DENTAL AND OTOLOGIC PROBLEMS IN CLEFT LIP AND PALATE PATIENTS FROM NORTHERN FINLAND

CLEFT ASSOCIATED PROBLEMS

Ville Lehtonen
VILLE LEHTONEN

DENTAL AND OTOLOGIC PROBLEMS IN CLEFT LIP AND PALATE PATIENTS FROM NORTHERN FINLAND

Cleft associated problems

Academic dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium 3 of Oulu University Hospital (Kajaanintie 50), on 2 September 2016, at 12 noon

UNIVERSITY OF OULU, OULU 2016
Lehtonen, Ville. Dental and otologic problems in cleft lip and palate patients from Northern Finland. Cleft associated problems
University of Oulu Graduate School; University of Oulu, Faculty of Medicine; Medical Research Center Oulu
University of Oulu, P.O. Box 8000, FI-90014 University of Oulu, Finland

Abstract
Patients with orofacial clefts must overcome problems associated with their deformity including multiple surgeries, facial scarring, speech difficulties, dental problems and hearing loss. This study considered dental and hearing problems faced by cleft lip and palate patients in Northern Finland. The research aimed to determine prevalence of dental anomalies in cleft children, assess restorative treatment need and examine dental treatment necessary under general anesthesia. Other aims were to identify middle ear problems, need for ventilation tubes (VTs) among cleft children and examine the relationship between cleft severity, palatoplasty technique and hearing outcomes in cleft children aged between 3 and 9-years.

The material comprised 214 cleft patients treated at Oulu University Hospital. In the dental study 26.6% had at least one dental anomaly while 17.9% had 2 or 3, most commonly missing or supernumerary teeth. In the general anesthesia study 11.5% had a syndrome and 52.4% of those with a syndrome aged 6-years-old needed restorative treatment. General anesthesia was required for dental treatment in 17.5% of cleft patients, mostly in those with a syndrome. In the middle ear study 79% had secretions in the middle ear during the study period. On average 3 VTs were placed in each patient. The prevalence of tympanic perforation was 35.9% and cholesteatoma occurred in 3.3%. In the hearing study pure tone average did not significantly differ between right and left ears and was unrelated to cleft severity or palatoplasty technique.

Based on the dental study the severity of clefting increased with the prevalence of dental anomalies. The general anesthesia study found that need for restorations increased with cleft severity. The presence of a syndrome increased the need for dental treatment under general anesthesia. The middle ear study found that patients with cleft lip and palate and isolated cleft palate had more extensive clefts affecting Eustachian tube function with more frequent middle ear problems requiring more VTs than isolated cleft lip patients. Continuous presence of VTs increased the prevalence of tympanic perforation and cholesteatoma. The hearing study concluded that most of the 3 to 9-year-old cleft patients had normal hearing thresholds unaffected by cleft severity or palatoplasty technique.

Keywords: caries, cholesteatoma, cleft lip and palate, dental anomalies, hearing outcomes, tympanic perforation, ventilation tubes
Lehtonen, Ville, Pohjois-Suomessa hoidettujen huuli- ja suulakihalkiolasten korvien ja Hampaidon ongelmat. Halkio-ongelmat Pohjois-Suomessa
Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Medical Research Center Oulu
Oulun yliopisto, PL 8000, 90014 Oulun yliopisto

Tiivistelmä

Aineisto koostui 214 halkiopotilaasta jotka hoidettiin Oulun yliopistollisessa sairaalassa. Potilaista 26,6%:lla oli vähintään yksi ja 17,9%:lla kaksi tai kolme hammasanomaliaa. Yleisin anomalia oli puuttuvat tai ylilukuiset hampaat. Yleisanestesiassa hoidetuista potilaista 11,5%:lla oli syndrooma eli oireyhtymä, kaikkiaan yleisanestesiä tarvitsi 17,5%. 6-vuotiaista syndroomapotilaista 52,4% tarvitsi hampaiden korjaavaa hoitoa. Korvien tutkimuksessa 79%:lla potilaista oli erittävä välkorvissa tutkimusjakson aikana. Jokaiselle potilaalle liitettiin ilmastointiputket keskimäärin 3 kertaa. Tärykalvon perforaatio havaittiin 35,9%:lla ja kolesteatooma todettiin 3,3%:lla. Oikean ja vaseman korvan välillä ei ollut merkittäviä eroja kuulontutkimustuloksissa eikä niillä havaittua yhteyttä halkion vakavuuden tai suulaen leikkaustekniikan kanssa.


Asiasanat: hammasanomaliat, huuli- ja suulakihalkio, ilmastointiputket, karies, kolesteatooma, kuulotulos, perforaatio
To my family, friends and colleagues
Believe you can and you’re halfway there. –T.R.
Acknowledgements

This thesis work was carried out at the Department of Oral and Maxillofacial Surgery, Institute of Dentistry, Faculty of Medicine, University of Oulu and University Hospital of Oulu, during the years 2014-2016. I wish to express my thanks to these institutes for providing excellent research facilities.

I owe my deepest gratitude to my supervisors and mentors Professor György K. Sándor, M.D., D.D.S., Ph.D., Leena Ylikontiola, M.D., D.D.S., Ph.D., and Professor Vuokko Anttonen, D.D.S., Ph.D., who provided me an opportunity to join their team as a student, and who gave access to the research facilities. Without their precious support, enthusiasm, encouragement and continuous optimism it would not have been possible to carry out this project.

I am grateful to my main supervisor, Professor György Kálmán Sándor, for his patience and support which helped me overcome many difficult problems and situations in order to finish this dissertation. I am indebted to Professor Sándor for teaching me how to do research, for holding me to a high research standard and enforcing strict confirmations for each research result. I have learned a great deal from him, which I am sure will be useful in different stages of my life. I respectfully express my honest and humble thanks to Professor Sándor for bringing my dreams into reality. Köszönöm szépen barátom.

I am so very grateful to my second supervisor, Dr. Leena Ylikontiola, for all her patience, guidance, encouragement and advice which she provided freely throughout my time as her student. Her leadership into the world of cleft surgery has been an invaluable input for this thesis and for my future studies and career.

I take immense pleasure in expressing my sincere and deep sense of gratitude to my third supervisor, Professor Vuokko Anttonen. Vuokko was the reason why I decided to begin this project and my research career. She has been helpful in providing advice several times during my graduate school career. I am also thankful to her for encouraging the use of consistent notation and correct grammar in my writings and for carefully reading and commenting on several revisions of this study.

My sincere thanks are due to the reviewers of this dissertation, Professor Richard Welbury, D.D.S., Ph.D. and Docent Tero Soukka, D.D.S., Ph.D., for their careful revisions and valuable criticism of the manuscript, for which I am most grateful. They greatly improved this work at its final stages.

I wish to express my deepest gratitude and thanks to my co-authors Riitta Lithovius D.D.S., Ph.D., Virpi Harila D.D.S., Ph.D., Sari Koskinen D.D.S. and
Timo Autio M.D., for their always friendly and most valuable help with the four publications of this thesis. My special thanks are due to Paula Pesonen MSc, for her valuable input into the statistical analysis and Seija Leskelä, for her assistance in the illustration of this thesis.

I am deeply grateful to all my colleagues and other staff in the Department of Oral and Maxillofacial Surgery at the University of Oulu and especially the personnel of the Husu cleft team. It has been a wonderful time to work with you all.

I would like to thank my former employer Jyväskylä Public Health Care Centre, and chiefs from there Pirkko Paavola, D.D.S., Ph.D. and Teemu Taipale, D.D.S., Ph.D., for giving me the opportunity to work full time and to work with this thesis at the same time. I am also very grateful to my current employer Jyväskylä Central Hospital and all my colleagues from there, especially my chief, Veikko Tuovinen D.D.S., Ph.D. for his kind patience during this process.

I am sincerely thankful to all my close friends, the relaxing moments together with them was worth more than I can express on paper.

Finally, I express my warmest thanks to my mom and dad for all love and support during my life. They selflessly encouraged me to explore new directions in life and let me pursue my own interests. I also want to thank my both sisters for our great time together and trust in me to have the opportunity to be godfather of their lovely children Lilia and Mila.

This work has been financially supported by Finnish Dental society Apollonia, EVO grants from Oulu University Hospital and Medical Research Center Oulu. I sincerely thank for them for their support.

Jyväskylä, May 2016

Ville Lehtonen
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCLP</td>
<td>Bilateral cleft lip and palate</td>
</tr>
<tr>
<td>CL</td>
<td>Cleft lip</td>
</tr>
<tr>
<td>CLA</td>
<td>Cleft lip and alveolus</td>
</tr>
<tr>
<td>CLP</td>
<td>Cleft lip and palate</td>
</tr>
<tr>
<td>CP</td>
<td>Cleft palate</td>
</tr>
<tr>
<td>DGA</td>
<td>Dental general anesthesia</td>
</tr>
<tr>
<td>DMFT</td>
<td>Decayed missing and filled teeth</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile Range</td>
</tr>
<tr>
<td>LCLP</td>
<td>Left cleft lip and palate</td>
</tr>
<tr>
<td>MIH</td>
<td>Molar incisor hypomineralization</td>
</tr>
<tr>
<td>mtDNA</td>
<td>Mitochondrial DNA</td>
</tr>
<tr>
<td>NSCLP</td>
<td>Non-syndromic cleft lip and palate</td>
</tr>
<tr>
<td>OHRQL</td>
<td>Oral health related quality of life</td>
</tr>
<tr>
<td>OME</td>
<td>Otitis media with effusion</td>
</tr>
<tr>
<td>OUH</td>
<td>Oulu University Hospital</td>
</tr>
<tr>
<td>PCL</td>
<td>Partial cleft lip</td>
</tr>
<tr>
<td>PTA</td>
<td>Pure tone average</td>
</tr>
<tr>
<td>RCLP</td>
<td>Right cleft lip and palate</td>
</tr>
<tr>
<td>SCP</td>
<td>Soft cleft palate</td>
</tr>
<tr>
<td>SMCP</td>
<td>Submucous cleft palate</td>
</tr>
<tr>
<td>TGFβ</td>
<td>Transforming growth factor beta</td>
</tr>
<tr>
<td>UCLP</td>
<td>Unilateral Cleft lip and palate</td>
</tr>
<tr>
<td>VT</td>
<td>Ventilation tube</td>
</tr>
<tr>
<td>VWS</td>
<td>Van der Woude syndrome</td>
</tr>
</tbody>
</table>
List of original papers

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals: I to IV


Contents

Abstract
Introduction
Acknowledgements
Abbreviations
List of original papers
Contents
1 Introduction
2 Review of the literature 19
  2.1 Cleft classifications ................................................................. 19
  2.2 Normal lip and palatal anatomy and anatomy in clefts ................. 19
  2.3 Palatal development ................................................................. 21
  2.4 Cleft etiology ........................................................................... 22
     2.4.1 Genetics ........................................................................... 23
     2.4.2 Syndromes ........................................................................ 23
     2.4.3 Environmental factors ....................................................... 24
  2.5 Incidence of clefting ................................................................. 24
     2.5.1 Cleft palate (isolated) ......................................................... 25
     2.5.2 Cleft lip and palate ............................................................ 27
     2.5.3 Cleft lip (isolated) ............................................................. 28
     2.5.4 Cleft lip and alveolus ......................................................... 29
     2.5.5 Submucous cleft palate ...................................................... 30
  2.6 Cleft related problems ............................................................. 31
     2.6.2 Dental Problems ............................................................... 31
     2.6.3 Otologic problems ............................................................ 42
  2.7 Cleft management ................................................................. 44
3 Aims of the study
4 Material and methods
  4.1 Subjects and methods ............................................................ 49
  4.2 Dental anomalies (study I) ...................................................... 49
  4.3 Caries and dental general anesthetics (study II) .......................... 50
  4.4 Middle ear findings and the need for ventilation tubes (study III) .... 51
  4.5 Cleft severity and hearing outcomes (IV) .................................. 51
  4.6 Statistics (studies I, II, III & IV) ............................................... 52
5 Results
  5.1 Dental anomalies (study I) ...................................................... 55
5.2 Caries and dental general anesthetics (study II) ........................................ 56
5.3 Middle ear findings and the need for ventilation tubes (study III) .......... 58
5.4 Cleft severity and hearing outcomes (study IV) ..................................... 59

6 Discussion

6.1 Dental anomalies (study I) ................................................................. 61
6.2 Caries and dental treatment under general anesthesia (study II) .......... 63
6.3 Middle ear findings and the need for ventilation tubes (study III) ....... 66
6.4 Cleft severity and hearing outcomes (study IV) ..................................... 68
6.5 Strengths and Weaknesses of the four current studies (studies I, II, III & IV) ........................................................................................................... 70
6.6 Future directions .................................................................................. 71
   6.6.1 3D photography of infants with CLP ............................................. 71
   6.6.2 Tissue engineering in cleft care .................................................... 72
   6.6.3 Mitochondrial DNA and genetics .............................................. 73
   6.6.4 Eurocleft .................................................................................. 73
   6.6.5 Oral health related quality of life study ...................................... 74
   6.6.6 Future longitudinal continuation of studies I, II, III & IV .......... 74

7 Conclusions
References
Original Publications
1 Introduction

Clefting deformities, particularly isolated cleft palate (CP) are unusually common in Northern Finland (Lithovius et al. 2014a). Patients with orofacial clefts including cleft lip and palate (CLP), cleft lip (CL), cleft lip and alveolus (CLA) as well as cleft palate must cope with a heavy burden of care together with their families. This is due to the numerous potential problems associated with their congenital deformity. Quality of life measures reflect their burden with poorer scores compared to their non-cleft peers (Kortelainen et al. 2015).

Cleft patients may face many problems. They include infant feeding problems (Britton et al. 2011), multiple surgeries, visible facial scarring, nasolabial deformity and problems with appearance. This may subject cleft individuals to cruel teasing by their peers of school (Bennun et al. 2015).

Speech problems, specifically difficult to understand hyponasal speech may be found in those patients with tissue deficiency or abnormal anatomic relationships in the orpharynx and nasopharynx following palatoplasty (Lithovius et al. 2014b). Hyponasal speech may also be found in patients with residual oral-nasal fistula (Lithovius et al. 2014c).

Dental problems including oligodontia, supernumerary teeth, malformed teeth, hypoplastic teeth and hypomineralized teeth have been noted in cleft patients (Al Jamal et al. 2010). From an orthodontic point of view the presence of a repaired palatal cleft may result in severe transverse and antero-posterior maxillary hypodevelopment (Harila et al. 2013).

Palatal clefts may result in abnormal nasopharyngeal anatomy and give rise to abnormal muscle attachments. These abnormal attachments may cause impaired Eustachian tube function, leading to chronic middle ear effusion and conductive hearing loss (Bütow et al. 1991). While advances have been made in cleft care (Semb et al. 2005, Behnia et al. 2009) there are still many areas where the understanding of this complex deformity and its far reaching consequences needs to be expanded.

