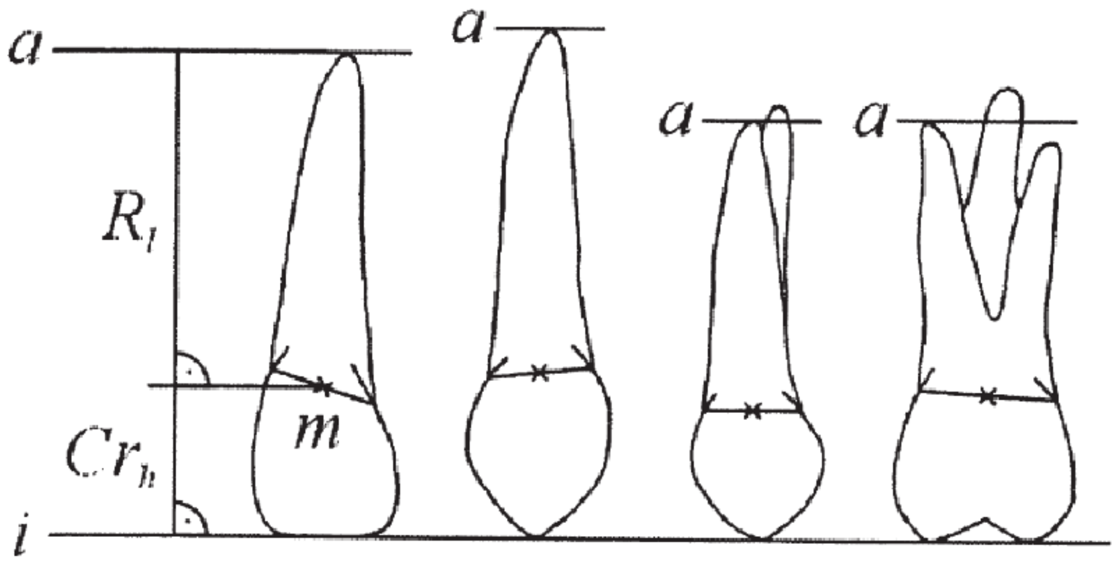
Root-crown ratios of permanent teeth in long-term survivors after acute lymphoblastic leukemia treated during childhood and adolescence

A research study



Hölttä P, Nyström M, Evälahti M, Alaluusua S. Root-crown ratios of permanent teeth in a healthy Finnish population assessed from panoramic radiographs. European Journal of Orthodontics 2004 26:491-497.

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Co-supervisor: PhD candidate Petter Wilberg

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FORORD

Denne forskningsstudien er del av et stort forskningsprosjekt som er et samarbeid mellom Oslo Universitetssykehus HF (Rikshospitalet) og Det odontologiske fakultet, Universitet i Oslo. Resultatene fra denne artikkelen vil inngå i doktorgradsavhandlingen til stipendiat Petter Wilberg og vil publiseres når overnevnte forskning er avsluttet.

Sommeren 2010 ble vi tildelt NRFs sommerstipend for å starte vår del av dette forskningsprosjektet som etter mye tid og arbeid har endt med masteroppgave. Ca. 400 timer hver har vi lagt ned i dette mastergradsarbeidet som kan deles i tre deler. Den første delen besto av å lese oss opp på relatert forskning og emnet generelt, samt planlegging. Veilederne satt oss inn i det overordnede forskningsprosjektet og vi tok del i datainnsamlingen fra pasientene som foregikk på Rikshospitalet. Her ble det blant annet tatt OPG av pasientene. Hoveddelen av masteroppgaven lå i selve målingene av rot- og kronedelene av tenner på OPG. I prosjektbeskrivelsen ble det antatt at ca. 40 OPG ville bli inkludert, men pga stor tilbakemelding fra pasientgruppen, ble det hele 141 OPG totalt. Dette ga oss et svært godt grunnlag for resultatene vi har kommet frem til, og gjorde at oppgaven ble mer tidkrevende enn først forventet. Den siste delen av arbeidet besto av å gjøre målingene om til resultater vha av SPSS, tolke disse og tegne dem ned i og utforme denne artikkelen.

