PREVALANCE OF SLEEP-DISORDED BREATHING AND EFFICACY OF TWIN BLOCK APPLIANCE TREATMENT IN SAUDI CHILDREN WITH CLASS II MALOCCLUSION AND OBSTRUCTIVE SLEEP APNOEA

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by

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LIST OF ABBREVIATIONS

AHI	Apnoea Hypopnea Index
AI	Apnoea Index
AT	Adeno-tonsillectomy
BMI	Body mass index
CBCT	Cone-beam computed tomography
CPAP	Continuous positive airway pressure
CRP	C-reactive protein
PSG	Polysomnography
OSA	Obstructive sleep apnoea
URS	upper airway resistance syndrome
CSA_{min}	minimum cross-sectional area
RME	Rapid maxillary expansion
MAS	Mandibular advancing splint
3D	Three-dimensional
SPSS	Statistical Package for the Social Sciences
QoL	Health quality of life
SDB	Sleep disordered breathing
PAP	Positive airway pressure
TB	Twin block
TFH	Total face height
uLTE	Urinrary luiokotrienes

TNF	Tumor necrosis factor alpha (TNF)
REM	Rem sleep
NREM	Non-Rem sleep
MAD	Mandibular advancement device
DM	Diabetes mellitus
LDL	Low density lipoprotein
HDL	High density lipoprotein
EEG	Electroencephalogram
EOG	Electrooculogram
EMG	Extremity electromyogram
PSQ	Paediatric Sleep Questionnaire
PT	Palatine tonsils
AASM	American Academy of Sleep Medicine
TST	Total sleep time
SOL	sleep-onset latency
ODI	Oxygen desaturation index
NE	nocturnal enuresis
COHIP	Child Oral Health Impact Profile
URT	Upper respiratory tract
2D	Two-dimensional
FH	Frankfort horizontal
QS	Quiet sleep
DICOM	Digital imaging and communications in medicine
MDT	multiple detector computed tomography

ANS	Anterior nasal spine
PNS	Posterior nasal spine
FRC	Functional Residual Capacity
BEP	Base of the epiglottis
TUV	Tip of the uvula
TEP	Tip of the epiglottis
RME	Rapid Maxillary Expansion
SPSS	Statistical Package for the Social Sciences.
SPO^2	Oxygen desaturation as measured by pulse oximetry.
Go	Gonion,
Gn	Gnathion.
S	Sella,
N	Nasion
A	A point
B	B point
ODI	Oxygen desaturation index
TGF	Transforming Growth Factor
SNA	Maxillary plane angel
SNB	Mandibular plane angel
MRI	Magnetic resonance imaging
NHP	Nottingham Health Profile
LC	locus coeruleus
TMN	Tuberomammillary nucleus

LH	lateral hypothalamus
UFH	Upper Face Height
LFH	Lower Facial Height
TFH	Total Face Height
SD	Standard Deviation

LIST OF APPENDICES

PREVALEN GANGGUAN PERNAFASAN KETIKA TIDUR DAN KEBERKESANAN RAWATAN APLIAN TWIN BLOCK DALAM KALANGAN KANAK-KANAK ARAB SAUDI MALOKLUSI KELAS II DAN APNEA TIDUR OBSTRUKTIF

ABSTRAK

Apnoea tidur obstruktif kanak-kanak merupakan satu kebimbangan utama kesihatan awam yang semakin meningkat di seluruh dunia, sebahagiannya disebabkan oleh kadar obesiti yang telah merangkumi populasi kanak-kanak. Individu dengan maloklusi tulang kelas II mengalami dengkuran akibat kedudukan retrognatik mandibel, yang mengakibatkan kedudukan lidah berada dalam kedudukan retro-glossal, yang menyekat ruang saluran udara farinks posterior yang boleh menyebabkan apnoea tidur obstruktif. Patologi tidur ini membawa kesan kesihatan yang serius seperti hipertensi, penyakit jantung iskemik, strok, dan dikaitkan dengan rintangan insulin. Kanak-kanak yang kurang tidur sering menunjukkan enuresis nokturnal, keletihan siang, hiperaktiviti, dan prestasi yang lemah di sekolah. Pengesanan awal terhadap keadaan ini melalui pemeriksaan klinikal gigi yang berkala, soal selidik saringan standard, dan analisis kraniofasial cephalometrik lanjutan mungkin dapat membantu dalam diagnosis dan rawatan awal. Terdapat banyak bukti yang menunjukkan peranan efektif alat miyofungsional dalam pengurusan apnoea tidur obstruktif yang dikaitkan dengan maloklusi tulang kelas II. Penggerakan anterior mandibel yang dipandu oleh alat ini mampu melebarkan ruang saluran udara farinks posterior, mengurangkan rintangan saluran udara di atas , dan meningkatkan aliran udara semasa bernafas sepanjang malam.

Tujuan kajian ini adalah untuk menentukan prevalens ganguan penafasan tidur dalam kanak kanak sekolah di Arab kajian populasi menggunakan Soal Selidik Tidur Pediatrik (PSQ) dan kedua, untuk menilai kesan penggunaan twin block terhadap dimensi CBCT saluran udara atas , parameter orofaring,tahap biokimia dan dan kualiti hidup dalam kanak-kanak apnea tidur obstruktif dengan maloklusi skeletal Kelas II pernafasan, Kajian kohort prospektif ini melibatkan 34 kanak-kanak yang sedang membesar dengan OSA yang telah dibuktikan melalui polisomnografi, mempunyai maloklusi skeletal kelas II dan retrognathia mandibula dalam lingkungan umur 8 hingga 12 tahun yang telah melengkapkan rawatan blok kembar/ "twin block" dan kumpulan kawalan sepadan. Hasil kajian menunjukkan bahawa dua puluh tiga peratus kanak-kanak sekolah di Arab Saudi berisiko tinggi untuk mengalami SDB dengan predileksi lelaki sebagai faktor risiko. Berdengkur, apnoea tidur, dan pernafasan melalui mulut adalah perkara biasa dalam kalangan kanak-kanak SDB yang berisiko tinggi. Terdapat hubungan yang kuat antara peningkatan indeks jisim badan (BMI) dan SDB. Peningkatan kadar obesiti dalam kalangan kanak-kanak sekolah di Arab Saudi dan kesan negatifnya memerlukan perbincangan serius dalam strategi kesihatan masa depan. Jantina lelaki, peningkatan BMI, markah tonsil dan Mallampati yang tinggi, adalah petunjuk klinikal petanda apnoea tidur obstruktif.Walau bagaimanapun, hanya skala Mallampati yang dikaitkan dengan keterukan OSA. Disebabkan oleh beban kewangan untuk polysomnografi (PSG), penunjuk diagnostik klinikal harus diwujudkan dan digalakkan terutamanya dalam kajian berasaskan komuniti. Hasil analisis imbasan CBCT menunjukkan bahawa kanak-kanak dengan apnoea tidur obstruktif mempunyai ruang orofaring yang lebih kecil, CSA_{min}, kawasan keratan rentas minimum (CSA_{min}) dimensi anterio-posterior dan lateral CSA_{min}, CSA_{min} hypofaring, dan panjang saluran udara atas yang lebih tinggi berbanding

