Pneumopedics: Non-surgical upper airway remodeling for Obstructive Sleep Apnea

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Objectives

• Gain information about Pneumopedics®
• Appreciate the principles of craniofacial epigenetics, which includes epigenetic orthopedics as well as the concept of epigenetic orthodontics
• Understand significance of biomimetic oral appliance therapy

Apply these concepts as a potential cure for Obstructive Sleep Apnea in a multi-disciplinary, dental setting

Marked interaction between craniofacial morphology and upper airway adequacy

Guilleminault and Stoohs, 1990

Do I snore?

Do I need mandibular advancement?

Can we change these phenotypes non-surgically?

Conflict of interest disclosure

Dr Singh is President of Vivos BioTechnologies, Inc.

Vivos has a medical device facility registered with the FDA
All the DNA appliances are FDA registered
The mRNA appliance is FDA cleared for mild to moderate OSA

World Association of Sleep Medicine, Seoul, South Korea
March 2015

A fat mouse (New Zealand Obese) seems to be sleeping upright to protect its upper airway

The standing sleeping mouse
Courtesy: Dr Alan Pack
What about teeth?

Epigenetics is the study of phenotypic changes that occur via mechanisms other than DNA sequence alteration. These changes are mediated by covalent attachments of chemical groups to the DNA and its associated proteins, histones and chromatin.

Types of epigenetic modification include: ADP-ribosylation, acetylation, methylation, phosphorylation, sumoylation and ubiquitination.

WHAT IS EPIGENETICS?


Researchers release most complete mapping of the Human Epigenome to date

The New York Times (February 19, 2015) reports that 200 scientists working on an ambitious federal project have begun to understand the complicated system of switches that regulates genes, turning some on and others off. The scientists hope these discoveries will eventually lead to a deeper understanding of diseases and new ways to treat or cure them.

Their findings are published in 24 papers in Nature and other journals.

WHAT IS PNEUMOPEDICS?

Pneumopedics is the process of non-surgical, upper airway remodeling that may result from treatment with a biomimetic oral appliance.

How does Pneumopedics work?

The biomimetic oral appliance system uses the principles of Epigenetics to activate a person’s naturally-occurring genes to correct deficiencies in the craniofacial region. The tissues in the craniofacial region are slowly redeveloped and remodeled over time, making corrections to the structure of the upper airway, non-surgically. It is a pain-free, minimally invasive process, which uses no drugs, medication or injections.

During the Pneumopedic process, the craniofacial region undergoes structural changes so that the functional space of the upper airway increases volumetrically, allowing for improved function of basic, physiologic processes, such as breathing during sleep. This is the reason that this system of biomimetic oral appliances can be used to treat, reduce and eventually eliminate OSA.

WHAT IS CRANIOFACIAL EPIGENETICS?

Craniofacial epigenetics uses a person’s natural genes to correct and straighten the jaws, teeth, soft tissues and functional spaces, painlessly, using biomimetic appliances

WHAT IS BIOMIMETICS (BIOMIMICRY)?

A science that studies natural models and then uses these designs and processes to solve human problems.
Craniofacial epigenetics is aimed at the overall health of the craniofacial region by providing appropriate treatment protocols that address the underlying etiology of the signs and symptoms of OSA, TMD, malocclusions, etc.

What makes craniofacial epigenetics different from traditional dentoalveolar orthodontics and from rapid palatal expansion?

What makes pneumopedics different from mandibular advancement devices?

Results from midfacial distraction osteogenesis:
Finite-element analysis shows similarity with MMA

Spatial matrix hypothesis

- During growth, spatial and functional alignment of skeletal elements is maintained through remodeling of bony surfaces (including the periodontium) to permit function
- Environmentally- (or genetically-) induced changes (e.g. tooth extraction, digit-sucking etc.) produce changes in early morphologic relationship → new solution (phenotypic variation)
- This ‘new solution’ represents departure from the genetically encoded ‘developmental body plan’ (temporo-spatial patterning)
- Developmental compensation occurs to permit compromised function → malocclusion, TMD, OSA, tori, etc
- Decompensation required through treatment with appropriate spatial signaling to re-establish (genomic) pattern formation for optimal form and function

Singh, GD. Michigan Craniofacial Growth Series, 2004
Singh, GD. British Dental Journal, 2007
What is the dental arch morphology in adults with OSA?