Arbeidet er utført av stud.odont. Betina Adriana Lind van Pelt og Julie Wilberg (kull V-07).

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Betina Adriana Lind van Pelt, Julie Wilberg, Petter Wilberg, Bente Brokstad Herlofson

ABSTRACT

Anti-cancer treatment may affect developing teeth by growth retardation

Aim: The aims of the present cross-sectional, descriptive study was to assess the root-crown (R/C) ratios in permanent teeth in long-term childhood cancer survivors (CCSs) treated for acute lymphoblastic leukemia (ALL) during childhood, and to compare them to R/C ratios from a healthy Finnish population.

Patients and methods: In total 141 CCSs were included in this study of which 72 were males. They were diagnosed with ALL before the age of 16, observed for a minimum of five years after diagnosis and > 18 years at the time of survey. There were 3942 teeth in total and after exclusions 3179 were measured. The results were compared to the R/C ratios of a healthy Finnish population using a method described by Hölttä and coworkers. Crown height and root length were measured on panoramic radiographs (PRGs).

Results: Except from maxillary central incisors, the results show no difference in R/C ratios between genders ($P < 0,05$). In male CCSs there was a lower R/C ratio in maxillary and mandibular premolars and molars compared to the healthy Finnish population ($P < 0,05$). In female CCSs there was a lower R/C ratio in maxillary laterals, canines, premolars and molars and mandibular premolars and first molars ($P < 0,05$). When comparing the age groups; <5, 5-13, ≥13, there was a significant difference between maxillary second molars, mandibular premolars and second molars. For maxillary second molars the R/C ratio was lowest in the age groups 5-13 and ≥13. For mandibular premolars and second molars the R/C ratio was lowest in the group 5-13.

Conclusion: The results in this study show that R/C ratios of permanent teeth in CCSs are lower for several of the tooth pairs. This indicates that ALL treatment may affect tooth development.

INTRODUCTION

Childhood cancer account for around 2 % of the total number of cancer cases worldwide. ALL is the most common malignancy diagnosed in children, representing nearly one third of all pediatric cancers [1]. ALL is a malignant transformation of lymphoid progenitor cells displayed in childhood [2]. Before 1950, the literature showed that nearly all children diagnosed with cancer died [3]. Significant advances in the treatment of most pediatric cancers have been achieved since the early 1970s in terms of overall survival. Especially an improved survival rate amongst children with ALL has been seen [2]. The risk of dying from ALL between 1983-1994 decreased by 5-6 % per year [3], and the survival rate for children with ALL is approximately 80% [2]. This means that there will be a large number of long-term CCSs with possible long-term side effects of their treatment during childhood in the future. The majority of the patients with ALL are diagnosed at the age of 2-3 [2]. In Norway the incidence of ALL diagnosed before the age of 15 was at average per year 33 patients during the years 1992-2000 [4].

The treatment of ALL involves a sequential combination of chemotherapy during a period of several months even years [5]. Haematopoietic stem cell transplantation (HSCT) and radiotherapy may also be indicated in patients with ALL [5]. Oral complications are common in all ALL patients undergoing systemic chemotherapy, radiotherapy and/or HSCT [5]. Knowledge of acute and long-term oral side effects of cancer treatment in children and adolescents (overall incidence: 30-100%) are of significant importance also to dental health professionals [5]. The morphogenesis of teeth starts in utero and is normally completed by the age of 15 as seen in *figure* 1[6, 7]. One of the side effects of anti-cancer treatment given before the age of 16 is disturbed dental development as these patients are treated while the teeth are formed. Several types of disturbances have been reported ranging from increased frequency of agenesis, microdontia, hypomineralization and hypoplasia of enamel. Disturbances in root development have also been reported; short roots, malformed roots, V-shaped tapering roots and blunting of the apical area [6, 8-11]. Children treated before the age of 5-6, show the most severe dental disturbances [6]. On PRGs root development can be seen from the age of 3 (central incisors, permanent first molars) to 7,5 (permanent second molars) [11]. Objective measurements on R/C ratios cannot be made until the root development has been terminated [11]. Anti-cancer treatment for ALL may affect developing teeth by growth retardation. [8]. Root growth will continue after completion of therapy [8]. Depending on when the treatment was given, it is possible to estimate which teeth will be most affected [6]. The prognosis of teeth with unfavorable R/C ratios may be affected, especially if orthodontic or prosthodontic treatment is needed [12].