dengan kumpulan kawalan yang sepadan. CSA_{min} yang kecil menjadi pembolehubah anatomi yang paling relevan dalam patogenesis apnoea tidur obstruktif. Kajian ini menunjukkan bahawa pembetulan maloklusi tulang mandibel kelas II dan retrognathia dengan peranti twin block menghasilkan peningkatan signifikan dalam jumlah ruang saluran udara atas, CSA_{min}, jarak anterio-posterior dan lateral CSA_{min} pada tahap orofaring, CSA_{min} pada tahap hypofaring, peningkatan panjang saluran udara atas, dan pengurangan yang ketara dalam skor indeks apnoea hypopnea (AHI), tetapi ia tidak mempunyai kesan ke atas parameter nasofaring. Rawatan apnoea tidur obstruktif pediatrik dengan peranti twin block tidak mempengaruhi tahap Leukotrien E4 (LTE4) dalam air kencing dan tahap protein C-reaktif (CRP) dalam serum walaupun terdapat peningkatan yang signifikan dalam ciri-ciri dentoalveolar dan parameter tidur pernafasan. Di samping itu, terapi “twin block” memberi kes an positif terhadap kualiti hidup kanak-kanak yang sedang membesar dengan apnoea tidur obstruktif dan pesakit menunjukkan peningkatan ketara yang diukur dengan PSG dan gejala yang dilaporkan oleh ibu bapa. Kelemahan utama kajian ini berkaitan dengan kesan jangka panjang terapi “twin block” terhadap apnoea tidur obstruktif pediatrik yang masih belum jelas dan perlu ditangani dalam kajian masa depan. Pertumbuhan semula jadi dan regresi tisu limfoid dalam kumpulan umur ini mungkin telah mempengaruhi dimensi saluran udara dan hasil rawatan lain.

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ABSTRACT

Obstructive sleep apnoea (OSA) is a disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction that disrupts normal ventilation during sleep and normal sleep patterns. It is an increasing major public health concern worldwide, partly resulting from the obesity epidemic which has encroached into the pediatric population. Individuals with a Class II skeletal malocclusion may suffer from snoring due to a retrognathic position of the mandible resulting in a retro-glossal tongue position which restricts posterior pharyngeal airway space which may result in obstructive sleep apnoea. This sleep pathology carries devastating health consequences resulting in hypertension, ischemic heart disease and stroke and associated with insulin resistance. Children who are sleep deprived often demonstrate nocturnal enuresis, daytime fatigue, hyperactivity and poor performance at school. Early recognition of this condition through routine dental clinical examination, standard screening questionnaires, and further craniofacial cephalometric analysis may help in early diagnosis and treatment. There is a growing body of evidence that shows the effective role of myofunctional appliances in the management of obstructive sleep apnoea associated with Class II skeletal malocclusion. The anterior displacement of the mandible guided by this device is able to widen the posterior pharyngeal airway space, reducing the upper airway resistance and improves airflow while breathing throughout

the night. The aims of this study were first: To determine the prevalence of sleep disordered breathing among Saudi school children as a population-based study using the Pediatric Sleep Questionnaire (PSQ), and second: To evaluate the impact of twin block management on upper airway CBCT dimensions, oropharynx parameters, biochemical levels, and quality of life in OSA children with Class II skeletal malocclusion. This prospective cohort study comprised polysomnography-proven OSA growing children with class II skeletal malocclusion and mandibular retrognathia in the age range of 8 to 12 years who have completed twin block treatment and matched corresponding controls. Results showed that twenty three percent of Saudi school children were at high risk of developing SDB with male predilection as a risk factor. Snoring, sleep apnoea, and mouth breathing were prevalent in high-risk SDB children. There is a strong association between increased body mass index (BMI) and SDB. The epidemic spread of obesity among Saudi school children and its negative impacts merit serious discussion in future health strategies. Male gender, increased BMI, high tonsil and Mallampati scores were clinical indicators of the presence of OSA. However, only Mallampati scale was associated with severity of OSA. Due to the financial burden for of polysomnography (PSG), clinical diagnostic indicators should be established and encouraged especially in community based studies. The results of CBCT scans analysis showed that children with OSA have a smaller oropharynx volume, minimum cross-sectional area (CSA_{min}), anterio-posterior and lateral dimensions of CSA_{min}, hypopharynx CSA_{min}, and increased upper airway length compared to corresponding controls. A small CSA_{min} seems to be the most relevant anatomical variable in the pathogenesis of OSA. The current study shows that correction of class II skeletal malocclusion and mandibular retrognathia with twin-block appliance resulted in significant increase of upper air way parameters.

CHAPTER ONE

INTRODUCTION

1.1 Background of the Study

Orthodontic treatment had undergone a paradigm shifting on the basis of improving health-related quality of life by improving aesthetics and function and relieving medical conditions related to discrepancies in dentofacial complex. The airway, mode of breathing, and malocclusion are so inter-related during growth and development. Orthodontic and orthopedic treatments that positively impact the airway and breathing can absolutely lead to a healthier life. The oral cavity, pharynx, and larynx constitute the components of the anatomic upper airway structures which underline respiration, swallowing, and phonation in humans. In children, the upper airway is greatly influenced by the growth and development of head and neck structures along a temporal continuum spanning from the neonatal period through to the end of adolescence. Patency of the upper airway is controlled by complex interactions between upper airways resistance, pharyngeal collapsibility, the tone of the pharyngeal dilator muscles, and the negative intra-lumenal pressure generated by respiratory muscles.

Sleep-disordered breathing (SDB) is a continuum which encompasses a spectrum of disease of varying severity, ranging from habitual snoring, labored breathing, sleep disruption and/or gas exchange abnormalities. SDB is clinically characterized by snoring and physiologically by increased upper airway resistance and partial or complete upper airway obstruction which disrupts ventilation and oxygenation (Thorpy, 2012). Charles

Dickens was probably the first to describe the features of sleep disturbance in his famous comic narrative The Posthumous Papers of the Pickwick Club. “The fat boy Joe was snoring heavily, he was falling constantly asleep and was described as having slow perception. Damn that boy...!” (Dickens, 1837). In 1889, William Hill recognized the symptoms of the syndrome, describing the stupid lazy-looking kid who frequently suffers from headache at school, breathes through his mouth instead of his nose, snores and is restless at night. He speculated that some of their backwardness was secondary to some hampering of the cerebral functions rather than deafness. Hill also found adenotonsillectomy to be helpful for these children (Hill, 1889).