Mean upper arch OSA configuration 7-11% narrower
Mean lower arch OSA configuration 10-11% narrower

Banabilh, Singh et al., J Oral Rehabil. 2009

Case progress with biomimetic DNA appliance

October, 2010
Courtsey: Dr Dennis Alleman

October, 2011

July, 2015
Courtsey: Dr Gary Sacher

August, 2016

Craniofacial effects following DNA appliance treatment:
38 year old adult diagnosed with OSA

After 10 months minimum intermolar width increased from 34mm to 39mm

Singh, Wendling et al. Dent Today 2011

Change in upper airway after 15 months

3D CBCT scan transverse sections

71% increase in upper airway volume from 12889mm$^3$ to 22024mm$^3$
Change in upper airway after 15 months

Decrease in AHI from 24/hr to 2.8/hr after 10 months

38 year old: 12 months DNA appliance therapy

Enhanced craniofacial homeostasis

Case study: Non-surgical cosmetic treatment with health benefits

Singh GD et al. Dent Today 2011

Singh and Cress, Dent Today, 2013
Upper arch: Orthodontic changes

Initial 12 Months

Singh and Cress, Dent Today, 2013

Lower arch: Orthodontic changes

Initial 12 Months

Singh and Cress, Dent Today, 2013

3D CBCT SUPERIMPOSITION

POST = BLUE PRE = GREY

Singh and Cress, 2013

UPPER AIRWAY ANALYSIS

Pre-Treatment Airway Post Treatment Airway

Pneumopedic® effect with no appliance in mouth

Singh and Cress, Dent Today, 2013

Biomimetic effects in adults following epigenetic orthodontic treatment with the DNA appliance

Is there an increased bone width after DNA appliance therapy in adults?

Singh, Heit et al., J Ind Orthod Soc. 2014
Maxillary intermolar width (mm)

<table>
<thead>
<tr>
<th>Patient</th>
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<th>Post-treatment</th>
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<td>NN</td>
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<td>31.88</td>
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<tr>
<td>KR</td>
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<tr>
<td>JD</td>
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<tr>
<td>Mean</td>
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<td>35.55</td>
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</table>

P value = 0.002

---

Maxillary Bone Volume (mm³)

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<td>HF</td>
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<td>21289</td>
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<td>KH</td>
<td>18884</td>
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<td>16689</td>
</tr>
<tr>
<td>KR</td>
<td>12389</td>
<td>17287</td>
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<tr>
<td>JD</td>
<td>21536</td>
<td>21858</td>
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<tr>
<td>Mean</td>
<td>17.3 cm³</td>
<td>19.1 cm³</td>
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</table>

P value = 0.02

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**WHAT MAKES PNEUMOPEDICS DIFFERENT FROM MANDIBULAR ADVANCEMENT DEVICES?**

**Dentoskeletal effects of oral appliance wear in OSA**

**OBJECTIVES**: To evaluate dentoskeletal changes associated with long-term mandibular advancement device (MAD) use in patients with sleep-disordered breathing.

**RESULTS**:

- The maxilla revealed a significant decrease in horizontal position and a significant retroclination of the upper incisors.
- The mandible displayed a significant downward rotation and a proclination of the lower incisors.

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**ABSTRACT**

- To evaluate the long-term effects of tooth-borne and bone-borne surgically assisted rapid maxillary expansion (SARME).
- **Hypotheses**: This prospective cohort study compared 45 consecutive skeletal misshapen non-syndromic patients with transverse maxillary hypoplasia. In 28 patients, a tooth-borne distractor (Maxflex) was used for expansion, whereas in the remaining 17 a bone-borne distractor (transpalatal distractor, TPD) was used. Cone beam computed tomography (CBCT) scans were performed before treatment (T1) and 22 months later, after fixed appliance treatment (T2). 3D models were constructed from CBCT data and superimposed using voxel-based matching. Distance maps between the superimposed models were compared to evaluate the amount of skeletal changes.

**Results**: The distance maps of the superimposed models showed positive distances on the right and left anterior maxillary segments of the maxilla indicating a forward movement of the anterior maxillary segment. There was a statistically significant difference between T1 and T2 for the three anterior segments (p values ranged between 0.001-0.02). Conclusions: Bone-borne and tooth-borne SARME were found to produce comparable results at the end of fixed appliance treatment regarding skeletal changes.

