any age with treatment modalities which are predictable and have a high chance of success in resolving the problems related to airway inadequacy. Exciting times lie ahead for the profession, but dramatic changes must be made. Retraction in any form must end. This requires a complete change in the orthodontic profession because many (if not most) treatment plans are retractive in nature. A complete discussion of these treatment plan changes is in an article by Hang and Gelb [46]. Orthodontic research to find better ways to help patients develop their faces forward must replace research on how to straighten teeth more efficiently and effectively to the "gold standard" Class I occlusion without regard to the position of the jaws in the face or to the airway. Orthodontists must embrace the goal of optimizing airway for all if the profession is to escape the often-cited image of being "oral cosmetology" and take its rightful place in the healthcare profession.

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10 CBCT and MRI of Temporomandibular Joint Disorders and Related Structures

Tammy L. Balatgek, G. Gary Demerjian, Anthony B. Sims, and Mayoor Patel

Abbreviations

CBCT	Cone beam computed tomography
MRI	Magnetic resonance imaging
TMD	Temporomandibular joint disorder
TMJ	Temporomandibular joint

10.1 Introduction

Clinical assessment of patients presenting with temporomandibular joint (TMJ) symptoms includes radiographic examination. There are several imaging modalities available to visualize the TMJ, and this chapter will focus specifically on cone beam computed tomography (CBCT) and magnetic resonance imaging (MRI). CBCT has revolutionized oral and maxillofacial radiology and offers low-dose, high-spatial resolution characteristics of the bony structures. In addition to anatomy seen on traditional TMJ radiographs of transpharyngeal, transcranial, panoramic radiograph, or tomographic section of the TMJ, CBCT will offer additional detailed information about bony alterations. These bony alterations may include flattening, sclerosis, erosions, osteophytes, resorption of the condylar head, ankyloses, erosion of the mandibular fossa, and reduced joint space. CBCT is also useful to visualize fractures, infection, invasion by tumor, and congenital abnormalities [1].

MRI is an advanced imaging modality that provides high-quality images of soft tissues without the use of ionizing radiation and without the invasiveness of arthrography. Information gathered from an MRI includes detection of disc displacement, assessment of disc configuration, inflammation, joint effusion, formation of a pseudo disc, perforated disc, loose bodies, and even subtle osseous changes [1].

The goal of this chapter is to give an overview of the imaging modalities of CBCT and MRI and to include sample films of TMJ anatomy, pathologic conditions, and explain what they mean regarding diagnosis. This chapter does not contain all anatomy or conditions seen on the imaging discussed; it is intended to provide an overview of the most common conditions encountered in daily practice.

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10.2 Cone Beam Computed Tomography (CBCT)

10.2.1 Description and Implications

Cone beam computed tomography (CBCT), or volumetric computed tomography (VCT), has become the standard of care to visualize hard tissue and surrounding anatomical structures when diagnosing and treating TMJ disorders (TMD).

This technology uses a cone-shaped X-ray beam instead of a collimated fan beam as used in spiral CT. The tube detector system performs a 180–360º rotation around the head of the subject using a constant beam angle. This rotation acquires basis images ranging from 150 to 600 in number depending on the degree of rotation and time of acquisition. The initial raw data consisting of the basis images is displayed into a primary image which is then used for reconstruction of secondary images. The secondary images, which may be reconstruction images in all three orthogonal planes (axial, sagittal, and coronal), specific views used in dentistry such as panoramic or lateral cephalometric, and 3D images, can then be used for diagnosis and treatment planning [2] (Fig. 10.1).

The radiation risk from many newer CBCT machines is below that for the most common intraoral full mouth series; thus, it may be possible when indicated to use a CBCT with select intraoral images as an option for dental treatment planning in the future. Clinicians must abide by the ALARA (as low as reasonably achievable) principle when ordering an imaging modality for a patient [3]. Exposing the patient to the radiation must provide an image whose diagnostic value is greater than the detriment the radiation exposure may cause [4]. Not every patient requires a CBCT as CBCT does expose the patient to radiation and results in increased cost. The American dental association (ADA) council on scientific affairs suggests that CBCT use should be based on professional judgment and clinicians must optimize technical factors such as using the smallest field of view (FOV) necessary for diagnostic purposes and using appropriate personal protective shielding [3].

Adjacent anatomy outside of the region of interest is usually captured with a CBCT. Given this volume of tissue is exposed and readily available for review, there is a moral, ethical, and legal responsibility of interpreting the volumetric data set. Due to the complexity of the anatomy of the maxillofacial area, review of the images by an appropriately trained radiologist is prudent [3].

10.2.2 Anatomic Structures Seen on a CBCT (Fig. 10.2)

CBCT imaging provides for multiplanar information and diagnostic imaging in different planes. Figure 10.2 shows the 3 basic tomographic planes (axial, coronal, and sagittal) with anatomy of the maxillofacial region demonstrated in each view.

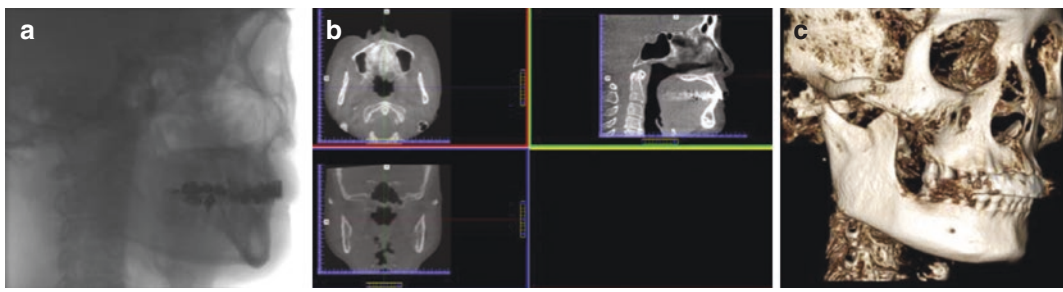

Fig. 10.1 (**a**) Primary image. (**b**) Secondary 3D volume multiplaner view reconstruction. (**c**) Secondary 3D reconstruction

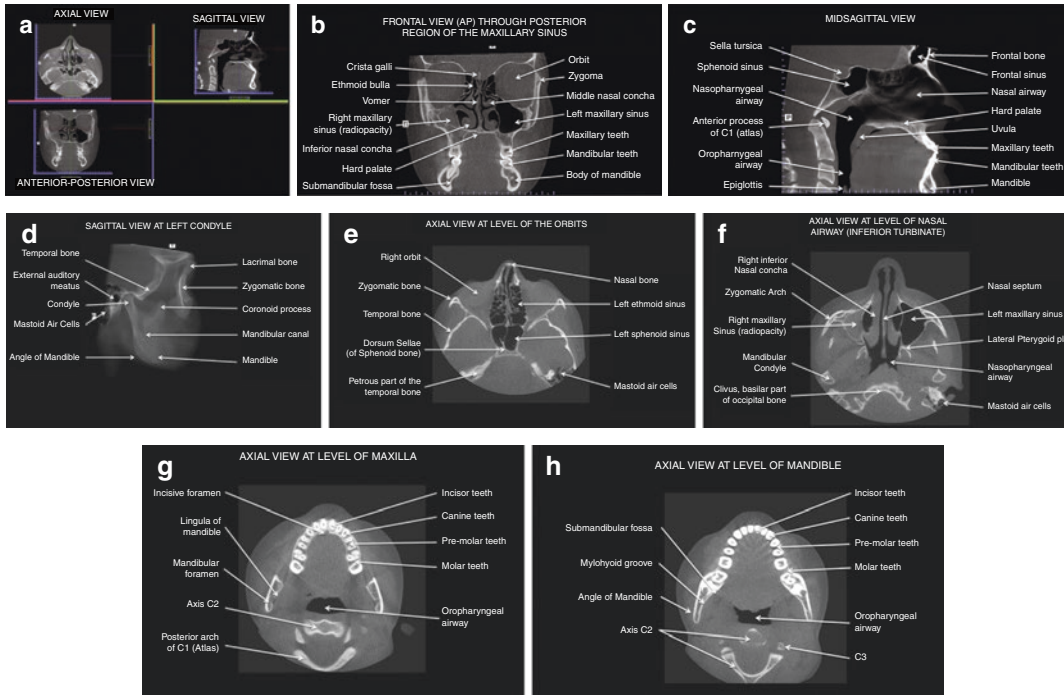

Fig. 10.2 (**a**) A composite layout of the various views in which a CBCT scan may be viewed in secondary reconstructions. (**b**) Frontal view (AP). (**c**) Midsagittal view. (**d**) Sagittal view left condyle. (**e**) Axial view orbit. (**f**) Axial view nasal airway. (**g**) Axial view maxilla. (**h**) Axial view mandible

10.2.3 TMJ Bony Information

The temporomandibular joint is made up of three bony structures: the condylar head of the mandible, the glenoid fossa of the temporal bone, and the articular eminence of the temporal bone (Fig. 10.3a).

The glenoid fossa is a shallow, oval depression in the infratemporal area and is located between the base of the zygomatic process anteriorly and the external acoustic meatus posteriorly. Normal anatomy of the glenoid fossa has an angle made by the midsagittal plane and the long axis of the fossa of approximately 70°.

The articular eminence is anterior to the glenoid fossa and is the lateromedial, cylindrical elevation in the base of the zygomatic process of the temporal bone. The function of the eminence, assisted by the articular disc, is to guide condylar movement during jaw opening. There are two slopes to the eminence and are covered by fibrocartilage. The anterior slope is anterior to the top of the eminence, and the posterior slope is posterior to the fossa [5].

The optimal position of the condyle in the glenoid fossa for normal function is a fundamental question that has yet to be quantitatively standardized. Several studies have assessed the joint space and condylar position in normally functioning TM joints and asymptomatic subjects and have found that the centric position of the condyle in the glenoid fossa is the most common presentation [6, 7].

A sagittal view of optimal joint position with the right condyle centered in the joint is seen in (Fig. 10.3b). There is spacing between the mandibular condyle and the articular eminence which allows room for the proper positioning of the articular disc. When a patient has dentition that occludes, the final condyle position is dictated by the dentition, making the TM joint different than other joints in the body and adding clinical significance to treatment [8].

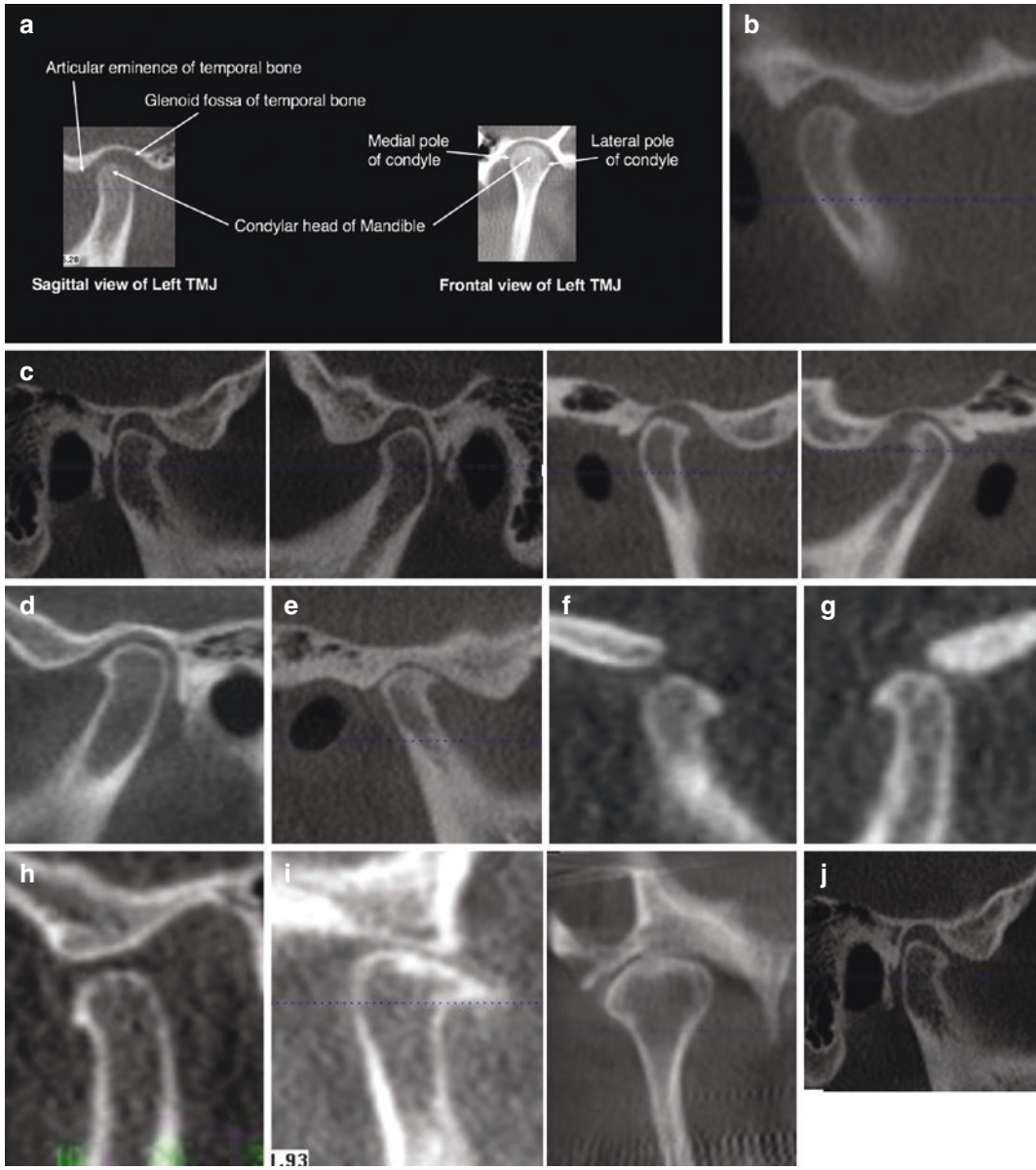

Fig. 10.3 (**a**) Bony Anatomy of TMJ. (**b**) Optimal TM joint position in sagittal view. (**c**) Posterior displacement of condyle. (**d**) Posterior and superior displacement of condyle. (**e**) Osteoarthritis, (**f**) Normal translation of the condyle upon maximum joint extension with ideal disc space, (**g**) Absence of disc space upon maximum joint extension. (**h**) Partial translation of condyle upon joint extension. (**i**) Lack of translation of condyle on joint extension. (**j**) Condylar flattening—anterior and posterior surface. (**k**) Anterior/posterior view of the condyle. (**l**) Condylar flattening—lateral pole and medial poles. (**m**) Flattening of the articular eminence and the superior surface of the condyle. (**n**) Condylar peaking. (**o**) Condylar beaking. (**p**) Condylar beaking and peaking. (**q**) Degenerative joint disease (osteoarthritis) of the condyle and articular eminence in frontal and sagittal views. (**r**) Left side photo: Degenerative arthritis of condyle and articular eminence. Right side photo: Normal eminence, posterior and superiorly displaced condyle. (**s**) A reconstructed panoramic view showing osteoarthritic changes on the right TMJ condyle (left side of photo). (**t**) Subchondral cyst formation and subchondral sclerosis of the condylar head. (**u**) Advanced osteoarthritic changes of condylar pitting/cratering. (**v**) Condylar osteophyte formation (lateral). (**w**) Artifact in joint space. (**x**) A healed condylar fracture, caused by a major trauma to the jaw

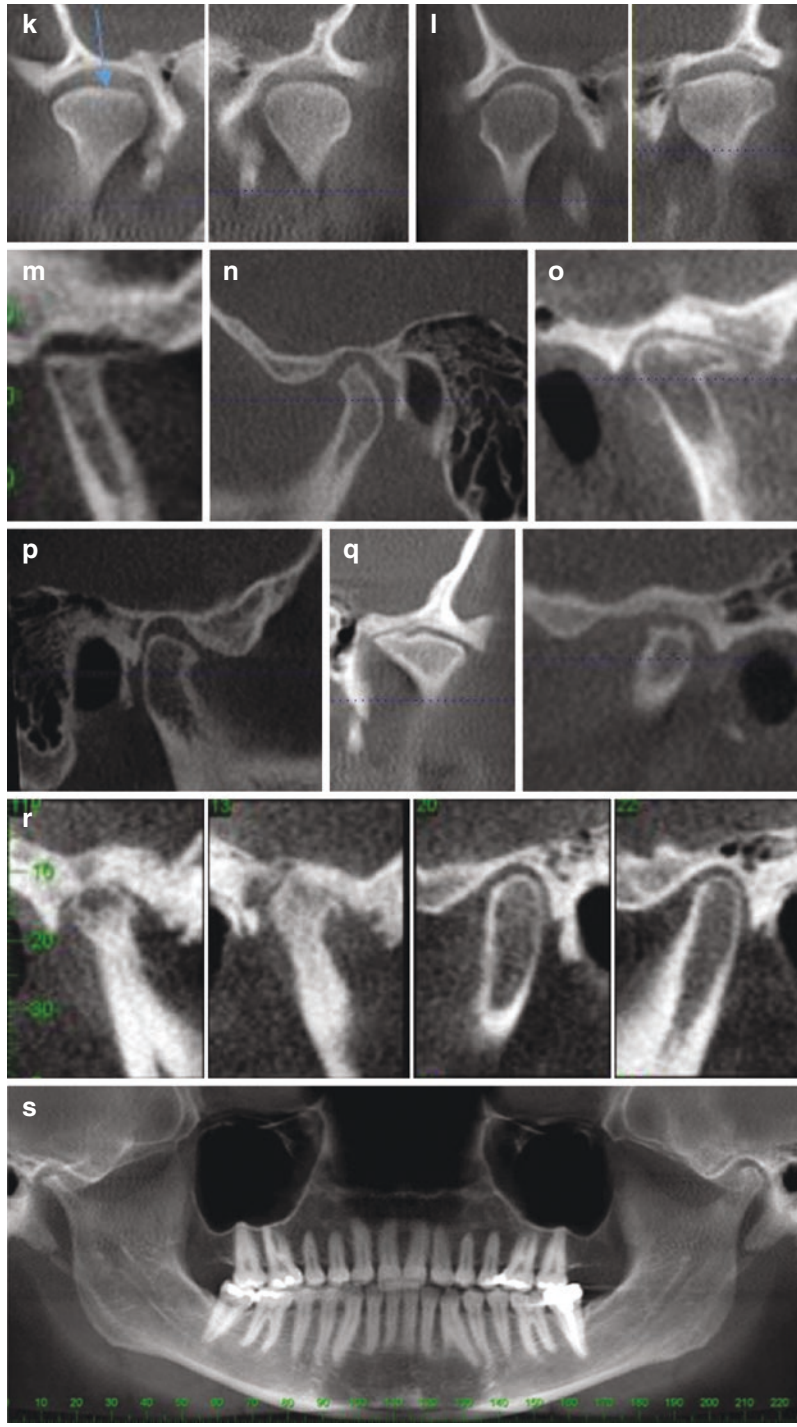

Fig. 10.3 (continued)

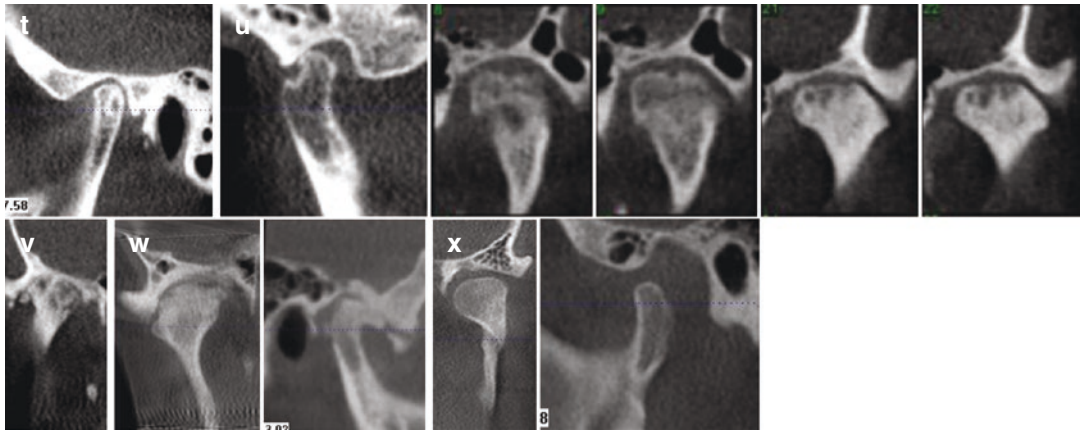

Fig. 10.3 (continued)

10.2.4 Local Pathological Temporomandibular Joint Conditions as seen on CBCT

A posteriorized (see Fig. 10.3c) or posterior and superiorly positioned condyle (see Fig. 10.3d) may indicate an anterior disc displacement [9], which can cause compression of the retrodiscal tissue resulting in pain and inflammation. This compression or irritation may lead to an overload of the central nervous system leading to central sensitization and neurologic conditions.