1.2 Regulation of Sleep

Sleep is a state of reversible unconsciousness in which the brain is relatively more responsive to internal than external stimuli and is characterized by sleep cycles with specific electroencephalogram (EEG) patterns and physiological changes. Non-rapid eye movement (NREM) sleep transitions into rapid eye movement (REM) sleep, which follows a regular cycle lasting about 90 minutes in adults. The cycles may be separated by a period of wakefulness and are repeated 3–6 times each night (Troynikov et al., 2018). The wakeful state is characterized by low-voltage, high-frequency electroencephalogram (EEG) activity and high muscle tone. In NREM sleep, high-amplitude, low-frequency EEG activity occurs, accompanied by decreased muscle tone; whereas REM sleep exhibits low-voltage, fast EEG activity coupled with muscle atonia and characteristic rapid eye movements (Bassetti et al., 2021). Wakefulness is mediated by the ascending arousal systems in the brainstem and posterior hypothalamus, which project to the forebrain. Cholinergic neurons in the pedunculopontine and laterodorsal

tegmental areas (PPT/LDT) activate the thalamus and other forebrain targets (Espana and Scammell, 2004)

Activation of the cerebral cortex to facilitate processing of thalamic inputs arises from monoaminergic neurons in the tuberomammillary nucleus (TMN) containing histamine, the dorsal and median raphe nuclei containing serotonin, and the locus coeruleus (LC) containing noradrenaline. Inputs are also received from peptidergic neurons in the lateral hypothalamus (LH) containing orexin and melanin-concentrating hormone, and from basal forebrain (BF) neurons that contain γ-aminobutyric acid (GABA) or acetylcholine. Cholinergic activation of the thalamus is necessary for thalamocortical activation, which results in the low-amplitude, high-frequency EEG characteristic of wakefulness. Other neurotransmitters that are active in wakefulness include histamine, dopamine, serotonin, noradrenaline, and orexins (Siegel, 2004).

The preoptic area in the anterior hypothalamus contains neurons that help produce NREM and REM sleep. These cells are located within the ventrolateral preoptic area (VLPO), and within adjacent regions of the preoptic area and basal forebrain, and are active during sleep. VLPO neurons contain inhibitory neurotransmitters γ-aminobutyric acid (GABA) and galanin that produce sleep by inhibiting wake-promoting brain regions such as the tuberomamillary nucleus (TMN), lateralhypothalamus, locus coeruleus (LC), dorsal raphe, laterodorsal tegmental nucleus (LDT), and pedunculopontine tegmental nucleus (PPT) (Espana and Scammell, 2004).

The interaction of cholinergic and aminergic brainstem neurons controls REM sleep. Cholinergic neurons in the LDT and PPT are active during REM sleep and

depolarise thalamic neurons, thereby activating thalamocortical signalling to produce high-frequency cortical EEG activity. During wakefulness and NREM sleep, these REM-active cholinergic cells are inhibited by noradrenaline, serotonin, and histamine. However, the REM sleep-generating neurons are disinhibited during REM sleep

1.3 Sleep Homeostasis and the Circadian Clock

The timing, quality, and duration of sleep are controlled by the duration of prior wakefulness (homeostatic control - process S) and by the interaction of time of day (circadian control - process C) (Borbely, 1982). The suprachiasmatic nucleus regulates circadian rhythms through local hypothalamic circuits via signals that are conveyed to the supraventricular zone and dorsomedial nucleus of the hypothalamus. The output from the subparaventricular zone and dorsomedial nucleus of the hypothalamus is integrated with behavioural and endocrine information to drive circadian cycles of sleep, feeding, activity, and corticosteroid secretion. Excitatory wake signals are relayed to arousal regions such as the lateral hypothalamus and locus coeruleus, and arousal inhibitory projections extend to the sleep-promoting VLPO (Arrigoni and Fuller, 2022).

Adequate sleep is essential for children. Sleep disturbances can burden normal development during childhood. Children who are sleep deprived often demonstrate daytime fatigue, restlessness, hyperactivity, and poor schooling performance. In severe cases, sleep pathology carries devastating health consequences resulting in hypertension, heart diseases, insulin resistance, and other metabolic disturbances (Lévy et al., 2015; Spruyt et al., 2011). Psychological deficits associated with untreated OSA include depression, anxiety, and daytime sleepiness. The etiology of this condition is

multifactorial. Possible risk factors include obesity, allergy, sex, ethnicity, exposure to cigarette smoke, low-socioeconomic status, and family history of snoring (Jordan et al., 2014; Hobzova et al., 2017).

The mildest form of SDB is habitual snoring or primary snoring, which was described by the American Academy of Pediatrics as 'snoring without obstructive apnoea, frequent arousals from sleep, or gas exchange abnormalities' (Clinical Practice Guideline, 2012). This suggests that neuromuscular compensation is able to sustain stable breathing and maintain the breathing effort below the threshold level of arousal (Kheirandish and Gozal, 2012). Nevertheless, primary snoring has been found to be associated with significant neurobehavioral deficits in a subset of children, suggesting it may not be benign (O'Brien et al., 2004).

The intermediate form of SDB includes obstructive hypoventilation and upper airway resistance syndrome (UARS). Obstructive hypoventilation is habitual snoring without apnoea and hypopnea, but with a stable increased respiratory effort and hypercapnia. In order to maintain stable sleep, there is increased neuromuscular compensation. However, this effort is not enough to maintain baseline minute ventilation, resulting in hypercapnia. It is hypothesized that these children have moderate anatomical predisposition towards the most severe form of SDB which is obstructive sleep apnoea (OSA).

UARS was first described by Guilleminault et al. in 1993 as brief, repetitive respiratory effort-related arousals, and daytime sleepiness without overt sleep apnoea, hypopnoea, or gas exchange abnormalities. It was observed that compared with children

with OSA, children with UARS aroused with less respiratory effort, suggesting that a reduced arousal threshold may be a possible aetiology. Nevertheless, as children with UARS have similar daytime neurobehavioural symptoms to those with OSA and respond similarly to treatment, it is likely that they share common pathophysiology (Lumeng and Ronald, 2008). However, whether UARS needs to be regarded as a distinct disease is controversial. The American Academy of Sleep Medicine (AASM) concluded that the current clinical and pathophysiological data are not sufficient to specify UARS as a distinct condition; instead, it was defined as a mild form of obstructive sleep apnoea (AASM, 2012).