This study investigated disturbed tooth development in only one specific cancer diagnosis; ALL. Other studies have shown a significant impact of cancer treatment on tooth development in young children, but none of them studied one diagnose in particular [8- 11]. Even though studies have shown long-term dental growth disturbances after treatment, it has been given little attention [9]. At present, new dental healthcare rights for hospitalized patients are in preparation by the Norwegian Government. It is therefore important to study long-term treatment needs in ALL patients since late side effects may occur after many years [11]. The aims of the present study was to investigate if the R/C ratios in permanent teeth of long-term CCSs are influenced by ALL treatment during childhood, and to compare the results with the R/C ratios of a healthy Finnish population published by Höltta and coworkers in 2004 [12].

PATIENTS

This is a study on R/C ratios on permanent teeth in CCSs after treatment for ALL. The study is part of a major research project instigated by Oslo University Hospital HF (Rikshospitalet) in collaboration with Det odontologiske fakultet, University of Oslo. It includes CCSs from all health regions in Norway all diagnosed with ALL before the age of 16 between 01.01.1970 and 31.12.2002 and observed for a minimum of 5 years after diagnosis. The CCSs were identified by the Norwegian Cancer Registry and should be >18 years old at the time of the survey. Informed consent was obtained before inclusion. The data collection started in 2009 and was concluded in June 2011. In total 141 CCSs were included in the study of which 72 were men.

METHODS

The R/C ratios of fully developed permanent teeth were assessed in this descriptive, cross-sectional study by two investigators (BALP, JW) separately on PRGs. The PRGs taken at Rikshospitalet were anonymized and the investigators were blinded to type of treatment and at which age the CCSs were treated. The R/C ratio measurement method used in the present study is described by Hölttä and coworkers in 2004 after a modification of a method first established by Lind in 1972 [13]. The CCSs answered a questionnaire, was given a medical examination and interviewed by a physician. A dentist (PW) interviewed, examined orally and took a PRG of each CCS. The height of crowns and length of roots were measured to the nearest half or whole millimeter by a standardized transparent millimeter plastic grid [12]. Point *m* in all teeth was found on the border between the crown and the root [12, 13] (*Figure* 2). A perpendicular line from point *m* to the incisal/occlusal reference line (*i*) was the crown height (Cr_h) and it was assessed as followed according to Hölttä [12]:

1. Canines and most premolars which have one incisal tip or buccal cusp were measured by placing the measuring grid perpendicular to the long axis of the tooth on the tip or cusp
2. Incisors with an edge and molars with several buccal cusps were measured by placing the measuring grid on the incisal edge or to connect the buccal cusps

Root length (R_l) was measured from apex (*a*) to point *m*. For premolars with two roots the length was measured from the shortest root. For molars the longest buccal root was measured. In cases were only one root was visible this root was measured. All third molars were excluded.

Individual teeth were excluded if:

1. Apex was not closed (*n=0)*
2. Reference points not clearly visible (*n=432*)
3. Roots were markedly deviated (*n=4*)
4. History of dental trauma with or without tooth fracture (*n=6*)
5. Presence of attrition or abrasion of the crown (*n=181*)
6. Microdontia (*n=54*)
7. Teeth in cleft jaw (*n=0*)

8. Agenesis (*n=12*)
9. Missing tooth because of orthodontic treatment (*n=50*)
10. Missing tooth because of caries (*n=30*)

When in doubt considering exclusions, investigator and author PW made the final decision. To assess intra- and inter-examiner reproducibility, the two investigators measured all teeth on 5 PRG and re-assessed them after a week. The R/C ratio was calculated by dividing the root (*R*) length by the crown (*C*) height. The R/C ratios of the study group were then compared to the R/C ratios of the healthy Finnish subjects in the study by Höltta, from here called the control group.