Narrowing of the space between the condyle and the fossa and articular eminence (see Fig. 10.3e, g) is due to disc displacement without reduction or the thinning of the disc possibly caused by repetitive microtrauma forces from clenching and bruxism.

Partial translation of the condyle (see Fig. 10.3h) is due to an obstruction such as disc displacement, which does not reduce, or adhesions within the joint. This can also be due to a muscle spasm that does not allow the joint to move.

Lack of translation of condyle (see Fig. 10.3i) on joint extension can be due to a disc displacement that does not recapture or adhesions within the joint.

Figure 10.3c shows condylar bony changes typically seen with chronic disc displacement with reduction [10]. The anterior flattening is due to the disc moving in and out of position, while the condyle translates down the articular eminence. The posterior flattening is due to the posteriorization of the condyle against the posterior aspect of the fossa.

In the frontal view, condylar flattening of the superior surface is seen in Fig. 10.3k notice the difference between right (arrow, flattened superior surface) and left condyles.

Early-stage degenerative joint disease (DJD) or osteoarthritis showing flattening of the condylar head is seen in Fig. 10.3n, therefore causing a point at the top of the condyle, e.g., "peaking," This is a common presentation seen with disc displacement with reduction [10].

Condylar "beaking" (see Fig. 10.3o) refers to the bony change that occurs to the shape of the condyle, indicating advanced-stage TMJ dysfunction with osteoarthritic changes and lack of disc space.

In Fig. 10.3w, an artifact can be seen on the anterior of the mandibular condyle in the frontal view, and a small artifact can be seen in the posterior joint space and anterior to the condyle in the sagittal view.

10.3 Other Common Comorbidities Associated with TMJ Dysfunction

10.3.1 Coronoid, Styloid, and Angle of Mandible Presentations

Elongation of the styloid process or calcification of the stylohyoid ligament is called Eagle's

syndrome when it causes symptoms such as dysphagia, headache, pain on rotation of the neck, pain on extension of the tongue, change in voice, and hypersalivation. Approximately 4% of the population is thought to have an elongated styloid process; however, only a small percentage is thought to be symptomatic [12, 13] (Fig. 10.4a, b).

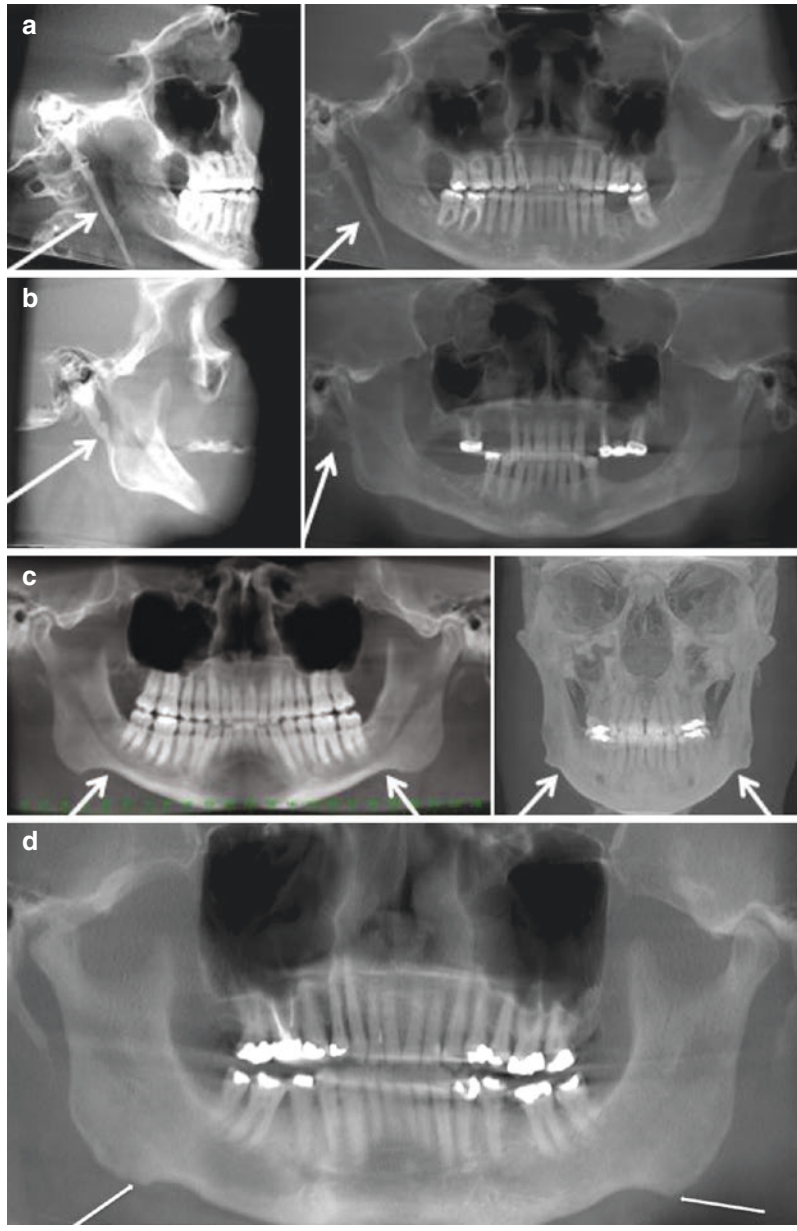

Fig. 10.4 Coronoid, styloid, and angle of mandible areas (**a**) Ossification, stylohyoid ligament. (**b**) Ossification, stylomandibular ligament. (**c**) Ante-gonial notching as seen on a reconstructed panoramic view and a frontal view, likely due to the forces put on the mandibular ramus from the masseter muscles due to clenching [11]. (**d**) Bone deposition indicated with the arrows. (**e**) 2D and 3D reconstructions of right and left elongated coronoid processes/coronoid hyperplasia. (**f**) Coronoid elongation on sagittal TMJ and panoramic views. (**g**) Coronoid process hypoplasia

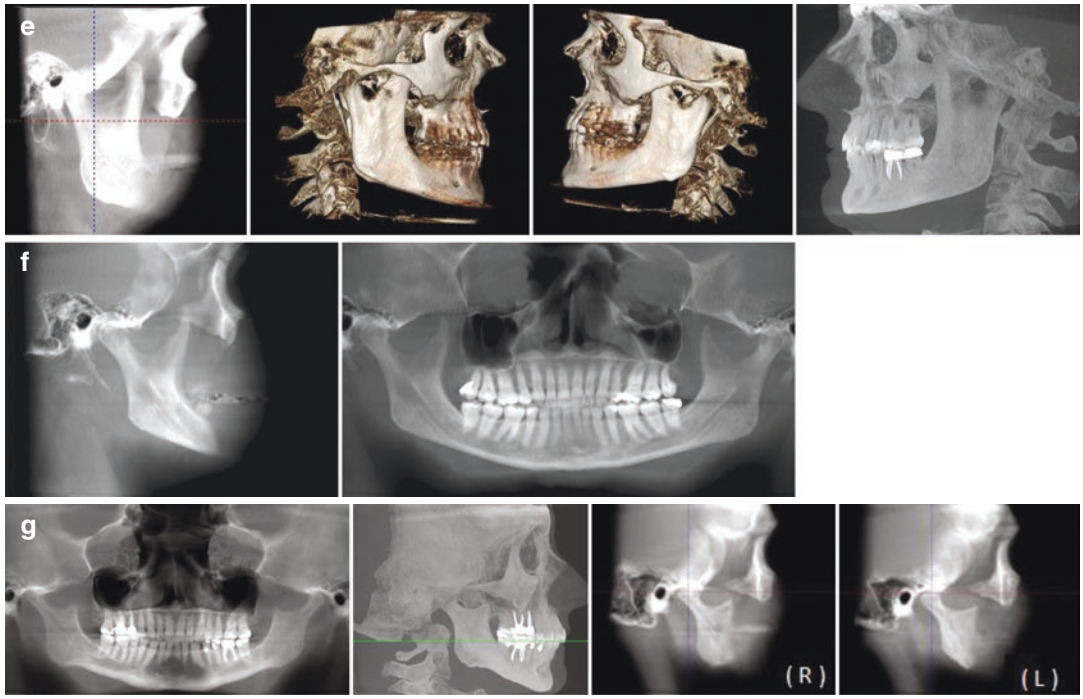

Fig. 10.4 (continued)

10.3.2 Airway Information as seen on CBCT

A high mandibular angle may signify downward and clockwise rotation of the mandible, which could cause airway impingement. Notice the cervical vertebrae are misaligned, and both patients have their lips parted, likely mouth breathers (Fig. 10.5a).

Small airway passage causes inadequate oxygen intake and is indicative of a posteriorized and collapsible tongue and soft palate. The photo on the right also shows retrognathia. These anatomic abnormalities have been recorded as risk factors for sleep-disordered breathing. CBCT scanning allows rapid, noninvasive assessment of airway variables [14] (Fig. 10.5b).

Tonsillar hypertrophy is due to increased immunologic activity. Acute tonsillar hypertrophy is associated with viral or bacterial infections. Chronic tonsillar hypertrophy can be asymptomatic which may lead to pharyngeal airway impingement causing obstructive sleep apnea, otitis media, sinusitis/rhinitis, underdevelopment of maxilla (narrow arch), and mandible (retrognathia) due to mouth breathing (Fig. 10.5c).

In Fig. 10.5.d, this patient had maxillary and mandibular osteotomies for orthodontic purposes when she was a teenager. Now in her fourth decade of life, dental relapse has occurred, likely due to airway issues and muscle forces on the teeth from altered breathing posture (e.g., tongue protruded and resting between her left side teeth to stay out of her airway). The left posterior and anterior open bite is seen on these films.

10.3.3 Developmental Bone Deposition

Palatal torus is likely due to clenching and flexing the maxillary suture, causing bone deposition as a stability mechanism [11]. Figure 10.6a shows three different radiographic

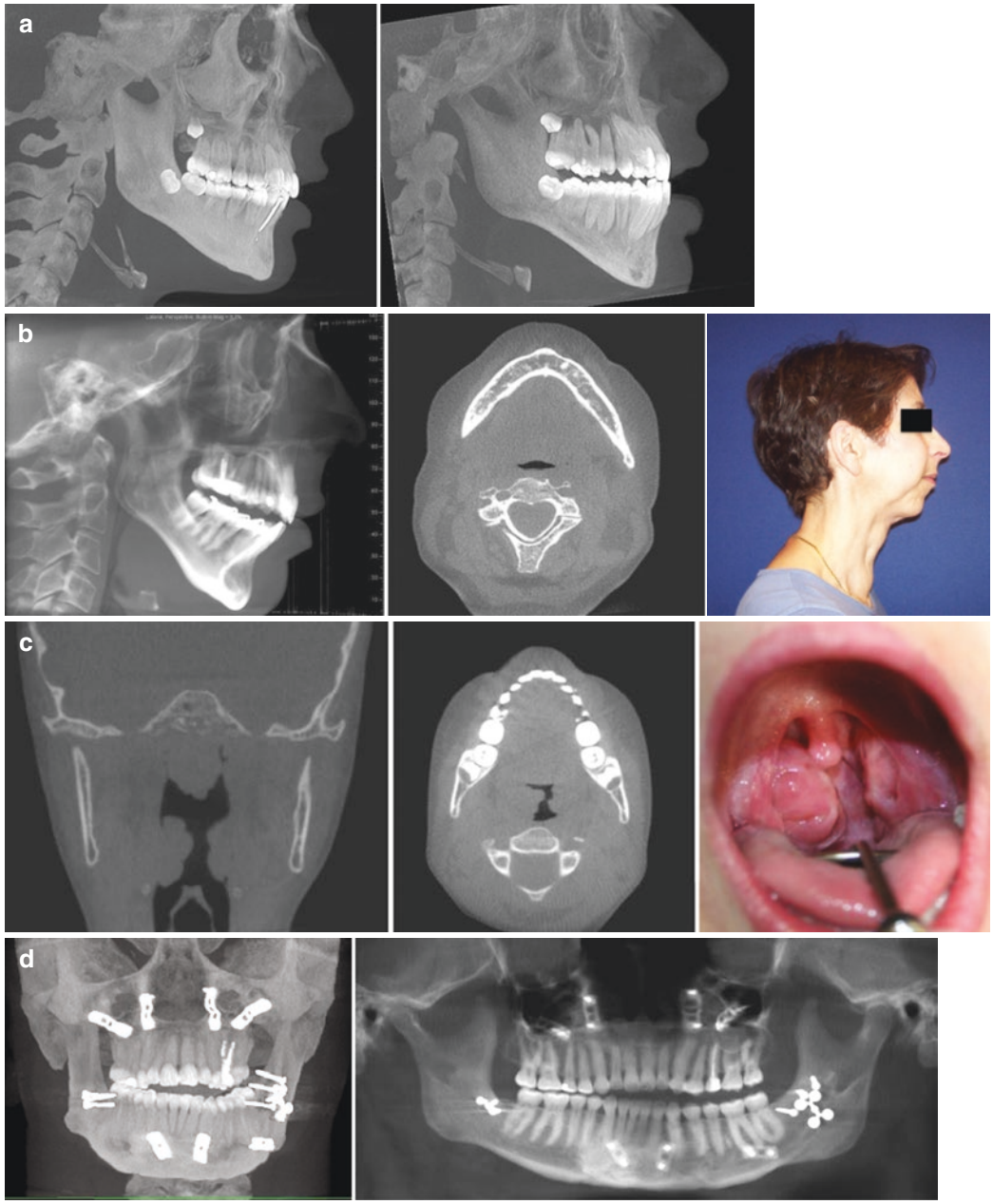

Fig. 10.5 Airway Information as seen on CBCT (**a**) High horizontal mandibular angle. (**b**) Pharyngeal airway impingement. (**c**) Enlarged tonsils. (**d**) Previous orthognathic surgery

views and an intraoral photo of the same patient.

Mandibular tori are a developmental phenomenon. One theory explains tori are caused by stimulation of the bone due to tooth clenching and grinding forces [11] (Fig. 10.6b).

Buccal exostosis seen on the left side of maxilla, right side of photo in Fig. 10.6c is caused by stimulation of the bone, due to clenching and bruxism. Worn occlusion can be seen on the left maxillary lateral incisor and cuspid [11].

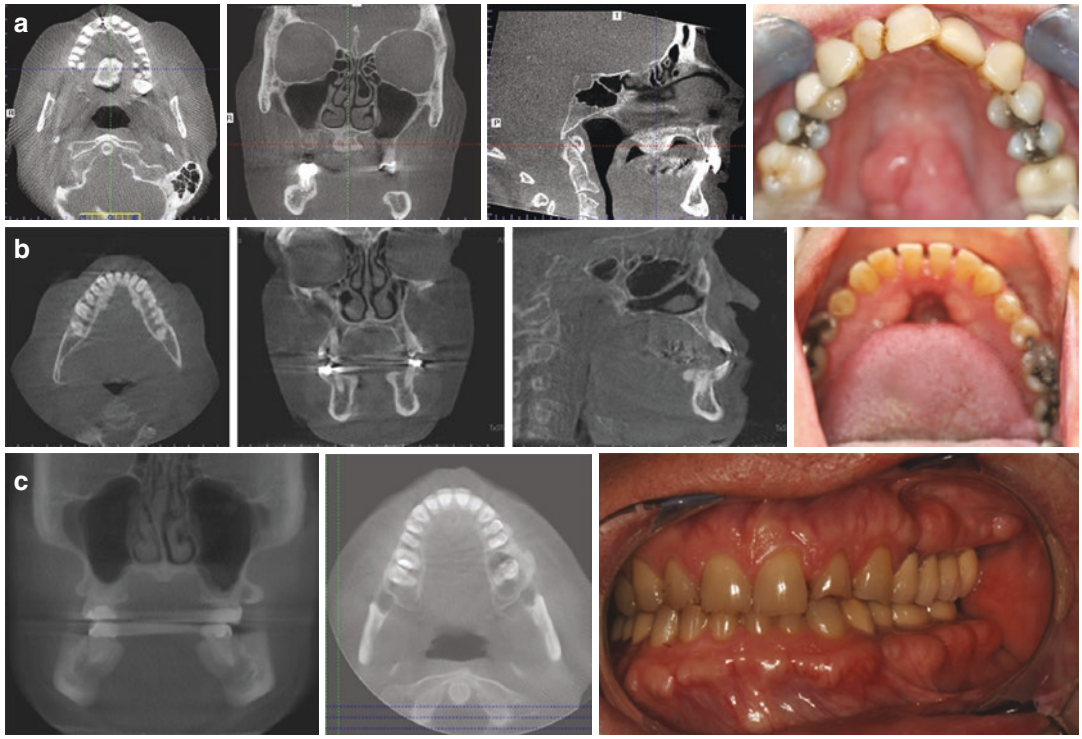

Fig. 10.6 (**a**) Palatal torus. (**b**) Mandibular Tori. (**c**) Buccal Exostosis

10.3.4 Other Calcifications Commonly seen on CBCT of TMJ Dysfunction patients

Salivary stone is a mass of crystalized minerals that form in the salivary tube which can cause blockage of the duct, therefore causing pain (see Fig. 10.7a).

Figure 10.7b shows physiologic calcification of the pineal gland in axial, coronal, and sagittal views.

The pineal gland is responsible for production of melatonin, which affects the circadian rhythm.