Obstructive sleep apnoea (OSA) was first described by Guilleminault and his team in 1976 using polysomnography and clinical symptoms. In 2012, OSA was defined by the American Academy of Pediatrics as a 'disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction that disrupts normal ventilation during sleep and normal sleep patterns'. The increased respiratory effort results in a reflex recruitment of upper airway muscles and serves as an arousal trigger (Fig. 1.1). As in adults, the gold standard for diagnosis of OSA in children is an overnight polysomnography study, which records sleep architecture, respiration, cardiac rhythm, muscle activity, gas exchange, and snoring (Aurora et al., 2011).

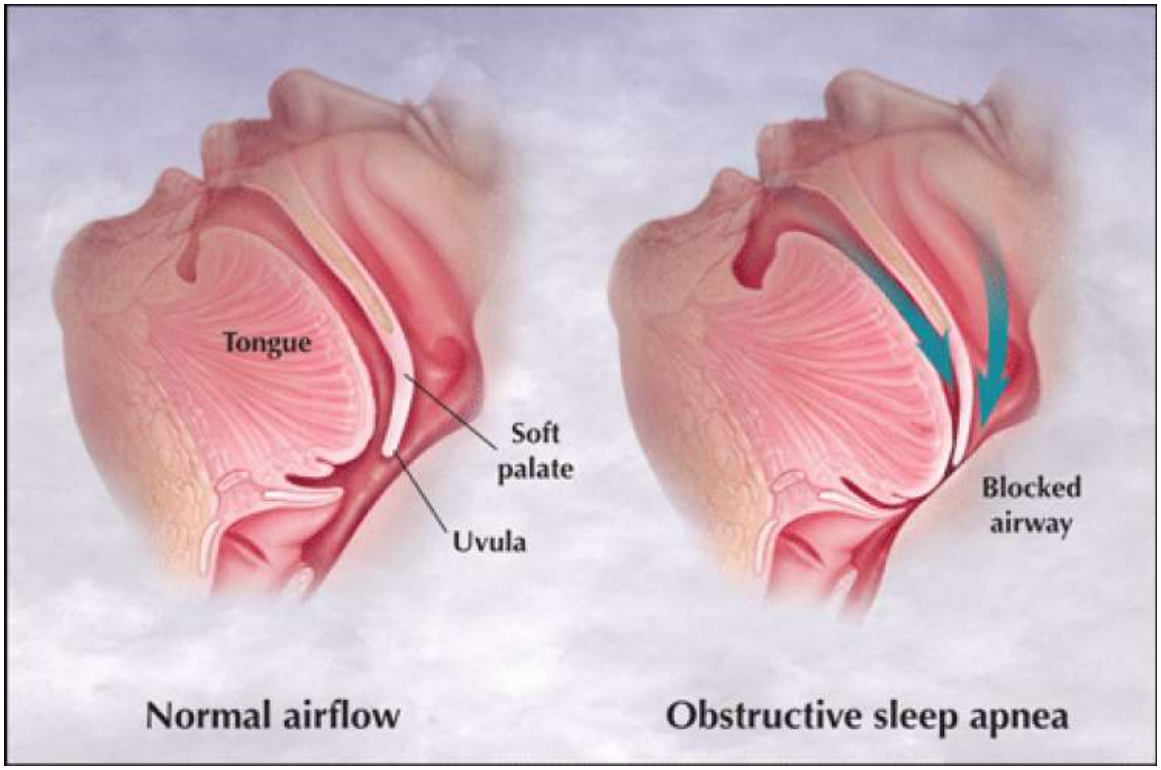

Figure 1.1 Obstructive Sleep Apnoea Pathophysiology (Morehead, 2014).

The most important index of polysomnography in defining the severity of OSA is the apnoea/hypopnoea index (AHI), which is defined as the number of apnoeas and hypopneas per hour of total sleep time. Apnoea in children is scored when a drop in the peak airflow is ≥ 90% of the pre-event baseline, with the drop lasting at least the duration of two breaths during baseline breathing and is associated with the presence of respiratory effort throughout the entire period of absent airflow (Berry et al., 2012). Hypopnoea is scored in children when the drop in peak airflow is ≥ 30% of the pre-event baseline, for the duration of at least two breaths in association with either ≥ 3% oxygen desaturation or an arousal (Sinha and Guilleminault, 2010). It was found that an apnoea/hypopnoea index (AHI) greater than 1 event per hour is abnormal in a child (Tam et al., 2014; Malhotra et al., 2018). However, diagnostic criteria for OSA are

defined as an apnoea-hypopnoea index (AHI) of 5 or greater events per hour on nocturnal PSG and evidence of disturbed sleep, daytime sleepiness, or other daytime symptoms. The severity of OSA is classified according to AHI as follows: Mild OSA: AHI of 5-15, moderate OSA: AHI of 15-30, severe OSA: AHI of more than 30 events per hour (Lumeng and Chervin, 2008)

1.4 Pediatric OSA vs. Adult OSA

Pediatric OSA differs from adult OSA in both clinical characteristics and determinants of its epidemiology. Consequently, diagnostic criteria and treatment protocols and methods differ from those in adults. In newborns, the daily sleep duration ranges from 14 to 16 hours, and newborns spend two-thirds of their total sleep time in active sleep (AS), which is equivalent to rapid eye movement (REM) sleep in older infants, children, and adults. Subsequently, the time spent in AS decreases to 20-25% at the age of 5 years to become similar to the percentage of REM sleep in adults. As the child grows, the sleep duration decreases. In newborns and infants, sleep is divided into multiple periods. At 5-6 months of age, nocturnal sleep consolidation occurs, and the infant sleeps at night more than during the day, with at least one nap per day. During development and maturation, several physiological changes occur during sleep (Guilleminault, 1987). Respiratory function changes with time. In adults, minute ventilation decreases during sleep by approximately 13-15% compared to the awake state (Berthon-Jones et al., 1982). The respiratory rate does not change substantially because the reduction occurs mainly in tidal volume (Krieger, 1985). By contrast, studies in children revealed a decrease in their respiratory rate during sleep (Carskadon et al., 1978). However, there are limited studies that assessed tidal volume and minute

ventilation in healthy children (Tabachnik et al., 1981). During sleep, the functional residual capacity decreases, and upper airway resistance doubles in normal humans (Hudgel et al., 1984).