This series of studies serves as a focused look at two of the major problems associated with clefting. Dental problems including dental malformations, restorative treatment need and the magnitude of dental treatment necessary under general anesthesia are analyzed. In addition middle ear findings, ventilation tube placement and hearing outcomes are considered and viewed with the backdrop being Northern Finland.
2  Review of the literature

2.1  Cleft classifications

Several methods have been used in attempts to classify clefts. Tessier described a landmark classification system of craniofacial clefting using 14 facial meridians (Tessier 1976). The meridian numbering corresponds to the extent and location of the cleft. This method can be used to describe all craniofacial clefts.

Later Kriens described the LAHSAL method for classification of orofacial clefts (Kriens 1989). The LAHSAL system is a diagrammatic classification of cleft lip and palate. The first character corresponds to the patient’s right lip and the last character corresponds to the left lip. LAHSAL codes refer to a complete cleft when capitalized or large characters are used. An incomplete cleft is referred to when a small character is used. Tolarová & Servenka classified orofacial clefts into nine different groups according to the best estimate of etiological origin or individual diagnosis (Tolarová & Servenka 1998).

Liu et al. described a simple and precise classification for cleft lip and palate. Five Arabic numerals denoted the anatomic description of the cleft components in the following order of right lip, right alveolus and primary palate, secondary palate, left alveolus and primary palate, and left lip. The extension of the cleft was marked using the numerals 0 to 4 (Liu et al. 2007). Elnassry divided clefts in seven different classes: Class I: Unilateral cleft lip Class II: Unilateral cleft lip and alveolus Class III: Bilateral cleft lip and alveolus Class IV: Unilateral complete cleft lip and palate Class V: Bilateral complete cleft lip and palate Class VI: Cleft hard palate Class VII: Bifid uvula (Shah et al. 2011).

At the present time clefts are divided in two different main groups: craniofacial and orofacial clefts. Orofacial clefts include cleft lip (CL), cleft lip and palate (CLP) and cleft palate (CP). The International Classification of Diseases (ICD-10) is used worldwide as a method for the classification of clefts and other diseases. Group Q35 involves a palatal cleft, Q36 includes a cleft lip and Q37 indicates a cleft lip and palate (Taub & Silver 2016).

2.2  Normal lip and palatal anatomy and anatomy in clefts

The upper and lower lip musculature mainly consists of the circular and sphincter like orbicularis oris muscle components. Facial muscles are also attached to the
corner of the mouth, which pull the corners up or down during the vast array of facial movements. The muscular ring is covered by soft connective tissue and skin. In the middle of the lip, under the nasal septum is the philtrum, a smooth notch between both raised right and left skin crests. The anterior nasal spine can be asymmetric in cleft patients and is indicated by the raised skin crests of the philtrum. This is where a cleft lip is found, present either on one side or bilaterally on both sides. Nasal cartilage forms the nostrils and the tip of the nose. The medial wall of the nose is the septum, being the wall between the two nostrils and the columella (Haapanen & Heliövaara 1998, Grabb et al. 1971).

In a unilateral cleft lip, the continuity of the muscle ring is broken and the muscle fibres attach incorrectly to the edges of the cleft. The counterforce is missing as the cheek muscles attach to the corners of the mouth, which is why cleft children have a wider smile than usual. The edge of the nostril on the cleft side is attached to the edge of the cleft, and it flattens out the lower lateral cartilage from its normally curved position. At the same time the tip of the nose is lower on the side of the cleft. On the opposite side of the cleft, the musculature is attached to the nasal septum, and as a result of muscular tension, the front of the nasal septum is drawn towards the healthy side. The structure of the nasal septum is mainly normal, but skewed, as is the cartilage in the septum (Haapanen & Heliövaara 1998, Grabb et al. 1971).

The front of the palate consists of thin but solid bone. The hard palate is part of the upper jaw. Its upper side forms the floor of the nasal meatus and nasopharynx. The back of the palate is the soft palate. The hard and soft palate are covered by mucous membrane. In the hard palate this consists of attached mucosa whereas in the soft palate the lining mucosa is loose or mobile unattached mucosa which covers the muscles that allow movement of the palate. At the back of the soft palate is the uvula. The soft palate’s musculature includes the levator veli palatini, the tensor veli palatini, the palatoglossus, the palatopharyngeus and the musculus uvulae (Hansen 2010, Bardach et al. 1999). The muscles of the soft palate and throat form a ring, which lifts the palate towards the posterior wall of the nasopharynx as it contracts (Haapanen & Heliövaara 1998) (Table 1).

Regardless of the cleft type, an important structural anomaly in a cleft palate is that the muscles of the soft palate are attached to the wrong part of the hard palate. The interference from the clefting renders the muscles to be unable to attach to each other in the midline. This means that the muscular rings of the oropharynx and nasopharynx are not closed and cannot function properly (Haapanen & Heliövaara 1998, Grabb et al. 1971).
Table 1. The extent of complete clefts.

<table>
<thead>
<tr>
<th>Cleft type</th>
<th>Nostril</th>
<th>Lip</th>
<th>Dental arch</th>
<th>Incisive Foramen</th>
<th>Hard palate</th>
<th>Soft palate</th>
<th>Uvula</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLP</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CLA</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CL</td>
<td>X</td>
<td>X</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CP</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SMCP</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>X*</td>
<td>X*</td>
<td>X*</td>
<td></td>
</tr>
</tbody>
</table>

X*=Palate is covered by mucosa, CLP=Cleft lip and palate, CL=Cleft lip, CP=Cleft palate, CLA=Cleft lip and alveolus, SMCP=Submucous cleft palate.

2.3 Palatal development

The human face develops during the first weeks of pregnancy. The development of the head and face is one of the most complex and tightly controlled events during embryonic development (Reddy et al. 2014, Garib et al. 2015).

The maxillary process (MXP) and frontonasal process (FNP) are composed of mesenchyme derived from the neural crest, and bound externally by a thin layer of epithelium derived from ectoderm. Development of the midface begins with formation of the MXP and FNP. Fetuses develop the FNP by the end of 5 weeks of pregnancy in humans. The forehead forms by the frontal portion of the FNP. The FNP is separated into frontonasal process, medial nasal process (MNP) and lateral nasal process (LNP) (Table 2).

The primary palate forms by the growth and fusion of the lateral nasal, medial nasal and maxillary process (Agrawal et al. 2014, Graf et al. 2015, Wu et al. 2011). Secondary palate formation begins at the sixth week of pregnancy in humans with the emergence of palatal primordia from the maxillary process (MXP). The palatal shelves grow vertically alongside the tongue and reorganize to assume a horizontal position when the mandible begins growing in length providing space for the tongue to descend. The palatal shelves then fuse to form the secondary palate (Parada et al. 2012, Agrawal et al. 2014).

Incorrect fusion or growth of the palatal shelves may result in a cleft of the secondary palate phenotype (Agrawal et al. 2014). During the 9th week in pregnancy, the right and left palatal shelves grow toward each other and make contact in the midline. The secondary palate meets the posterior part of the primary palate and fuses together forming the final palate, including both soft and hard parts. Fusion of the palatal shelves is completed by the 12th week of pregnancy (Parada
et al. 2012). Interruption of any stage during palatal development for example blocked fusion, failed or delayed elevation, and defective palatal shelf growth, can result in cleft palate with or without cleft lip (Wenli Yu et al. 2009).

Table 2. Timetable of lip and palatal development.

<table>
<thead>
<tr>
<th>W</th>
<th>Lip and palatal development</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Development of facial structures begins</td>
</tr>
<tr>
<td>5</td>
<td>Primary palate formation</td>
</tr>
<tr>
<td>6</td>
<td>Closure of the lip is completed</td>
</tr>
<tr>
<td>7</td>
<td>Secondary palate formation</td>
</tr>
<tr>
<td>8</td>
<td>Development of the hard palate is completed</td>
</tr>
<tr>
<td>9</td>
<td>Completion of palate</td>
</tr>
<tr>
<td>10</td>
<td>Fusion of the soft palate and uvula is finished</td>
</tr>
</tbody>
</table>

W=Weeks of pregnancy

2.4 Cleft etiology

CLP is an abnormality whose etiology is considered to be multifactorial (Tolarova & Cervenka 1998). Several genes and environmental factors contribute to its occurrence. CLP is also associated as a part of numerous syndromes (Wiechkowska et al. 2015).

Non-syndromic CLP (NSCLP) is genetically different from those of syndromic clefts and the prevalence of NSCLP is 70% of all cases with oral clefts (Murthy et al. 2014).

There is contradictory information regarding the distribution of the aetiology. According to Reddy et al. 30% of factors resulting in CLP are genetic, and 70% are related to environmental factors (Reddy et al. 2014). In a cross-sectional study conducted in Pakistan, the aetiological factors of the clefts could not be identified in 82% of the cases. In 6% of the cases the cause was environmental and in 12% it was genetic (Yaqoob et al. 2013). The etiology of NSCLP is unclear with both environmental and genetic contributions. It is hard to identify etiologic specific factors. While multiple potential risk factors have been studied strong risk factors have not yet been identified (Xu et al. 2015).
2.4.1 Genetics

Genetics play an important role in the etiology of the clefts although most of the causative genes are unknown (Rautio et al. 2010). Chromosomal abnormalities and mutations in single genes are the most common reason underlying syndromic CLP (Brito et al. 2012).

There can be a strong family history as a cleft deformity can be inherited. The risk of inheritance from a cleft parent to a child and from a cleft child to a sibling is approximately 4%. The risk is 0.6% for second degree relatives. If several family members have clefts, the inheritance risk is increased. An inherited cleft palate can only result in a cleft palate, but an inherited cleft lip can also result in a cleft palate (Sivertsen et al. 2008).

The MSX1 gene includes instructions for preparing a regulatory protein, which adjusts the activity of other genes and works in early developmental stages by controlling the morphogenesis and development of the skull during dental development. TGFβ is involved in the development of the palate, and isoforms 1, 2 and 3 are expressed at this stage in development. It has been found that a mutation in these genes predisposes to the development of a cleft (Mehrotra 2015, Reddy et al. 2014, Wang et al. 2016).

The IRF6 gene encodes a member of the IRF family. Mutations in this gene can result in X-linked CLP, Van der Woude syndrome (VWS), ectodermal dysplasia and popliteal pterygium syndrome. This IRF6 gene has an important role in palate formation (Mehrotra 2015, Ibarra-Arce et al. 2015).

The RUNX2 gene is a potential factor for the emergence of NSCLP (Wu et al. 2012). Both genetic and molecular studies on humans and mice have shown RUNX2 to be a critical regulator of bone and tooth formation. Heterozygous mutations in RUNX2 may result in supernumerary teeth, delayed eruption and cleidocranial dysplasia which includes skeletal defects (Mehrotra 2015).

2.4.2 Syndromes

Lip and palate clefts are just one sign among many others which are present in more than 300 syndromes (Rautio et al. 2010, Cameron & Widmer 2008). In fact cleft associated syndromes are thought to number over 500 (Brito et al. 2012). Studies on CLP have reported that the range of cleft patients with syndromes is 14.8% to 59.5% (McDonnel et al. 2014, Monillé et al. 2015). For example in Ireland the rate was reported as 14.8% of cleft patients being afflicted with a syndrome (McDonnell
et al. 2014). Previously published reports indicated that the clefts among the children with syndromes were not more complex than those in non-syndromic patients. Commonly reported cleft associated syndromes included Pierre Robin, Treacher Collins, Fragile X, Blepharo-cleido, Kabuki, Apert, Van der Woude, CATCH22 or Down syndrome (Venkatesh 2009, Martelli-Junior et al. 2009, Leslie & Marazita 2013, Gangopadhyay et al. 2012, Lee et al. 2013). The most common syndrome found in Finnish cleft children was VWS. Its prevalence was estimated at 1:34,000 births. In Finnish cleft children, the prevalence of VWS was 2% (Koillinen et al. 2001).

2.4.3 Environmental factors

Many congenital deformities have been found to be linked with environmental factors such as maternal smoking and alcohol use during pregnancy (Aizenbud et al. 2013). Clefts may also be associated with low birth weight, diet, vitamin hypoconsumption and drug use during pregnancy (Gonzales et al. 2008).

There were also reports linking several environmental factors which increased the risk of clefting (Wieckowska et al. 2015). Those factors included maternal exposure to smoking, medications, contact with chemicals at home or at work, drinking contaminated water, alcohol use, living in a lead, sulfur or air-polluted area, living near dangerous waste disposal areas, or having folic acid or vitamin deficiencies.

Also late maternal age or multiple pregnancies have been found to have a negative impact on the risk of clefting (Wieckowska et al. 2015). Still others reported that antibiotic use during pregnancy, twin births, the use of antiemetic medication, frequent morning sickness, severe colds or flu, and also passive smoking were associated with non-syndromic clefts (Sabbagh et al. 2015).

Environmental factors varied in different parts of the world. For instance the prevalence of diabetes, a considerable risk factor during pregnancy for development of clefts, varied greatly (Yaqoob et al. 2013).

2.5 Incidence of clefting

The incidence of clefts varies between countries and racial or ethnic groups (Schutte & Murray 1999). It was estimated to be between 1 and 2.21/1,000 live births (Derijicke et al. 1996, Alper et al. 2012, Khan et al. 2006). The respective figure is about 1/2,000 births among black persons, 1/800 births among white
persons, and 1/500 births in Indian or Japanese persons. A study from Mississippi, USA found that the incidence of clefts in live-born infants was 0.54/1,000 for non-whites and 1.36/1,000 for whites. White boys had a higher incidence of CLP than white girls. Black boys had an extremely low incidence of CL, whereas black girls showed a higher incidence of CP alone (Das et al. 1995).

In Finland about 130 children are born every year with a cleft from a total of 60,000 newborns for an incidence of approximately 2:1000 (NIHW statistics, 2012) and the prevalence of CP is 0.97/1000 (Harila et al. 2013). The overall incidence of clefts in Finland is 2.56/1,000 live births and abortions. The incidence of isolated CP in Finland is amongst the highest on the globe, at 1.36/1,000 (Lithovius et al. 2014b). Non-syndromic cleft palate incidence in Finland is about 1.01:1000 livebirths (Koillinen et al. 2001). In a study from Northern Finland analyzing the records of a total of 214 cleft patients and CP (68.7%) was found most frequently, followed by CLP (18.7%) and CL with or without alveolus (12.6%) (Lithovius et al. 2014a). In Europe the incidence of clefts is 1:1000 (Dixon et al. 2011) and the incidence of clefts in Asia and America is reported to be approximately one in 500 newborns (Lithovius et al. 2014a). The numbers of CL or CLP patients are large in Asia and parts of Latin America and minor in Israel, southern Europe and South Africa. Amounts of isolated CP were large in parts of northern Europe and Canada and minor in South Africa and Latin America (Harila et al. 2012). Cleft lip and palate was more frequent in male infants, but CP most frequently affected female infants (Damle 2002, Matthews et al. 2014).