© 2012 European Association for Cranio-Maxillo-Facial Surgery
Example of non-surgical, biomimetic procedure:

Pre-treatment conditions

Pre-treatment and progress comparison

Example of non-surgical, biomimetic procedure:

Singh GD. Dental sleep medicine in the 21st Century. Sleep Scholar, 2015

Superimposition of 3D CBCT scan mid-sagittal section

Increase in upper airway (retropalatal/retroglossal) distances
Further research questions

- Is there an increased nasal cavity width after DNA appliance therapy in children/adults?
- Is there an increased nasal cavity volume after DNA appliance therapy in children/adults?

First pediatric case: One year progress

Distance between nasal septum and inferior conchae

First adult case: One year progress

Distance between nasal septum and inferior conchae

Patients with rhino-sinusitis are more likely to develop it on the side with a more laterally positioned uncinate process

The natural maxillary sinus has a sophisticated defense system

- Uncinate/membranum effectively isolates the maxillary from nasal airflow
- Maxillary sinus is protected from contaminated environmental air
- Maxillary sinus produces and stores high concentrations of Nitric Oxide (NO)
- NO kills bacteria, viruses, fungus
- NO stimulates ciliary activity

Courtesy: Brian H. Weeks, MD

Research questions
- What about nasal obstruction in adults?
- Why does nasal collapse happen?

Ostia are widely patent
Sinus is well-ventilated
Clearly not functional

Objective
The aim of this study is to evaluate changes in nasal airway volume in adult patients following biomimetic oral appliance therapy.

Methods
After obtaining informed consent, we undertook 3D cone-beam (CBCT) scans of 11 consecutive, adult patients (mean age approx. 38 years) prior to and 18 months after biomimetic oral appliance therapy.

These cases had all been diagnosed with clinical midfacial hypoplasia without congenital malformation.

Volumetric reconstruction of the nasal cavity
To acquire the nasal cavity volume, volumetric, 3-D reconstruction of the nasal cavity was undertaken between the anterior and posterior nasal spines, extending superiorly from the palatine process of the maxilla and the palatine bone to the cribiform plate of the ethmoid bone.

Laterally, the maxillary sinuses were trimmed out at their junction with the nasal cavity on the 3D CBCT data.
Volumetric reconstruction of the nasal cavity

Measurement of nasal cavity volume

The nasal cavity volume was calculated in all cases. The findings were subjected to statistical analysis, using paired t-tests.

Improved nasal symmetry and functional space

Volumetric changes of the nose and nasal airway 2 years after tooth-borne and bone-borne surgically assisted rapid maxillary expansion

Nasal airway changes in adults (cm³) after 18 months

<table>
<thead>
<tr>
<th>Subject</th>
<th>Pre-Treatment</th>
<th>Post-Treatment</th>
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<tbody>
<tr>
<td>ASE</td>
<td>33.596</td>
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<tr>
<td>FE</td>
<td>56.001</td>
<td>55.344</td>
</tr>
<tr>
<td>HF</td>
<td>50.067</td>
<td>43.624</td>
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<tr>
<td>CH</td>
<td>55.534</td>
<td>30.381</td>
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<tr>
<td>KH</td>
<td>43.624</td>
<td>36.756</td>
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<tr>
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<tr>
<td>AT</td>
<td>47.144</td>
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<td>Mean</td>
<td>39.8 cm³</td>
<td>42.3 cm³</td>
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<tr>
<td>p value</td>
<td>&lt; 0.05</td>
<td></td>
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</table>

Table Clinic Prize 2014


Surgical procedure:

The non-surgical procedure was applied to all patients and has been described in detail in a previous study. Briefly, non-surgical maxillary expansion was performed using two miniscrews placed buccal to the lateral incisors. Each screw was connected to a modified acrylic miniscrew splint. Non-surgical maxillary expansion was performed using a modified acrylic miniscrew splint which was designed to cater for the individual patient’s needs. The acrylic splint was connected to a modified acrylic splint which was designed to cater for the individual patient’s needs. The acrylic splint was connected to a modified acrylic splint which was designed to cater for the individual patient’s needs.
Comparison of Hyrax and DNA appliance protocols