While respiration is regular during NREM sleep, REM sleep is characterized by irregular breathing in terms of the variable respiratory rate and tidal volume. In children, the suppression of the tonic muscle activity of the intercostal muscles leads to a further decrease in functional residual capacity, while the concurrent activity of the diaphragm muscle remains stable. This mechanism results in paradoxical chest and abdominal movements during sleep that usually disappear by 3 years of age (Papastamelos et al., 1995). Because children have a high percentage of REM sleep, they are prone to REM-associated sleep disorders such as OSA. Additionally, chest wall compliance during infancy is nearly triple that of lung compliance, resulting in paradoxical inward rib cage motion during REM sleep. In normal children, high chest wall compliance continues until 3 years of age, and by the second year of life, chest wall stiffness gradually increases until the chest wall and lungs have almost equal compliance, as in adulthood (Gaultier et al., 1987). Moreover, the shape of the rib cage movement contributes to tidal breathing during quiet sleep (QS) and is only one-third in neonates compared with two-thirds during NREM sleep in older children (Hershenson et al., 1990). Due to increased chest wall compliance in infancy, infants have a lower functional residual capacity and are more prone to atelectasis compared with older children and adults. To actively increase their Functional Residual Capacity (FRC), infants utilize a mechanism termed laryngeal braking until 6 to 12 months of age (Wheeler et al., 2007).

Moreover, the cephalic location of the larynx during infancy allows the epiglottis to overlap the soft palate and thus enables infants to make a better seal for suckling (Tonkin, 1975). However, this mechanism makes them at risk for upper airway obstructions if the nasopharynx is partially obstructed. During the prepuberty period, there is no gender difference in the incidence of OSA; however, after puberty, the incidence increases in boys more than in girls. Theoretically, this difference could be explained by the testosterone-induced changes in upper airway morphology, as testosterone flow in boys during puberty leads to muscle mass enlargement. This difference may increase the risk for OSA in adolescent and adult males compared with females (Redline et al., 1999). The increase in muscle mass could explain the reappearance of OSA in teenagers with relatively small upper airways. However, not all children with abnormal craniofacial morphometric features will develop OSA as teenagers (Guilleminault et al., 1989). Other maturational changes include an increase in the lymphoidal tissues of the upper airway from birth until the age of 12 years, accompanied by the gradual growth of the skeletal boundaries of the upper airway (Jeans et al., 1981). Compared with adults, infants have an extreme response to hypoxia, initially expressed as increased ventilation, followed by a reduction of ventilation below the baseline, which may lead to apnoea (Henderson-Smart, 1992).

Unlike adults with OSA, adenotonsillectomy (TA) is the first-line treatment in most paediatric OSA cases. TA results in subjective (symptoms) and objective (PSG parameters) improvements in the majority of paediatric OSA patients, with a cumulative cure rate of 80% and a significant reduction in healthcare utilization (Lipton and Gozal, 2003; Tarasiuk et al., 2004). On the other hand, in adult patients, positive airway

pressure (PAP) therapy is the mainstay treatment of OSA. However, in children with OSA, PAP therapy has an important role, but only in a small group of paediatric OSA children who do not respond to TA or in whom the major cause of the upper airway obstruction is not adenotonsillar hypertrophy (such as patients with obesity or craniofacial abnormalities). Table 1.1 summarises the major differences between adult and paediatric OSA.

Table 1.1 paediatric OSA vs. Adult OSA (Lee, 2012).

Polysomnography	Child	Adult
Respiratory related cortical arousal	Less than 50% of respiratory events	At termination of each respiratory events
Slow wave sleep	Normal	Decreased slow wave sleep
REM sleep dependency of respiratory events	REM dependence	REM or non-REM
Characteristics of airway obstruction	Cyclic obstruction or prolonged obstructive hypoventilatioin	Cyclic obstruction
Definition in duration of obstructive apnea and hypopnea	More than two respiratory cycles	More than 10 seconds
Definition in duration of central apnea	Either duration more than 20 seconds, or more than two respiratory cycles and associated with arousal, awakening or more than 3% desaturation	More than 10 seconds
OSA definition as AHI	More than 1 per hour with OSA symptoms	More than 5 per hour with OSA symptoms or more than 15 per hour

REM, rapid eye movement; OSA, obstructive sleep apnea; AHI, apnea-hypopnea index.

A mutual interaction has been reported between the nasopharyngeal airway and the craniofacial complex. Jaw malposition and anomalies are correlated with changes in airway morphology and respiratory problems. Conversely, obstruction of the airways has an influence on the development of the stomatognathic system. The first-line and most common treatment for paediatric OSA is adenotonsillectomy, particularly for moderate to severe cases with adenotonsillar hypertrophy and no contraindication to surgery (Marcus et al., 2012). However, the cure rate of OSA after the operation (defined as a post-adenotonsillectomy AHI event/hour) ranges from 27% to 60% (Friedman et al., 2009). Thus, further orthodontic treatment may be required to address the problem.

Orthodontic oral appliances have been widely used for the treatment of OSA, mainly in adults. These appliances aim to increase the posterior oropharyngeal airway by reducing upper airway collapsibility during sleep and by triggering the stretch receptors, which in turn activate the airway supporting muscles (Ferguson et al., 2006). Due to improved comfort, quietness, and portability, oral appliance treatment could potentially result in better patient adherence and acceptance than other treatment modalities. The orthodontic interventions introduced for the treatment of paediatric SDB include mandibular advancement splints (MAS), rapid maxillary expansion (RME), and facial masks.

MAS is the most common type of oral appliance used in the treatment of SDB. Evidence supporting their use and efficacy in adults is increasing, but their use in children for SDB treatment is less common, and they are usually designed as a functional appliance for growth modification and alleviating skeletal malocclusion in children. Skeletal malocclusion is a common birth defect that occurs due to the distortion of the maxillary and/or mandibular development that may have an impact on the positioning, alignment and health of the primary and permanent teeth (Joshi et al., 2014). Malrelationship of the dental arches relative to the normal occlusion: may occur in any of the three planes of spaces: anteroposterior, vertical or transverse (Hassan and Rahimah, 2007). It is generally accepted that advancing the mandible in growing patients may improve jaw skeletal and dentoalveolar relationships, as well as increase nasopharyngeal airway dimensions. Therefore, it may improve OSA symptoms based on the significant relationship between paediatric OSA and craniofacial morphology (Flores-Mir et al., 2013). Twin block is a kind of oral functional appliance used for

early treatment of children with mandibular retrognathia. With its effect of the forward position of the mandible, twin block may be a suitable oral appliance to treat children with OSA.