Patients with suspected carotid calcifications should be referred to their primary care physicians for hypertension and stroke risk evaluation. Cervical carotid artery atherosclerosis commonly occurs in older individuals with a history of hypertension and smoking and is a major cause of cerebrovascular accident (stroke). Dentists treating at-risk patients must be able to recognize these lesions and differentiate them from other anatomical and pathological radiopacities observed in the carotid artery territory [15] (see Fig. 10.7c).

Occipital protuberance is the point at which the ligamentum nuchae and the trapezius muscle attachment to the skull. The growth of the protuberance has to do with the pulling forces of the trapezius muscles (Fig. 10.7d).

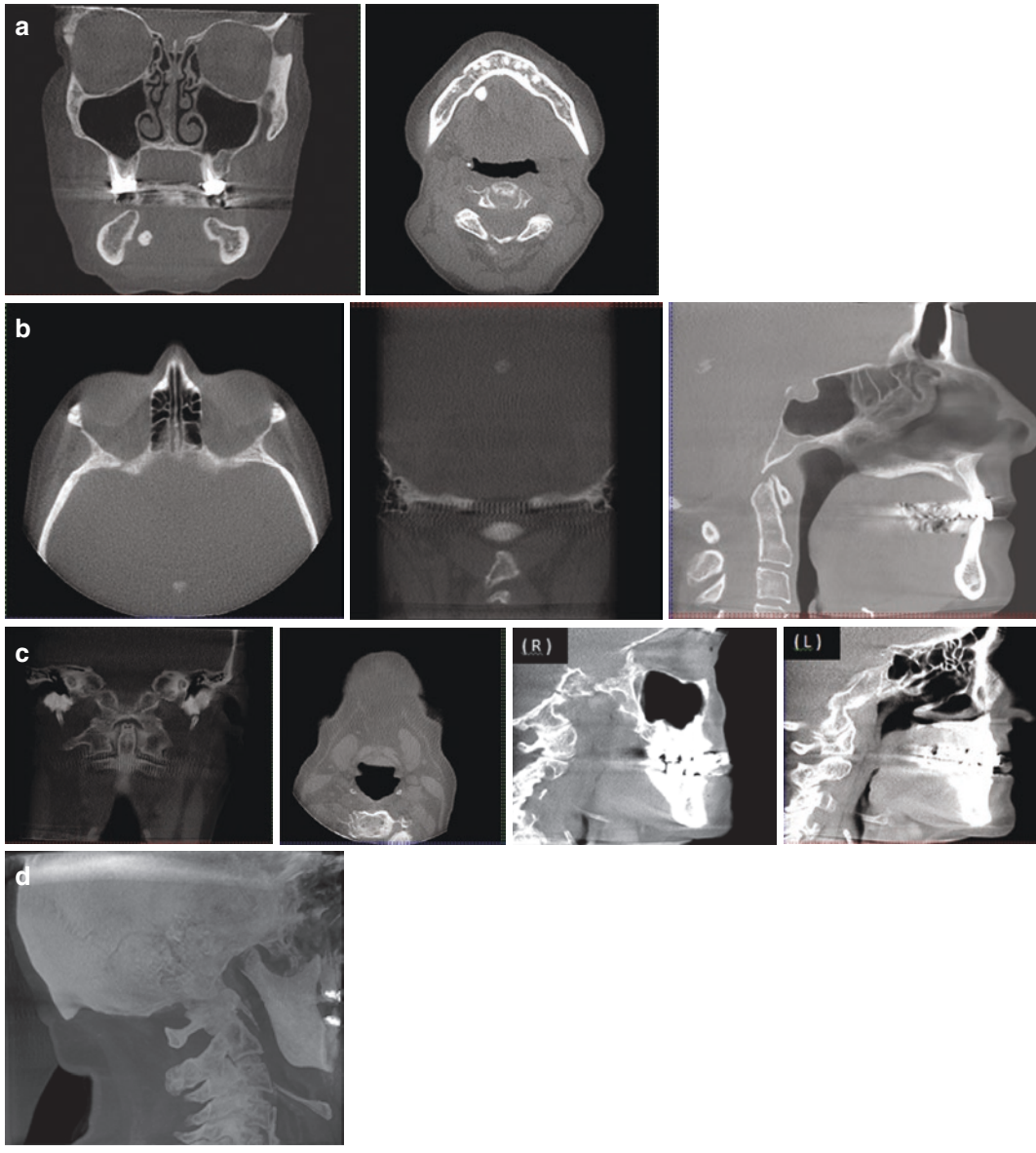

Fig. 10.7 (**a**) Right side submandibular Salivary Stone. (**b**) Calcified Pineal Gland. (**c**) Rt and Lt carotid artery calcifications. (**d**) Occipital protuberance

10.4 Sinus Pathology Seen on a CBCT

Sagittal, axial, and frontal views of different levels of sinus inflammation which may be due to allergies or a sinus infection. Sinus infections can cause facial pain and mimic a dental toothache (Fig. 10.8).

Deviation or obstruction of the nasal sinus can cause limited nasal breathing which can decrease oxygen intake during sleep.

10.5 Magnetic Resonance Imaging (MRI)

Twenty-eight percent of the population is affected by TMJ dysfunction according to the *New England Journal of Medicine* [16]. The National Institute of Dental and Craniofacial Research has estimated that there are ten million people that have been impacted by TMJ dysfunction [17]. Internal derangement, which is an anomalous relationship of the meniscus to the mandibular condyle, is the most frequent cause for TMJ dysfunction. MRI is

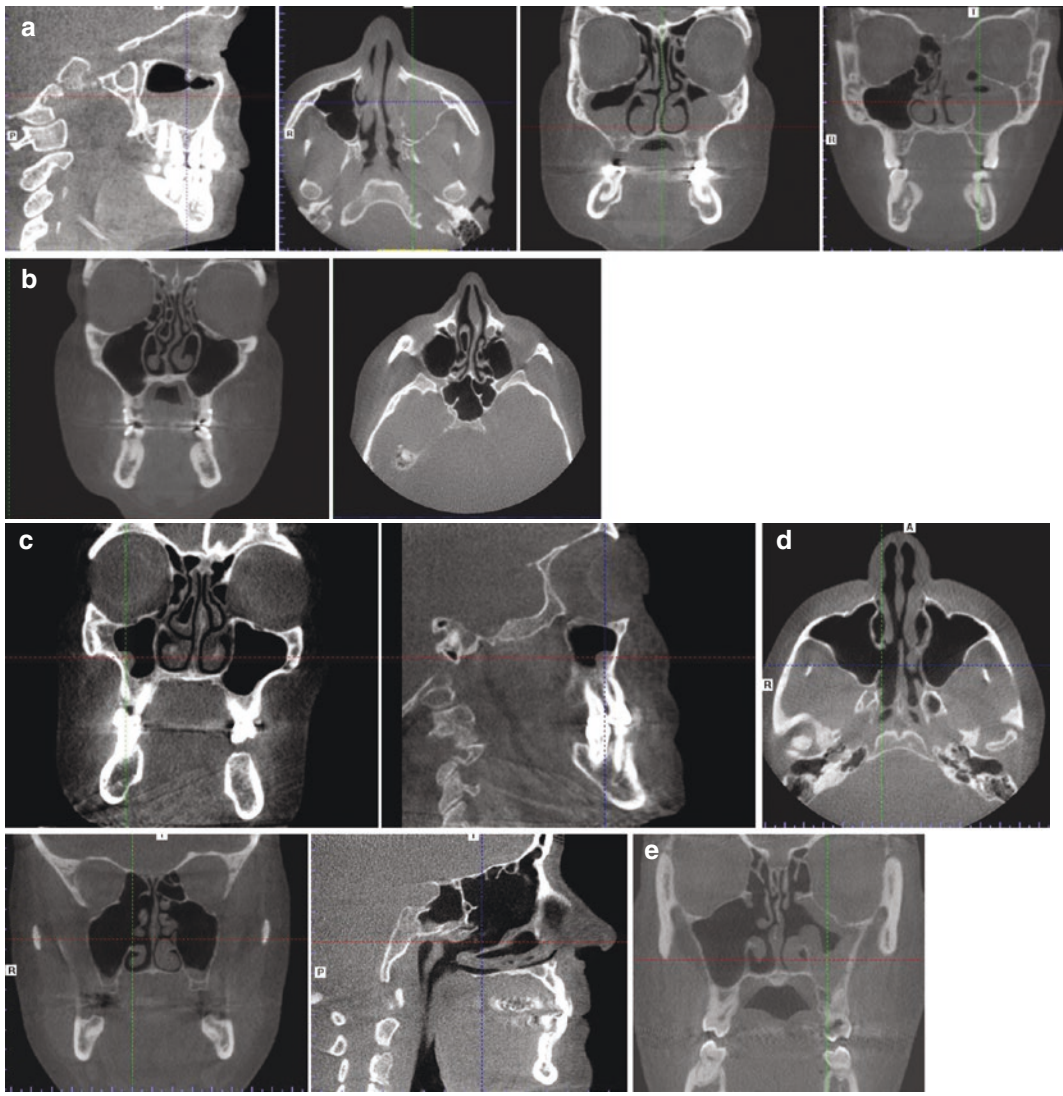

Fig. 10.8 (**a**) Sinus inflammation. (**b**) Deviated nasal septum. (**c**) Nasal polyp. (**d**) Previous sinus surgery in axial, frontal, and sagittal view. (**e**) Sinus and nasal airway pathology from cocaine use

the best technique for imaging the soft tissue of the TMJ and can be done in either a static or dynamic mode to show tissue and meniscus changes. Menisci relationship and position within the TMJ is most important and can only be seen with an MRI. The diagnostic accuracy of the clinical examination is variable, ranging from 54 to 90% [18].

The TMJ is a ginglymoarthrodial synovial joint (a hinge-gliding motion) that allows both backward and forward translation [19] with the disc having a biconcave fibrocartilaginous anatomy located between the mandibular condyle, the glenoid fossa, and articular eminence of the temporal bone of the joint. The disc is round to oval and avascular with thicker anterior and posterior bands and a thin center or the intermediate zone that separates them. The disc is attached to the temporal bone and condyle posteriorly by elastic and loose connective tissue; this tissue is also known as the *retrodiscal soft tissue* or the *bilaminar zone*. The lateral pterygoid muscle, the only muscle of mastication serving to open the jaw, inserts on the mandibular condyle inferior to the articular surface but is partially inserted on the joint capsule and disc. When the mandible is in the closed-mouth position, the thick posterior band of the meniscus lies immediately above the condyle near the 12 o'clock position. When the opening the mouth, rotation occurs first, followed by translation, in which the disc and condyle move under the articular eminence.

10.6 Anatomy Seen on an MRI (Fig. 10.9)

Figure 10.9 shows a typical MRI frame and the anatomy visualized in the sagittal view of a closed and open mouth position. It is vital to understand normal anatomy and biomechanics of the TMJ in order to assess for pathology.

10.7 Pathology of TMJ

10.7.1 Disc Injuries

MRIs are currently the standard for imaging and diagnosing disc injuries, which can manifest as innate disc lesions (changes in shape and signal intensity) or disc displacement [20]. At the early onset of an internal derangement, the disc shape is retained as normal. As the displacement progresses, the displaced disc becomes deformed by the thickening of the posterior band and the reduction in size of the anterior band and the intermediate zone becomes thinner, resulting in a biconvex-shaped disc. During the process of disc displacement and reduction, a reciprocal click can be audible. Chronic progression of disc displacement sometimes results in a perforation of the meniscus (disc). During the process of disc displacement without reduction, no click is present. If the disc is chronically worn between the condyle and the fossa, a perforation may develop usually in the intermediate zone. Abnormal disc displacement has been categorized as anterior, medial, lateral, posterior, anterolateral, and anteromedial displacements. Disc displacement can be further subclassified as anterior displacement with reduction or anterior displacement without reduction based on the normalizing relationship of the condyle and the disc in the open-mouth position.

10.7.2 TMJ Dysfunction Progression

Osteoarthritis (degenerative joint disease) of the TMJ is more prevalent and common in older individuals; however, it is not relegated to gender or dentition [21]. Osteoarthritic changes may appear in young individuals in which longstanding internal disc derangement without reduction should be ruled out. Osteoarthritic changes tend to appear as advanced-stage TMJ dysfunction and may be interpreted as signs of disease progression. Osteoarthritis can be demonstrated when the condyle exhibits one of the following imaging signs: flattening, osteophytes, erosions, and sclerosis [22]. MR imaging has demonstrated osteophytes and condylar flattening were seen in 27% of cases, erosions in 13%, and sclerosis in 9% [10].

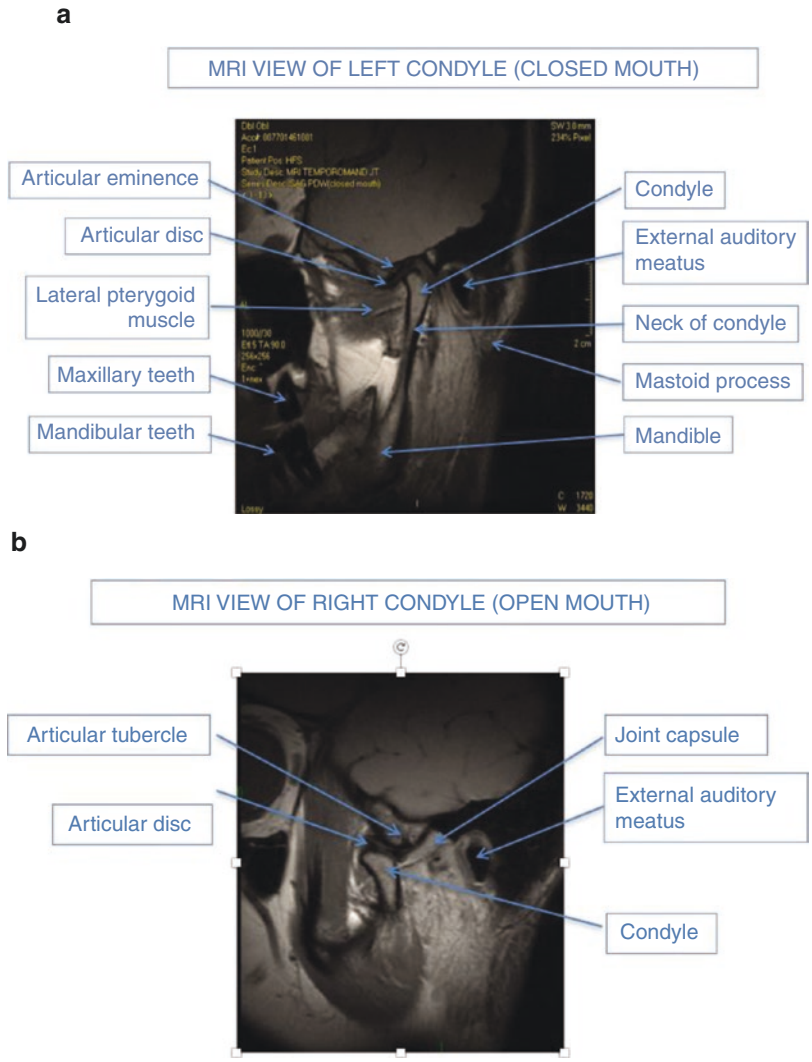

Fig. 10.9 (**a**) MRI lateral view of condyle (closed mouth). (**b**) MRI lateral view of condyle (open mouth)

10.8 Supplemental MRIs of the TMJ

Figure 10.10 includes various pathological features often seen on an MRI. The following should be assessed for evaluation of the TMJ: position and morphology of the articular disc, any disc deformity or perforation, joint effusion and marrow edema, osteoarthritis and other bony changes, the lateral pterygoid muscle, and the retrodiscal tissues.

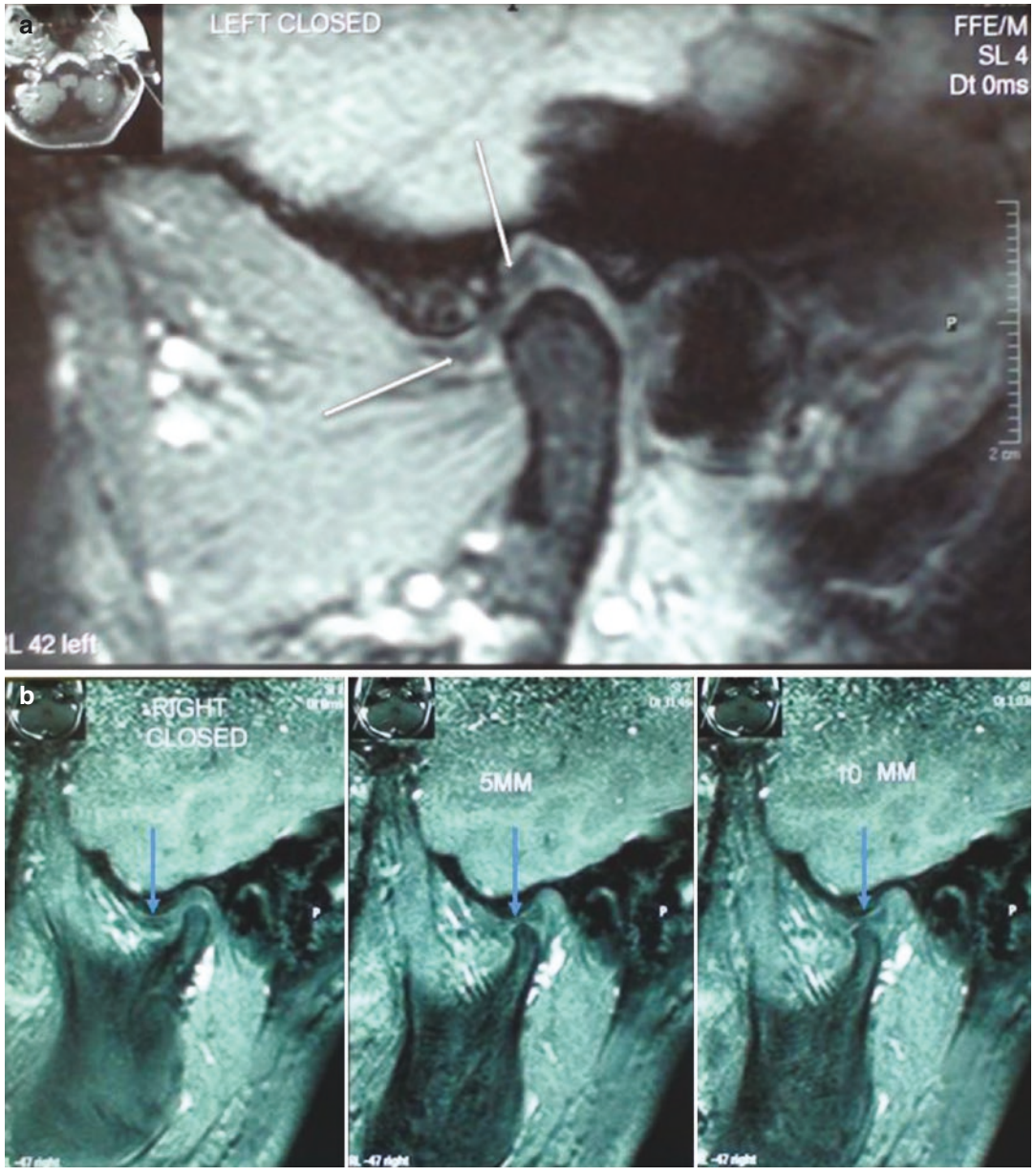

Fig. 10.10 (**a**) Anterior and posterior disc bands of the meniscus (disc) within the glenoid fossa in front of the condyle and behind the articular eminence. Posterior band in the 12 o'clock position. (**b**) Anteriorly displaced disc with recapture as mandible translates. (**c**) Anteriorly displaced disc (closed mouth). (**d**) Anteriorly displaced disc without recapture (open mouth). (**e**) Sagittal view of anteriorly displaced disc without recapture. (**f**) Laterally displaced disc in the frontal view. (**g**) Laterally displaced disc in the frontal view. (**h**) Anteriorly displaced disc with chronic condyle distalization resulting in bending of condylar head. Also early osseous degeneration with osteophyte formation and "beaking" of condyle. (**i**) Chronic osseous erosion with deterioration of glenoid fossa and articular eminence and complete disc degradation. (**j**) Chronic condylar degeneration with anterior disc displacement. (**k**) Sagittal view of condylar breakdown with osteophyte formation and articular eminence and glenoid fossa degeneration. Torn meniscus without recapture. Clinically, subject would present with limited opening due to incomplete translational movement. (**l**) Mandibular condyle with early osteophyte formation and early bone erosion (left photo) and in a posterior-superior position (right photo)