STATISTICS

All data will be registered and analyzed using The Statistical Package for the Social Sciences, version 18.0 (IBM SPSS for Windows, IBM corporation, Armonc, New York, USA). Mean values were compared using independent-samples T-test when analyzing two independent groups, and the Kruskal-Wallis test was used when the results from three subpopulations were compared.

ETHICAL CONSIDERATIONS

The overall study protocol was approved by the Regional Ethics Committee (Regional komitè for medisinsk og helsefaglig forskningsetikk (REK sør-øst)) with reference number S-07094b.

RESULTS

141 CCSs were included in the study of which 72 were men. There were 3942 teeth in total, after exclusions by the investigators 3179 teeth (80,5 %) of the total amount were measured. R/C ratios for males and females are described in *Table* 1. Except from maxillary central incisors, the results show no difference in R/C ratios between genders ($P < 0,05$). *Table* 3 and 4 present a comparison of R/C ratio in CCSs (study group) and the control group. There was a lower R/C ratio in maxillary and mandibular premolars and molars in male CCSs ($P < 0,05$). In female CCSs a lower R/C ratio in maxillary laterals, canines, premolars and

molars and mandibular premolars and first molars were seen (*P < 0,05*). Between the age groups defined in *Table* 5 there was a significant difference between maxillary second molars, mandibular premolars and second molars (*P < 0,05*). For maxillary second molars the R/C ratio was lowest in the groups 5-13 and ≥13 years. For mandibular premolars and second molars the R/C ratio was lowest in the age group 5-13.

DISCUSSION

The present study showed that treatment of pediatric ALL patients before the age of 16 induced long-term dental side effects with reduced R/C ratios of developing teeth. Our study showed a mean value of contralaterals in each CCS, while Hölttä's study included both teeth in each tooth pair (*Table* 1-4). The R/C ratios of contralateral tooth pairs are very much alike, so the mean value of contralaterals will not differ much from the mean value of the control group [12]. The number of CCSs (*n*) in this study and number of teeth in the control group (*n*) may therefore be compared (*Table* 1-4). Almost no difference in R/C ratios was seen between genders in our study population compared to several differences in the healthy Finnish population in the study by Hölttä. The discrepancy may be due to the fact that our study included more patients compared to the Finnish study population. The subjects included in our study had been given cancer treatment which influenced tooth development and this may have induced more even R/C ratios between genders.

Studies have shown that reduction in root size is more pronounced than the reduction in crown size following multimodal chemotherapy [8].The results in our study showed that there are lower R/C ratios in certain tooth pairs in CCSs compared to healthy individuals. Chemotherapy given at a certain age may affect different teeth due to different stages in tooth development. The results show lower R/C ratio in premolars, but many of the affected teeth also had more than two roots. This indicates that teeth with several roots may be more severely affected with disturbed root development than teeth with a single root. As shown in *Figure* 1, second molars and mandibular premolars have root development from approximately 6 years. This may explain the significant results shown in *Table* 5. It is important to take into consideration individual differences in tooth development and other factors such as orthodontic treatment and unknown trauma which can lower the R/C ratio. Fifty-one (36.7%) CCSs had orthodontic treatment during childhood. Traumatized teeth were excluded but there might have been unknown episodes of trauma not recognized by the young cancer patient.

There are several limitations to the method used in this study. The quality of the PRGs varied all though they were taken with the same machine by the same operator (PW). PRGs often overlap in the premolar region in the upper jaw which could lead to difficulties finding the cemento-enamel junction [12]. This affected the overall exclusion rate because an unclear reference point was one of the criteria for exclusion. Even though the PRG procedure can be the source of error, the main problem may be the investigators' inability to recognize the same reference points [12, 14]. The goal of the intra- and inter-examiner reproducibility test was to eliminate these errors. Another limitation to the method is the age at which the PRGs were taken. In this study the study population was between 18-47 years compared to a mean of 18 year in the study by Hölttä. Most likely this has resulted in a high DMFT value and more attrition in the study group and possibly increased the number of excluded teeth. If the PRGs in our study had been taken at an earlier age, the results may have been even clearer. The most favorable control group for comparison of results would have been healthy Norwegians with the same distribution of gender and age. There is also a chance that some of the most affected teeth have been excluded due to the fact that many of them have had extensive conservative or prosthodontic treatment.