1.5 Statement of the Problem

Obstructive sleep apnoea is a prevalent global disorder and is increasingly becoming a significant public health concern, primarily due to the escalating prevalence of obesity, particularly among the paediatric population in Saudi Arabia. Narrowing of the upper airway has been identified as a physiological characteristic in growing patients with Class II skeletal malocclusion and mandibular retrusion. The retruded mandible induces a retro-displacement of the tongue and hyoid bone, potentially resulting in a reduction in upper airway volume. The twin block appliance has been proposed as a potential oral treatment for OSA in children with Class II skeletal malocclusion and mandibular retrognathia. There is an urgent need to investigate the impact of twin block appliance treatment on craniofacial features, upper airway dimensions, respiratory parameters, quality of life, and circulating inflammatory biomarkers in children with OSA and Class II malocclusion with mandibular retrognathia. Currently, there is a lack of evidence, particularly regarding inflammatory biomarker levels and quality of life, which have not been assessed in the paediatric population. This data may aid in predicting and diagnosing paediatric OSA and other sleep disturbances globally. Additionally, the results of this research may improve interdisciplinary treatment planning for children with OSA, offering alternatives to primary treatments. Furthermore, it is intriguing to determine the prevalence of SDB and its correlation with obesity among Saudi schoolchildren

1.6 Objectives of the Study

1.6.1 General Objective

To evaluate the prevalence of SDB among Saudi schoolchildren and study the impact of twin block treatment on respiratory, oropharynx parameters, biomarkers levels, and quality of life in OSA children with Class II skeletal malocclusion and mandibular retrognathia.

1.6.2 Specific Objectives

1. To determine the prevalence of SDB symptoms and its association with obesity among Saudi school children.

Phase One (Clinical Part; Cross-sectional Study)

2. To compare oropharyngeal size and morphology of Class II skeletal malocclusion and mandibular retrognathia children with and without OSA using the tonsil size and Mallampati score.

3. To compare upper airways dimensions in Class II skeletal malocclusion and mandibular retrognathia children with and without OSA using cone-beam computed tomography.

Phase Two (clinical Part- Interventional Study)

4. To evaluate the effect of twin block treatment on upper airway dimensions and respiratory parameters in OSA children with class II skeletal malocclusion and mandibular retrognathia using cone-beam computed tomography.

5. To determine the effect of twin block treatment on urine leukotriene E4 (uLTE4) and serum C-reactive protein (CRP) levels in OSA children with class II skeletal malocclusion and mandibular retrognathia.

6. To determine the impact of twin block treatment on quality of life in OSA children with class II skeletal malocclusion and mandibular retrognathia.

1.7 Hypothesis

1. There is difference in oropharyngeal size and morphology of Class II skeletal malocclusion children presented with OSA and without using the tonsil size and Mallampati score.

2. The upper airways dimensions in OSA children with Class II skeletal malocclusion and mandibular retrognathia are different from those without OSA.

3. The twin block appliance therapy can change upper airway dimensions and respiratory parameters in OSA children with class II skeletal malocclusion and mandibular retrognathia.

4. The twin block appliance therapy can change leukotriene E4 (uLTE4) and serum C-reactive protein (CRP) levels in OSA children with class II skeletal malocclusion and mandibular retrognathia.

5. The twin block appliance therapy has a significant impact on quality of life in OSA children with class II skeletal malocclusion and mandibular retrognathia.

CHAPTER TWO

LITERATURE REVIEW

2.1 Epidemiology

Lumeng and Chervin reviewed 48 articles worldwide, including studies from the USA, Europe, Asia, the Middle East, and Australia. They reported that the overall prevalence of parent-reported SDB in children by any definition was 7.45%, while parental report of apnoea varied from 0.2 to 4%. They also found that the prevalence of SDB identified by parent-reported symptoms on questionnaires was estimated to be between 4 to 11%, while the prevalence of OSA diagnosed by diagnostic polysomnography studies was reported to be 1 to 4% by most studies (Lumeng and Chervin, 2008).

In 2009, Bixler et al. investigated the prevalence and risk factors of OSA in a representative sample of primary school children using a full polysomnogram and complete history/physical examination. They found that the prevalence of moderate OSA (AHI $\geq$ 5) was 1.2% in the USA, and waist circumference/BMI, nasal abnormalities, and ethnic minority (non-Caucasian) are the main risk factors. Li et al., in 2009, reported similar numbers. They noted that 9 to 10% of children are habitual snorers, while 1-3% of children were estimated to have UARS. In the 2012 guideline published by American Academy of Pediatrics (AAP), Marcus et al. 2012, reported that the prevalence of habitual snoring varied widely, depending on the study and definition used, from 1.5% to 27.6%, while the prevalence of OSA is found to be in the range of 1% to 5%.

It has been reported in various studies in the United States that SDB is more prevalent among African American children than Caucasian children, and Asians have more severe OSA than matched Caucasians (Ong and Clerk, 1998); the difference between races is less clear in other populations. Moreover, SDB is more common among boys and heavier children. SDB was reported to present most commonly in 2 to 5-year-olds, but it can present in all ages. OSA does run in families, and it is likely that both genetic and environmental factors play a role (Lumeng and Chervin, 2008).

2.2 Predisposing Factors for Pediatric OSA

2.2.1 Anatomical Structure

The patency of the airway depends on the balance between the collapsing forces, which include the intraluminal negative pressure and airway anatomy, and the dilating forces from the pharyngeal muscles and changes in lung volume. These forces are affected by factors such as the anatomical structure, neuromotor tone, and inflammation (Dempsey et al., 2010).

Patients with OSA have been shown to have increased upper airway collapsibility when awake, and it is plausible that these patients may have an anatomically small pharyngeal airway. Using computerised tomography on awake patients, Haponik et al., 1983, observed a reduced cross-sectional area in the nasopharynx, oropharynx, and/or hypopharynx of patients with OSA. CT imaging was also used by Schwab et al., 1993, who reported that an enlarged tongue and lateral pharyngeal wall size independently increased the risk for OSA. Moreover, the physical size of the craniofacial and dentofacial skeleton and the amount of soft tissue within and surrounding the airway

also affect the airway size. It is known that adenotonsillar tissue is largest in relative size in the first few years of life and gradually involutes by adolescence and adulthood (Fig. 2.1). Using magnetic resonance imaging (MRI), Ni et al., 2007, observed that in children with OSA and primary snoring, the upper airway is restricted by both the adenoids and tonsils; the soft palate is also larger in children with OSA, adding further restriction.