A study of a Nigerian Teaching Hospital analyzing 360 cleft lip and palate patients found that the proportion of CL only was 49%, CP only was 19% and CLP was 32% (Iregbulem 1982). A cross-sectional study in Mashhad, in North-Eastern Iran, documented 28,519 infants born between 1982 and 2011 at three major hospitals in Mashhad which were screened for oral clefts. CLP was the most prevalent type of cleft 50%, followed by isolated CL 35.2% and isolated CP 14.8% (Kianifar et al. 2015).

2.5.1 Cleft palate (isolated)

Isolated cleft palate is the most common orofacial cleft in Finland (59%-63.3%) (Haapanen & Heliövaara 1998, Lithovius et al. 2014a). It is found in the centre line of the palate. The extent of the cleft varies. It can extend to the soft palate (Fig. 1), but may also reach both the soft and hard palates (Fig. 2). The uvula is usually divided. A cleft of the soft palate may include the whole length of the soft palate or
just part of it (Fig. 1). There are large individual differences in the soft tissue of the soft palate, and some patients may have a quite a short palate. A cleft of the hard palate is either incomplete or complete (Fig. 2). An incomplete cleft extends to the hard palate in varying lengths and widths, but never to the incisive foramen. A complete cleft extends to the incisive foramen and the nasal septum is clearly visible in the middle of the cleft (Haapanen & Heliövaara 1998, Grabb et al. 1971).

![Fig. 1. Cleft palate (soft palate).](image1)

![Fig. 2. Cleft palate (hard and soft palate).](image2)
2.5.2 Cleft lip and palate

Cleft lip and palate is the second most common orofacial cleft (18.7%-25%) in Finland (Haapanen & Heliövaara 1998, Lithovius et al. 2014a). A cleft lip and palate can be unilateral (Fig. 3) or bilateral (Fig. 4), with varying degrees of severity depending on the extent of involvement of the lip, alveolus and palate. A unilateral cleft lip and palate is usually complete, and it is most commonly found on the left side. A complete cleft lip and palate does not leave an observable tissue bridge between clefts in the lip, alveolus or palate. The cleft is therefore wide, and the nasal deformity is also greatly accentuated. The nasal septum is strongly tilted. The dental arches are often twisted in comparison to each other.

A bilateral cleft lip and palate is also usually complete. The upper jaw and middle of the dental arch, or premaxilla, grows without normal muscular stimulation from facial muscles or other structures, and twists forwards and up. The middle part of the dental arch is often found up to two centimetres in front of the sides of the palate. The nasal tip is very flat and wide, and the nostril wall appears almost non-existent. The edges of the nostrils are pulled back to the sides. The nasal septum is clearly visible in its whole extent between the palate halves (Haapanen & Heliövaara 1998, Grabb et al. 1971).

Fig. 3. Unilateral cleft lip and palate.
2.5.3 Cleft lip (isolated)

If the cleft does not reach the palate and is limited to the lip, it is called an isolated cleft lip (Fig. 5). Incidence of cleft lips in Finland varies from 12.6% to 16% of all orofacial clefts (Haapanen & Heliövaara 1998, Lithovius et al. 2014a). The underlying bone structure is intact in cleft lips. Cleft lip can also occur in varying severities both unilaterally and bilaterally. A unilateral cleft lip is more common than a bilateral cleft lip, and it is usually found on the left side. A more mild form of cleft lip is a small tract in the lip forming an incomplete or forme fruste cleft lip, while more severe clefts split the whole lip and cause a significant asymmetry to the nostril on the side of the cleft. Cleft lips are divided into partial and complete cleft lips (Haapanen & Heliövaara 1998, Grabb et al. 1971).
2.5.4 Cleft lip and alveolus

In cleft lip and alveolus the palate is intact, and the cleft is located in front of the incisive foramen (Fig. 6). A cleft lip and alveolus is usually found in varying degrees of severities in the lip and alveolar area, either unilaterally or bilaterally. A bilateral cleft lip and alveolus is rare and rarely complete. It may look like a cleft lip in milder cases, but the cleft alveolus causes changes in the dental arch around the cleft. Mild cases are found as a small indentation in the dental arch. A severe cleft lip and alveolus can be wide and reach the nasal and upper dental arch area, causing severe nasal deformity. The dental arches are twisted in comparison to each other, and the cleft lip is complete (Haapanen & Heliovaara 1998, Grabb et al. 1971).
2.5.5 Submucous cleft palate

A submucous cleft palate (SMCP) only affects the underlying bone and muscle. The overlying mucous tissue remains intact (Fig. 7). Since the palatal mucosal tissue is intact, a submucous cleft palate may present with only a divided or bifid uvula with an accompanying translucent blueish colored groove in the midline of the soft palate representing a muscular diastasis. This diastasis can also be felt by finger palpation, by touching the groove at the posterior edge of the hard palate.

Frequently a notch of the posterior aspect of the bony hard palate in the area of the posterior nasal spine is also palpable. A SMCP is usually found clinically at a later stage than the obviously visible CLP or CP deformities which tend to be noted at birth. The muscles of the soft palate may not work properly, which may lead to speech, middle ear and swallowing problems and these may be the late presenting features that alert parents and astute clinicians to the presence of these otherwise hidden clefts (Haapanen & Heliövaara 1998, Grabb et al. 1971). Rarely SMCPs may split or dehisce spontaneously or following trauma. This might be another reason for the late presentation of submucous cleft palates.
2.6 Cleft related problems

Cleft patients may face numerous problems including issues with their appearance, speech problems with difficult to understand hyponasal speech, many dental and occlusal problems and otologic problems with impaired Eustachian tube function, leading to chronic middle ear effusion and conductive hearing loss.

2.6.2 Dental Problems

Cleft patients may have dental problems including missing teeth or oligodontia, supernumerary teeth, malformed teeth, hypoplastic teeth and hypomineralized teeth (Al Jamal et al. 2010) (Figs. 8 and 9).
Dental anomalies

Patients with CLP commonly exhibit various dental anomalies including abnormal tooth shape, abnormal tooth size, and abnormal tooth position (Fig. 9). The extent of these dental anomalies varies according to cleft type, gender and ethnicity (Paradowska-Stolarz et al. 2014, Al-Kharboush et al. 2015). The occurrence of
cleft palate and the development of tooth germs are closely related during embryological development, both chronologically and anatomically. The association between the dental anomalies and CLP may result from their proximate anatomy, the timing of dental development and the timing of cleft formation. Research has shown that genetic factors have a major role in dental anomalies. Some genes may be responsible for the induction of both congenital dental anomalies and orofacial clefts. Two examples are PAX9 and Msx1 which are signaling molecules that affect the shape and position of teeth (Wu et al. 2011, Schwartz et al. 2014).

The prevalence of dental anomalies was recently reported to be 11.7% in a study on panoramic radiographs in children from the general population aged 5 to 12 years. The most prevalent anomalies were missing and supernumerary teeth, occurring at a rate of 4.6% and 3.3%, respectively (Souchois et al. 2013). Minor morphological disturbances in deciduous teeth were found to be frequent in children with cleft lip and palate (Pöyry & Ranta 1985a, Pöyry & Ranta 1985b). Other commonly observed dental anomalies included impacted teeth, microodontia, macrodontia, taurodontism, and dilaceration (Al-Kharboush et al. 2015, Paradowska-Stolarz et al. 2014, Wu et al. 2011). It has been proposed that the prevalence of dental anomalies is greater in children with clefts than in the general population. The severity of the cleft malformation has been reported to be related to the amount of dental anomalies (Schwartz et al. 2014). Anomalies in the deciduous dentition were more common in children with clefts than in non-cleft children.

The types of dental anomalies in cleft patients are multiple missing teeth, hypodontia, tooth agenesis, ectopic teeth, impaction, supernumerary teeth, microodontia, transposition of maxillary canines and premolar teeth, delayed dental development, crown and root malformation, and multiple decayed teeth. Missing maxillary lateral incisors, supernumerary teeth, and missing lower incisors are the three most common dental anomalies which vary by cleft severity (Schwartz et al. 2014).

The common types of dental anomalies in non-cleft patients were noted to be palatally ectopic maxillary canines, congenitally missing teeth, polydiastema, germination, fusion, tooth impaction, persistent teeth, peg-shaped lateral incisors, hypodontia, persistent deciduous teeth, transpositions, and supernumerary teeth (Islam et al. 2015). Yamunadevi et al. reported that prevalence of dental anomalies in the Dravidian population in the southern Indian subcontinent was 31.55% with the exclusion of third molars. Shape anomalies were more prevalent (22.1%),
followed by size (8.6%), number (3.2%) and position anomalies (0.4%). Two percentage of study population had hypodontia and 1.2% had hyperdontia (Yamunadevi et al. 2015).

The types of dental anomalies common in syndrome patients were malformed teeth, enamel hypoplasia, hypodontia, supernumerary teeth (Subasioglu et al. 2015, Wong et al. 2015).

Mineralization defects

Cleft patients are at a higher risk of molar–incisor hypomineralization (MIH) and the permanent maxillary lateral incisor has been reported to be the most commonly affected tooth with MIH (Fig. 10). In a study regarding mineralization defects 83.1% of the children with CLP were found to have some form of enamel hypomineralization compared to 23.3% in the control sample of children without CLP (Allam et al. 2015). According to previous studies, the prevalence of MIH in the general population varies between 2.9 and 25% depending on the geographic location and the age of the study population. In a retrospective study, 14.3% of the Dutch 9-year-old children had at least one affected tooth with a hypomineralization defect. In Brazilian children, MIH was found in 19.8% of the population. In a group of 5 to 12 years old Greek children, the prevalence was 10.2% (Allam et al. 2015).

One reason for generalized hypomineralization defects and dental erosion can be an acquired digestive disorder called gastroesophageal reflux disease (GERD). GERD affects the tone of the lower esophageal sphincter. Many people suffer from acid indigestion and heartburn caused by GERD. The estimated prevalence of GERD ranges from 6% to 10% (Barron et al. 2003). However, the pattern of hypomineralization in GERD is dramatically different from that seen in MIH.
Fig. 10. Mineralization defect.

**Hypoplastic teeth**

Enamel hypoplasia may be caused by pathological or developmental disturbances during amelogenesis or by mechanical trauma during enamel maturation. Disturbed enamel formation is most frequently seen in the permanent teeth in the central incisor on the cleft side (Pegelow et al. 2012) (Fig. 11). Among 5-year-old Swedish children, the prevalence of hypoplasia was reported to be 61% in the cleft group compared to 26% in the non-cleft control group. The values for 10-year-olds were 75% in the cleft group and 47% in the non-cleft control group. The most common presentation of hypoplasia was demarcated opacities on permanent anterior teeth (Sundell et al. 2016). Several studies of enamel hypoplasia in the primary dentition in the general population have been carried out. The results show that enamel hypoplasia of primary canines varies from 0.5% to 45% (Mukhopadhyay et al. 2014).
Fig. 11. Enamel hypoplasia with opacity.

*Morphological changes*

A talon cusp is an uncommon dental anomaly presenting as an accessory cusp on an anterior tooth. It can be seen in the primary and permanent dentition and this disorder is more common in maxillary incisors than in the mandibular incisors. The etiology of the talon cusp is unknown and while not restricted to cleft patients, the anomaly is known to occur in cleft patients (Maia et al. 2015). Talon cusp has also been reported to occur as part of Rubinstein-Taybi syndrome and has also been noted as an isolated finding (Acs et al. 1992).

Shovel shape of upper incisors is a common characteristic in indigenous American and Asian populations but is rare or absent in European and African populations (Kimura et al. 2009). Affected teeth are called shovel-shaped incisors because the lingual marginal ridges enclose the lingual fossa and give the tooth the appearance of a shovel (Haseqawa et al. 2009). While these anomalies can occur in cleft patients, they have also been observed in non-cleft patients.

Mulberry molars and those peg-shaped teeth which have a crescent-shaped notch in the cutting or incisal edge are called Hutchinson’s teeth. While Hutchinson’s teeth are seen in cleft patients, they are more often described as one of the main dental characteristics of congenital syphilis. Mulberry molars are irregularly formed teeth generally affecting the first molars and are characterized by rounded enamel nodules on their occlusal surfaces with alternating nonanatomic depressions (Sedano et al. 2009) (Fig. 12). Hutchinson’s teeth present as enamel
hypoplasia of the maxillary incisors with a semilunar notch on the incisal edge of mandibular incisors (Pessoa & Galvão 2011).

Fig. 12. Morphological changes with peg-shaped teeth.

Missing teeth

Missing teeth present with degrees of severity. Hypodontia is defined as a condition in which the patient is missing at least one or more but less than six teeth (Figs. 13 and 14). Oligodontia is a more severe form of hypodontia in which 6 or more permanent teeth excluding the third molars are missing (Sândor et al. 2001). Anodontia is a term which is defined by the total absence of permanent teeth. Hypodontia has been reported to be one of the most common developmental dental anomalies. The prevalence of hypodontia varies from 0.3% to 11.3% (Isman et al. 2015) and it occurs 1.37 times more frequently in females than males. Hypodontia was reported to be more prevalent in Europe (females: 6.3%; males: 4.6%) and in Australia (females: 7.6%; males: 5.5%) than in North American whites (females: 4.6%; males 3.2%) (Carmichael & Sándor 2008a). In a cleft population missing teeth or hypodontia varies from 26.8% to 70.2% (Haque & Alam 2015). There are 126 syndromes which are associated with oligodontia or anodontia. The syndromes most frequently associated with agenesis of teeth include Down syndrome and ectodermal dysplasia (ED). In Sweden it has been estimated that 15% of children and adolescents missing eight or more permanent teeth have a syndrome such as
ED (Carmichael & Sândor 2008b). The more severe the oligodontia, the more probable it is associated to be with a syndrome (Carmichael & Sândor 2008a).

Studies have shown that some genes are known to have a potential for producing non-syndromic oligodontia. Mutations of genes such as Msx-1 (muscle segment homeobox1) cause specific oligodontia or hypodontia. Nonsense mutations of the Msx-1 gene are associated with combinations of tooth agenesis and CLP. Mutations in the Pax-9 gene loci (paired box gene 9) are related to agenesis of permanent molars with or without involving primary teeth. Tooth agenesis and colorectal cancer are associated with mutations in AXIN 2 (axis inhibition protein) gene (Yamunadevi et al. 2015, Isman et al. 2015). At least four candidate genes show positive associations for clefting with hypodontia including: Msx-1, IRF6, Pax-9 and TGFB3s (Aspinal et al. 2014).