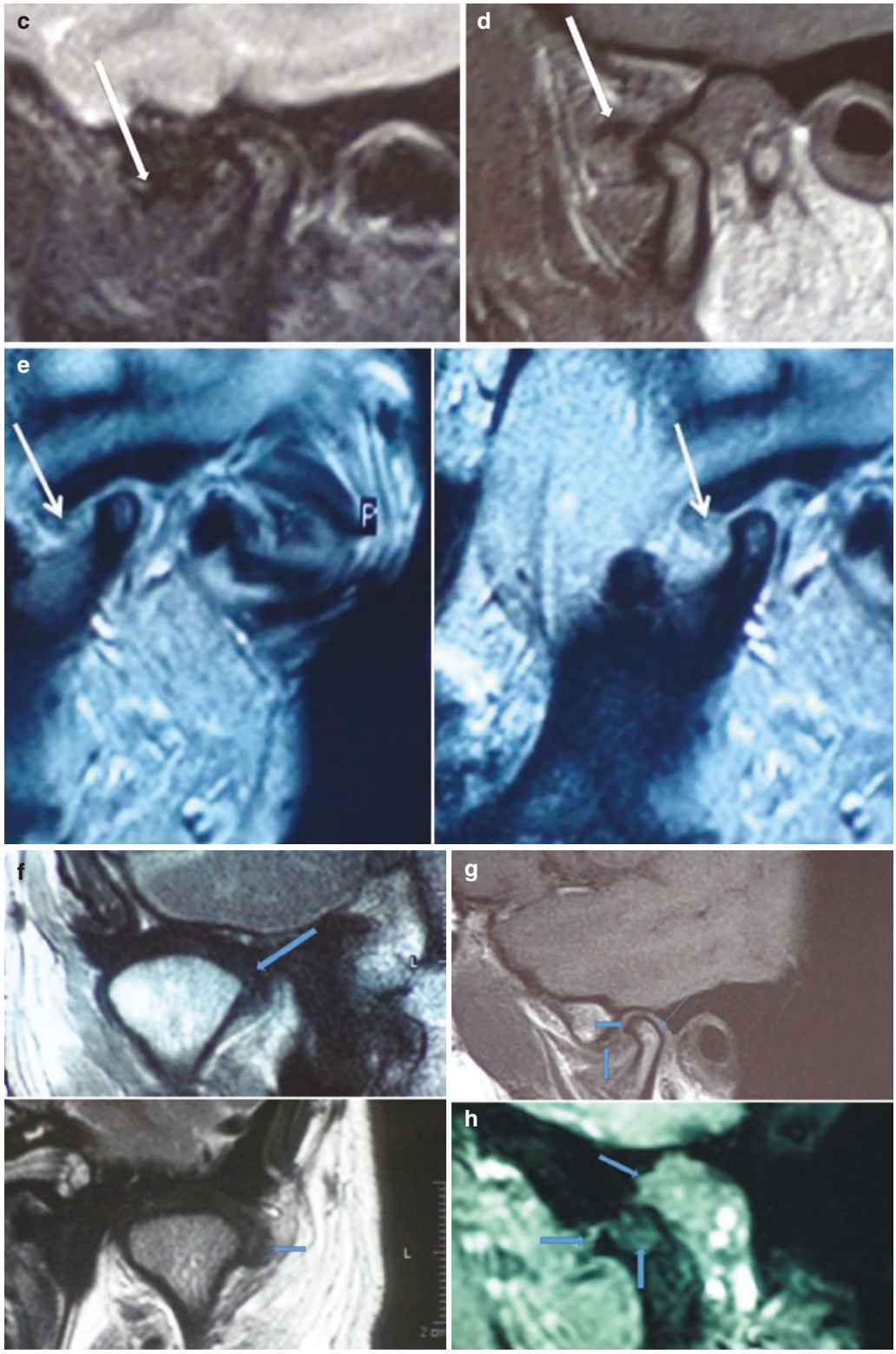

Fig. 10.10 (continued)

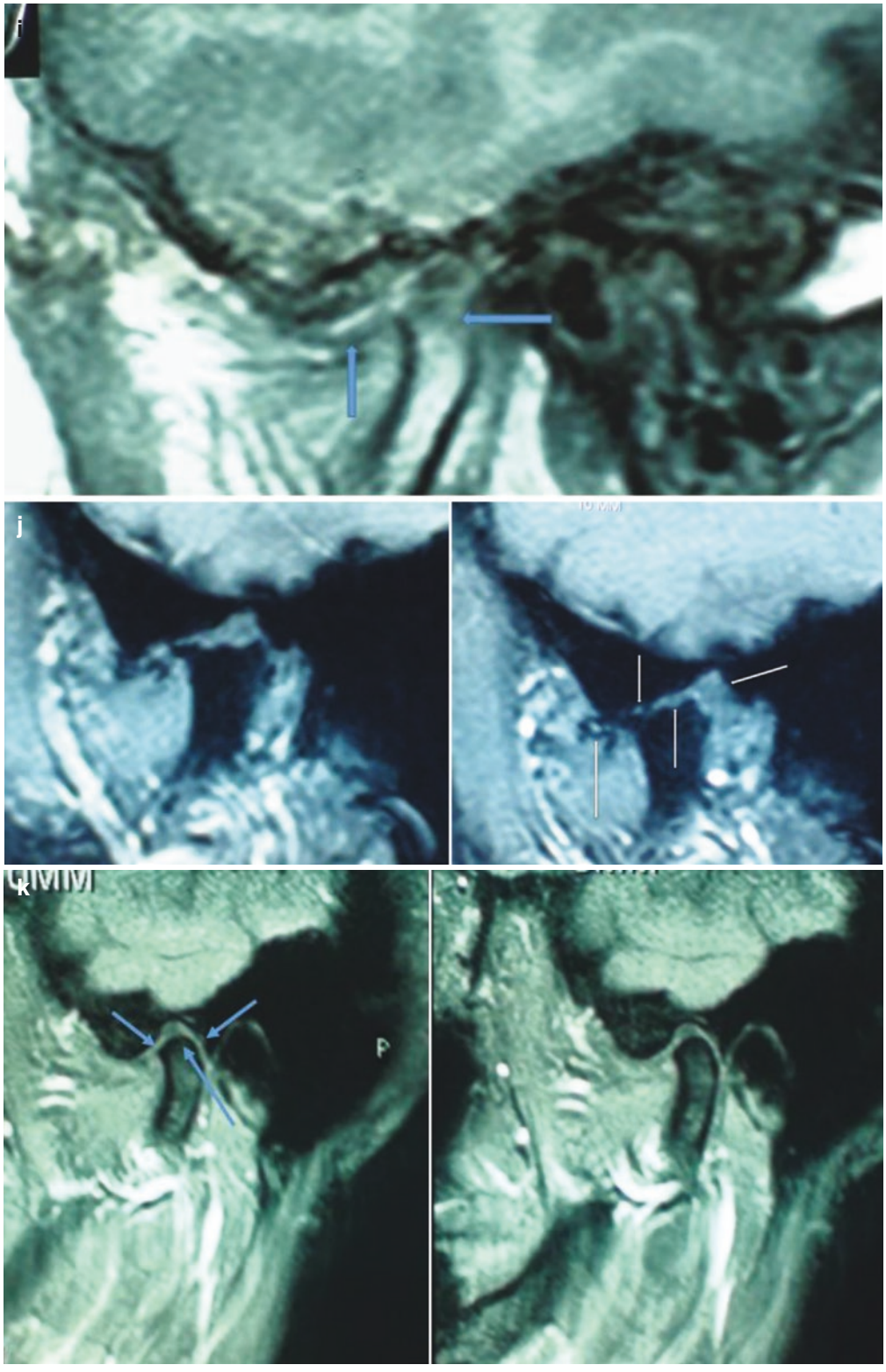

Fig. 10.10 (continued)

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11 Patient-Centered Outcomes Research and Collaborative Evidence-Based Medical and Dental Practice for Patients with Temporomandibular Joint Disorders

Francesco Chiappelli, André Barkhordarian, and G. Gary Demerjian

Abbreviations

EBD	Evidence-based dentistry
EBDM	Evidence-based clinical decision-making
EBrCPGs	Evidence-based revisions of clinical practice guidelines
fMRI	Functional magnetic resonance imaging
PCOE	Patient-centered outcomes evaluation
TMD	Temporomandibular joint disorders
TMJ	Temporomandibular joint
WHO	World Health Organization

Core Message

The novel discipline of research synthesis and translational effectiveness pioneers a fresh conceptualization of clinical practice in dentistry in the context of translational science that is grounded on the pursuit and the utilization of the best available evidence. This chapter examines specific facets of this novel model of evidence-based clinical decision-making (EBDM) in health care in general and in evidence-based dentistry (EBD) in particular and specifically for patients with temporomandibular joint disorders (TMD).

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11.1 The Temporomandibular Joint

The body is endowed with two temporomandibular joints (TMJ): one on the right and the other on the left of the facial skeleton. The TMJs are the dual articulation of the mandible with the maxillary bone of the frontal aspect of the skull. The TMJs are ginglymoarthrodial joints in that they

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consist of a hinge-type joint (i.e., ginglymal[1]) and a sliding arthrodial[2] component [1].

The joint itself is encapsulated by a fibrous tissue and is composed of the condylar process of the mandible below and the glenoid fossa (i.e., the articular face) of the temporal bone above. Between these articular surfaces lies a biconcave, transversely oval disc composed of dense fibrous connective tissue referred to as the articular disc, also called the meniscus. Tight fibers connect the mandible to the disc from below, whereas looser fibers hold the meniscus to the temporal bone superiorly. This anatomical distinction results in the property of the temporomandibular joint consisting of two distinct capsules, an upper and a lower joint space, that are separated by the meniscal disc. A synovial membrane lines the inner facet of this fibrous capsule apart from the articular surfaces and the disc and secretes temporomandibular synovium,[3] which fills and lubricates the upper and lower spaces and distributes essential growth factors, cytokines, and nutrients to the tissues within the joint.

The meniscus is concave, which produces an anterior band, an intermediate zone, and a posterior band. Posterior to the disc is loose vascular tissue termed the bilaminar region. It is a relatively loose tissue that sits posterior to the articular disc and that is rich in vascularization. It provides posterior attachment of the meniscus and extensive blood and lymph circulation.

The movement of the joint has two phases:

- When the mouth is first opened, the initial movement of the mandibular condyle is rotational and involves primarily the lower joint space.
- When the mouth is opened further, the movement of the condyle is translational and involves the upper joint space.

The overall translational movement of the temporomandibular joint therefore is obtained by a sliding downward motion of the condylar head along the articular eminence, which constitutes the front border of the articular fossa. The articular eminence prevents and limits the excessive forward movement of the condyle and is aided in this function by the stylomandibular and the sphenomandibular ligament that are not directly associated with the joint capsule as well as the temporomandibular ligament (i.e., lateral ligament), which is the lateral extension of the fibrous capsule itself. The movement of the joint acts similar to a pump, such that circulation is particularly increased when the head of the condyle translates down the articular eminence.[4]

The regulation of TMJ movements—that is to say, the opening and closing of the mouth—is directed by the muscles of mastication. Therefore, TMD is often taken as an umbrella term that describes dysfunction of the masticatory musculature,[5] which can severely impair TMJ movement, and eventually its anatomy. Because of its anatomical architecture, the resting position of the joint is determined by occlusion principles—that is, how the upper teeth sit upon the lower teeth when the mouth is closed. When the adequate support is not provided by the relative occlusal position of the upper and lower molars, in particular, the structure of the joint is progressively and chronically altered, which can have serious consequences on the balance of the powerful masticatory muscles.

[1]From Latin, derived from Greek, *ginglumos* for hinge.

[2]From Greek, *arthrodia* for a synovial joint which allows a gliding motion.

[3]The synovium is specialized mesenchymal tissue that facilitates the functionality of the arthrodial joints.

[4]Cf., Gray's anatomy: the anatomical basis of clinical practice. (39th ed.). Edinburgh: Elsevier Churchill Livingstone; Clemente's Anatomy: A Regional Atlas of the Human Body (6th ed., 2011). Philadelphia: Lippincott.

[5]On each side: the masseter, the temporalis (the sphenomandibularis is considered a part of the temporalis by some sources and a distinct muscle by others), the medial pterygoid, and the lateral pterygoid. The muscles of mastication originate in the maxilla and insert into the mandible and allow for TMJ movements during contraction. They are all derived from the first branchial arch during embryonic development and are all innervated by the mandibular (i.e., third) branch of the trigeminal cranial nerve V (V3).

Innervation of the TMJ is provided by the mandibular branch (V3) of the trigeminal nerve, the cranial nerve V. Cranial nerve V is the largest of the 12 cranial nerves that consist of three main branches, hence "trigeminus"—born three at birth—and trigeminal implies three parts. It is responsible for sensation in the face, but it also has certain motor functions such as regulating the masticatory musculature for opening and closing the jaw, as well as the tensor tympani,[6] tensor veli palatini,[7] mylohyoid,[8] and anterior belly of the digastric muscle.[9] The motor division of the trigeminal nerve is derived from the basal plate of the embryonic pons,[10] while the sensory division originates from the cranial neural crest and provides tactile, proprioceptive, and nociceptive afferents to the rostrum.

The three trigeminal branches originate from the trigeminal ganglion,[11] which sits in Meckel's cave[12] and contains the cell bodies of incoming sensory nerve fibers. Whence, a single large sensory root enters the brainstem at the level of pons, and, adjacent, the smaller motor root also emerges. The motor fibers are functionally distinct from sensory nerves. Thus, the mandibular branch of the trigeminal nerve, V3, is said to have general somatic afferent (sensory) components and special visceral efferent (motor) components, the latter is responsible for controlling the muscles[13] of mastication and of swallowing. These muscles have bilateral cortical representation, meaning that any unilateral pathology, arising from neural lesion (e.g., a stroke) or inflammation, is likely to cause unilateral deficits on one side of the TMJ and by compensatory action on the other side: the net result often being deficits that are observable[14] by dentists with special interest of the TMJ.

The main trigeminal nucleus in the pons is anatomically adjacent to the entry site of cranial nerve V. From this nucleus, secondary fibers cross the midline and ascend in the trigeminal lemniscus to the contralateral thalamus. The trigeminal lemniscus runs parallel to the medial lemniscus, which carries touch/position information from the rest of the body to the thalamus. Information from V3 is represented bilaterally in the thalamus[15] and hence in the cortex. The mesencephalic trigeminal nucleus is embedded in the brainstem and regulates the symmetrical coordination of TMJ, the simultaneous actions of both sides of the body, which need essentially little conscious attention.

[6]The larger of the two muscles of the tympanic cavity responsible for dampening sounds, such as those produced by chewing.

[7]Tenses and elevates the soft palate thus protecting the nasopharynx during swallowing.

[8]Depresses the mandible and elevates the hyoid during swallowing.

[9]Elevates the hyoid during swallowing.

[10]The pons, better referred to as pons Varolii (the connection, the bridge of Varolius, because it was first described by Italian anatomist and physician to Pope Gregory XIII, Costanzo Varolio [1543–1575]), is a component of the brainstem that links the medulla oblongata to the thalamus. The pons is considered to be a critical neuroanatomical structure in that it regulates signals, through its specialized nuclei, that control a vast array of functional behaviors, including sleep, respiration, swallowing, bladder control, hearing, equilibrium and movement, taste, eye coordination, facial expressions, facial sensation, and posture. Pontine pathologies lead to difficulty with balance, walking, touch and other senses, swallowing, and speaking (cf., Pritchard and Alloway, 1999, Medical neuroscience; Gray's anatomy; Clemente's anatomy, among others).

[11]Aka semilunar ganglion, gasserian ganglion, after the Austrian anatomist Johann Lorentz Gasser (1723–1765).

[12]Named after Johann Friedrich Meckel the Elder (1724–1774).

[13]Masseter, temporalis, medial pterygoid, lateral pterygoid; and tensor veli palatini, mylohyoid, anterior belly of digastric.

[14]For example, injury to peripheral branches of V3 nerve may cause partial or total, transient, or chronic paralysis of certain muscles on TMJ, thus leading to a deviation of the jaw on that side and a compensation on the TMJ of the other side (cf., Wallenberg syndrome).

[15]The thalamus distributes information between subcortical areas and the cerebral cortex, such as sensory information from V1, V2, and V3. For this purpose, almost every sensory system has a thalamic nucleus that receives sensory signals and sends them to related primary cortical area.

11.2 Worldviews of Temporomandibular Joint Disorders (TMD)

Temporomandibular joint dysfunction (or disorder) (TMD)[16] is a complex symptom of clinically recognizable manifestations, a syndrome[17] rather than a single condition. To be clear, even though it is a generally accepted agreement among TMJ specialists that TMD can be caused by multiple factors, it is also accepted that the relative relevance of these factors to the clinical profile of TMD is still poorly understood and actually forcefully debated [2, 3]. Consequently, many treatments have been proposed, each based on one or the other particular worldview of TMD etiology, sometimes acrimoniously defended but often without the benefit of hard scientific and clinical evidence. Common treatments for TMD include adjustment of occlusal balance (e.g., splints) and masticatory muscle relaxation by means of various techniques ranging from pharmaceutical muscle relaxants, acupuncture/acupressure, and psychosocial and psycho-cognitive therapy. These three forms of myotherapy are often supplemented with analgesics and other forms of pain control intervention.