<table>
<thead>
<tr>
<th></th>
<th>Nada et al. 2013</th>
<th>Singh et al. 2014</th>
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<tbody>
<tr>
<td>Surgical procedure</td>
<td>LeFort I osteotomy</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Midline osteotomy</td>
<td>Pterygomaxillary osteotomy</td>
</tr>
<tr>
<td>Treatment time</td>
<td>22 months</td>
<td>18 months</td>
</tr>
<tr>
<td>Wear time</td>
<td>24hrs per day</td>
<td>16hrs per day</td>
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<tr>
<td>Sample size</td>
<td>13</td>
<td>11</td>
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<tr>
<td>Nasal volume increase</td>
<td>9.7%</td>
<td>5.6%</td>
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<td>Diastema formation</td>
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<td>No</td>
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Further research questions

What are the effects of increased nasal cavity volume after DNA appliance therapy in adults diagnosed with OSA?

The aim of this study is to test the hypothesis that the upper airway can be enhanced in adults diagnosed with OSA so that CPAP therapy might potentially become avoidable.

Methods

• 11 consecutive adults aged >21yrs.
• Diagnosed with mild to moderate OSA, following HST interpreted by a Board certified sleep physician.
• Each subject was treated using biomimetic oral appliance therapy by a dentist (TG) with advanced training in dental sleep medicine.
• The mean AHI of the study sample was calculated prior to and after treatment with no appliance in the mouth when both sleep studies were done.

Results

<table>
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<tr>
<th>Subject</th>
<th>Pre-AHI</th>
<th>Post-AHI</th>
<th>Months</th>
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<tr>
<td>A</td>
<td>5.4</td>
<td>3.1</td>
<td>16</td>
</tr>
<tr>
<td>B</td>
<td>18.9</td>
<td>7.1</td>
<td>19</td>
</tr>
<tr>
<td>C</td>
<td>21</td>
<td>2.5</td>
<td>13</td>
</tr>
<tr>
<td>D</td>
<td>13.7</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>E</td>
<td>8.2</td>
<td>3.7</td>
<td>4</td>
</tr>
<tr>
<td>F</td>
<td>21.3</td>
<td>12.8</td>
<td>1</td>
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<td>G</td>
<td>5.7</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>H</td>
<td>5.1</td>
<td>5.4</td>
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<td>7</td>
</tr>
<tr>
<td>J</td>
<td>12.3</td>
<td>1.7</td>
<td>4</td>
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<tr>
<td>K</td>
<td>7.4</td>
<td>1.0</td>
<td>6</td>
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<td>Mean</td>
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<td>7.8</td>
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<tr>
<td>Std</td>
<td>6.9</td>
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<tr>
<td>Mean AHI improvement</td>
<td>68.4%</td>
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</table>

Patient History and Physical Findings

• A 27 year old female reported to our office with TMD symptoms, was screened for OSA and was diagnosed with severe obstructive sleep apnea with an initial AHI of 105/hour
• Level 1 sleep study showed AHI 118/hr
• Referred to ENT for tonsillectomy. Reduced AHI 70/hr and controlled on CPAP, which she did not like.
• Initiated DNA appliance therapy for 9 months (combined with CPAP).
• Resulted in AHI of 1/hour without CPAP or DNA appliance in situ.

Pulmonologist’s Report

<table>
<thead>
<tr>
<th>Appliance</th>
<th>Pre AHI</th>
<th>Post AHI</th>
<th>Mths</th>
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<tbody>
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<td>DNA 56.5</td>
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<td>DNA 40</td>
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<td>DNA 41</td>
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<td>DNA 35.5</td>
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<td>10</td>
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<td>DNA 39.1</td>
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<td>DNA 50.7</td>
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<td>mRNA 50.8</td>
<td>Severe</td>
<td>26.6</td>
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Mean 45.9 16.5 9.7
Std 10.5 8.8 1.9

p value  p < 0.001

Singh, Griffith and Cress, J Sleep Disorders Therapy, 2016
More recent data: Long-term follow-up

CONCLUSIONS

• Non-surgical upper airway remodeling can be obtained in adults, and suggests that genetically-encoded developmental mechanisms may be epigenetically modulated by biomimetic oral appliances to enhance the upper airway in patients with OSA.

• These findings may help dentists in the management of adults and children diagnosed with obstructive sleep apnea, using Pneumopedics® and craniofacial epigenetics.

Thanks for your attention!