![Image of tooth and implant](image)

**Fig. 13.** Congenitally absent maxillary lateral incisor in CLP patient restored with a dental implant.
Supernumerary teeth

Supernumerary teeth or hyperdontia may be defined as the presence of any extra tooth substance in excess of the usual configuration of twenty deciduous and thirty-two permanent teeth. In the literature the age of patients with supernumerary teeth ranges from 5 to 70. Most cases are reported between 7 and 10 years of age. Supernumerary teeth can appear in any region of the maxilla and mandible but they most commonly occur in the maxilla. In the literature mesiodens are the most common supernumerary teeth in young adolescents and children occurring at a rate of 30%-80% of all supernumerary teeth (Demiriz et al. 2015) (Fig. 15). The prevalence of supernumerary teeth has been estimated as 0.5-5.3% in the permanent dentition and 0.2-0.8% in the deciduous dentition in various populations (Demiriz et al. 2015, Subasioglu et al. 2015). Hyperdontia is usually associated with some other disorder such as CP, CL, CLP, or syndromes such as Down syndrome, Gardner syndrome, cleidocranial dysplasia, Zimerman-Laby syndrome, Ehlers-Danlos syndrome, Fabry-Anderson syndrome or Noonan syndrome (Ata-Ali et al. 2014, Demiriz et al. 2015). Studies have reported that supernumerary teeth vary from 4.97% to 35.5% in a cleft population (Haque & Alam 2015, Jamilian et al. 2015).
Fig. 15. Supernumerary tooth at maxillary lateral incisor site.

Dental caries

In Finland, about one-third of 5-yr-old children and one-half of 12-yr-old children have dental caries-related tooth damage with approximately 0.5 caries lesions per individual (or 500 carious lesions per 1,000 individuals) (Suominen-Taipale et al. 2009, Tanner et al. 2013). The proportion of children with CLP and CP 6 to 36 months of age with dental caries lesions, were recently reported to be an alarming 18.9% in an article assessing the dental health of Brazilian children (Moura et al. 2013). A study in West Scotland found that the prevalence of dental caries was more common in children with clefts than in non-cleft children (Britton & Welbury 2010). Children with CLP and CP have a high risk of developing dental caries, with a reported decayed missing and filled (dmf) score ranging between 2.35 and 13.5 worldwide (Shashni et al. 2015).

The common risk factors associated with dental caries have been reported as irregularity of teeth, the anatomy of cleft area, tightly repaired lip with a tendency for food to accumulate in the cleft area, deep pits or fissures in the teeth, nasal discharge through the cleft which acts as a reservoir of cariogenic microorganisms, hypoplastic defects, presence of orthodontic appliances, prolonged feeding especially at night time, frequent eating of carbohydrate snacks, increased consumption of sugar containing foods, developmental delay and low socioeconomic status (Shashni et al. 2015, Gaudilliere et al. 2014).

The previous studies concerning dental caries in non-cleft children shows that more than 40% of primary and preschool school aged children in western
industrialised countries and other middle income countries, including children in the United States of America, Sweden, Australia and Brazil have a high prevalence of dental caries. It has recently been reported that 2.4 billion people worldwide have untreated dental caries (Fernando et al. 2015). Research in Latvia in the period of 1970-1980 suggested that 2% of the children of 1 year of age had caries. In the period from 1989-2000, the prevalence of caries increased from 17.3% to 20.3% in 2-year-old children, and in 2001, 48% of children at the age of 2-3 years had caries (Skrīvele et al. 2013).

According to previous studies in Estonia the caries prevalence among children aged 2 to 4 years in 2006 was 41.6%. In 2007, 38% of children at the age of 2 to 5 had caries in Sweden. In 2001, 14.7% of children at the age of 2 to 3 years had caries in Germany. In Poland, 43.8% of 3-year-old children had caries in 2002. In 2009, 50.6% of 3-year-old children had caries in Lithuania (Skrīvele et al. 2013). Approximately 49% of Australian 6 years of age children have evidence of caries in their deciduous teeth. In Australian children aged 6 to 7 years the prevalence of dental caries was 32.4% in 2011 (Fernando et al. 2015). In a recent study 1,204 Brazilian children aged 8 to 10 years were examined and a total of 278 (23.1%) children had at least one carious lesion (Martins et al. 2015).

Children with CLP tend to have a higher prevalence of dental caries than non-cleft children when considering studies worldwide. This holds true for both deciduous and permanent teeth (Wells 2014, Chopra et al. 2014, Hasslöf & Twetman 2007, Antonarakis et al. 2013).

**Dental care under general anesthesia**

Both cleft and non-cleft patients may be uncooperative, either because of the sheer magnitude of the dental work required, or as a result of psychological or emotional immaturity (Sari et al. 2014). Such patients may present a scenario where routine dental care is more difficult, if not impossible, to deliver without sedation or even general anesthesia. Sedative premedication and/or nitrous oxide/oxygen sedation may be used as the first line of treatment (Hulland et al. 2002). In more difficult cases, dental care is performed under general anaesthesia (DGA) (Sari et al. 2014). In 2010, approximately 160,000 non-cleft patients were treated in the public sector in Helsinki, Finland, with 0.22% of these patients receiving care under general anaesthesia (Savanheimo et al. 2012). Almost the same number was reported in the city of Oulu, Finland, in 2014, when 2/1,000 (0.2%) children in this age group were treated under DGA; there were 18,791 children 0 to 6 years of age, of whom 46
were treated under DGA (statistics from the City of Oulu). These findings are supported by the retrospective study from Hospital Universiti Sains Malaysia which found that the most treated patients receiving dental treatment under general anesthesia were syndromic children and cleft lip and palate patients (Karim et al. 2008).

2.6.3 Otologic problems

Palatal clefts may result in disrupted nasopharyngeal anatomy and give rise to abnormal muscle attachments. These abnormal attachments may result in impaired Eustachian tube function, leading to chronic middle ear effusion and conductive hearing loss (Bütow et al. 1991).

**Otitis media with effusion (OME)**

Secretory otitis media (SOM), otitis media with effusion (OME) or glue ear is a condition in which serous or mucous fluid accumulates in the middle ear cavity behind an intact tympanic membrane instead of pus without signs or symptoms of ear infection, and can lead to conductive hearing impairment (Varsak et al. 2015, Kucur et al. 2015). Hearing impairment in usually slight and often parents notice it when children exhibit abnormal behaviour. Without proper treatment OME may lead to various complications, such as tympanosclerosis, retraction pockets, adhesive otitis media, impairment in the development of language and permanent hearing loss (Kucur et al. 2015). The etiology of OME for non-cleft children is multifactorial. It includes infection, adenoid hypertrophy, allergies, social and environmental factors (Varsak et al. 2015). For children with a cleft involving the palate, there is a tendency towards Eustachian tube dysfunction because of an abnormal insertion of tensor veli palatini and levator veli palatini muscles into the posterior margin of the hard palate as well as the associated muscular hypoplasia and palatal aponeurosis. Eustachian tube dysfunction can affect the development and persistence of negative middle ear pressure and the accumulation of serous or mucoid fluid within the middle ear cavity (Harman et al. 2015, Khan et al. 2006). CP individuals should always be investigated thoroughly for otological problems, which is one of the common complications (Khan et al. 2006).
How ventilation tubes (VT) work and the need for ventilation tubes

OME in the presence of an effusion with duration longer than three months is usually treated with VT placement. VT insertion is the most common surgical treatment in young children under general anesthesia (Lee et al. 2014). The tubes allow the middle ear effusion to drain to the external auditory canal while the tubes remain in place. The benefits of tympanostomy and VT insertions are removal of the secretion products from the middle ear, ventilation of middle ear and improvement of conductive hearing loss (Reiter et al. 2009). A Finnish study showed that 8.5% of non-cleft children under the age of 7.5 years have suffered from OME and had had VTs placed (Karma et al. 1988). OMEs resulting from a malfunction of the Eustachian tube are reported to be even more common among cleft patients (Klockars & Rautio 2012). Before the first year of age, OME appears at least once in 90% of children with cleft palate and increasing to 97% by the second year of age (Kuo et al. 2014). Harman et al. found that approximately 75% of children with CP have histories which include OME and therefore need for VT (Harman et al. 2015).

Ventilation tubes and their risks

The possible adverse effects of repeated VT insertions includes hearing loss, tympanic membrane atrophy, tympanosclerosis, relapse of effusion, eardrum perforations and cholesteatoma (Moller 1981, Shehan & Blayney 2002, Härtzell & Dornhoffer 2010, Saki et al. 2012). Middle ear infections and conductive hearing loss are also closely related.

Speech development in cleft patients, can be affected by velopharyngeal structural abnormalities and hearing loss. Early VT placement in children with clefts may improve their speech ability, reduce hearing loss and improve the long-term clinical, audiologic and radiologic outcomes (Klockars & Rautio 2012). Closing the cleft palate and placing VTs concurrently has been reported to be effective treatment for cleft patients with OME (Huang et al. 2012). Hubbard et al. showed that early elective VT placement leads to reduced hearing loss in comparison to placing the VT as symptoms appear (Hubbard et al. 1985). However, in the long run early VT placement has not been shown to result in a better hearing and may result in morbidity including otorrhea and persistent perforation (Robinson et al. 1992).
2.7 Cleft management

Patients with CLP may experience feeding, swallowing, speech, hearing, and cosmetic problems, as well as poor dental health (Bian et al. 2001). In Finland, the management of cleft patients begins early in the maternity hospital. The successful treatment of a cleft patient consists of multidisciplinary surgical and nonsurgical care that is continued from birth to adulthood (Fitzsimons et al. 2013). A cleft lip is normally repaired at the age of 3 to 6 months, and a cleft palate at the age of approximately 9 months. However, the exact timing of surgical treatments varies with each case (Rautio et al. 2010). The goal of the cleft-related surgical treatments is to ensure normal development, facial growth, and appearance for the patient, as well as normal hearing, speech and normal respiration abilities (Pearson & Kirschner 2011).

The core of the cleft treatment is multidisciplinary care, being provided by the members of the cleft team including anesthesiology, dentistry, oral and maxillofacial surgery, craniofacial and plastic surgery, otolaryngology, phoniatry, speech therapy, paediatric dentistry, orthodontics as well as psychiatry, nursing and genetics (Bennun et al. 2015). In Finland patients with lip and palate clefts are treated at two centres, Oulu and Helsinki University Hospitals. In Oulu the patients are monitored in the Oulu University Hospital regularly until they are 18 years of age (Tables 3 and 4). Orthodontic and basic dental treatment can also be performed at health centers or in the private sector with financial support from the community as cleft care in Finland is free of charge to the individual until the age of 18.

The treatment of a particular cleft is defined by its type. Isolated lip clefts and separate palatal clefts often do not require any treatment other than primary surgery. Lip and palate clefts usually require several other operations, such as a bone grafts and possibly orthognathic surgery to correct jaw growth deficits. Severe clefts can also affect tooth development and the development of speech and treatment of children with clefts usually includes speech therapy possibly combined with speech improving operations.

Many cleft patients also have problems with their ears, mostly with recurrent acute otitis media. Therefore, in many cases, cleft patients also need tympanostomy surgery. The benefit of tympanostomy is the drainage and ventilation of middle ear with improvement of conductive hearing loss (Reiter et al. 2009). Cleft patients also require orthodontic treatment in addition to treatment for morphological anomalies (Rautio et al. 2010).
The edentulous space left by the cleft and missing teeth can be restored prosthodontically after growth has ceased or with orthodontic treatment during growth. Also surgical treatment, such as tooth transplantation, can be used for filling gaps with other teeth (Aizenbud et al. 2013). Dental implants can be used later after growth cessation during adulthood (Carmichael & Sándor 2008c, Sedlackova et al. 2011, Aizenbud et al. 2013). Clefts require long and challenging multidisciplinary treatment plans and their precise execution. The treatments are physically and mentally demanding both for the patients and their parents as well as the treatment team.

Table 3. Cleft lip and/or palate timing of records according to Oulu University Hospital treatment protocol.

<table>
<thead>
<tr>
<th>Timing</th>
<th>Dental casts</th>
<th>Optg*</th>
<th>Lateral cephalogram</th>
<th>Photos</th>
<th>Phoniatric cl*</th>
<th>Hearing examination</th>
<th>Children’s psychiatry examination</th>
<th>Final examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 yr</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 yr</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X*</td>
<td>X*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/6 yr</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 yr</td>
<td>X</td>
<td></td>
<td></td>
<td>X*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 yr</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 yr</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X*</td>
<td>X*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 yr</td>
<td>X</td>
<td></td>
<td></td>
<td>X*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15/16 yr</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X**</td>
<td>X**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 yr</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X*</td>
<td>X*</td>
<td>X*</td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 yr after</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 yr after</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Optg*=orthopantomogram, Phoniatric cl*=phoniatric control, X*=cleft lip and palate only, X**=cleft palate only
Table 4. Cleft lip timing of records according to Oulu University Hospital treatment protocol.

<table>
<thead>
<tr>
<th>Timing</th>
<th>Dental casts</th>
<th>Optg*</th>
<th>Lateral cephalogram</th>
<th>Photos</th>
<th>Phoniatric cl*</th>
<th>Hearing examination</th>
<th>Children's psychiatry examination</th>
<th>Final examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary surgery</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>3 yr</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>5/6 yr</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>8 yr</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 yr</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 yr</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14yr</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15/16 yr</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 yr</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Optg* = orthopantomogram, Phoniatric cl* = phoniatric control
3 Aims of the study

This thesis aimed to study some of the clinical problems faced by CL, CLP and CP patients. The goal of the first study was to determine the prevalence of dental anomalies in cleft children treated in Northern Finland when comparing the age, gender and cleft types. In the first hypothesis, the number of dental anomalies was assumed to be higher in cleft children than in the general population. In the second hypothesis, missing and supernumerary teeth were assumed to be among the most prevalent dental anomalies. It was also assumed that the cleft type and gender had an impact on the prevalence of dental anomalies.

The aim of the second study was to determine the need for restorative treatment in Northern Finnish cleft patients of different age groups, genders, and cleft types also considering the concurrent existence of syndromes. Another aim was to determine the amount of restorative treatments performed under general anesthesia among the cleft patients included in the research material. The first hypothesis was that Finnish children with clefts have a higher caries rate due to difficulty in hygiene because of cleft anatomy and scar tissue, making access more challenging than among non-cleft Northern Finnish children. The second hypothesis was that the existence of a syndrome can increase the risk of dental caries in cleft patients. Thirdly, it was assumed that a significant number of dental treatments of cleft children were carried out under general anesthesia due to dental caries.

The aim of the third study was to identify middle ear problems among cleft children treated in Northern Finland. Another aim was to identify the need for ventilation tube (VT) placement, as well as the problems it caused, such as perforation and cholesteatoma. The findings in different cleft types, age groups and genders were assessed. The first hypothesis was that cleft patients treated in Northern Finland suffered from more middle ear problems than non-cleft children. It was also hypothesized that the cleft children in the study group had more VTs than non-cleft children.