It is interesting to note that there are two principal national organizations for orofacial pain related to TMD, which each follow these fundamentally distinct conceptualizations of TMD:

- The American Academy of Orofacial Pain (AAOP) was established in the 1980s, a time when the field of TMD treatment was disorganized and many different treatment and examination modalities were being utilized. Research focused on what the most effective treatments were for the constellation of problems associated with TMDs. The drive to determine the etiology of TMDs sought to confirm the proposed role of dental occlusion, which was based on clinical reports that established about 80% of the population had occlusal interferences but no pain. Jaw bruxing behavior was believed to be increased because of occlusal interferences and that it caused the onset of pain, although bruxism[18] can often (80–90% of the population) occur without pain. Based on those associations, it was deemed that malocclusion alone could not be the main etiologic factor for TMD. The identification of an unambiguous universal cause of TMDs is lacking. For this reason, they await future research to document TMDs etiologic significance.[19]
- The American Academy of Craniofacial Pain (AACP), established in 1985, by contrast "believes that TMD's are primarily structural in nature. They believe that TM disorders can cause headache, neck ache, shoulder ache, dizziness, equilibration problems and a myriad of symptoms that are sometimes not routinely associated with TMD." In the *Craniofacial Pain: A Handbook for*

[16] The term *temporomandibular disorder* refers to a group of similarly symptomatic conditions and thus provides a rather vague description of a state, rather than a specific syndrome or condition that affects the temporomandibular joints. Thus, the term temporomandibular joint dysfunction is described as the most common form of temporomandibular disorder. Yet, temporomandibular disorders have been defined as *a group of conditions with similar signs and symptoms that affect the temporomandibular joints, the muscles of mastication, or both*. It is also the case that TMD is distinct, albeit overlapping somewhat with related syndromes such as the temporomandibular pain and dysfunction syndrome, which is characterized by aching in the muscles of mastication, occasional brief severe pain on chewing, and associated with restricted jaw movement and clicking or popping sounds (Classification of Chronic Pain, International Association for the Study of Pain; Classification of Chronic Pain, Part II, B. Relatively Localized Syndromes of the Head and Neck; Group III: Craniofacial pain of musculoskeletal origin).

[17] A syndrome (Greek, syn, together + dromos, course, progression) describes a constellation of manifestations, clinically recognizable features, which collectively indicate or characterize a condition. These signs can occur together or in a recognized timeline.

[18] Bruxism (sleep or wake bruxism) is an oral para-functional activity where there is excessive clenching and grinding of the teeth. The etiology of bruxism is unclear: psychosocial factors may be implicated, and dopaminergic dysfunction and other central nervous system mechanisms may be involved in sleep bruxism.

[19] Cf., "Orofacial Pain Fourth Edition. Guidelines for Assessment, Diagnosis, and Management."

Assessment, Diagnosis, and Management, this approach follows in broad lines Costen's early recommendations.[20]

To be clear, TMD is an umbrella term used to describe pain and dysfunction of the muscles of mastication that control and regulate movement of the TMJ. In an early study, 31.4% of patients with TMD complaints were found to have masticatory muscle dysregulation (Group I), internal disc displacement was noted in about 15.5% of patients (Group II), and arthralgia, arthritis, and arthrosis disorders were observed in close to 13% of patients (Group III). Among all TMD patients, almost 40% manifested Axis II moderate to severe depression, and 48% showed moderate to severe nonspecific physical symptom of stress [4]. A more recent study confirmed this pattern of patient distribution, Group I (muscle disorders), 57.5%; Group II (disc displacement), 42.5% and 47.1% of the right and left joints, respectively; and Group III (arthralgia, arthrosis, arthritis), 19.5% and 23.0% of the right and left TMJ, whereas 42.5% of patients had moderate/severe depression scores and 60% moderate to severe somatization scores [5].

However, the occluding opposing molars must find appropriate position and support, lest the TMJ may be chronically imbalanced, which will lead to progressively impaired function. TMD prevalence among the young and adult populations is high, and it is estimated that TMD afflicts close to a third of the individuals in mid-adulthood (40–50 years of age), although teenage girls and women are generally more prone to develop TMD than their male counterparts [6].

The primary[21] symptoms of TMD in most patients are:

- Clicking, grating (i.e., crepitus), and popping noises at the TMJ: most often intermittent and unilateral during functional movement of the joint. Most joint sounds are due to internal derangement of the joint, which is a term used to describe instability or abnormal position of the articular disc.
- Clicking indicates that the articular disc has moved to and from a temporarily displaced position (disc displacement with reduction) to allow completion of a phase of movement of the mandible.
- Locking reflects the situation where the disc displaces and does not reduce (move back into position).
- Crepitus reveals arthritic changes in the joint and occurs at any time during mandibular movement, especially lateral movements.
- Restricted mandibular movement: Limited range of movement may lead to difficulty in eating or talking. In more severe cases, there may be locking of the jaw or stiffness in the jaw muscles and the joints. Often bilateral, these manifestations can be unilateral, resulting in asymmetry and deviation of mandibular movement.
- Pain[22]: Pain and tenderness on palpation in the muscles of mastication or of the joint itself (preauricular pain), usually aggravated by function (chewing, clenching, yawning). The pain is mostly dull or aching, poorly localized, and intermittent or constant in more severe cases. Typically unilateral, the pain can also be manifested bilaterally. TMD pain may be referred to the teeth and shoulder and may be associated with headache in the temporal, frontal, and occipital region, migraines (including ocular migraines), tension headache, and myofascial pain.

A recent systematic review established that for most patients, a disc displacement is just a pain-free, lifelong-lasting, "noisy annoyance"

[20] An older name for TMD is "Costen's syndrome," after James Bray Costen (1895–1962), who, in 1934, described disorder systematically. He suggested that malocclusion, specifically mandibular over-closure, caused TMD and involved ear symptoms, such as tinnitus, otalgia, impaired hearing, and dizziness, including as well burning sensation of the throat, tongue, and side of the nose. He recommended TMD treatment interventions involving correcting occlusion by building up the bite, thus balancing TMJ [35].

[21] Secondarily, and because of the proximity of the auriculotemporal nerve to the TMJ, symptoms involving hearing may become evident, including diminished auditory acuity (hearing loss), occasional tinnitus (ringing in the ear), and dizziness.

[22] TMD is the second most frequent cause of orofacial pain after dental pain.

from their TMJ. A disc displacement with reduction is relatively stable, pain-free, chronic, and lifelong. In a few patients, the disc loses its capacity to reduce on opening, and in even fewer cases, the loss of disc reduction follows closed lock, painful, and limited mouth opening. These symptoms may spontaneously resolve within months [7].

We also discussed TMD from the perspective of the arthrokinetic reflex [8]. A typical joint movement, including TMJ, can reflexively cause neuromuscular activation or inhibition. Clinical research and observations of patients with TMD have established the wide spectrum of the arthrokinetic reflex in TMD, mediated largely by retrograde transport from the V3 terminal branch to the joint (auriculotemporal nerve) and the central nervous system, which can contribute and exacerbate neuromuscular disorders, including, as we discuss throughout this book, Tourette's syndrome, cervical dystonia, complex regional pain syndrome, gait or balance disorders, Parkinson's disease, middle and inner ear dysfunction, impaired eye movement, sleep disturbances, pain, and related neurological symptoms. In this context, sleep is particularly important because lack of quality sleep has been associated with increased risks of several health issues including obesity, heart disease, and diabetes. Individual patient measures of sleep quality should include the patient's quality of sleep that can be assessed with a polysomnography in an experimental sleep study and confirmed with the two critical blood or salivary biomarkers, oxalic acid and diacylglycerol 36:3, whose levels decrease significantly following sleep deprivation and normalize upon sleep recovery, and functional MRI (fMRI).

Our initial studies of the overarching arthrokinetic reflex in TMD are grounded on the working hypothesis that by expanding the joint anatomical space, the arthrokinetic reflex is reduced. In the context of individual patient-centered translational research (cf., Chap. 10), a broad spectrum of clinical independent patient data can be obtained from patients diagnosed clinically, by palpation as well as imaging (X-rays, CT) with mild-severe TMD. Salivary and synovial levels of proinflammatory cytokines replicate the findings reported in the literature [9] and are found to correlate with significant impairments ($p < 0.05$) in neuropsychological testing (e.g., Brief Visuospatial Memory Test, Grooved Pegboard, Hopkins Verbal Learning Test, Stroop), polysomnography, and fMRI, in the state of jaw joint space constriction, compared to when the joint space is expanded [8].

TMD is very common, as 20–30% of the adult population between age 20 and 40 are affected to some degree. TMD has a substantially greater relative prevalence in women, compared to men.

11.3 Principles of Patient-Centered, Effectiveness-Focused, and Evidence-Based Intervention

The new model of health care is patient-centered, effectiveness-focused, and evidence-based [9, 10]. The depth of meaning of this statement is still only barely understood. It is fair to say that its fundamental root can be traced several centuries back, perhaps as far as Aristotelian philosophy, as we discussed elsewhere [9, 10]. In the modern era, we recall the observation of the Marquis de Vauvenargues to the effect that it is in fact easier to state concepts anew than to reconcile statements made previously by others.[23] Seeking a consensus of the evidence is often a more complex process than obtaining new evidence. That is precisely the purpose and ultimate goal of the research design of the research synthesis model in evidence-based health care: to reconcile research evidence toward obtaining the best available evidence (evidence-based) for effective and efficacious treatment intervention (effectiveness-focused) for addressing clinical issues in specific patients (patient-centered).

The position that holds the ideology that the Western approach to delivering health care is

[23] Luc de Clapiers, Marquis de Vauvenargues (1715–1747), *Réflexions et Maximes* "…il est. plus aisé de dire des choses nouvelles que de concilier celles qui ont étés dites…."

superior because it rests on research evidence is, in and of itself, a fallacy simply because it ignores[24] the self-evident fact that there is good research evidence and there is bad research evidence. If research evidence is tainted by a suboptimal research methodology, if bias and error abound, if data is mis-analyzed and misinterpreted, then it is possible and even probable that the utilization and integration of that evidence in the clinical decision-making process will be unacceptable for safe utilization in patient care.

That, in and of itself, seems self-evident and routine. But in fact, it is a typical case of onus probandi[25]—that is to say, the complex process of research synthesis engages a series of articulated steps that lead to sophisticated statistical analysis and inference, which together build the case for or against the acceptability of the best available research evidence for patient care. The burden of proof for the elaboration of the consensus of the best available evidence rests squarely on research synthesis. That is the reason why it is critically important that research synthesis be a hypothesis-driven endeavor anchored in the reliable, valid, and unbiased scientific process.

The medical literature is gargantuan. We could not exhaustively peruse the published reports in the manner just outlined, even if we had the expertise to do so, and still have the material time to take care of our patients. Therefore, we would become selective on which report we are going to peruse. By doing so, inevitably, we insert into the very process the gravest fault of all research: the bias of selection. By selecting what report we shall consider in our perusal, we de facto select the kind of evidence we will be willing to utilize in the process of sharpening our skills and expertise: we de facto taint the very process of our clinical decision-making with a bias that is inappropriate because it is not related to the condition of the patient, to the intervention we are considering, or to the outcome sought. We de facto fall into one of the most dangerous fallacies of science, in which we tend to demonstrate this; well simply because of the conditions, we selected to make the case (post hoc ergo propter hoc; selection bias).

Health care based on the evidence suffers from an unalienable bias. The best available evidence emerges from a concerted process of systematically synthesizing and analyzing all the available evidence that pertains specifically to the patient under consideration, the interventions under consideration, and the clinical outcome under consideration. Thus, when the systematic process of research synthesis is applied to the entire body of the available evidence, such that the acceptable evidence can be obtained, from which a consensus of the best available evidence can be derived, evidence-based health care is procured. Evidence-based health care is the optimal and safest manner to update skills and expertise to provide effective and efficacious health care to each individual patient in a patient-centered paradigm.

In brief, evidence-based health care, therefore, entails making fully informed clinical decisions that integrate not only the patient's medical history and clinical test results but also the training of the clinician and his/her skills and expertise updated by the consensus of the best available research evidence, itself derived from a systematic process of research synthesis.

Research synthesis [11–13] follows the scientific method, which can be outlined in brief as follows:

- Statement of the hypothesis and research question
- Crafting of the research approach to test the hypothesis and answer to the research ques-

[24] Fallacy consequential to mere ignorance of the facts (*argumentum ad ignorantiam*), that is, the assumption that a claim is true (here, that all research evidence is equally acceptable for safe use on patients – note: the oath calls health-care providers to do no harm first and foremost [primum non nocere]) simply on the basis of the lack of clearly establishing that in fact that evidence is not safe to be used in patient care; in addition, fallacy consequential to mere adherence to previously held beliefs (*argumentum ad antiquitam*) (here again, that all research evidence is equally acceptable and safe for patient care) despite cutting edge protocols designed to distinguish acceptable vs. non-acceptable research evidence.

[25] "…onus probandi incumbit ei qui dicit, non ei qui negat…" the burden of proof is on the person who makes the claim, not on the person who denies it.

tion (i.e., research design, sampling issues, tools of measurement)
- Presentation of the findings and summary of the results by means of descriptive statistics
- Statistical analysis of the data
- Inferences, discussion of limitations and intervening variables, identification of future research toward further testing the hypothesis, and answering the research question in greater details

It is critical to set the question of the research at hand and to realize that a research question, when stated in the affirmative, is nothing but the study hypothesis. Thus, for instance, one could set out to test the research query of whether *orthotic intervention is an effective and efficacious in correcting TMD with internal derangement associated with TMJ inflammation and pain*.

The search for the best available evidence, which is obtained through the research synthesis design, is hypothesis-driven because it addresses a specific type of research question that is rendered by the acronym PICOTS (patient, interventions under consideration, outcomes, timeline, clinical setting). The PICOTS research questions direct the search for evidence about which intervention under consideration may, or may not, be more effective or efficacious for the particular patient population targeted in the study and in light of the specific clinical outcome of interest.

The distinction between the "effectiveness" and the "efficacy" of a clinical intervention is critical at this juncture. The US Federal Coordinating Council for Comparative Effectiveness Research Report to the President and the Congress, dated June 30, 2009, stated that *"…because it (comparative effectiveness research) …[applies]… to real-world needs and decisions faced by patients, clinicians, and other decision makers [generally including assessment of risks, costs vs. benefits]…."* By contrast, in *"… efficacy research, …the question is typically whether the treatment is efficacious [i.e., works clinically] under ideal, rather than real-world, settings …[and]….[t]he results … are … not necessarily generalizable to any given patient…."* Simply stated, whereas effectiveness pertains to risk, benefits, and cost assessment, efficacy pertains to whether or not a given clinical intervention works clinically and brings about the clinical outcome sought.

The PICOTS questions drive the process of search and analysis of the *best available* evidence by means of the research synthesis design. It defines and determines the sample of publication to be scrutinized to obtain the *available* evidence, the tools of evaluations that serve to assess the *best* evidence, the statistical analysis required to establish reliability and validity of the results, and the inference of the findings for immediate implication to clinical practice. The PICOTS question sets the criteria for deductive reasoning leading incremental progress of research in the future. In brief, it instructs and informs the creation of new knowledge obtained through systematic research driven by the scientific method to the ultimate aim—the *causa prima* (cf., Aristotelian teleology)—providing the best available treatment intervention to individual patients in the most cost- and benefit-effective manner.

The sample of a research synthesis design is obtained in a manner that is in no way different from what is done in a clinical trial, where the investigator determines and establishes beforehand what is the accessible and what is the target sample of the study. In the research synthesis design, the sample consists in the peer-reviewed and non-peer-reviewed published research literature, as well as unrecorded observations. The term "available" underscores the fact that we limit the subjects of study in a piece of research synthesis investigation, in the same manner as any other piece of research, to the accessible sample: that is to say, the accessible research literature that specifically targets the question under study. Unpublished evidence and evidence that is published in non-peer-reviewed journals are often excluded from a research synthesis design, in part, because it is exceedingly difficult to obtain these types of evidence in a valid and reliable manner. The literature available through the proceedings of scientific meetings, dissertations, and non-peer-reviewed journals, the "gray litera-

ture," is likewise often not part of the research synthesis process, because it is generally agreed that the evidence that has not been sifted through the widely accepted peer-reviewed process is likely to be fraught with issues of validity, quality, and bias, which will interfere with the research synthesis process. In brief, the research synthesis process is most often focused, otherwise indicated, on peer-reviewed literature. The search for that sample is obtained by utilizing the medical subject headings (MeSH terms) and keywords that can be derived from the PICOTS question.

Case in point, for the PICOTS question proposed above, typical keywords could be:

- (Dental, oral) orthotic
- Temporomandibular joint disorder
- Internal derangement
- Inflammation
- Pain

Of these, "orthotic device," "temporomandibular joint disorder," and temporomandibular joint" are actual MeSH words: MeSH (medical subject headings) being the vocabulary thesaurus used for indexing articles for PubMed controlled by the National Library of Medicine.

A typical search on PubMed would develop as follows:

> orthotic [All Fields] AND ("temporomandibular joint disorders"[MeSH Terms] OR ("temporomandibular"[All Fields] AND "joint"[All Fields] AND "disorders"[All Fields]) OR "temporomandibular joint disorders"[All Fields] OR ("temporomandibular"[All Fields] AND "joint"[All Fields] AND "disorder"[All Fields]) OR "temporomandibular joint disorder"[All Fields]) AND internal[All Fields] AND derangement[All Fields] AND ("inflammation"[MeSH Terms] OR "inflammation"[All Fields]) AND ("pain"[MeSH Terms] OR "pain"[All Fields]).

This search approach would yield three entries:

A. Observational Study—Imirzalioğlu P, Uçkan S, Güler N, Haberal A, Uçkan D. (Department of Prosthodontics, Baskent University, Faculty of Dentistry, Ankara, Turkey.) Synovial apoptosis in temporomandibular joint disc displacement without reduction. Oral Surgery Oral Medicine Oral Pathology Oral Radiology Endodontics. 2009 108:693–8.

> *Objective*: Our hypothesis is that increased apoptosis in synovium might contribute to temporomandibular joint (TMJ) degeneration. To investigate this, we measured soluble Fas (sFas) and nuclear matrix protein (NMP) levels in TMJ synovial fluid from patients with disc displacement without reduction as indicators of apoptosis in the synovium.
>
> Patients and Methods: Synovial fluid was obtained from 17 joints in 17 patients (11 females, 6 males; mean age, 31.5 ± 11.9 years; range, 19–55). Patients were referred to our clinic because of limited mouth opening, joint sounds, or TMJ pain. Synovial fluid obtained by arthrocentesis for therapeutic reasons was analyzed by enzyme-linked immunosorbent assays for APO-1/Fas and cell death detection (NMP).
>
> Results: We studied 12 left (71%) and 5 right (29%) joints with disc displacement without reduction. The chief complaint was pain on the affected side and limited mouth opening. Only two patients had a click in the affected joint, whereas 14 reported pain and 17 had the limited mouth opening. All patients experienced a significant ($P < .01$) increase in maximal mouth opening immediately after arthrocentesis. Mean sFas and NMP levels were 484.9 ± 466.7 pg/mL (range, 17–1501) and 29.2 ± 13.7 U/mL (range, 8–52.8), respectively.
>
> Conclusion: Considering reports that increased sFas blocks apoptosis by inhibiting binding of FasL to Fas on the cell membrane, low level of sFas in our patients' synovial fluid (compared with amounts reported in joint inflammation or degeneration) suggests vulnerability to apoptosis in patients with internal derangement.