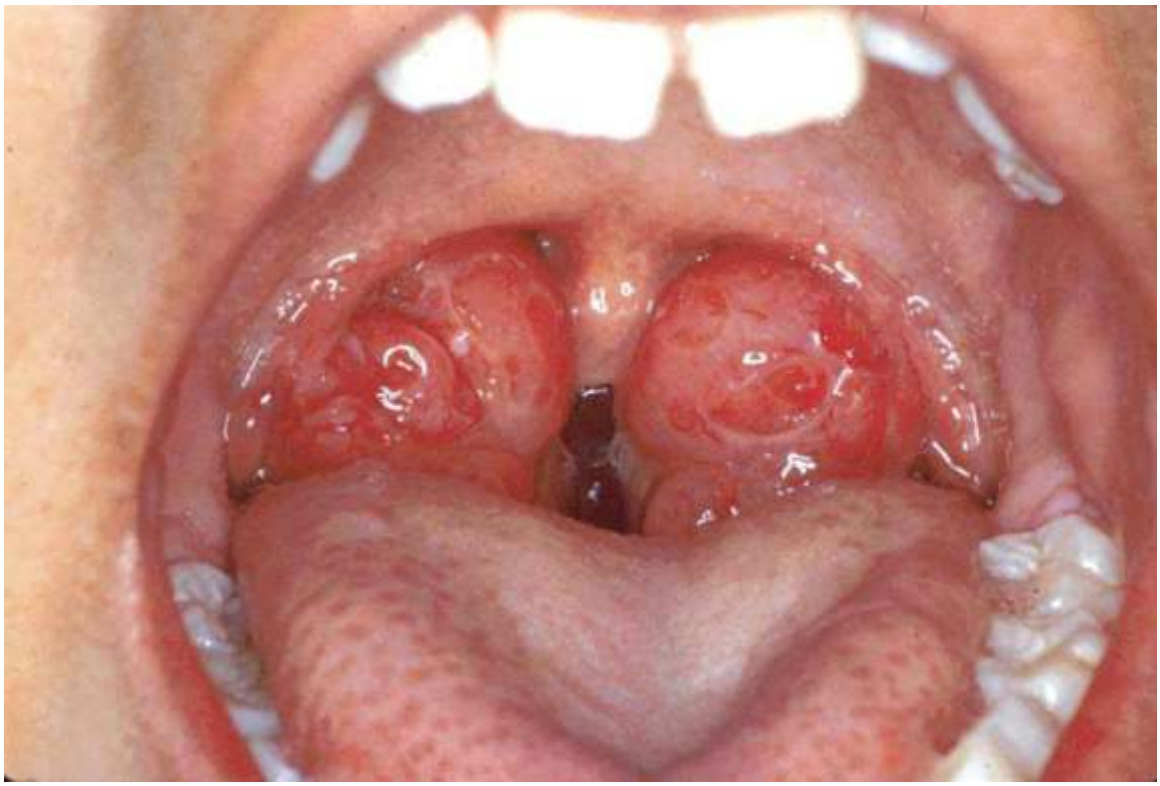

Figure 2.1 Hypertrophied Adenoid Tissues

Furthermore, the reduced size in craniofacial and dentofacial bony structures compromises the pharyngeal space and also contributes to the development of OSA. In a cross-sectional study of 604 paediatric patients, Huynh et al., 2011, found that SDB symptoms were primarily associated with morphologic features related to a long and narrow face (dolichocephalic facial profile, high mandibular plane angle, narrow palate,

and severe crowding in the maxilla and the mandible). Down Syndrome (DS) is an example of how anatomical structural deformities can lead to the development of OSA. These deformities include macroglossia, glossoptosis, hypopharyngeal collapse, tracheal stenosis, laryngomalacia, and recurrent enlarged adenoids. Studies showed that OSA was found in 63% and 79% of children with DS, respectively (Marcus et al., 1991; Dyken et al., 2003). In addition, children with Crouzon syndrome are at high risk of obstructive sleep apnoea (OSA), mainly due to midfacial hypoplasia and facial deformities. Those cases require major midface advancement to restore airway patency (Doerga et al., 2016).

2.2.2 Neuromuscular

Most OSA children are able to intermittently obtain a stable breathing pattern during sleep, suggesting that neuromuscular compensation below arousal level is possible and that anatomical properties are not the only determinants of airway patency (Katz and D'Ambrosio, 2008). Children with neurological disorders such as cerebral palsy may present with SDB and OSA. These neurological disorders contribute to OSA by reducing upper airway motor control with pharyngeal hypotonia, reduced ventilatory responses, and reduced ventilatory muscle strength. Elsayed et al., 2012, observed a 50% prevalence of SDB among 48 school-aged children with cerebral palsy. In another retrospective study using overnight polysomnography on children with cerebral palsy, Kotagal et al., 1994, found 5 out of 9 were diagnosed with OSA.

2.2.3 Pro-Inflammatory Factors

OSA also appears to cause low-grade systemic inflammation and local inflammation. This is thought to be the result of the intermittent hypoxia and sleep fragmentation leading to the production of free radicals and systemic oxidative stress. Studies have shown inflammatory changes in upper airway samples from children with OSA, and higher levels of cysteinyl leukotrienes (CYS LT) have been found (Goldbart and Tal, 2008; Punjabi et al., 2004). These are major inflammatory mediators and potent neutrophil activators. The expression of their receptors has been shown to be higher in children with OSA compared to children with recurrent infectious tonsillitis, suggesting an inflammatory process involving leukotriene expression and regulation occurs in children with OSA.

Systemic inflammation, as indicated by C-reactive protein (CRP) levels, has been shown to increase in patients with OSA and tends to decrease three months after adenotonsillectomy. Moreover, there is a significant correlation between the changes in CRP and reduction in the severity of OSA (Zucconi et al., 2003; Li et al., 2008). This elevation of systemic inflammation was thought to be triggered by episodic hypoxia and arousal. There is continued effort to understand whether local and systemic inflammation is a component or the cause of OSA. Most current evidence shows that adenotonsillectomy reduces the inflammation in OSA at the local or systemic level (Goldbart and Tal, 2008).

Cytokines play a part in sleep regulation and are part of the etiology of OSA as well. The body's immune response is regulated by cytokines. Levels of pro-inflammatory cytokines are highest at night. During illness, increased levels of pro-inflammatory cytokines correspond with increased fatigue, which makes a patient feel more tired. This natural response to the onset of an illness encourages more sleep and recovery from illness. Cytokines also increase and fragment deep, NREM sleep and decrease REM sleep, which can help explain why patients may sleep restlessly during illness. Two cytokines, interleukin-1 beta (IL1) and tumour necrosis factor alpha (TNF), are well characterised for their roles in sleep regulation. Evidence from animal studies has shown that systemic or central injection of either IL1 or TNF enhances the duration of NREMS and EEG delta wave power during NREMS (Krueger et al., 1984).