The aim of the fourth study was to examine the association between cleft severity, palate repair technique, VT placement and hearing outcomes in children with CLP and CP from Northern Finland who were between 3 and 9 years of age. The first hypothesis of the fourth study was that the surgical technique used for the primary palatoplasty had an impact on the hearing results. The second hypothesis was that clefts of varying severity had an impact on hearing results. It was also hypothesized that the severity of the cleft or the surgery technique had an impact
on the number of VT placements. Finally it was hypothesized that hearing improved significantly after the age of 6.
4 Material and methods

4.1 Subjects and methods

The study material consisted of 214 cleft patients treated at the Oulu Cleft Lip and Palate Center of the Oulu University Hospital (OUH) since 1996. The studies were retrospective follow-up studies, and the material was initially collected from the patient database of the OUH. The Ethics Committee of the OUH approved the study as a retrospective study, and the data were used in accordance with the principles of the Declaration of Helsinki.

4.2 Dental anomalies (study I)

In study I the material was collected covering a 15-year period (1996-2010), during which time cleft patients had been treated at the OUH. Those patients who had received treatment elsewhere were excluded from the study, because their material was not available. Those patients under 3 years of age were excluded because dental anomalies are not reliably detectable in such a young age group.

This study material consisted of 139 cleft patients after the exclusions (Table 5). The following factors were registered: age, gender and cleft type. The following dental anomalies were noted: missing teeth, supernumerary teeth, gemination, mineralisation defects, morphological changes and hypomineralization. The patients were divided into two groups; cleft patients older than 5 years and cleft patients 5 years or younger. This was because children under 3 years of age rarely had radiographs available and some deciduous tooth anomalies in the study population were anticipated to be in the cleft adjacent areas. The age of 5 was chosen because most cleft adjacent teeth are at least radiographically visible by 5 years of age. Cleft types were divided into 8 groups. Cleft palate (CP), soft cleft palate (SCP), right cleft lip and palate (RCLP), left cleft lip and palate (LCLP), bilateral cleft lip and palate (BCLP), cleft lip and alveolus (CLA), cleft lip (CL), submucous cleft palate (SMCP).
Table 5. Inclusion and Exclusion Criteria.

<table>
<thead>
<tr>
<th>Inclusion/exclusion</th>
<th>M</th>
<th>F</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Included</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Older than 5 years</td>
<td>53</td>
<td>55</td>
<td>108</td>
</tr>
<tr>
<td>5 years or younger</td>
<td>13</td>
<td>18</td>
<td>31</td>
</tr>
<tr>
<td>Excluded</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under 3 years old</td>
<td>30</td>
<td>33</td>
<td>63</td>
</tr>
<tr>
<td>Treated elsewhere</td>
<td>4</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>114</td>
<td>214</td>
</tr>
</tbody>
</table>

4.3 Caries and dental general anesthetics (study II)

In study II the material was collected covering the period 1997-2011, during which period cleft patients had been treated at the OUH. Patients who had received treatment elsewhere were excluded from the study, because their records were not available. Thus study II comprised 183 cleft patients after the exclusions were applied.

The following variables were recorded: age, gender, cleft type, occurrence of dental caries lesions needing restoration (yes/no) at 3 years and at 6 years of age. The dates of the Dental General Anesthetics were recorded as well as their associated diagnoses (ICD10) and the procedures performed. Cleft patients were divided into 9 groups: CP, RCLP, LCLP, BCLP, CLA, CL, SMCP, SCP, CLP (Table 6).

Table 6. Distribution of Cleft Types in Study II.

<table>
<thead>
<tr>
<th>Cleft types</th>
<th>M</th>
<th>F</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP</td>
<td>36</td>
<td>63</td>
<td>99</td>
</tr>
<tr>
<td>RCLP</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>LCLP</td>
<td>8</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>BCLP</td>
<td>9</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>CLA</td>
<td>5</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>CL</td>
<td>5</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>SMCP</td>
<td>8</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>SCP</td>
<td>9</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>PCL</td>
<td>5</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>88</td>
<td>95</td>
<td>183</td>
</tr>
</tbody>
</table>

CP=Cleft palate, RCLP=Lip and palate (right), LCLP=Lip and palate (left), BCLP=Lip and palate (bilateral), CLA=Cleft lip and alveolus, CL=Cleft lip (complete), SMCP=Submucous cleft palate, SCP=Soft palate, PCL=Partial Cleft Lip
4.4 Middle ear findings and the need for ventilation tubes (study III)

In study III the data were collected for the period including 1997-2011. Some patients had received treatment at their regional hospital, such as the Lapland Central Hospital and the hospitals of Kajaani, Kemi, Kokkola, Raah and Kuusamo. Data were also collected from the databases of the respective hospitals with the permission of the register holder. Exclusion criteria were: VT placements performed at hospitals other than the OUH, patients who moved during the follow-up period and patients with incomplete patient data. The material consisted of 156 patients after these exclusions. The following factors were registered: age, gender, cleft type, time of surgery, surgery type, number of VT insertions, tube material, middle ear findings and the date and time of the particular findings. Clefts were divided into four groups: CP, CLP, CL and SMCP (Table 7).

Table 7. Distribution of Cleft Types in Study III.

<table>
<thead>
<tr>
<th>Cleft types</th>
<th>M</th>
<th>F</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP</td>
<td>34</td>
<td>57</td>
<td>91</td>
</tr>
<tr>
<td>CLP</td>
<td>20</td>
<td>11</td>
<td>31</td>
</tr>
<tr>
<td>CL</td>
<td>13</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>SMCP</td>
<td>4</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>71</td>
<td>85</td>
<td>156</td>
</tr>
</tbody>
</table>

CP=Cleft palate, CLP=Cleft Lip and palate, CL=Cleft lip, SMCP=Submucous cleft palate.

4.5 Cleft severity and hearing outcomes (IV)

In study IV the data were collected covering the period 1998-2011. The following factors were registered: gender, age, cleft type, surgical technique used for primary repair, date of primary palatoplasty, number of VT placements, hearing test results with Pure Tone Average (PTA) and the dates of the audiologic measures. The participating patients range in age from 3 to 9 years and were divided into two groups: 3 to 5-year-olds and 6 to 9-year-olds. Forty-two patients had undergone hearing tests in both groups. The best hearing results were recorded and analysed in each group. The severity of palatal clefts was defined with a three-dimensional scanner using Jensen’s scale (Jensen et al. 1988). Exclusion criteria were as follows: patients who had received treatment at hospitals other than the OUH, patients who missed follow-up visits, patients under 3 years and patients without hearing tests. A total of 90 patients were included in the study after the exclusions. As in study III, the patients were divided into four groups. A one-stage cleft closure was
performed on all cleft patients. It is a three-layered technique, where the hard and soft palates are closed at the same time. VT placements were performed during or before the palatoplasty procedures. Patients met an ENT-specialist 1-3 times a year. The VT placements were repeated according to the protocol of the OUH, which requires a diagnosis of secretory otitis media and more than three middle ear infections within a year for VT placement to be scheduled.

The otolaryngologic protocol included audiological examination using standard pure tone audiometry. Ear-specific measurements were performed at 0.5 kHz, 1 kHz, 2 kHz and 4 kHz and registered in dB hearing level by a trained audiologist using headphones. The three-frequency Pure Tone Average (PTA) was calculated for each ear. Some of the audiograms were not in electronic format and the PTAs were calculated with the guidance of an otolaryngologist (T. Autio). In the PTA scale higher numbers represent worse hearing so that PTA scores greater than 20 dB was categorized as the abnormal hearing threshold.

4.6 Statistics (studies I, II, III & IV)

In study I & II the frequencies and proportions of different types of clefts were analysed from the data. The association between clefts and developmental dental disorders was analysed using cross tabulation and Chi-square test. Existence of dental caries lesions was registered using the cut-off points of 3 and 6 years of age. Gender, cleft-type and existence of a cleft-related syndrome were considered. The number of DGAs per patient were analysed from the data considering the age, gender, cleft type and presence of a cleft related syndrome. The association of the clefts and occurrence of dental caries was evaluated using Chi-squared test or Fisher’s exact test.

The number of DGAs was presented as a mean with Standard Deviation. The diagnoses leading to DGAs were presented as frequencies, as were the procedures done under DGAs. Logistic regression analysis was done to investigate association of different variables (cleft type, syndrome, gender) with the existence of dental caries at three and six years.

In study III the cleft children were counted and their cleft type determined. Data related to middle ear findings were gathered in connection with VT placements. The gender, age, tube material and fistula were registered separately. Dates were gathered separately for tympanostomies, VT placements, middle ear findings and surgeries including cleft repair surgery and speech improvement surgery.
The number of clefts, VT insertions and the association of middle ear findings were determined by using the Pearson’s Chi-squared test, Kruskall-Wallis test, T-test or Mann-Whitney test.

In study IV mean and standard deviation were used to describe the continuous variables. Frequency was used to describe categorical data such as gender and cleft type. A non-parametric paired-samples t-test and Wilcoxon signed rank test was used to compare hearing scores between two age groups, being the 3-5 year-olds and 6-9 year-old patients. Kruskal-Walls and Mann-Whitneys tests were used when comparing PTAs to the palatoplasty surgical technique and to the severity of cleft and the cleft type. Median and ranges were used when the latter tests were used. Anova was used to compare the number of tube insertions by surgical techniques. The Mann-Whitney test was used when analyzing the association between cleft severity and number of tube placements.

In studies I, II, III & IV the statistical differences between groups were considered by using the significant p-value (P<0.05) and were performed using the program IBM SPSS statistics 20.0 software for Windows (IBM SPSS, Chicago, Illinois, USA).
5 Results

5.1 Dental anomalies (study I)

A total of 139 patients were included in the study of which 108 were older than 5 years and 31 patients were 5-years-old or younger. Their mean age was 8.2 years. There were 18 patients who had been diagnosed with a syndrome, such as Pierre Robin, Treacher Collins, Fragile X, Blepharo-cleido, Kabuki, Apert, CATCH22 or Down syndrome.

Almost one quarter (26.6%) had at least one dental anomaly and 17.9% had two or three dental anomalies. The most common anomalies were missing teeth or supernumerary teeth (Table 8). Missing teeth were found in all cleft types with the exception of isolated CL patients. Supernumerary teeth were found in all cleft types with the exception of CP patients and SMCP patients. Cleft patients usually also had dental morphological changes and hypoplastic teeth. Such dental anomalies were most commonly observed in cleft lip and palate patients, patients with clefts of the hard palate and cleft palate patients, in that order. Missing teeth and supernumerary teeth were most commonly observed among CLP patients. The lowest prevalence of dental anomalies was observed in patients with SMCP or soft CP. A statistical relationship was observed between dental anomalies and cleft types. A total of 86 anomalies were observed in the group of over 5-year-olds, and 17 anomalies in the younger under 5-year-old group. There was a small difference in the prevalence of dental anomalies between the groups. Missing teeth were mostly observed in the older group, while supernumerary teeth and hypoplastic teeth were mostly observed in the younger group. A statistical relationship was observed between missing teeth and different cleft types.
Table 8. Prevalence of the cleft types and dental anomalies.

<table>
<thead>
<tr>
<th>Dental anomalies and clefts</th>
<th>CP</th>
<th>SCP</th>
<th>RCLP</th>
<th>LCLP</th>
<th>BCLP</th>
<th>CL</th>
<th>CLA</th>
<th>SMCP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of clefts</td>
<td>75</td>
<td>11</td>
<td>4</td>
<td>11</td>
<td>10</td>
<td>9</td>
<td>9</td>
<td>10</td>
<td>139</td>
</tr>
<tr>
<td>Dental anomalies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing teeth</td>
<td>17</td>
<td>1</td>
<td>2</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>36</td>
</tr>
<tr>
<td>(47.2)</td>
<td>(2.8)</td>
<td>(5.4)</td>
<td>(19.4)</td>
<td>(11.1)</td>
<td>(5.6)</td>
<td>(0.0)</td>
<td>(8.3)</td>
<td>(35.3)</td>
<td></td>
</tr>
<tr>
<td>Supernumerary teeth</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>(0.0)</td>
<td>(0.0)</td>
<td>(4.5)</td>
<td>(27.3)</td>
<td>(18.2)</td>
<td>(18.2)</td>
<td>(27.3)</td>
<td>(4.5)</td>
<td>(21.6)</td>
<td></td>
</tr>
<tr>
<td>Gemination</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>(0.0)</td>
<td>(0.0)</td>
<td>(0.0)</td>
<td>(0.0)</td>
<td>(0.0)</td>
<td>(100.0)</td>
<td>(0.0)</td>
<td>(0.0)</td>
<td>(1.0)</td>
<td></td>
</tr>
<tr>
<td>Mineralisation defect</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>(40.0)</td>
<td>(0.0)</td>
<td>(0.0)</td>
<td>(30.0)</td>
<td>(10.0)</td>
<td>(10.0)</td>
<td>(0.0)</td>
<td>(10.0)</td>
<td>(9.8)</td>
<td></td>
</tr>
<tr>
<td>Morphological changes</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>(31.6)</td>
<td>(0.0)</td>
<td>(5.3)</td>
<td>(10.5)</td>
<td>(21.1)</td>
<td>(15.8)</td>
<td>(15.8)</td>
<td>(0.0)</td>
<td>(18.6)</td>
<td></td>
</tr>
<tr>
<td>Hypoplastic teeth</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>(26.7)</td>
<td>(0.0)</td>
<td>(6.7)</td>
<td>(33.3)</td>
<td>(6.7)</td>
<td>(6.7)</td>
<td>(13.3)</td>
<td>(6.7)</td>
<td>(14.6)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>1</td>
<td>5</td>
<td>23</td>
<td>14</td>
<td>12</td>
<td>11</td>
<td>6</td>
<td>103</td>
</tr>
<tr>
<td>(30.4)</td>
<td>(1.0)</td>
<td>(4.9)</td>
<td>(22.3)</td>
<td>(13.7)</td>
<td>(11.8)</td>
<td>(10.8)</td>
<td>(5.9)</td>
<td>(100.0)</td>
<td></td>
</tr>
</tbody>
</table>

Cleft palate (CP), Soft cleft palate (SCP), Right cleft lip and palate (RCLP), Left cleft lip and palate (LCLP), Bilateral cleft lip and palate (BCLP), Cleft lip and alveolus (CLA), Cleft lip (CL), Submucous cleft lip (SMCP).