High dose chemotherapy and total body irradiation have been shown to induce disturbed root development when the treatment was given before the age of 10 [11]. This study has assessed R/C ratio, but other root/tooth anomalies could have been taken into consideration as well, like root development failure, V-shaped tapering roots, blunting of the apical area, microdontia and short crown [6, 8-11]. More research is necessary to elucidate the mechanism of action on developing odontogenic cells of the different drugs used in the treatment of ALL. Because of the different late effects on teeth after cancer treatment of ALL during childhood, it is important to assess dental treatment needs.

CONCLUSION

Treatment of childhood ALL affects developing teeth by lowering the R/C ratios of permanent teeth in CCSs compared to R/C ratios in healthy individuals.

ACKNOWLEDGEMENTS

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FIGURE 1.
The chronology of mineralization of permanent teeth.
Reprinted with the permission of Blackwell Publishing Ltd. from Koch G, Thesleff I. Developmental disturbances in number and shape of teeth and their treatment. (In: Koch G, Poulsen S, editors. Pediatric dentistry—a clinical approach, 1st ed. Copenhagen: Munksgaard, 2001:253–271.)

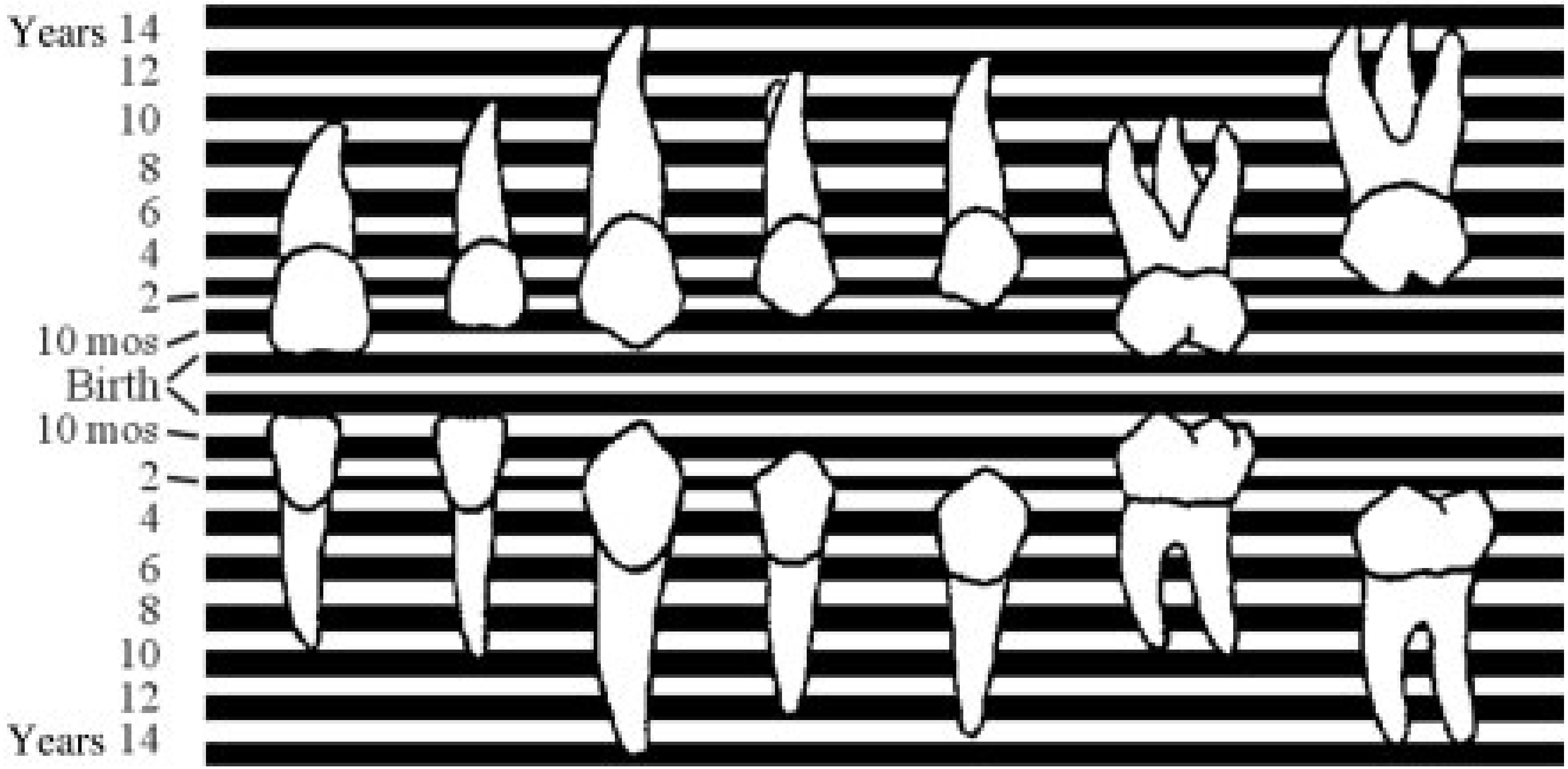

Figure 2. The method used for measuring Cr_h and R_l as described in the text (Hölttä 2004 normal, Lind 1972).