B. Observational Study—Sato J, Segami N, Yoshitake Y, Kaneyama K, Yoshimura H, Fujimura K, Kitagawa Y. (Department of Oral and Maxillofacial Surgery, Kanazawa Medical University, Daigaku, Uchinada-machi, Kahoku-gun, Ishikawa 920–0293, Japan. jun-s@den.hokudai.ac.jp) Specific expression of substance P in synovial tissues of patients with symptomatic, non-reducing internal derangement of the temporomandibular joint: comparison with clinical findings. Br J Oral Maxillofac Surg. 2007 45:372–7.

Our aim was to find out the extent of expression of substance P in synovial tissue from the human temporomandibular joints (TMJ), with symptomatic, non-reducing internal derangement, and to investigate the relationship between substance P and clinical findings. Fifty-four joints in 54 patients were examined immunohistochemically. Specimens of synovial tissue from 10 joints in 8 subjects with habitual dislocation of the TMJ with no pain were examined as controls. Cells that stained for substance P were found mainly among the endothelial cells in the blood vessels beneath the lining cells in synovial tissues from 47 of the 54 joints (87%) with internal derangement and from 5 of the 10 control joints. The extent score of cells that stained for substance P in joints with internal derangement was significantly higher than that in controls ($p = 0.02$). The extent score of these cells did not correlate with pain in the joint or the degree of synovitis. These results suggest that substance P may have some roles in both the physiological and pathological conditions in patients with symptomatic internal derangement of the TMJ.

C. Review (French)—De Laat A. (Département d'Odontologie, Université Catholique de Leuven) [Etiologic factors in temporomandibular joint disorders and pain]. Revue Belge Medice Dentaire 1997 52:115–23.

Parallel to the construction of better classifications and the identification of subgroups of temporomandibular disorders, an important development has taken place in research concerning its etiology. The etiological factors implied in muscle problems refer to more generalized disorders as myofascial pain syndrome and fibromyalgia. The role of occlusal and articular factors has been brought down to realistic proportions, indicating a minor contribution. Similarly, doubt has arisen concerning the existence of a vicious cycle of pain/spasm/pain. With regard to internal derangement, emphasis has been put on the high prevalence in an otherwise normal population and the fluctuating character of the symptom. Also here, developments point toward constitutional and systemic factors, more than local influences. Trauma, however, seems to play an increasing role. The development of osteoarthrosis has been studied more in depth revealing local processes of inflammation, neurogenic inflammation, and the existence of specific markers, which might be important in the future. The relationship between disc derangement and the development of osteoarthrosis remains unclear.

A similar search process through Google Scholar, which uses the keywords "oral orthotic temporomandibular joint disorder internal derangement inflammation pain," yielded those 3 reports and 165 additional ones, including reviews, case reports, and other types of study, that are not suitable for incorporation in a research synthesis design, save for background and interpretative purposes. This discrepancy serves to exemplify the fact that the search for a research synthesis project is generally actualized by accessing the National Library of Medicine (PubMed-MEDLINE, www.ncbi.nlm.nih.gov/pubmed) and at least two other search engines (e.g., Cochrane, www.cochrane.org; Bandolier, www.jr2.ox.ac.uk/bandolier; Embase, www.embase.com; Center for Reviews and Dissemination, www.york.ac.uk/inst/crd; Google Scholar; etc.). The purpose of the multiple search is to ensure comprehensive inclusion of all the available literature within the confines of the inclusion/exclusion criteria dictated by the research synthesis process while, at the same time, minimizing as much as possible dangers of selection bias and systematic sampling errors. The multiple search process produces a complete and exhaustive sample of the available evidence, as it pertains specifically to the PICOTS question, and following appropriate inclusion and exclusion criteria. The outcome of the search process is termed the bibliome.

The suffix *-ome* describes a series, or collection, of objects, or entities, that harbor a distinctive commonality. For example, the collection, the totality of the genes of an organism is termed the genome. In modern and contemporary terminology in the health and life sciences, *−omes* can provide a direct descriptor of a given field or subfield. In that sense, the proteome is the complex assembly of posttranslational products (i.e., proteins) of the organism, and the interactome describes the complex sets of gene-gene, protein-protein, or protein-gene and protein-ligand interactions that are necessary to support and maintain the survival, growth, and reproduction of the organism. By extension, the bibliome is the totality of the corpus of literature that harbors the distinctive commonality of describing the specific biological phenomena under study.

The systematic computer-driven methods for storing, retrieving, organizing, and analyzing the bibliome pertain to the research approach of bibliometrics. The systematic evaluation of the level and quality of the evidence contained within the bibliome is obtained through the research design of research synthesis and is disseminated in the form of

a research report called the systematic review. The term is meant to indicate not only that is all-encompassing of the bibliome derived from PICOTS question but also that it results from a systematic science-driven process of evaluation and quantification of the evidence level and quality, supported by stringent statistical analyses and inferences.

It must not be understated that the sampling process in research synthesis—that is, the process of establishing the bibliome—suffers from the same threats and limitations as the process of sampling in other research designs (i.e., observational designs, experimental designs, randomized clinical trials). For example, the threat of selection bias adulterates the sampling process in experimental studies when sampling is driven by convenience rather than by chance. Sampling of the literature suffers likewise from selection bias, when, for instance, our evaluation capabilities (i.e., critical reading, assessment tools) fail to be all-inclusive, including such barriers as language, search engine, and library availability, among others. That is one specific facet of the publication bias.

Case in point, a systematic review was conducted to describe the evidence for a relationship between diagnoses and findings of clinical examination and diagnoses and findings of magnetic resonance imaging (MRI) examination for degenerative and inflammatory temporomandibular joint disorders. The bibliome was obtained through the National Library of Medicine (PubMed) and the Cochrane Library. The Quality Assessment of Diagnostic Accuracy Studies (*QUADAS*) tool was used to evaluate the yielded literature. A total of 23 studies were obtained. Due to vast heterogeneity in study design, clinical examination methods, and diagnostic criteria, supportive evidence for a relationship between clinical and MRI diagnoses and findings was not established. Similarly, the relationship between clinical pain and internal derangement diagnosed with MRI could not firmly establish (odds ratio was in the low range of 1.54–2.04). The relationship between pain and disc displacement without reduction (4.82) or crepitation and disc displacement without reduction showed higher ORs (4.82 and 3.71), respectively [14].

The Cochrane Group, a leading organization in establishing the methodology of systematic reviews and research synthesis, describes the publication bias as spectrum of situations that taunt the bibliome and which may be summarized into five principal situations that favor the publication of positive data, over null or negative findings:

- More likely to be published (publication access bias)
- More likely to be published rapidly (time lag bias)
- More likely to be published in English (language bias)
- More likely to be published more than once (multiple publication bias)
- More likely to be cited by others (citation bias)

It must be acknowledged that some degree of publication bias cannot be avoided simply because, as a general rule, papers that are statistically significant, whether they demonstrate clinical relevance or not, tend to be preferentially published in the scientific literature, compared to reports that demonstrate clinical relevance but fail to reach statistical significance. The problem of publication bias is inherent to our present system of scientific literature and is an unavoidable issue of the research synthesis process, which is generally discussed as a limitation of the utilization of the best available evidence in consideration of the clinical relevance of the findings, and clinical decision-making for treatment intervention or diagnosis.

The second major domain of methodology in the research synthesis designs pertains to the assessment of the level and quality of the evidence. As the sample process described above yields the *available evidence*, the assessment of the quality of the evidence uncovers the *best evidence*.

In this context, two contemporary schools of thought can be succinctly described as such:

- One proposition is that a ranking system can be arbitrarily devised to evaluate the strength

of the results of a study purely on the basis of the nature of the design—i.e., the level of the evidence.
- Another view argues that the best research is that which most strictly adheres to the fundamental tenets and standards of research methodology, design, and analysis—i.e., quality of the evidence.

The level of the evidence paradigm is insufficient to establish whether the evidence is indeed "best," because it simply assigns a rank to the individual studies, based on the nature of the design, viz., clinical trial, observational, etc. Clinical trials are ranked second highest, the top position being assigned to systematic reviews. Some attempt is made to establish the quality of individual clinical trials by means of the checklist of the consolidated standards of reporting trials (CONSORT) [15], revised in 2010 (CONSORT 10) [16]. The criteria developed to ensure the strengthening and reporting of observational studies in epidemiology is referred to as the STROBE.

The level of evidence is established on the basis of the type of study design that was used to generate the evidence under evaluation. The US Preventive Services Task Force has established the following criteria:

- *Level I*: Evidence obtained from at least one properly designed randomized controlled trial.
- *Level II-1*: Evidence obtained from well-designed controlled trials without randomization.
- *Level II-2*: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
- *Level II-3*: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
- *Level III*: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

The UK National Health Service uses a similar system with categories labeled A, B, C, and D
- *Level A*: Consistent randomized controlled clinical trial, cohort study, with clinical decision rule validated in different populations
- *Level B*: Consistent retrospective cohort, exploratory cohort, ecological study, outcomes research, case-control study, or extrapolations from level A studies
- *Level C*: Case-series study or extrapolations from level B studies
- *Level D*: Expert opinion without explicit critical appraisal or based on physiology, bench research, or first principles

Proponents of the assessment of the level of evidence as the means to establish the "best available" evidence have improved the ranking process of research report with the strength of recommendation taxonomy (SORT). The SORT system was created to provide a simple, user-friendly system for grading the strength of diagnostic and prognostic studies but in effect may be a biased and rather cumbersome grading device yielding no or few effective and valid recommendations. In brief, SORT yields:

- Ratings (A, B, or C) for the strength of recommendation for a body of evidence
- Qualitative inferences about good or limited evidence and consistent or inconsistent evidence
- Ratings (1, 2, or 3) for the resulting ranking of studies

The Standards for Reporting of Diagnostic Accuracy (STARD) similarly seeks to establish the accuracy and completeness of reporting of studies of diagnostic accuracy, to allow readers to assess the potential for bias in the study (internal validity), and to evaluate its generalizability (external validity). The STARD statement consists of a checklist of 25 items and recommends the use of a flow diagram which describe the design of the study and the flow of patients.

Taken together, the fundamental limitation of the assessment of the level of evidence remains that research in the health sciences utilizes all the possible and available study designs. The choice of research designs must not be dictated by the

misconception that some designs are better than others. The choice of a design is driven purely by research methodology issues and concerns and reflects the optimal methodological approach to obtain a reliable and valid quantifiable answer to the research question in a manner that can withstand the rigors of statistical analysis and generate clinically relevant new knowledge. That is the call of the scientific method.

The "best available" evidence is that research evidence that emerges from the systematic process of evaluation as the most reliable and valid evidence for the simple reason that it was obtained with the strictest adherence to the very criteria and standards that define and establish the scientific process. It is that which emerges from a research methodology, design, and data analysis that answers the research question and tests the hypothesis in a scientific approach that is the most sound possible, considering the limitations, intervening variables, and possible confounders. The best evidence only emerges from the best research, and the best research only results from fulfilling the requirements of good research, as stipulated by the research process. In brief, it is that which is least biased.

The Agency for Healthcare Research and Quality (AHRQ) has established recommendations for strength (i.e., quality) of the evidence in terms of its immunity from the risk of inherent bias. For this assessment, AHRQ developed an instrument that consists of four principal domains:

(a) *Risk of bias*: the principal component in determining the strength-of-evidence (i.e., risk of bias) score and is intended to assess methodological limitations and systematic errors. Risk of bias results from issues of inappropriate design and performance of studies by the PICOTS bibliomic search. The risk of bias component assessment proceeds by, first, considering which study design is most appropriate to reduce bias for each question; second, it requires consideration of the risk of bias from available studies; and, third, it assesses the aggregate quality of studies within each major study design and integrates those assessments into an overall risk of bias score. Individual risk of bias scores can be high (elevated risk of bias lowers strength-of-evidence grade), medium, or low (low risk of bias scores raise strength-of-evidence grade).

(b) *Consistency*: related to precision of measurements and results; inconsistency refers to imprecision of results and lack of reliability of measurements and manifests as a rather large heterogeneity or variance. Consistency is best defined as the degree of similarity in the effect sizes of different studies within an evidence base and thus reflects the consistency among evidence bases. Consistency scores can be high consistency, low consistency (i.e., inconsistent), and unknown (or cannot be assessed on the basis of the data available).

(c) *Directness*: defined as whether the evidence being assessed: (a) reflects a single, direct link between the interventions of interest and the ultimate health outcome under consideration, (b) relies on multiple links in a causal chain, or (c) utilizes analytic frameworks (a priori structure planned for measurements and data analysis). By contrast, indirectness of evidence is reflective of lack of specificity. Evidence can only be scored as direct, if the evidence is based on a single link between the intervention and health outcomes, or indirect, if the evidence relies on surrogate/proxy outcomes or more than one body of evidence.

(d) *Precision*: related to consistency, such that lack of consistency refers to imprecision of results and consequentially high heterogeneity of outcomes and prohibitive variance. Precision is defined as the degree of certainty for estimate of effect with respect to a specific outcome and specifically pertains to what can evidence-based decision-makers conclude about whether one treatment is, clinically speaking, inferior, superior, or equivalent (neither inferior nor superior) to another. Precision typically considers the statistical significance for each effect estimate separately and the confidence intervals for

those effect estimates. Precision scores can be precise, when estimates allow a clinically useful evidence-based conclusion, and imprecise, when the confidence interval is so wide; it could include clinically distinct (even conflicting) conclusions.

In addition, the instruments have secondary additional domains, which include:

1. Dose-response association
2. Plausible confounders
3. Strength of association
4. Publication bias

The scores of the individual domains are combined into a single strength-of-evidence (i.e., risk of bias) score, taking scores on additional domains into account as needed. Standardized principles of scoring, such as explicit evidence-grading criteria, clearly established point system for combining ratings of each domain, qualitative consideration of the domains—that is to say, crafting of criteria to define and refine each domain—and clear documentation of all procedures aid in establishing and formalizing the process of grading the evidence.

To compare the effectiveness of splint therapy with that of minimal or no treatment in patients with TMDs, an extensive systematic review intended to examine a vast (n = 1567) bibliome obtained from MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials for studies up to and including August 2011. But a limited number (=11) were Level I studies and therefore eligible for further analysis. Quality assessment established overall moderate quality across the 11 reports indicated that splint therapy may reduce TMJ pain, but not improve function. Overall, the results of this systematic review were inconclusive due to the individual bias inherent to the bibliome [17].

With respect to evaluating the quality of systematic reviews, Shea and colleagues developed and characterized the assessment of multiple systematic reviews instrument, through a process of factor and cluster analyses of previously existing instruments for this purpose (e.g., OQAQ, Sacks' checklist, quality assessment of studies of diagnostic accuracy included in systematic reviews, QUADAS). This process resulted in the identification of 11 domains that are sine qua non of an adequate systematic review and which constitute the 11 items of the AMSTAR [18, 19]:

1. "A priori" design provided
2. Duplicate study selection and data extraction
3. Comprehensive literature search
4. Status of publication (i.e., gray literature) used as an inclusion criterion
5. List of studies (included and excluded) provided
6. Characteristics of the included studies provided
7. Scientific quality of the included studies assessed and documented
8. Scientific quality of the included studies used appropriately in formulating conclusions
9. Methods used to combine the findings of studies
10. Publication bias
11. Conflict of interest

Taken together, the principal elements of measuring the quality of the evidence lie in the fact that the tools used must be:

- Valid—assess what they are designed to assess
- Reliable—assess what they assess in a replicable manner

In our own work, we modified the original risk of bias instrument to obtain quantitative assessment, verified its criterion validity (r = 0.96, $p < 0.05$), and established its inter-rater reliability (r = 0.94, $p < 0.05$) [20]. For the same purpose, we also validate an expansion of the original GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) instrument [21] designed for grading the quality of underlying evidence and the strength of clinical recommendations and expanded to include quantifiable assessments and measures of clinical relevance [22]. A similar research tool is the AGREE[26] (Appraisal of Guidelines and Research

[26]AGREE is an instrument developed to provide a basis for defining steps in a shared development approach to

and Evaluation, Europe) measure and its update (AGREE-II) [23].

The next critical step in the pursuance of the best available evidence is the analysis of the data. Over a decade ago, it became apparent that standards must be established for the appropriate reporting of meta-analytical analyses [24], especially when these pertained to the identification of the best available evidence for health care. The original Quality of Reporting of Meta-analyses (QUOROM) statement outlines the optimal flow of presentation of the abstract, introduction, methods, results, and discussion sections of a report of a meta-analysis. They were structured and organized into 21 headings and subheadings, which had the advantage of providing a set of guidelines for investigators, but were often arduous to understand and follow for the neophytes. In a recent development, QUOROM was revised and improved and presented as the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA; prisma.org) [25]. Whereas longer and more complex than CONSORT, PRISMA consists of a 27-item checklist and a 4-phase flow diagram, which is actually more user-friendly than QUOROM. Whereas research synthesis is the structure by which the investigator obtains the systematic review, the meta-analysis is one of the protocols that the investigator will utilize judiciously to obtain one specific aspect of analysis of the data of the systematic review.

There may be instances where a meta-analysis is not needed or impossible to conduct in a given systematic review. That, in and of itself, does not diminish the value of the systematic review product and the strength of the evidence it presents.

In and of itself, meta-analysis is simply a statistical protocol, a combinatorial process of analysis that is extraordinary sensitive to several properties of the data. Two principal properties deserve to be mentioned in the context of this discussion are heterogeneity/homogeneity of outcome and data quality.

(a) Clinical outcomes, whereas they may seem to clear and crisp measurable entities, more often than not can be quantified in more than one way. The heterogeneity in outcome measure is one clear danger for the validity of any meta-analytical reasoning, because it speaks directly to what, really, are we combining together and what really are we making overall inferences about. There are statistical tests that we must run on the outcome measurements that establish whether homogeneity is verified (cf., Cochran Q and its transformation as the I^2 test)—that is to say, whether the extent of outcome measure heterogeneity is within the level of confidence and is, in fact, not statistically significant.

(b) The data pooled together into a meta-analysis be from reports that are deemed of good quality. If the data in the input are all high quality, then the variability due to residual inexplicable error will be small, and the effect, if there is one, will be apparent and clearly statistically significant. If, on the other hand, the data that are used in the meta-analysis originate from studies that are fraught with serious quality issues, then each of these sets of data will carry into the meta-analysis its contribution of residual inexplicable error, and the total overall variability will be large and negate the ability of a statistically significant overall effect to become apparent over this residual error "noise." Similarly, albeit not as dramatically, if a meta-analysis should incorporate some solid and good studies and a few studies with serious quality issues, the contribution of the former to the variability due to residual inexplicable error will be small, but the contribution of the latter to the overall error will be disproportionately large. That will, more often than not, mask a statistically significant overall effect [9, 10, 24].