5.2 Caries and dental general anesthetics (study II)

A total of 183 cleft patients were included in the study. Of these patients 11.5% (n=21) had been diagnosed with a syndrome. Dental treatment need was more common among 6-year-olds than 3-year-olds. In 3-year-olds, in the presence of a syndrome, 33.3% had need for dental treatment, while 14.2% of patients without a syndrome needed dental treatment for caries. In 6-year-olds, in the presence of a syndrome, 52.4% needed dental treatment, while 28.4% of patients without a syndrome needed dental treatment. Dental caries was observed most commonly in both groups in patients with bilateral cleft lip and palate and unilateral cleft lip and palate. In 6-year-olds dental caries was least prevalent in patients with submucous cleft palate. When comparing different cleft types in the younger group, the need for dental treatment of the younger group; the difference between groups was not statistically significant (Table 9).

Of the initial 183 cleft patients 17.5% (n=32) required dental treatments performed under general anaesthesia (DGA). DGA was performed as a one-time treatment for 17 patients. Redo DGAs, meaning more than one DGA in a particular
patient’s treatment history were required in 15 patients. Specifically DGAs were performed twice for seven patients, three times for two patients, four times for four patients, five times for one patient and eight times for one patient, for a total of 62 redo DGAs in 15 patients.

A total of 14.8% (n=24) of cleft patients without a syndrome received DGAs while the respective figure for patients with a syndrome was 38.1% (n=8). In all, 12 of 21 cleft patients with a diagnosed syndrome had caries between ages 3 and 6, and only 4 of them could be treated without general anaesthesia. Most of the treatments were performed on cleft palate children, especially among those who had a more severe cleft, such as a unilateral or bilateral cleft lip and palates.

Table 9. Distribution of gender, syndrome and cleft types according to their dental treatment need.

<table>
<thead>
<tr>
<th>Gender, syndrome and cleft type</th>
<th>Dental caries (3 years)</th>
<th>p</th>
<th>Dental caries (6 years)</th>
<th>p</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n)</td>
<td>Yes (n)</td>
<td>n (%)</td>
<td>No (n)</td>
<td>Yes (n)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>72 (81.8)</td>
<td>16 (18.2)</td>
<td>0.439</td>
<td>58 (65.9)</td>
<td>30 (34.1)</td>
</tr>
<tr>
<td>Female</td>
<td>81 (85.3)</td>
<td>14 (14.7)</td>
<td></td>
<td>68 (71.6)</td>
<td>27 (28.4)</td>
</tr>
<tr>
<td>Syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>139 (85.8)</td>
<td>23 (14.2)</td>
<td>0.015</td>
<td>116 (71.6)</td>
<td>46 (28.4)</td>
</tr>
<tr>
<td>Yes</td>
<td>14 (66.7)</td>
<td>7 (33.3)</td>
<td></td>
<td>10 (47.6)</td>
<td>11 (52.4)</td>
</tr>
<tr>
<td>Cleft type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP</td>
<td>77 (77.8)</td>
<td>22 (22.2)</td>
<td></td>
<td>71 (71.7)</td>
<td>28 (28.3)</td>
</tr>
<tr>
<td>RCLP</td>
<td>4 (66.7)</td>
<td>2 (33.3)</td>
<td></td>
<td>4 (66.7)</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>LCLP</td>
<td>14 (93.3)</td>
<td>1 (6.7)</td>
<td></td>
<td>7 (46.7)</td>
<td>8 (53.3)</td>
</tr>
<tr>
<td>BCLP</td>
<td>8 (80.0)</td>
<td>2 (20.0)</td>
<td></td>
<td>4 (40.0)</td>
<td>6 (60.0)</td>
</tr>
<tr>
<td>CLA</td>
<td>8 (88.9)</td>
<td>1 (11.1)</td>
<td></td>
<td>6 (66.7)</td>
<td>3 (33.3)</td>
</tr>
<tr>
<td>CL</td>
<td>6 (100.0)</td>
<td>0 (0.0)</td>
<td></td>
<td>5 (83.3)</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>SMCP</td>
<td>11 (100.0)</td>
<td>0 (0.0)</td>
<td></td>
<td>5 (45.4)</td>
<td>6 (54.5)</td>
</tr>
<tr>
<td>SCP</td>
<td>15 (93.8)</td>
<td>1 (6.2)</td>
<td></td>
<td>13 (81.3)</td>
<td>3 (18.7)</td>
</tr>
<tr>
<td>PCL</td>
<td>10 (90.9)</td>
<td>1 (9.1)</td>
<td></td>
<td>11 (100.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Total</td>
<td>153 (83.6)</td>
<td>30 (16.4)</td>
<td></td>
<td>126 (68.9)</td>
<td>57 (31.1)</td>
</tr>
</tbody>
</table>

CP=Cleft palate, RCLP=Lip and palate (right), LCLP=Lip and palate (left), BCLP=Lip and palate (bilateral), CLA=Cleft lip and alveolus, CL=Cleft lip (complete), SMCP=Submucous cleft palate, SCP=Soft palate, PCL=Partial Cleft Lip
5.3 Middle ear findings and the need for ventilation tubes (study III)

A cohort of 156 patients was included in the study of which 78.9% had secretions in the ear during the monitoring period. Mucous secretions were discovered in 69.2% of all subjects, serous secretions in 36.6% and purulent secretions in 23.7%. Mucous secretions referring to glue ear was detected in 96.8% of the cleft lip and palate patients, 69.2% of the cleft palate patients and 13.0% of the cleft lip patients.

One or more VTs were placed in 82.7% of the patients in the study group during the monitoring period. Differences in the need for VT placement were observed between cleft types. On average, 2.9 (min=0; max=15 SD 2.7) VT placements were performed for each cleft patient. The period between VT placement was (1.1 SD 1.2) years. However, there were variations in the VT placements between age groups. An average of 4.9 (SD 2.9) VT insertions were required for CLP patients, 3.1 (SD 2.5) for CP patients, 2.7 (SD 2.2) for SMCP patients, and 0.2 (SD 0.7) for CL patients. The mean period for the last VT insertion was 3.7 (SD 2.8) years. No statistically significant difference in the number of VT placements was found between genders. The mean age for the primary closure of a cleft was 0.6 years, which was almost the same as the mean age for the first VT insertion being 0.8 years. In accordance with current treatment practices, the first VT insertion was to be performed simultaneously with the cleft closure at palatoplasty. However, in 9.1% of patients, the VT was inserted before the primary closure of the cleft (Table 10).

A speech improvement surgery had been performed on 26 patients. The mean number of VTs required for these speech improvement patients was 3.7 (SD 2.8) compared to 2.9 (SD 2.7) VTs in the other cleft patients. In two of these 26 patients, a VT placement was not performed at all because those particular patients did not have middle ear problems. Each patient with a fistula (n=15) needed one or several VT insertions. For these patients, the mean number of VT insertions was 5.3 (SD 3.0) versus 3.0 (SD 2.7) for those patients without a fistula. During the monitoring period, 56 patients were observed to have a middle ear perforation, and 4 patients had a cholesteatoma. The prevalence of cholesteatoma in all cleft patients was 2.6%, and 3.3% for those cleft patients who had undergone VT insertions. The prevalence of tympanic perforation was 35.9% for cleft patients treated with VT insertion.
Table 10. Distribution of fistula, cholesteatoma and number of ventilation tube insertions according to cleft types

<table>
<thead>
<tr>
<th>Fistula, cholesteatoma, eardrum perforation and number of VTs</th>
<th>CP</th>
<th>CLP</th>
<th>CL</th>
<th>SMCP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fistula</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>No</td>
<td>86</td>
<td>21</td>
<td>23</td>
<td>11</td>
<td>141</td>
</tr>
<tr>
<td>Cholesteatoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>No</td>
<td>88</td>
<td>31</td>
<td>23</td>
<td>10</td>
<td>152</td>
</tr>
<tr>
<td>Eardrum Perforation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>31</td>
<td>22</td>
<td>0</td>
<td>3</td>
<td>56</td>
</tr>
<tr>
<td>No</td>
<td>60</td>
<td>9</td>
<td>23</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td>Number of VTs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5</td>
<td>0</td>
<td>20</td>
<td>2</td>
<td>27</td>
</tr>
<tr>
<td>1-6</td>
<td>79</td>
<td>21</td>
<td>3</td>
<td>9</td>
<td>112</td>
</tr>
<tr>
<td>&gt;=7</td>
<td>7</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Total number of VTs</td>
<td>91</td>
<td>31</td>
<td>23</td>
<td>11</td>
<td>156</td>
</tr>
</tbody>
</table>

CP=Cleft palate, CLP=Cleft lip and palate, CL=Cleft lip, SMCP=Submucous cleft, VTs=Ventilation tubes.

5.4 Cleft severity and hearing outcomes (study IV)

A total of 90 patients passed the inclusion criteria and participated in the study. The group consisted of 51 girls and 39 boys. Patients were 3 to 9 years of age and the mean age of 90 patients was 5.5 years. Of the 90 patients in the study 71 (78.9%) had CP and 19 (21.1%) had CLP. Of these patients 33 had minor to moderate clefts and 38 had severe palatal clefts. Patients with other cleft types not requiring VTs such as isolated CL and SMCP were not included in the study.

Three different one-stage palatoplasty techniques were used to close their clefts according to their cleft severity. A total of 44 patients were treated with a straight closure without lateral incisions, 12 patients treated with the von Langenbeck technique and 34 patients required a vomer flap. Three patients (3.3%) had abnormal PTA hearing results (less than 20 dB). The mean PTA of the entire cleft population included in this study IV was 10.7 dB (SD 8.9). The gender, cleft type, severity of the cleft and surgery techniques were not found to impact on the statistical significance of the PTA. PTAs were not significantly different (p=0.573) between the right or left ears with one (mean 9.3 dB (SD 3.8)) or more than one (mean 10.4 dB (SD 8.1)) VT insertions. Palatoplasty techniques were also not associated with the number of VT insertions required (p=0.57).
Almost half (n=42, 46.7%) of the 90 participants had abnormal hearing results in both groups 3 to 5 years and 6 to 9 years. It was noted that the hearing improved as the age increased, when the following factors were combined: surgery technique, cleft severity and cleft type. PTAs dropped significantly after the age of 6 representing an improvement in hearing after that age.
6 Discussion

6.1 Dental anomalies (study I)

The results of study I indicate that developmental dental disorders are more common among cleft patients than non-cleft individuals. For instance, in the general population missing teeth are found in 6 to 9% (Avellán et al. 2010) whereas in this study 25% of the cleft patients had missing teeth. In cleft patients older than 5 years the respective frequency was even higher (>30%). Similarly supernumerary teeth were found in 0.4% of Finnish children aged 3-4 years (Järvinen & Lehtinen 1981), whereas among cleft patients in this study the prevalence was 15.8%; being the same in patients older than 5 years. In comparison the prevalence of dental anomalies among Turkish cleft patients was 96.7%. Almost all of these patients were reported to have at least one dental anomaly (Akcam et al. 2010). In this study about half of the cleft patients from Northern Finland were reported to have at least one dental anomaly.

Based on this study, it may be concluded that the prevalence of dental anomalies is strongly influenced by the type of the cleft. Supernumerary teeth were found in all other types of clefts except those involving only the palate. Supernumerary teeth also seem to manifest earlier than missing teeth. Missing teeth can clearly be found significantly more often in patients with unilateral or bilateral lip and palate clefts than in patients with soft palate or submucous clefts. This can be explained by the fact that in uni- or bilateral lip and palate clefts the cleft interrupts the development of the alveolar bone and interferes with the development of the teeth (Sándor & Carmichael 2008), causing agenesis or deformation of teeth (Eslami et al. 2013).

The prevalence of dental anomalies in cleft patients seems to vary geographically. The prevalence of supernumerary teeth among the cleft patients in this study was 15.8%. This is in agreement with the results of Al Jamal et al., who reported supernumerary teeth among 16.7% of the cleft patients in Jordan. However, the prevalence of missing teeth reported by Al Jamal et al. was much higher (66.7%) than that found in the present study (Al Jamal et al. 2010). This was also true among Chinese cleft patients (12 to 16 years) with a prevalence of 57.6% of missing teeth (Wong et al. 2012). Missing teeth were reported to be the most frequent dental anomaly also among Iranian and Turkish cleft patients (70.8 to 97.1%) (Akcam et al. 2010, Eslami et al. 2013). The authors could not find any Northern European
studies reporting the prevalence of dental anomalies among cleft patients. This enhances the value of the present study.

Morphological changes as well as hypoplastic teeth comprised approximately one third of the anomalies. Satisfactory appearance is an issue of major concern for development of good self-esteem. Therefore these dental anomalies and especially anterior morphological changes should be treated as early in life as possible. If permanent treatment cannot be carried out, temporary solutions should be considered. Composites combined with fiber offer a good temporary treatment alternative even for developing dentition (Sándor & Carmichael 2008).

Lip and palate clefts are one symptom among many others which are present in more than 300 syndromes (Rautio et al. 2010, Cameron & Widmer 2008). In the current study the proportion of syndromic children with clefts was 11.5%, being similar to proportions reported in Ireland (14.8%) (McDonnell et al. 2013). According to the results of the current study the clefts among the children with syndromes are not more complex than in non-syndromic children. The prevalence of dental anomalies is similar in both groups as well.

It seems that genetics play an important role in the etiology of clefts. However, many other congenital deformities have been found to be linked with environmental factors such as maternal smoking and alcohol use during pregnancy (Alzenbud et al. 2013). In the present study population clefts were more common among girls than boys. Girls had significantly more hard palate clefts whereas boys had a significantly higher incidence of serious bilateral lip and palate clefts. Genetics may have a role in these phenomena, which should be studied further in future.

Studies on cleft lip and palate patients indicate that clefts may also be associated with diet, vitamin consumption and drug use during pregnancy. Low birth weight is also connected with the incidence of palate clefts (Gonzales et al. 2008). In a cross-sectional study conducted in Pakistan, the aetiological factors of the clefts could not be tracked in 82% of the cases. In 6% of the cases the cause was environmental and in 12% it was genetic. In that study 18% of the patients also had dental anomalies.

Environmental factors vary in different parts of the world. For instance the prevalence of diabetes, an important risk factor during pregnancy for the development of clefts (Yaqoob et al. 2013), varies greatly. The presence of dental anomalies, such as molar incisor hypomineralisation disorder (MIH) has been connected to environmental toxins. The original aetiological factor for both the cleft and dental anomalies can be the same, but the physical existence of the cleft
may also affect the developing tooth buds causing a dental anomaly. This might explain the wider prevalence of dental anomalies among severe clefts and their non-existence among the less severe soft palate and sub mucous clefts.