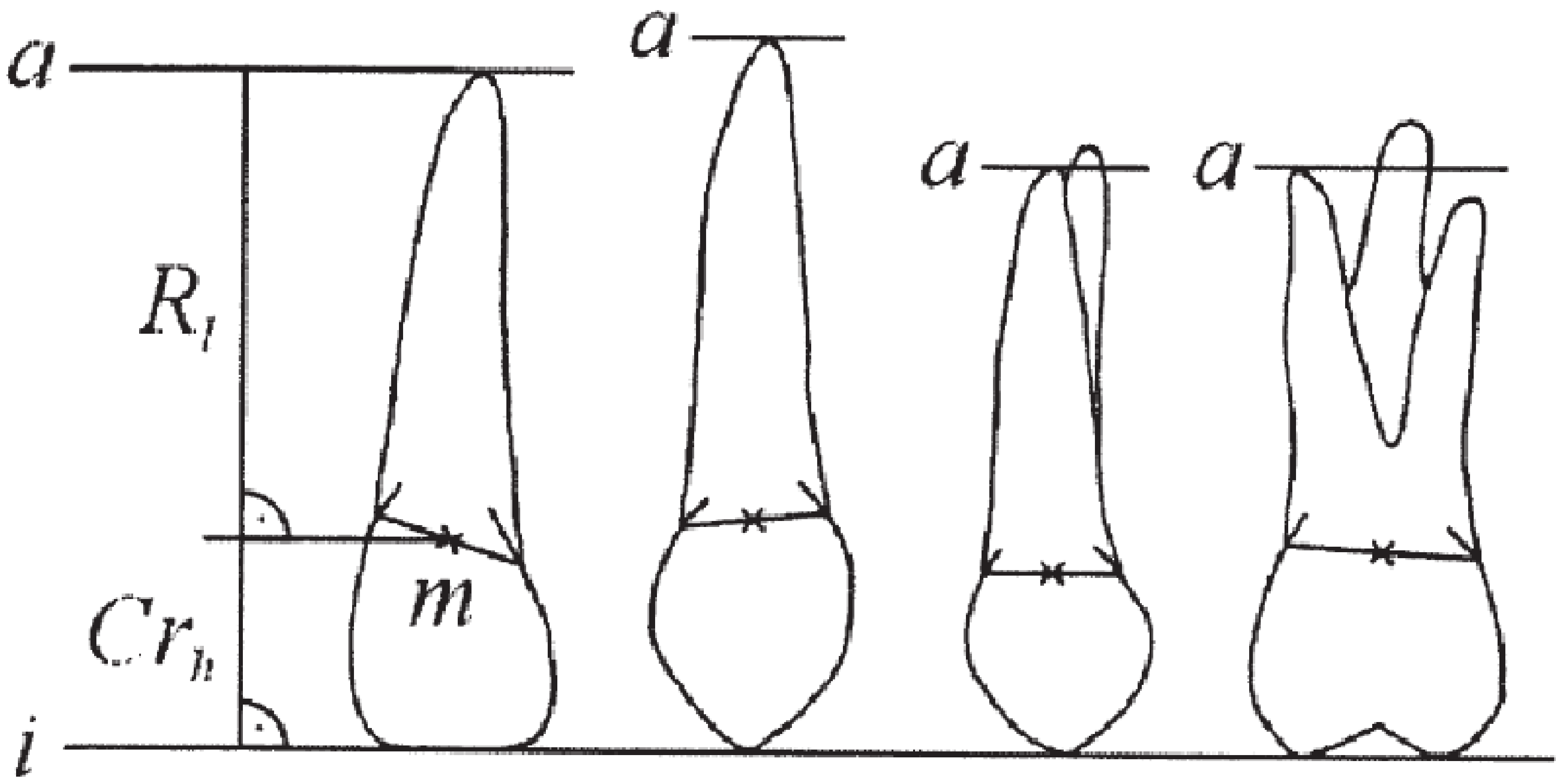

TABLE 1

Mean R/C ratios of male and female in study group

n= number of patients

Independent-sample T-test was used to compare the mean values

Teeth	n		mean		SD		P males vs females
	Male	Female	Male	Female	Male	Female	
11,21	52	56	1,90	1,76	0,27	0,25	**
12,22	56	53	2,00	1,91	0,23	0,22	NS
13,23	53	56	2,02	2,00	0,30	0,27	NS
14,24	26	43	1,61	1,65	0,33	0,24	NS
15,25	44	44	1,90	1,86	0,28	0,26	NS
16,26	52	44	1,58	1,54	0,24	0,22	NS
17,27	49	51	1,69	1,72	0,27	0,22	NS
31,41	52	58	2,04	1,94	0,38	0,33	NS
32,42	52	59	2,09	2,04	0,27	0,35	NS
33,43	47	48	2,25	2,16	0,35	0,36	NS
34,44	59	60	2,13	2,07	0,31	0,26	NS
35,45	57	53	2,32	2,34	0,31	0,31	NS
36,46	56	48	2,02	1,99	0,24	0,24	NS
37,47	59	53	1,92	1,92	0,25	0,27	NS

*P ≤ 0,05; **P ≤ 0,01; ***P ≤ 0,001; NS, P > 0,05

TABLE 2

Mean R/C ratios of male and female in control group

n= number of teeth

Independent-sample T-test was used to compare the mean values

Teeth	n		mean		SD		P males vs females
	Male	Female	Male	Female	Male	Female	
11,21	105	106	1,86	1,78	0,17	0,16	**
12,22	102	105	2,04	1,97	0,21	0,18	**
13,23	103	102	2,10	2,10	0,22	0,21	NS
14,24	78	68	2,16	2,15	0,22	0,22	NS
15,25	88	92	2,19	2,21	0,22	0,25	NS
16,26	101	92	1,87	1,80	0,15	0,15	**
17,27	105	100	1,99	1,94	0,17	0,18	*
31,41	95	105	1,97	1,92	0,16	0,14	**
32,42	102	107	2,05	2,02	0,17	0,16	NS
33,43	92	101	2,22	2,23	0,23	0,20	NS
34,44	101	105	2,43	2,42	0,27	0,25	NS
35,45	99	105	2,44	2,46	0,26	0,24	NS
36,46	105	101	2,11	2,07	0,17	0,18	NS
37,47	106	108	2,01	1,98	0,18	0,19	NS