For that reason, many—most, but not all—investigators argue in favor of a two-step process of data analysis for systematic reviews, which involves establishing first the quality of the

produce high-quality clinical practice guidelines revised based upon the best available evidence.

research evidence by acceptable sampling analysis and, then, based on these assessments, eliminating the studies that demonstrate excessive flaws, as determined by the score of the quality of evidence assessment tools (i.e., acceptable sampling analysis; [18, 20]). For the studies that remain, the second step involves testing for homogeneity, and if no significant heterogeneity is noted with the accepted studies, then run the meta-analysis. The forest plot thus generated has the best likelihood of evincing overall significance, if there is one to be shown.[27] Stated in statistical terms, it is necessary to perform both acceptable sampling and homogeneity analyses in order to ensure power of a meta-analysis.

11.4 Evidence-Based Revision of Clinical Practice Guidelines for Treating TMD

The consensus statement that follows these analyses must be clear statement of the clinical implication and relevance of the research synthesis and meta-synthesis. It must present clearly the strength of the clinical recommendation thusly conceptualized [26–28].

Efficacy refers to whether or not a clinical intervention tested in the context of a clinical trial yielded valid and replicable outcomes. In lay language, we might say that efficacy tells us whether the treatment "worked," and it does so because of its inherent dependence upon the effort the investigator in constructing the research project correctly and fractionating as much as the random error as possible. In that regard, efficacy establishes the replicability of the clinical outcome. By contrast, effectiveness relates to the experiential reality of the clinical practice and pertains to whether or not the intervention minimizes risk, maximizes benefit, and yields these outcomes at the lowest (or at least the most reasonable) cost. It is fair to say that effectiveness does not pertain to a clinical trial study per se, but rather to the pragmatic implementations of its findings to the intricate complexities of clinical treatment. Careful consideration of effectiveness seeks to evaluate costs, benefits, and harms of clinical interventions; in such complex clinical situations as temporomandibular joint disorders, it is particularly critical to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. Its purpose is to assist consumers, clinicians, purchasers, and policymakers to make informed decisions that will improve health care at both the individual and population levels.

In brief, perhaps the single most important use of the science of research synthesis and research meta-synthesis in the health sciences, including dentistry, head neck and oral biology, pertains to empowering the clinician to make fully informed decisions for treatments that rest not only on the patient's wants and needs, clinical tests, medical history and clinician's experience and personal awareness of the available research, but also on the best available evidence. It is important to stress the summative quality of this sine qua non: in addition to all the previous, which equate the best current clinical practice, reliance on the science of research synthesis and meta-synthesis signifies adding to the decision-making process of the best available evidence. Hence, there is the need to have reliable instruments to assess and to establish the strength of the clinical relevance and recommendations for the uncovered *best available* evidence.

Case in point, in an effort to assess the efficacy of intraoral orthotic appliances to reduce pain in patients with TMD affecting both the masticatory muscle and the joint compartment, a systematic review of clinical trials designed to compare patients who had received placebo control, no treatment, vs. other treatments was conducted. The bibliome was obtained through a stringent search strategy that included MEDLINE, the Cochrane Central Register, and manual search. Publication bias restricted the search to English language publications between January 1966 and March 2006. Inclusion/exclusion criteria included RCTs designed to assess the efficacy of hard and soft stabilization appliances, anterior positioning appliances, anterior bite appliances, and other appliance types for TMJD pain. The

[27] That is to say, statistical power even in the case of a meta-analysis performed with few papers.

main outcome measure was pain relief. CONSORT and QUORUM criteria were used to evaluate the bibliome. A total of 44 RCTs (evidence Level I) with 2218 subjects were included. Two distinct meta-analyses were conducted, as determined by homogeneity of outcomes measures: In the first meta-analysis of seven studies with 385 patients, a hard stabilization appliance was found to improve TMJD pain compared to non-occluding appliance (odds ratio (OR) = 2.46, $p = 0.001$; CI95: 1.56–3.67). In the second meta-analysis of three studies (216 patients), a hard stabilization appliance was found to improve TMJD pain compared to no-treatment controls (OR = 2.15, $p > 0.05$, CI95: 0.80–5.75). Taken together, these analyses demonstrate that hard stabilization appliances, when adjusted properly, have good evidence of effectiveness in the treatment of TMJD pain compared to non-occluding appliances and to no treatment [29].

Translational effectiveness refers to the translation of the best available evidence gathered in systematic reviews in specific clinical settings (6–9). These stringent research synthesis protocols proffer recommendations about clinical practice guideline revisions, decisions about standard of care and health information technology policy, and new research and funding directions and to fully empower patients by ensuring patient empowerment and participation through increased health literacy.

Decision-making of the best available evidence can be both qualitative and quantitative. Qualitatively, the clinical relevance of the resulting consensus of the best available diagnostic or prognostic evidence is discussed in the framework of the logic model and is described along (a) patient-centered criteria of satisfaction and quality of life, (b) practitioner satisfaction of clinical efficacy, (c) patient and clinician satisfaction about cost-effectiveness and risk-benefit ratio effectiveness, and (d) public health values and concerns, such as translation of the findings and the data into the specific clinical setting presently attending to the patient (i.e., translational effectiveness). Quantitatively, the outcomes of the research synthesis process can be utilized in a probabilistic mode of clinical decision-making that is directed to computing the probabilities of cost and risk, compared to benefits in a utilitarian model of decision-making (cf., Markovian tree). Consensus of the best available evidence will be analyzed in light of limitations of each independent systematic review and of threats to internal and external validity of the research synthesis protocol itself [9, 10].

For the purpose of dissemination of knowledge, critical summaries (i.e., "evidence reviews") of each generated systematic review are developed in a user-friendly format for the researcher, the clinician, and the policymaker, as much as the patients themselves. These summaries serve as the foundation for recommendations about each intervention reviewed to ensure that the highest-quality evidence can inform practice, policy, research, and funding decisions. These summaries also become key instruments to empower the patients by raising health literacy. Current work in our research group (cf., EBD-PBRN.org) aims at standardizing and validating the quality and value-added of evidence reviews recommendations.

One principal purpose of evidence-based revisions of clinical practice guidelines obtained from systematic reviews is to generate and analyze further directed data systematically, to address gaps in the evidence base and expansion to a global database of pathogen distribution, with the aim of improving syndrome management of TMD, prioritizing diagnostic development, and producing a guide to empirical therapy for the benefit of all stakeholders.

Despite the rapid advancement in information and communications technology over the last decade, there is limited evidence suggesting improvements in the ability of health professionals to communicate effectively. Given the critical nature of communication, it is timely and critical to initiate further evaluation of information and communication technology designed to improve communication between clinicians [30]. A framework was recently proposed by AHRQ in that respect, which was derived from a systematic patient-centered outcomes evaluation (PCOE) [9, 10] protocol that consisted of six distinct steps:

1. Focused literature review
2. Development of draft framework
3. Workshop with technical experts
4. Refinement of framework
5. Development of two case studies
6. Pilot test of framework on case studies

In brief and discussed elsewhere in greater depth [9, 10], PCOE is distinct from PCOR in that the former pursues the goal of improving existing programs, whereas the latter seeks to prove the superiority over other programs. In this process, PCOE generates new hypotheses, whereas PCOR is structured to test existing hypotheses. Both PCOE and PCOR employ the scientific process to reach the conclusions of their respective endeavors, the former obtains conclusions that are specific to the programs under evaluation, but the latter generates conclusions, which, provided the study has strong external validity, will be generalizable beyond the sample under test to the population. Researchers principally disseminate their research outcomes to their peers and fellow researchers in a constant strive to obtain a better, more precise, and more accurate understanding of fundamental mechanisms and principles. By contrast, evaluators seek to disseminate their findings to the various stakeholders who are affected, either directly or indirectly by the program under evaluation, with the primary concern of increasing cost-effectiveness of the program under evaluation or its benefit-effectiveness. That is to say, research and evaluation are two complementary aspects of the science of health care, whose interdependence is all the more timely and critical in the context of the contemporary new model of translational science in health care, in which translational research and translational effectiveness are inextricably intertwined. PCOE and PCOR are the fundamental and indispensable pillars of patient-centered, effectiveness-focused, and evidence-based health care.

The resulting framework can be characterized as having several important features combining work from a variety of fields that represent an important step forward in the rigorous assessment of such evidence because it:

- Integrates a definition of evidence based on inferential effect, not study design
- Separates evidence about the biological and physiological mechanisms from evidence derived from research synthesis aimed at linking the intervention to a given clinical outcome and evaluating efficacy and effectiveness
- Proffers the sine qua non, the essential, and the minimum sufficient set of steps for building a logic-based process based on the best evidence; is adaptable and generalizable across the health-care domains

In conclusion, this approach, developed and advocated by AHRQ for dissemination of the best evidence [31], integrates and expands previously proposed models [2, 20, 32, 33] by mirroring in the evidential framework the conceptual framework for translational medicine, thus linking the fields of basic science, evidence-based medicine, and comparative effectiveness research.

In that context, it is important to note the principal threads of intervention for TMD currently address three primary areas of work:

(a) Socioeconomic status (i.e., living conditions)
(b) Community-based (i.e., educational interventions)
(c) Biological (e.g., neuroendocrine-osteoimmunology, cf., Chiappelli [34]).
(d) Evidence-based clinical intervention.

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12 Future Avenues of Translational Care for Patients with Temporomandibular Joint Disorders

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Abbreviations

CRSWBCT	Cluster randomized stepped wedge blinded controlled trial
IPR&A	Individual patient research and analysis
miRNA	MicroRNA
RANKL	Receptor activator of nuclear factor κB ligand
STAT3	Signal transducer and activator of transcription 3
TLRs	Toll-like receptors
TMD	Temporomandibular joint disorders
TMJ	Temporomandibular joint

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Core Message

Contemporary translational healthcare dictates a two-level approach, which consists of translational research, going from the patient to the laboratory and back to the patient, and translational effectiveness, synthesizing research in the pursuit and dissemination of the best evidence base for treatment. This chapter proposes future avenues of research in both domains, with implication specifically for patients with temporomandibular joint disorders.

12.1 Translational Healthcare for Temporomandibular Joint Disorders (TMD)

As discussed in detail in a previous chapter (cf., Chap. 7), the temporomandibular joint (TMJ) is the synovial ginglymoarthrodial articulation of the mandible with the maxillary bone of the

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frontal aspect of each the right and the left side of the facial skeleton [1]. TMJs on both sides of the face are endowed with powerful masticatory musculature and extensive motor and sensory (trigeminal, V3) innervation.

The synovial articular disc composed of dense fibrous connective tissue that attaches to the joint capsule, a dense fibrous membrane surrounding the joint, connecting to it by strong ligaments. The disc is positioned between the two bones that form the joint and forms two anatomical spaces through which the disc glides during normal articulation of the joint.

Wear and tear due to age as well as trauma contribute to alter the thickness of the disc, which brings about thinning of the cartilage in its central part and related chondropathology, progressively compromise the normal movement of the joint, and can lead to osteoarthritis of the joint and related osteopathology. TMJ disorders (TMDs) include disc displacement. Associated synovial inflammation; local pain and myalgias of the face, head, neck, and shoulders; and migraine-type headaches are often observed as discussed in Chap. 6.

The current view of translational healthcare proposes two primary facets [2–5]. Translational research (T1) is conceived as incorporating laboratory protocol of basic biology and physiology on specific biopsies to better define and characterize the pathological mechanism that underlies the patient's condition. Translational effectiveness (T2) integrates the research synthesis design into the comparative effectiveness research and meta-analysis protocols to generate systematic review reports, which contribute to craft and establish the consensus of the best evidence base for electing the most appropriate mode of therapeutic intervention to treat the patient's condition. A third level of translational science (T3) may be conceptualized that is meant to ensure quality improvement of individual patient research and analysis (IPR&A) for community-based participatory and action research and clinical practice [4, 6].

This chapter explores possible and probable future avenues of research in translational care for patients with TMD. Specifically, it presents arguments in support for a T1-T2-T3 transaction for the effective incorporation of comparative effectiveness research and patient-centered outcome research toward the optimization of the dissemination and diffusion of the best available evidence for treatment of such conditions as TMD.

12.2 Current and Future Avenues of Translational Research in TMD

Bone and cartilage metabolisms are highly dynamic and complex processes that are modulated in part in response to mechanical loading, such as tooth grinding and normal chewing. The cellular mechanisms that regulate bone formation and resorption involve the stimulation of osteoclast and osteoblast populations and the participation of bone marrow mesenchymal stem cells. Osteoclast differentiation is determined by the ratio of receptor activator of nuclear factor κB ligand (RANKL) to the soluble decoy receptor osteoprotegerin. Inflammatory cytokines, including IL6, and hormones including parathyroid hormone, 1,25-dihydroxyvitamin D, glucocorticoids, and estrogen work in concert to control bone metabolism. The recognition that the continuous formation and resorption of bone is regulated by neuroendocrine and cellular immune events led to the establishment of osteo-(neuroendocrine) immunology as a rich interdisciplinary domain with obvious and direct implications for TMD [7]. Recent evidence further indicates that bone is more than just a structural scaffold: osteoblasts and osteoclasts work together in response to exercise and presumably other bone-loading situations (e.g., chewing and grinding) to secrete endocrine factors, such as osteocalcin, sclerostin, and lubricin, which can act as a circulating hormone systemically to promote insulin sensitivity and reduce body fat mass, among other metabolic outcomes of significance. Osteocalcin, sclerostin, and lubricin are but examples of factors now recognized as "osteokine" that contribute to systemic homeostasis [8].

Osteocalcin, a gamma-carboxyglutamic acid-containing protein, is a noncollagenous vitamin K-dependent protein found in bone and dentin. It is encoded by the BGLAP gene in osteoblasts and is secreted into body fluids, including saliva

and blood serum, and presumably synovial fluid as well. In the circulation, osteocalcin acts as an osteokine and contributes to the regulation of glucose homeostasis by stimulating insulin release in pancreas and directing adipocytes to release adiponectin, which in turn increases insulin sensitivity. Taken together, the concerted evidence to this date suggests that osteocalcin promotes bone formation, bone mineralization, and calcium ion homeostasis and simultaneously regulates energy metabolism systemically. Because higher serum osteocalcin levels are relatively well correlated with increases in bone mineral density during treatment with anabolic bone formation drugs for osteoporosis such as teriparatide, osteocalcin has strong potential as timely and critical biomarker for establishing the effectiveness of treatment interventions aimed at promoting bone formation. In point of fact, osteocalcin is an important marker of bone activity and is increasingly routinely used to diagnose joint disease and to evaluate the effects of pharmaceuticals on bone metabolism [8–11].

In an experimental setting, adult male Sprague-Dawley rats were injected with 50 μL of complete Freud's adjuvant bilaterally into the anterosuperior compartment of the TMJ and monitored for signs of local TMJ inflammation at 1–4 weeks posttreatment. Enhanced osteoclast activity, expanded bone marrow cavity, increased RANKL/osteoprotegerin ratio in the cartilage and subchondral bone, and upregulation of osteocalcin peaked 2 weeks following injection. Meanwhile, TMD symptoms also increased in the 2-week complete Freud adjuvant injection [12]. Taken together, these molecular data show the putative role of osteocalcin in the intimate interactive relationship between muscle action and bone in joints [13] such as the TMJ.

Sclerostin, a glycol protein secreted mainly, but not exclusively, by osteocytes, is encoded by the SOST gene. At the molecular level, sclerostin binds to LRP5/6 receptors and inhibits the Wnt signaling pathway, thus contributing to decreased bone formation. It expressed relatively late during osteoblast differentiation temporally coinciding with the expression of osteogenic marker osteocalcin. Sclerostin production by osteocytes is inhibited by parathyroid hormone, mechanical loading, and inflammatory cytokines, but it is upregulated by calcitonin. Sclerostin deficiency is associated with high bone mass phenotype, but elevated serum sclerostin levels appear to be predictive of prediabetic metabolic condition. Increased serum sclerostin levels appear to be predictive of bone resorption. In brief, whereas sclerostin may not be a typical osteokine, it clearly emerges as a clinically significant biomarker for bone resorption [8, 14].

Based on this molecular knowledge base, preclinical and early clinical studies (i.e., clinical trials phase I and II) have gathered promising data in support of the efficacy of monoclonal humanized neutralizing antibodies (e.g., romosozumab, AMG 785 [Amgen], blosozumab [Elli Lilly], BPS804 [Novartis]) in a new treatment paradigm toward bone re-building for the management of patients with osteoporosis [15].

Lubricin is a 345 kDa proteoglycan (i.e., proteoglycan-4) encoded by the PRG4 human gene. It acts as a joint lubricant in synovial fluid and on the surface and the superficial layer of articular cartilage. It is synthesized by chondrocytes located at the surface of articular cartilage and by fibroblastoid synovial lining cells [16, 17]. Preclinical phase I trials indicate that intra-articular lubricin treatment retards progression of cartilage degeneration in early osteoarthritis. This anti-inflammatory effect of lubricin is obtained mechanistically by its binding to toll-like receptors 2 and 4 [18]. Toll-like receptors (TLRs) are a class of molecular receptors primarily found on white blood cells of the innate immune system, including monocytes/macrophages and dendritic cells, and principally function to induce cell-mediated immune activation. Related experimental research has established that inflammatory cytokines of the TH17 family (i.e., IL17) significantly upregulate the expression of toll-like receptors 2, 3, and 4 in fibroblast-like synoviocytes from patients with rheumatoid arthritis and osteoarthritis by a molecular mechanism that specifically involves the signal transducer and activator of transcription 3 (STAT3). Another cytokine of the same TH17 family, IL23, augments the IL17-induced expression of these toll-like receptors by fibroblast-like synoviocytes obtained from patients with rheumatoid arthritis.

Treatment of fibroblast-like synoviocytes from these patients in vitro with the STAT3-specific inhibitor, S3I-20, which selectively prevents the phosphorylation and activation of STAT3, blunts this IL17 effect [19]. Toll-like receptor 3 had been previously shown to promote osteoclastogenesis in rheumatoid arthritis synovium by inducing RANKL production by the fibroblast-like synoviocytes, which in turn favors the differentiation of osteoclasts in the arthritis synovium [20]. It follows that targeting the TLR3 pathway may be a promising approach to preventing inflammatory bone destruction in arthritic pathologies that evolve as complications of TMD.

Ongoing proof of concept experiments are generating new compelling evidence in support of the hypothesis that IL6 as well as IL17 and related TH17 inflammatory cytokines significantly depress the expression of lubricin by synoviocytes [21]. Phase I trials will therefore follow to test whether injections of recombinant human lubricin in situ might alleviate joint pathology in TMD patients with internal derangement. Together, these will open new avenues of translational research on the molecular biology of TMD, including genomic engineering involving microRNA or the CRISPR-Cas9 genome editing technology.

MicroRNAs (miRNAs) are endogenous noncoding RNA molecules of 20–24 nucleotides, which function to silence mRNA translation and therefore blunt posttranscriptional regulation of gene expression. Most miRNAs are intracellular, but some miRNAs are released extracellularly and can be detected in body fluids, including serum, saliva, and presumably synovial fluid. Case in point, miRNA-155, which has critical immune regulatory functions, is upregulated in the synovial membranes and in synovial fluid from patients with rheumatoid arthritis. In fact, miRNA-155 is crucial for the proinflammatory activation of human myeloid cells and antigen-driven inflammatory arthritis. Taken together, these lines of evidence suggest that miRNA-155 may be a strong candidate for therapeutic target in joint disease [22].