The youngest children operated in the OUH were excluded from the study group because many dental anomalies such as missing teeth become manifest only later on in life. To assess differences in the prevalence of anomalies in different age groups, the authors decided that the data were to be dichotomised, having cleft patients older than 5 years and 5 years or younger as the cut-off point. The majority of anomalies were anticipated to be in cleft-adjacent teeth. The crowns of the cleft-adjacent teeth being incisors and canines, are generally developed to the point of being radiographically detectable by the age of 5 years. The authors understood the negative side of the timing of this dichotomous division, being that some findings in the non-cleft adjacent premolar areas of the jaws might not be detected. This meant that the true incidence of dental anomalies might in fact be underestimated by this analysis. Further sub-stratifying the data to more age groups did not add to the analysis. Generally studies on dental anomalies are cross-sectional in a variety of older age groups. There are not many studies that compare younger and older age groups regarding dental anomalies among cleft patients (Pöyry & Ranta 1986, Pöyry et al. 1989).

There was a significant difference in prevalence of missing teeth between the two age groups. Teeth were detected as missing less frequently among those 5 years of age or younger compared to the older group. The disorders of the permanent dentition become manifest only after the permanent dentition develops, for example, all teeth excluding third molars develop generally by the age 13. This explains the lower frequency of missing teeth in the younger age group compared to the older ones in the present study. Also mineralisation defects and morphological changes may be diagnosed reliably only at a later age. However, detection of any anomalies as early as possible is beneficial to estimate the patient’s future dental treatment plan needs. Documenting the presence of dental anomalies is important in predicting the costs related to dental care used for understanding the budgetary projections of such comprehensive cleft treatment programmes.

6.2 Caries and dental treatment under general anesthesia (study II)

Study II investigated dental treatment need in patients with clefts in Northern Finland, according to the age and gender of the subject, as well as their cleft types. The results indicated that about one-third of the 6-yr-old cleft children in the study
had dental treatment need, which is in agreement with the outcome reported by Jindal et al. (Jindal et al. 2011). This is almost two-fold more than that noted in non-cleft 5-yr-old children from Kallio public Dental Health Services, Finland. The present study group was slightly dominated by female patients; of the 183 patients, 95 were girls and 88 were boys. Restorative treatment need, however, was more common among boys than among girls, which is also true among the population-based studies involving Finnish adults (Suominen et al. 2003). The difference between genders is the opposite of that suggested by Jindal et al., who reported that female subjects were more likely to experience dental caries during their lifetime than male subjects (Jindal et al. 2011). Distributions of dental caries between the genders maybe culture specific.

These results suggest that dental caries is quite common in Finland in children with clefts, especially in those with an increased degree of cleft severity. For instance, in patients with BCLP, an alarming two-thirds of 6 year old subjects had dental caries lesions; however, it should be borne in mind that the number of participants in the study was limited and therefore great caution must be exerted when making any generalizations. However, the observation of the current study is supported by the results of a Vietnamese study, which analyzed 4 to 6 year old children with clefts. The Vietnamese authors observed that CLP patients have dental caries lesions significantly more often compared with patients with an isolated CP or CL (Besseling & Dubois 2004).

The current study’s data showed that patients with BCLP and patients with UCLP are at increased risk for developing caries lesions. Consequently the more severe the cleft deformity, the more frequently children require dental treatment. In addition to the risk for dental caries, clefts of greater severity also increase the risk for other oral health problems, such as malpositioned teeth, occlusal problems, and jaw-growth disturbances.

Severe CLP patients may require multiple surgical procedures, orthodontic treatment, and speech therapy (Cameron & Widmer 2008). Milder cases, such as isolated CL, may not require any other operation except a lip closure. During their more extensive treatment, patients with a severe cleft may find it difficult also to perform adequate daily oral hygiene. For example, the surgical site may be sensitive for a long period of time, making toothbrushing unpleasant.

Also, orthodontic treatment may make it difficult for patients to clean all areas. From a dental care perspective, a cleft patient requires the same, if not more, preventive and restorative dental treatment compared with a non-cleft child. Again, those with bilateral clefts may require even further attention. Careful oral health-
risk evaluation followed by caries control ensures a healthy dentition for cleft children. Some children only require preventive measures, whereas others require additional restorative treatment, or even extractions.

In the current study, the proportion of syndromic children with clefts was 11.5% of the study population, similar to that reported in Ireland (14.8%) (Mcdonnel et al. 2014). According to the results in this study, clefts among children with syndromes were not more complex than clefts in non-syndromic children, but the prevalence of dental caries was different for the two groups. In syndromic cleft patients, more than half (54.5%) had dental caries lesions compared with those without a syndrome, for whom only less than a third (28.6%) had a need for dental treatment need. A Vietnamese study also found that dental caries was more common in cleft children 4 to 6 years of age with a syndrome than in cleft patients without an associated syndrome. Thus, syndromic patients with cleft deformities are at an increased risk for dental caries (Besseling & Dubois 2004). Of specific syndrome patients, patients with Down syndrome have shown a variable prevalence of dental caries. Sharath et al. noted that 38.1% of 0 to 5 year old Indian children with Down syndrome had dental caries. Portuguese children with Down syndrome, on the other hand, have been shown to have lower dental caries prevalence rates than non-cleft children (Sharath et al. 2008). It is presumed that the reason for this is a heightened concern by the parents for the child’s dental health, with a lower threshold for taking the child for dental care (Areias et al. 2011). In contrast, CATCH 22 patients have been found to have a negative attitude towards oral hygiene, which adds to their potential dental caries risk in this unique group of patients (Kulan et al. 2013).

The present study investigated the number of dental treatments required under general anesthesia in cleft patients in Northern Finland. Both cleft and non-cleft patients may be unco-operative, either because of the sheer magnitude of the dental work required, or as a result of psychological or emotional immaturity (Sari et al. 2014). Such patients may present a scenario where routine dental care is more difficult, if not impossible, to deliver without sedation or even general anesthesia. Sedative premedication and/or nitrous oxide/oxygen sedation may be used as the first line of treatment (Hulland et al. 2002). In more difficult cases, dental care is performed under general anaesthesia (Sari et al. 2014).

Generally, comprehensive dental care of the entire dentition is performed when using general anaesthesia. In the current study, 17.5% of the cleft patients required dental care under general anaesthesia (DGA) for the provision of their dental treatment. Of those patients with a syndrome and dental caries (n=12), only four (33.3%) could be treated without DGA.
In 2010, approximately 160,000 non-cleft patients were treated in the public sector in Helsinki, Finland, with 0.22% of these patients receiving care under general anaesthesia (Savanheimo et al. 2012). Almost the same number was reported in the city of Oulu, Finland, in 2014, where 2/1,000 (0.2%) children in this age group were treated under DGA. There were 18,791 children 0 to 6 years of age, of whom 46 were treated under DGA (statistics from the City of Oulu). These values are significantly lower compared with the 17.5% of patients in this study who required DGAs. It may be speculated that the threshold for referring cleft patients for DGA is lower than for non-cleft patients. In Finland, cleft patients, especially those with bilateral or unilateral cleft lip and palate, are treated under general anesthesia more often than are non-cleft children. The treatments comprise mainly restorative treatments and extractions for dental caries.

The combination of increased caries prevalence in the more severely deformed cleft patients or in those cleft patients with syndromes, plus the increased requirement for DGAs in cleft patients, underscores the increased burden of care that these patients and their families face. The provision of DGAs is an important service for this patient group. The information from this study can be useful for future resource management and planning that is required for this special patient group. One deficiency in the study protocol is missing information at the tooth level, such as decayed, missing, or filled teeth (DMFT) scores, caries status, and the presence of restorations.

6.3 Middle ear findings and the need for ventilation tubes (study III)

Study III analysed the middle ear findings of cleft patients treated in Northern Finland and compared them among groups of different cleft types. The results showed that some secretion, such as mucous, serous or purulent secretions in the middle ear, was found in 78.9% of the patients. Mucous secretion suggestive of OME was discovered in 69.2% of all cleft patients. When comparing cleft types, mucous secretions were found in 96.8% of CLP patients, 69.2% of isolated CP patients and 13.0% of CL patients.

Research published from Finland in 1988 revealed that OME findings were discovered in 8.5% of non-cleft children under 7.5 years of age (Karma & Sipilä 1988). A similar result was obtained in a cross-sectional study in Saudi Arabia, which studied the prevalence of OME and risk factors in school children aged 6 to 12 years. A total of 1488 patients were analysed, and OME was found in at least in one ear in 7.5% of the patients. The criteria for the diagnosis of OME was the
presence of secretions in the middle ear for longer than three months, an average air-bone gap of 10dB, and a deviating tympanogram (Humaid et al. 2014). The prevalence of OME has been studied also elsewhere. It was reported to be 16% in Turkey, 9.5% in the Netherlands, 6.8% in Italy and 6.5% in Greece (Humaid et al. 2014).

The difference is significant when comparing the prevalence of OME between non-cleft children in Finland and other countries, and that in cleft patients treated at OUH. The worldwide prevalence of OME in non-cleft children ranges from 6.8 to 16%, while the prevalence in cleft children of Northern Finland was 69.2% in the current study. This difference can be explained by the fact that cleft patients have different anomalies in the craniofacial area that affect the function of the Eustachian tube. The Eustachian tube cannot function normally and the ventilation of the middle ear is either impaired or non-existent, leading to the accumulation of secretions in the middle ear (Kopcsányi et al. 2015, Ceponiene et al. 2000).

Middle ear ventilation problems are treated by removing the secretion products from the middle ear and by inserting VTs. A Finnish study found that VT insertions were performed for one in every 12 non-cleft children (8.3%) during the follow-up (Karma & Sipilä 1988). A Danish study reported that in three cases out of 10 non-cleft children (30%) VTs were inserted at least once before the age of five (Djurhuus et al. 2015). A Swedish study followed 146 non-cleft child patients in total for a period of 10 years. Twelve of these patients (8.2%) required VT insertions (Håkansson et al. 2015). In the current study 82.7% of all cleft children required VT insertions at least once during their clinical follow-up. In addition to the middle ear findings, VT insertions are notably higher for cleft children in Northern Finland than for non-cleft children in general. Significant differences were found in tube insertion rates between cleft types in this study. VTs were inserted for all (100%) of the CLP patients and for 94.5% of isolated CP patients, while only 13.0% of CL patients required VT placements.

The extent of clefting in isolated CL patients is less severe than with isolated CP or with CLP patients. Therefore in isolated CL patients the Eustachian tube is not involved in the cleft deformity and functions normally in most cases. This explains the need for less frequent tube insertions in cleft lip patients. The data associated with cleft lip patients approximated the rates reported for the non-cleft children (Karma & Sipilä 1988).

According to the treatment protocol, the first VTs were to be inserted in connection with the initial cleft palate repair. These data showed that the first VT placements were performed at the same time as the initial palate repair and 9.1%
required VTs to be inserted even before palate repair surgery. The reason for earlier tube insertions were continuing ear problems preceding palate repair or because of a delay in the timing of the palate repair surgery.

Speech improvement surgery was performed for 26 patients. VT insertion was not performed in two of these 26 children, and the mean tube insertion value of 3.7 was only slightly higher than the mean value of 2.9 for all cleft patients.

A residual palatal fistula was present in 15 patients in this study. The presence of a fistula had an important impact on the number of VT insertions required. Each patient with a residual fistula had VT insertions. The mean number of VT insertions was 5.3, representing the greatest number of required tube insertions in any group analysed in this study.

A study from a Western Australia Hospital followed 56,946 children born after 1980 who had at least one VT insertion from 1980 to 2009. There were 869 children who had cleft conditions and of those patients with cleft conditions 6.9% developed cholesteatoma by 18 years of age while the patients without cleft conditions only 1.5% developed cholesteatoma (Spilsbury et al. 2013). In the current study the prevalence of cholesteatoma was 3.3% of all subjects with tube insertion. Close otolaryngologic follow-up is necessary in cleft patients due to the frequent need for VT placement and since the Interquartile Range (IQR) is 1.5-6.0 years of age. Such follow-up could continue to the age of 8 years thus ensuring that cleft patients with VT are followed during the time they are most likely to be replaced.

6.4 Cleft severity and hearing outcomes (study IV)

The data consisted of cleft patients treated in Northern Finland, where the incidence of CP is known to be common (Lithovius et al. 2014). The goal was to determine hearing results after the first palatal closure surgery. The palate surgery technique was chosen according to the severity of the cleft. Least severe clefts were corrected with the simple straight closure method, moderately severe clefts with the von Langenbeck method and severe clefts required vomer flaps (Bütow 1987).

The objective of the primary palatoplasty is to ensure normal facial development and appearance, normal speech and hearing, as well as to restore a normal level of ventilation in the middle ear. The results of previous studies have varied between different surgery methods and hearing outcomes. Carrol et al. showed that the average PTA was lower in patients whose surgery technique was double-reverse Z-plasty than in patients whose surgery technique was V-Y pushback or von Langenbeck (Carrol et al. 2013). The study by Antonelli et al.
found no differences in hearing results, when they compared the double-reverse Z-plasty method and the von Langenbeck method (Antonelli et al. 2011). The current study found no statistically significant differences between different surgical methods and the PTA. Our results are supported by other studies (Carrol et al. 2013, Paliobei et al. 2005, Tuncbilek et al. 2003). The current study included young children aged 3 to 9 years of age. Adolescents and young adults have not been studied yet. Hearing results should be monitored on a longer-term, into adulthood. This means that the continuation of the study could provide important future material.

The severity level of the cleft or the surgical technique did not affect the number of VTs required in patients 3-9 years who had undergone primary cleft surgery. Other studies compared the severity of the clefts and number of VTs required after primary surgery. They did not find any association, however, in some reports the surgical technique did have a statistical effect on the number of VT insertions required (Carrol et al. 2013, Smith et al. 2008). Smith and associates reported that the need for VT insertions decreased in patients who had been treated with the double-reverse Z-plasty method compared to the four-flap method (Smith et al. 2008). Patients treated with the four-flap palatoplasty needed VTs in fewer cases than patients treated with the V-Y pushback or the von Langenbeck method (Carrol et al. 2013).

The current study showed that hearing improved significantly as the age of the patient increased. Other studies have also found similar improvements in hearing as the age increases (Flynn & Lohmander 2014, Flynn et al. 2013, Skuladottir et al. 2015, Handzic-Cuk et al. 1996). Almost all patients in the research had normal hearing results in the current study. Abnormal hearing results (PTA >20 dB) were only found in 3.1% of the patients with CLP or CP. Two Finnish studies (Marttila 1986, Haapaniemi 1997) examined non-cleft school-age children and their hearing results. One study found hearing loss in 2.5% (at a PTA screening threshold of 20 dB) of patients, and the other study found hearing loss in 20.1% (at a PTA screening threshold of 15 dB) of patients. On the basis of these results it can be concluded that in the current study, the PTA level is better in cleft patients than in non-cleft children in Finland in general. This provides justification to perform VT insertion concurrently with the primary closure of the cleft in accordance with the treatment protocol adopted by the Oulu cleft center.