*P ≤ 0,05; **P ≤ 0,01; ***P ≤ 0,001; NS, P > 0,05

TABLE 3

A comparison of mean R/C ratios in the male study group and control group

This study, n= number of patients; Hölltä, n= number of teeth

Independent-sample T-test was used to compare the mean values

Teeth	n		mean		SD		P this study vs Hölltä
	this study	Hölltä	this study	Hölltä	this study	Hölltä	
11,21	52	105	1,90	1,86	0,27	0,17	NS
12,22	56	102	2,00	2,04	0,23	0,21	NS
13,23	53	103	2,02	2,10	0,30	0,22	NS
14,24	26	78	1,61	2,16	0,33	0,22	***
15,25	44	88	1,90	2,19	0,28	0,22	***
16,26	52	101	1,58	1,87	0,24	0,15	***
17,27	49	105	1,69	1,99	0,27	0,17	***
31,41	52	95	2,04	1,97	0,38	0,16	NS
32,42	52	102	2,09	2,05	0,27	0,17	NS
33,43	47	92	2,25	2,22	0,35	0,23	NS
34,44	59	101	2,13	2,43	0,31	0,27	***
35,45	57	99	2,32	2,44	0,31	0,26	*
36,46	56	105	2,02	2,11	0,24	0,17	*
37,47	59	106	1,92	2,01	0,25	0,18	*

*P ≤ 0,05; **P ≤ 0,01; ***P ≤ 0,001; NS, P >0,05

TABLE 4

A comparison of mean R/C ratios in the female study group and control group

This study, n= number of patients; Hölltä, n= number of teeth

Independent-sample T-test was used to compare the mean values

Teeth	n		mean		SD		P this study vs Hölltä
	this study	Hölltä	this study	Hölltä	this study	Hölltä	
11,21	56	106	1,76	1,78	0,25	0,16	NS
12,22	54	105	1,92	1,97	0,23	0,18	*
13,23	56	102	2,00	2,10	0,27	0,21	*
14,24	43	68	1,65	2,15	0,24	0,22	***
15,25	44	92	1,86	2,21	0,26	0,25	***
16,26	44	92	1,54	1,80	0,22	0,15	***
17,27	51	100	1,72	1,94	0,22	0,18	***
31,41	58	105	1,94	1,92	0,33	0,14	NS
32,42	59	107	2,04	2,02	0,35	0,16	NS
33,43	48	101	2,25	2,23	0,36	0,20	NS
34,44	60	105	2,13	2,42	0,26	0,25	***
35,45	53	105	2,32	2,46	0,31	0,24	**
36,46	48	101	2,02	2,07	0,24	0,18	*
37,47	53	108	1,92	1,98	0,27	0,19	NS

*P ≤ 0,05; **P ≤ 0,01; ***P ≤ 0,001; NS, P >0,05

TABLE 5

The age groups in this table indicate the age when treatment was given.

The table shows a comparison of mean R/C ratios in the different age groups.

n= number of patients

Kruskal-Wallis Test was used to find significant differences between the age groups

Teeth	n			mean			SD			P significance
	<5	5-13 years	≥13	<5	5-13 years	≥13	<5	5-13 years	≥13	
11,21	50	51	7	1,83	1,83	1,81	0,27	0,26	0,29	NS
12,22	50	52	8	2,00	1,93	1,89	0,21	0,24	0,26	NS
13,23	49	51	9	2,04	1,98	2,05	0,28	0,30	0,21	NS
14,24	32	33	4	1,68	1,59	1,61	0,26	0,31	0,08	NS
15,25	42	38	8	1,92	1,81	1,94	0,28	0,26	0,24	NS
16,26	44	44	8	1,53	1,59	1,54	0,22	0,25	0,23	NS
17,27	41	47	12	1,77	1,66	1,66	0,23	0,25	0,19	**
31,41	50	51	9	1,96	2,01	1,98	0,29	0,43	0,24	NS
32,42	51	52	8	2,04	2,07	2,16	0,30	0,28	0,53	NS
33,43	46	41	8	2,19	2,20	2,30	0,40	0,30	0,42	NS
34,44	55	54	10	2,16	2,01	2,26	0,27	0,28	0,31	**
35,45	47	53	10	2,42	2,24	2,39	0,26	0,32	0,36	**
36,46	50	46	8	2,00	1,99	2,11	0,25	0,23	0,22	NS
37,47	47	54	11	2,00	1,83	2,02	0,25	0,24	0,27	***

*P ≤ 0,05; **P ≤ 0,01; ***P ≤ 0,001; NS, P > 0,05