Recoquillon et al., 2018, assessed changes in serum levels of the inflammatory biomarkers before and after 2 months of treatment with a mandibular advancement device (MAD) or a sham device. The biomarkers test included C-reactive protein, interleukin-6, tumour necrosis factor-α and its receptors, adiponectin, leptin, and P-selectin), glucose and lipid metabolism, N-terminal pro-brain, and natriuretic peptide. MAD reduced the Apnoea–Hypopnoea Index ($p<0.001$) but had no effect on circulating biomarkers compared with the sham device, despite high treatment adherence (6.6 hours/night). Salivary cytokine concentrations seem to be associated with respective blood levels although this association is not very strong. In a recent study, night workers seemed to produce less salivary TNF and IL-1β compared to day workers due to circadian disruption (Reinhardt et al., 2018).

Primary insomnia is usually considered a result of long-term stress, and sleep behaviour is usually closely related to stress. Cortisol levels are increased after a few days of partial sleep loss. Indeed, any awakening from sleep will be associated with a burst of cortisol, and cortisol levels are increased in insomnia (Spath-Schwalbe et al., 1991; Vgontzas et al., 2001). Dahlgren et al., 2005, found very strong relations between subjective sleepiness and the diurnal pattern of salivary cortisol.

Increased oxidative stress can induce damage to the cellular structure and potentially destroy tissues. The relationship between inflammation and oxidative stress is close because the stress could be initiated by the signaling inflammatory biomarkers (Meliante et al., 2023). On the other hand, inflammation could contribute production and secretion of biomarkers, and vice versa, establishing an auto-toxic loop that helps develop a pathophysiologic mechanism in OSA (Lavalle et al., 2024). However, it should be noted that although inflammation is the main stimulus for biomarkers production and secretion, other stimuli also exist, such as intermittent hypoxia, alterations in the expression of genes involved in inflammation, metabolism, adiposity, cigarette smoke, chronic stress, oxidative stress, exposures to toxins and other environmental factors.

2.2.4 Obesity

Obesity is a known risk factor for OSA in adults. From the results of some epidemiological studies, the prevalence of OSA in obese children is in the range of 46% to 55% (Kalra et al., 2005). The mechanism on how obesity contributes to the development of OSA is both mechanical and functional. Using volumetric analysis of

the upper airway in obese children with OSA, Arens et al., 2011, noted larger adenoids, tonsils, and parapharyngeal fat pads in OSA children compared to matched controls. Additionally, obese children may have excess deposition of adipose tissue within the muscles and tissue surrounding the airway, which may alter chest wall (Figure 2.2).

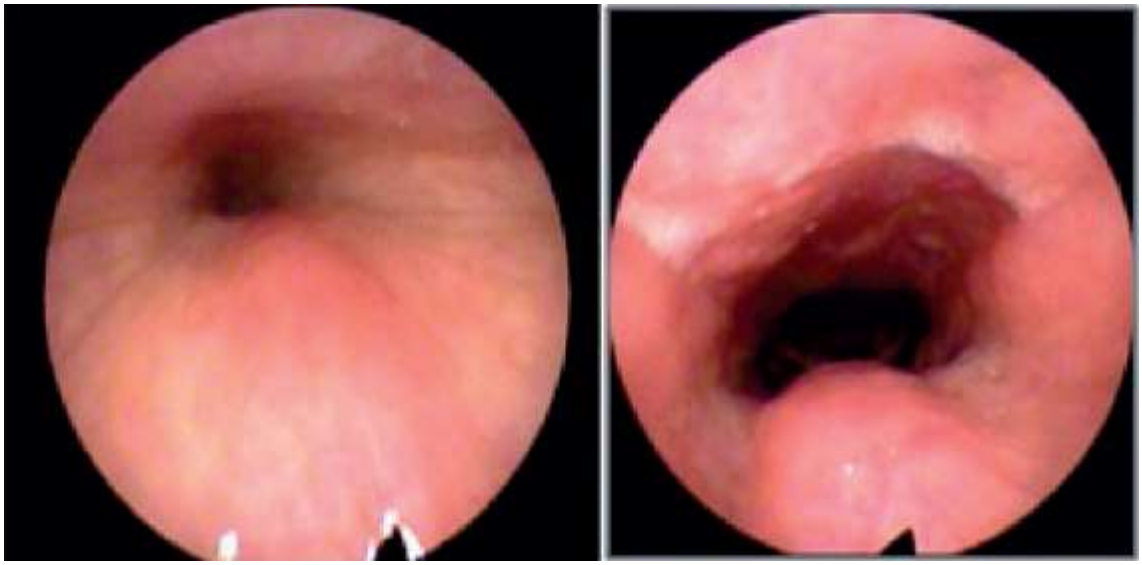

Figure 2.2 Airways at the Level of Oropharynx Constricted (Left) due to Fats Infiltration vs. Normal (Right).

2.3 Diagnosis

2.3.1 Screening Questionnaires for Sleep-Disordered Breathing

Questionnaires are generally considered as screening tools to identify patients who are at higher risk of developing OSA. Phase I screening tools generally include specific preliminary questions to be asked during healthcare maintenance visits. These are developed to help paediatricians recognise the symptoms of snoring and other sleep problems in children. Examples of screening tools include BEARS, Epworth Sleepiness

Scale, and the Ten-Item Sleep Screener (TISS) (Marcus et al., 1992); and the Paediatric Sleepiness Questionnaire (Chervin et al., 2000).

The BEARS is a simple, 5-item paediatric sleep screening tool to detect and identify sleep problems. The BEARS refers to: B – Bedtime: Does my child have trouble going to bed? Or trouble falling asleep?; Excessive Daytime Sleepiness: Is my child difficult to awaken in the morning?; Does my child seem sleepy or groggy during the day?: Does my child often seem tired during the day? (In children, tired may mean moody, hyperactive, "out-of-it", as well as sleepy); A - Awakening During the Night: Does my child awaken during the night and have trouble going back to sleep?; Is anything else interrupting my child's sleep?; R - Regularity and Duration of Sleep: How many hours of sleep does my child need at this age?; What time does my child go to bed and get up on weekdays? On weekends?; Does this allow my child to get enough sleep every day?; S – Snoring: Does my child snore? Loudly? Every Night?; Does my child stop breathing, gasp, or choke during sleep?

The Paediatric Daytime Sleepiness Scale (PDSS – Iowa Sleep Disorder Center) is a self-administered questionnaire with 8 questions. Respondents are asked to rate, on a 5-point scale (0-4), their usual chances of dozing off or falling asleep while engaged in eight different activities. Most people engage in those activities at least occasionally, although not necessarily every day. The ESS score (the sum of 8 item scores) can range from 0 to 24. The higher the ESS score, the higher that person's average sleep propensity in daily life (ASP), or their 'daytime sleepiness'. The questionnaire takes no more than 2 or 3 minutes to answer. It is available in many different languages. Scoring