Almost all patients of the study had undergone a tympanostomy with VT placement, and almost all patients had good hearing results. The study has a statistical problem because of the absence of a control group. As there was no
control group, a cause-and-effect relationship cannot be determined. A group that has not undergone tympanostomies and VT placement would be needed for comparison. However, this would have been ethically not possible since the exclusion of routine practice would not be permitted.

6.5 Strengths and Weaknesses of the four current studies (studies I, II, III & IV)

The four current studies have both strengths and weaknesses. The main strength of the four studies is that their questions are well defined and they have a thematic fit in a unique and well defined population. The weakness is that the population base of the four studies is limited by small numbers of participants. As the cleft program grows so will its study material.

Study I is valuable because prior similar studies in North-Europe and Finland are lacking. A further strength is in recording of data. Because of the priority given to patient electronic records the OUH patient files are up to date and accessible. Each patient's data was accurately identified in the patient files so that erroneous data entry was limited during data collection. The weakness of the study was the limited number of participants. It would have been interesting to determine cleft severity using the same methodology as in study IV with three-dimensional scanning and this will be done in a future study.

Study II provided valuable information because it was the first study in Finland which examined the need for DGAs with cleft lip and palate patients. The weakness was missing information in the DMFT scores. The occurrence of dental-caries lesions were recorded using only yes/no answers.

In study III the patients had detailed files with records of their otologic history because they were closely followed by an otolaryngologist at least 1-3 times per year or more often if necessary. This yielded valuable information regarding middle-ear findings. The weakness of study III was that cleft lip patients should have been excluded from the study. The Eustachian tube is not involved in the cleft deformity of the isolated cleft lip patients and functions normally in most cases. This distorted the results when determining the need for VTs in cleft patients. On the other hand isolated cleft lip patients could serve as a control population that do not require more VTs than a non-cleft population.

One of the strengths of study IV was the multitude of perspectives in the multidisciplinary team analyzing the data. Also cleft severity grades were determined using three-dimensional scanning which provided a unique perspective.
The weakness of study IV was the absence of a control group. Since there was no control group, a cause-and-effect relationship could not be examined. Another weakness was the small study population numbers because only 90 patients met the inclusion criteria of the study.

6.6 Future directions

There are several exciting areas of development which may change the approach to problems faced by patients with CLP as time progresses.

6.6.1 3D photography of infants with CLP

Usual 2-D radiographic imaging, including posteroanterior, oblique cephalometric and panoramic radiographs, has suffered from distortion and magnification errors. Its reliability has been limited, especially in the determination of facial asymmetry (Lin et al. 2015, Suomalainen et al. 2014). Cone Beam Computerized Tomography (CBCT, 3D imaging) scans provide more information than conventional dental radiographs but ionizing radiation dosages should not only be minimized, avoidance would be preferable.

3D CBCT imaging has been used to better determine the grafted bone mass, spatial placement, it has also been used to monitor the orthodontic treatment of the cleft-adjacent teeth, the position of prosthetic treatment with dental implants and the subsequent eruption of the canine or incisor. 3D imaging has been first achieved by the use of conventional computed tomography and, more recently, with lower radiation dosages using CBCT (Suomalainen et al. 2014). 3D photographic imaging of infants with CLP can be used to quantify improvements not only following primary surgery in three dimensions but also during and after the use of dynamic nasoalveolar molding appliances. 3D photography also makes it possible to collect long-term follow-up images to document whether changes in symmetry (Vuollo et al. 2016) have appeared during subsequent growth. In the future 3D photography of infants with CLP will be an effective clinical tool for pre-operative severity determination, pre-operative diagnosis, for surgical planning, for the documentation of results and to analyze the quality of the treatment outcomes (Harila et al. 2015).


6.6.2 Tissue engineering in cleft care

In 2005 Carstens et al. reported on the reconstruction of seven different lateral facial clefts by implanting a collagen sponge soaked with recombinant human BMP-2 and distraction into the expanding periosteum. Carstens et al. reported abundant bicortical bone production. They named the technique distraction-assisted in situ osteogenesis (DISO) (Carstens et al. 2005).

In 2009 Behnia et al. reported on the first use of human mesenchymal stem cells (MSCs) in two CLP patients (Behnia et al. 2009). Patients were treated using scaffolds of demineralized bone matrix (DBM) and calcium sulphate. The authors reported 25.6% maintenance of bony integrity in one case and 34.5% regenerated bone in the other case. In 2012 the same authors reported on a new approach. In three cleft patients MSCs were placed on biphasic calcium phosphate scaffolds with platelet derived growth factor (PDGF), forming the tissue engineering triad: cells, scaffold and a growth factor. Post-operative cleft volumes were measured using CT scans. Three months after surgery the fill of the bone defect was a mean of 51.3% where no bone graft had been used.

Another approach that Bueno et al. reported was that an alternative stem cell source for potential osteogenesis can be found by using orbicular oris muscle (OOM) fragments, which have been found to contain muscle stem cells (Bueno et al. 2009). OOM fragments are normally discarded during cheiloplasty. After the production of suitable culture conditions, these cells were able to exhibit adipogenic, chondrogenic, osteogenic, and skeletal muscle cell differentiation. The authors also demonstrated that, together with a collagen membrane, these cells could lead to the formation of bone tissue in non-immunocompromised rats with critical-size skull defects. The presence of human DNA in the new bone was confirmed with PCR. The authors concluded by pointing out that it is characteristic to OOM cells that their phenotype and behaviour are similar to other stem cells of adults in vitro and in vivo. This approach gives hope for the reinvigoration of bone and offers possibilities for forming new lip muscles in corrective lip surgeries.

Other possible sources of stem cells are the bone chips collected with a vacuum fitted with a filter during the removal of the third lower jaw molar or during the osteotomies in a cranioplasty. The advantage of this technique is that stem cells can be collected during routine oral surgical and cranio-maxillofacial procedures. The removal of the third molar can also present new opportunities. Its evolving follicle can also lead to follicular cells, which can be cultivated and studied along with
other dental stem cells. These include dental pulp stem cells, periodontal ligament stem cells and stem cells of the apical papilla (Sândor 2015).

6.6.3 Mitochondrial DNA and genetics

Although most DNA is packaged in chromosomes within the nucleus of the cell, mitochondria contain their own DNA in a single circular chromosome. This genetic material is known as mitochondrial DNA (mtDNA). In humans, mtDNA spans about 16,500 DNA units to represent a small part of the total DNA in cells. The mitochondrial genome contains 37 genes. Thirteen of these genes encode subunits of the electron-transfer chain, 2 ribosomal RNAs and 22 transfer RNAs. It has become well known that mtDNA mutations are associated with several syndromes. Common mtDNA diversity may have increased the risk of developing multifactorial neurodegenerative disorders (Chu et al. 2015).

Mitochondrial haplotypes have been suggested as a potential tool to help in the gene identification of the susceptibility to clefts and East Europe is represented by several mitochondrial haplotype groups (H, V, U, J, T, N1b, I, W, and X). MtDNA variants may not play a direct role in the development of CL or CLP but they may be a substitute for population substructure and used as a tool to increase homogeneous and statistical power (Vieira et al. 2011). MtDNA may also explain why UCLP has a left sided predilection (Mittwoch 2008). A study from Latvian cleft population reported that the mtDNA haplogroups U4 and U5 may be ideal for use to perform a whole-genome linkage disequilibrium screen.

Haplogroups may show the same genetic causes of cleft lip and palate because it has theoretically the same maternal founder (Vieira et al. 2011). Lace et al. found that the phenotype of patients with non-U haplotypes was associated with markers in wingless-type MMTV integration site family, collagen, member 3 (WNT3), type XI, alpha 2 (COL11A2), and fibroblast growth factor receptor 1 (FGFR1) (Lace et al. 2011). Patients with U4 and U5 haplotypes showed prominent association with COL11A2 and WNT3. Future studies should consider these findings based on mtDNA haplotypes when analyzing genetic variations and their possible association with CLP susceptibility.

6.6.4 Eurocleft

Protocols for the treatment of CLP can vary significantly in the burden of treatment imposed (Semb et al. 2005). The Eurocleft Project spanned 1996-2000 and was a
follow-up of the original Eurocleft study from 1992. The follow-up project was known as standards of care for CLP in Europe (Singh et al. 2014). Cleft services, treatment and research have certainly suffered from random implementation through Europe. Attainment of even minimum standards of cleft treatment remains a big challenge in some regions and both the will to reform and a basic strategy to follow are left behind.

It is hoped that the Eurocleft Consensus Recommendations will assist in improving the opportunities for future patients (Shaw et al. 2001, Singh et al. 2014). Standardized common treatment protocols between cleft centres helps in cooperation and assessment of outcomes. The standardization and timing of follow-up visits and the orderly taking of records including clinical photographs, dental models and radiographs helps avoid unnecessary duplication and repeated radiation exposure. Such structure will ensure that protocols will become more comparable so that advantageous outcomes can be recognized.

6.6.5 Oral health related quality of life study

The existence of clefts influences all fields of life. The OUH team is already collecting data for an ongoing oral health related quality of life (OHRQL) study in this particular cleft study population. It may well be that this specific group of children and adolescents need more active support during their growth and development. It is most beneficial to have a psychiatrist with specialized interest in the issues of children and adolescents as part of the team. All adolescents attending the cleft multidisciplinary clinic in the year when they turn 18 years of age are asked to complete a modified CPQ, previously tested among 14-year-olds in OUF (Luoto et al. 2009). This data collection is planned to continue until the end of 2017.

6.6.6 Future longitudinal continuation of studies I, II, III & IV

In study I dental anomalies were found to be more common in cleft children than in non-cleft children. Anomalies were more common in children with more severe clefts. Future research could be focused on children with more severe clefts and multiple dental anomalies. The purpose of such a study would be to determine what treatment the patients have received, and the situation of the teeth at adulthood when compared to the situation of the teeth at the time of the current study. Patients’ satisfaction with the treatment could also be determined.
It was reported in study II that treatment is free of charge for cleft children aged under 18 years in Finland. Cleft patients see experts from multidisciplinary fields related to cleft treatment. Dental examinations, as well as follow-up visits take place frequently, especially in severe cleft cases. As a result, these children are at the best indicators of the need for dental treatment. DGAs are more common in cleft patients than in non-cleft children. A similar study a few years following the end of cleft treatment would provide valuable information on how the need for dental treatment changes when regular cleft follow-ups are no longer provided free of charge. Will patients who had previously received dental treatment under general anaesthesia continue to seek dental treatment in adulthood independently? The purpose of the study would be to determine the need for dental treatment in adulthood after the coverage for cleft treatment has ended.

In study III numerous tympanostomies were performed for several cleft patients in the study. In the future, a further study would focus on these multiply re-operated patients. The purpose of the study would be to determine whether the several tympanostomies and VT placements performed at a young age had an effect on the status of the middle ears in adulthood. This study would compare cleft patients who have undergone several repeated tympanostomies versus VT placement in cleft patients who have undergone no more than one tympanostomy with VT placement. The study results would provide valuable information regarding the current treatment protocol of the OUH, which states that tympanostomies must be replaced if glue ear is diagnosed at least three times in 6 months or over four times in a year.

In study IV the current study included only young children aged 3 to 9 years of age. Adolescents and young adults were not studied as of yet. Hearing results should be monitored on a longer-term basis, into adulthood. This would provide long-term results that include older aged groups with valuable longitudinal information.
7 Conclusions

In study I cleft patients treated in the Northern Finland were found to suffer from more dental anomalies than non-cleft children in general. Missing and supernumerary teeth were the most common anomalies. The severity of the cleft increases the prevalence of dental anomalies. Clefts were more often found in females, and isolated CP was the most common cleft type. CLP was more common on the left side in this population. The cause of this left sided predilection is unknown. It may be concluded that whether the cleft is a result of genetic factors, environmental factors or a part of a syndrome, clefts are often associated with the developmental disorders of teeth presenting as oligodontia, supernumerary teeth, hypoplasia or hypomineralisation. These must be taken into consideration in treatment and resource planning.

In study II the presence of a cleft was not directly found to increase the need for dental treatment of cleft patients. The need for dental treatment, however, increased with the severity of the cleft. The presence of a syndrome increased the need for dental treatment. Northern Finnish cleft patients treated at the OUH received dental treatment under general anaesthesia significantly more often than non-cleft children. Caries control must be an essential part of the management among non-cleft as well as cleft patients.

In study III cleft patients treated in the North Finland were found to suffer from more middle ear problems and had more middle ear secretions and required more tympanostomies and VT placements than non-cleft children in Finland. CLP patients and patients with isolated CP had more extensive clefts affecting Eustachian tube function and consequently had more frequent middle ear ventilation problems and required a greater number of VTs than patients with isolated CL who had less severe clefting. Continuous presence of VTs increased the prevalence of tympanic perforation and cholesteatoma. Close otolaryngologic follow-up was necessary in CP patients due to frequent need for VT placement. Since the IQR is 1.5-6.0 years of age such follow-up could continue to the age of 8 years thus ensuring that cleft patients with VTs are followed during the time they are most likely to be replaced.

In study IV the majority of 3 to 9 year old cleft patients had a normal hearing threshold ($\leq$20 dB). The surgical technique or severity of the cleft did not affect the hearing results or the number of VT placements. Hearing improved significantly after the age of 6 years. Care of cleft children involves multidisciplinary management from birth to adulthood. Continuous follow-up, with early diagnosis
and treatment should improve dental, hearing and speech outcomes and support the social development of cleft children in general.
References


Wells M (2014) Review suggests that cleft lip and palate patients have more caries. Evid Based Dent 15: 79.


Original Publications


Reprinted with permission from the publisher.

Original publications are not included in the electronic version of the dissertation.
1361. Hannila, Iikka (2016) T2 relaxation of articular cartilage: normal variation, repeatability and detection of patellar cartilage lesions
1362. Pihlaja, Juha (2016) Treatment outcome of zirconia single crowns and fixed dental prostheses
1365. Aro, Jani (2016) Novel load-inducible factors in cardiac hypertrophy
1366. Mäkynen, Mikko (2016) Hypoxia-inducible factor prolyl 4-hydroxylase-2 in Tibetan high-altitude adaptation, extramedullary erythropoiesis and skeletal muscle ischemia
1368. Krökki, Olga (2016) Multiple sclerosis in Northern Finland: epidemiological characteristics and comorbidities
1369. Mosorin, Matti-Aleksi (2016) Prognostic impact of preoperative and postoperative critical conditions on the outcome of coronary artery bypass surgery
1372. Helkkula, Anne (2016) Ketoacidosis at diagnosis of type 1 diabetes in children under 15 years of age

Book orders:
Granum: Virtual book store
http://granum.uta.fi/granum/
Ville Lehtonen

DENTAL AND OTOLOGIC PROBLEMS IN CLEFT LIP AND PALATE PATIENTS FROM NORTHERN FINLAND

CLEFT ASSOCIATED PROBLEMS