Clustered regularly interspaced short palindromic repeat (CRISPR)-associated protein 9 (Cas9) is a novel technology of genomic engineering that is used to functionally inactivate genes in human cell lines and cells with a high degree of fidelity and relatively simple construction. Studies are emerging that utilize CRISPR/Cas9 for better understanding the genomic underpinnings of potential drug targets [23] for a variety of bone and joint pathologies, including TMD. The miRNA-155 is a key proinflammatory regulator in clinical and experimental rheumatoid arthritis and putatively in TMD as well. In vitro experiments have shown that CRISPR/CAS9 genomic editing of miRNA-155 significantly blunts the production of inflammatory cytokines [24].

12.3 T3: From Translational Research (T1) to Translational Effectiveness (T2)

In principle, translational care proposes two rather well-defined facets of interrelated activities, as we and others have noted elsewhere. In the context of patients with TMD, for instance, translational research may involve obtaining synovial biopsies from each patient's TMJs and analyzing those samples for lubricin, or osteocalcin, in conjunction with the measurement of IL6 and cytokines of the TH17 family. These assessments, ideally, would be obtained at the patient's first visit to inform the clinician of certain aspects of the fundamental molecular pathology underlying each individual patient's case. Based on that information, the clinician may elect to supplement the orthotic intervention with, say, miRNA-155; monoclonal humanized neutralizing antibodies, such as romosozumab; or other such molecular-based interventions.

Translational research of this kind, however, is only valid if the molecular-based interventions are fully vetted for efficacy and effectiveness. The evidence in support of the use of miRNA-155 for a given patient who displays a particular molecular pathology of TMD, for example, must be carefully evaluated and systematically reviewed. The research must be cumulatively synthesized and a consensus of the best available qualitative and quantitative evidence obtained. In brief, the process of

establishing the rationale for the utilization of any given molecular-based intervention—that is to say, the predicate of the clinical decision-making that determines what molecular-based intervention is optimal for supplementing the orthotic intervention for a given patient based on his/her fundamental molecular pathology as determined by translational research—is itself obtained through a systematic process of research, which involves synthesizing all the available research evidence (i.e., research synthesis) and determining its level, quality, acceptability, and overall consensus of effectiveness (i.e., comparative effectiveness research).

To be clear, translational healthcare rests on these two distinct modes of acquisition of knowledge about the needs of each individual patient: the characterization of the fundamental molecular pathology that defines and characterizes his/her clinical case (i.e., translational research, T1) and obtaining the best available evidence for treatment of his/her clinical case based on this molecular pathology profile (i.e., comparative effectiveness research, T2). From this perspective, it is self-evident that translational healthcare is patient-centered, focused on achieving optimal effectiveness, and grounded on the evidence-based paradigm.

It is also painfully manifested, however, that the translational healthcare paradigm suffers from one principal caveat. That is to say, it must integrate a component of evaluation by which hard data can be obtained to verify the efficiency of the translational treatment plan. In a previous chapter (cf. Chap. 6), we outlined some principles of such patient-centered outcome evaluation process and suggested, as reiterated above, the need for a third sine qua non step for translational healthcare, T3.

To illustrate the point, we might suggest the following specific example: We [25] confirmed and expanded the early reports by others [26] that proximally synovial fluid obtained from the TMJs with clinical signs and symptoms of internal derangement, as determined by examination and confirmed by CT imaging, contains elevated levels of IL6 and other inflammatory cytokines, in addition to certain pain neurotransmitters (e.g., substance P). These biomarkers were also elevated in whole saliva, confirming the possibility of integrating the measurement of these and related molecular markers in the diagnosis of TMD by means of noninvasive collection of salivary samples.

To ensure quality of care, we propose that T3 ought to operate in the context of community-based participatory and action research through a research model that we defined as individual patient research and analysis (IPR&A) [6]. The IPR&A protocol is conceptualized as incorporating the utilization of the cluster randomized stepped wedge blinded controlled trial design [27, 28] to test systematically and selectively clinically relevant variables for obtaining continuous quantification of the individual patient clinical outcomes.

In brief, following collection of baseline synovial samples from patients with TMD for measurements of IL6 and substance P, repeated measure samples should be collected at regular intervals for each patient participant. Baseline measurements might best be processed as means ± standard deviation, a difference, deltas (Δ) obtained at each repeated measure time point, and the statistical analyses run on the δΔ values. Thus, for each participating subjects, individual patient data ought to be obtained and independently analyzed as repeated measures. The optimal clinical research design for IPR&A approach might be the adaptive trial design where, for instance, all patients will first be in the placebo group and then sequentially rolled out into the treatment arm in a quasi-crossover paradigm. To be clear, the treatment arm must consist of the routine clinical intervention determined by the clinician's expertise and judgment, supplemented—as per the judicious determination of the clinician—with the best available evidence produced by comparative effectiveness research.[1] Different clusters will cross over and switch

[1]The American Dental Association defines evidence-based dentistry as "an approach to oral healthcare that requires the *judicious integration* of systematic assessments of clinically relevant scientific evidence, relating to the patient's oral and medical condition and history, with the dentist's clinical expertise and the patient's treatment needs and preferences."

treatments at the different time points of the repeated measure analysis.

The first time point—placebo for all patients—will yield the individual baseline measurements. At subsequent time points, clusters switch over to the treatment group, following random ordering, and individual patient measurements are obtained and analyzed as Δ. Within each cluster, patients must be randomized, thus yielding a trial structure notorious for its stringency, power, and strength in preserving equipoise, as well as benefit- and cost-effectiveness. Analysis of the data will be required by repeated measure ANOVA, with Newman-Keuls post hoc comparisons and Bonferroni corrections for comparative purposes, with either a frequentist (Fisherian) or a Bayesian inference model. For predictive purposes integrating other patient characteristics in the model, analysis commonly entails hierarchical regression.

The IPR&A paradigm to test and verify the T1-T2-T3 transaction in translational healthcare is evidently not limited to clinical situations that involve TMD patients with internal derangement. We have showed that it has a wide range of clinical applicability, from Alzheimer's disease to psychoneuroimmunopathologies [29].

As critical as the choice of the design and statistical analysis, a timely and critical IPR&A endeavor must rest on the sound selection of variables that are adequate and relevant to individual patient data outcomes research and analysis. Case in point, and returning to the focus of this writing on TMD patients with internal derangement, individual patient research outcomes, which must be repeated at every visit to constitute a body of individual patient data, and integrated in the IPR&A research paradigm and analysis, might include, in addition to the neuroendocrine immune and molecular biomarkers (IL6, TH17 cytokines, substance P, lubricin, miRNA-155, etc.) in synovial fluid, saliva, serum, and other body fluids, as discussed above:

- Behavior and movement: tremors, dystonias (gait, posture), apraxia, and aphasia—duration, intensity, severity, quality of life (pre- and posttreatment)
- Psycho-cognitive: fear, anxiety, and phobias, including the STAI and the POMS tests and neurocognitive tests, including the Stroop test
- Sleep: getting to sleep, in min, and staying asleep, in min, and sleep disturbances (number and duration of snoring and sleep apnea events); polysomnogram measures including brain wave activity, eye movement, muscle tone, heart rhythm and rate, apneas, hypopneas, sleep position, oxygen saturation, and limb movements; Epworth Sleepiness Scale for quality of sleep assessment [30]
- Pain: self-report of perceived face pain, jaw pain, ear pain, headaches, neck pain, and shoulder pain; Visual Analog Scale
- TMJ function: jaw range of motion, measured as inter-incisal opening (in conjunction with pain assessment); clinical palpitations of the head and neck and neck rotations (in mm) before and after treatment; side effects of traditional pharmaceutical interventions (e.g., Serenase, Haldol) such as paralysis of buccolingual and mandibular voluntary movements (dyskinesias) that interfere with proper temporomandibular joint function, via their effects on the striatum and cortical projections
- Imaging: X-rays, CT scans (i.e., anatomical pathology of the temporomandibular joint, which would best lend itself to surgical treatment), and functional MRI (i.e., neurological pathology) neuro-inflammation attributed to the secondary effects of TMD on the terminal trigeminal [V3] auriculotemporal branch

12.4 Caveats, Fallacies, and Related Limitations

One primary caveat of the T1-T2-T3 symbiotic relationship for translational healthcare, as depicted in Fig. 12.1, is its reliance on informed stakeholders. The three-legged stool depiction seeks to render the notion not only of the fact that T1, T2, and T3 are intertwined, interrelated, and interdependent for the translational healthcare outcome but also that if one of the three components is conducted suboptimally, the

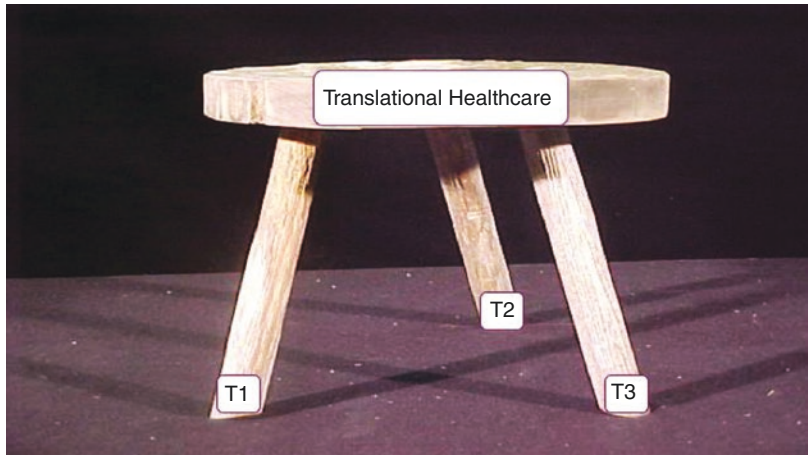

Fig. 12.1 Schematic representation of the translational healthcare paradigm. In this conceptualization, the translational healthcare paradigm is represented as a three-legged stool to show that if one of the three components that sustain it, T1, T2, or T3, is either incomplete or improperly conducted, then the paradigm collapses. Collapse in the translational healthcare paradigm manifests in a variety of outcomes that range from decreased quality of life and satisfaction of care for the patient, increased risk and harm to the patient, increased cost to the patient, etc

translational healthcare paradigm collapses. Faltering of this paradigm becomes manifest along several variables that range from unsuccessful clinical outcomes; increased risks and harm to the patient; increased cost; decreased quality of life; decreased job satisfaction for healthcare providers, including clinical and nursing staff; and the like.

The focal point of the T1-T2-T3 transaction in translational healthcare must rest, therefore, in ensuring the involvement of the stakeholders with respect to several timely and critical issues, such as:

- Clear and unambiguous intent and purpose of translational healthcare, as well as its procedural protocol
- Active engagement of the stakeholders—be they the clinical and nursing staff, allied healthcare providers (e.g., pharmacist, optometrist), patient's caregiver, patient's immediate and distant family, patient's social support system, pastoral support and care, and health insurance carriers—at every appropriate and necessary step of the care along the T1-T2-T3 transaction
- Stakeholders' understanding of the patient's condition, diagnosis, and prognosis, as well of the best available evidence for treatment options, to ensure active participation of the stakeholders as appropriate and permitted by law, and together with the patient when possible, in the clinical decision-making process judiciously led by the primary clinician
- User-friendly dissemination of the T1-T2-T3 transaction, the best available evidence, the IPR&A protocol, and stakeholder engagement and health literacy procedure in a structure that is as informative, and at the same time as protective of patients' rights and privacy, as the current clinical trial registry

That is to say, we identify four primary domains of the T1-T2-T3 transaction for translational healthcare that require timely and critical research endeavors:

1. Teleology[2] of translational healthcare [31, 32]
2. Stakeholder engagement [25, 33]
3. Health literacy [21, 34]
4. Dissemination [35, 36]

[2]Teleology (Greek: telos, purpose + logos, knowledge) improves and expands the knowledge and understanding of the purpose of translational healthcare and of how it is to be performed.

One important component of the T1-T2-T3 transaction for translational healthcare, which permeates throughout and across these four domains and which demands concerted work of optimization and wide application, is telehealth,[3] particularly as we increasingly seek to distribute translational healthcare across industrialized nations, as well as in remote and rural areas and in developing countries. Telehealth presents solutions for better disease prevention, improved disease management, more reliable emergency services, and overall optimization of healthcare practices. Nonetheless, many challenges and barriers remain, which will slow down the progress of the T1-T2-T3 transaction for translational healthcare globally.

Telehealth currently entails two modalities: store-and-forward telehealth surpasses the need for a face-to-face meeting between the primary clinician and the patient or caregiver. Rather, individual patient clinical data are collected (e.g., laboratory tests, imaging data) and transmitted to a clinical specialist at a specialized clinical site for prompt evaluation. For example, a patient with TMJ problem could be seen by a general dentist in a remote province of one developing country. The general dentist would have access to the necessary equipment and protocol to obtain the required CT images and synovial samples, in addition to all other necessary clinical assessments. The samples would be shipped frozen to the TMJ specialist, together with all the gathered clinical data and images. In a timely fashion, the TMJ specialist would process the samples (T1 modality), access the best available evidence with respect to the evidence-based revisions of clinical practice guidelines for the T1-identified underlying molecular pathology (T2 modality), verify the registry of ongoing related IPR&A protocols (T3 modality), and judiciously integrate this information with his/her expertise to propose a clinical intervention to be communicated back to the general dentist who originated the request.

The second modality of via telehealth occurs real time and is often described as interactive telehealth. It provides the opportunity for immediate interaction among clinicians at both the remote and the specialized site, patients, caregivers, and other stakeholders as needed.

In both modalities, telehealth has the potential of ensuring consultation with specialists thus optimizing treatment intervention, reducing the patients' cost and harm, while decreasing the time to get the needed healthcare services, when patients must otherwise travel large distances to have face-to-face consultation with the specialist. Another substantial advantage of telehealth involves the provision of in-the-home advice and consultation to patients with chronic or terminal diseases.

To be clear, telehealth is not limited only to the delivery of specialized care in remote or isolated areas; indeed, one primary benefit of telehealth protocols lies in the timely and critical contribution they proffer to the dissemination of the latest new knowledge in each domain of the T1-T2-T3 transaction. To be sure, telehealth must be structured to expand and improve dissemination of translational research outcomes (T1), of the best available evidence for treatment interventions under consideration (T2), and of ongoing or completed IPR&A protocols (T3). That is to say, telehealth is the central core of the dissemination of health information to the stakeholders, which in turns strengthens and ensures their continued commitment and engagement and secures their increased health literacy.

Together, telehealth benefits clinicians and patients and other stakeholders not only along these dimensions but also because it may be expected:

- To enhance healthcare quality overall, as measured by the Institute of Medicine (IOM) six major indexes for health promotion: effectiveness, timeliness, equity, patient-centeredness, safety, and efficiency
- To decrease clinician's workload and ensure higher efficiency

[3]The authors thank Melissa Nachivan for her timely and critical insight and contribution to our research in the area of telehealthcare, which is discussed in greater depth in Chiappelli et al. [38].

- To reduce medical errors and associated risks of medical error-related morbidities and mortalities
- To improve clinician-patient relationship by increasing transparency, access to shared information, and shared participation in the clinical decision-making process
- To cross cultural barriers, to break language barriers, to improve web connectivity worldwide, and to improve professional communication and networking globally

Telehealth and translational healthcare in general suffer from validity threats and fallacies, which distract us from the true teleological design of the T1-T2-T3 transaction, and impair the effectiveness of stakeholder engagement and increase health literacy and efficiency of health information dissemination. To cite only a few:

- Threats to internal validity uncover alternative explanation instead of treatment for the outcomes and include:
  - History: events occurring to certain but not all individual patients during the study may impact the outcome.
  - Maturation: processes of growth and development that may confound the measured outcome in some individual patients, and not others, and some time points but not others.
  - Testing: the effects of sensitization and fatigue on the performance of certain individual patients, but not others, at certain time points, but not others.
  - Instrumentation: changes in the selection of tools of measurement during the course of the study.
  - Statistical reasoning (or inference model): the movement of post-intervention measures toward the mean, independent of the treatment effect on individual patients.
  - Contamination: the differential effect of the differential sets of activities individual patients undergo between the repeated measure time points, which can uniquely interact or interfere with treatment and alter the measured outcomes.
  - Hawthorne effect: the effect of receiving attention from the researcher or clinician on the individual patient's response.
- Threats to external validity by interfering with the reliability, replicability, and implications of the findings in the real world. More often than not, threats to the external validity of IPR&A point to fundamentally fallacious reasoning and errors of judgment.
- Fallacies that may impact upon the T1-T2-T3 transaction in translational healthcare include:
  - Hindsight: foretelling the responses of a given patient on the basis of related clinical outcomes and observations obtained from that patient and setting a hypothesis to confirm those very predictions
  - Recomposing: inferring that a given observation at one time point, or in one specific patient, fully describes the whole just because it is true of that one patient
  - Ecological inference: interpreting the IPR&A data on the basis of the means and standard deviations and of the norms that characterize the group to which the patient may (or may not) belong
  - Ad hominem: shifting the blame of an inconclusive observation or measurement to an unrelated cause
  - Ad populum (group of people) et ad verecundiam (authoritative knowledge): generalizing and globalizing IPR&A data, which in fact has then the result of washing out and diluting the individual patient differences
  - Ad ignorantiam et non sequitur fallacy: making a given set of inferences, not so much based on IPR&A observations, but for no other reason than ignorance of better alternatives

In conclusion, the Affordable Care Act, passed by the Congress and signed into law by President Obama on March 23, 2010, and further upheld by the US Supreme Court on June 28, 2012, has, over the past 6 years, proffered more affordable and higher-quality healthcare to millions of Americans [37]. Arguably, this piece of legislation is by no means perfect and demands additional concerted work toward its improvement.

One important transformation that this Act brought to the health sciences nationally and globally is a new and improved view about how healthcare research and delivery should be brought forth. In brief, the concerted forces that led to this legislation included a trend toward "translational research," a term that originally, in the early 1990s, indicated work that spanned across (i.e., that "translated across") different types of fields of medicine, dentistry, and nursing, such as might be the case for the neuropathological symptomatology and neuroendocrine immune derangements that appear to result from injury and inflammation of the auriculotemporal innervation of the TMJ and which are not uncommon in TMD patients.

The development, testing, and evaluation of novel patient-targeted therapies rest and require a patient-centered outcome research and evaluation paradigm, as we explored in a previous chapter (cf., Chap. 7). New and improved research protocols must be tailored to the needs and characteristics of individual patients, and patient-centered, effectiveness-focused, and evidence-based methodological standards and guidelines must be developed and tested.

The variables, prospects, limitations, and fallacies of the T1-T2-T3 paradigm in translational healthcare, which integrates translational research of the underlying molecular pathology and comparative effectiveness research of the best available evidence for treatment, to optimize the prognosis of TMD patients with internal derangements, discussed in this chapter are neither exhaustive nor fully descriptive. It simply raises new questions and opens new avenues of timely and critical research for the translational care of TMD patients.

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