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The rate and the type of orthodontic tooth movement is influenced by bone turnover in a rat model

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SUMMARY The influence of bone metabolism on both the rate and the type of orthodontic tooth movement was investigated. A rat model in which high (n = 16) and low (n = 17) bone turnover was pharmacologically induced was used. A non-pharmacologically treated group (n = 19) served as the control. A mesially directed constant single force of 25 cN was applied to the upper left first molar for a period of 3 weeks. The study was performed as a split-mouth design, the contralateral side of each animal serving as its control. The displacement of the molar crown was measured with an electronic calliper, while changes in inclination of the teeth were measured from micro-CT scans of the excised maxillae.

The bone turnover significantly affected the rate of tooth movement. In the case of high turnover, the rate of tooth movement was increased while it was reduced in the case of low turnover. A controlled mesial tipping in all three groups was observed, but the actual location of the centre of rotation seemed to be influenced by the metabolic state of the bone.

Based on the results it can be concluded that deviations in bone turnover influence the response to orthodontic forces, and should be taken into consideration when planning orthodontic treatment in patients with metabolic bone disease or those on chronic medication influencing bone metabolism.

Introduction

Tissue reactions occurring during orthodontic tooth displacement are a product of the generated changes in the stress/strain distribution of the periodontal tissues and the biological state of these tissues. Bone turnover in the alveolus is, on the other hand, influenced by both local factors related to teeth and occlusion, and the general metabolism characterizing the total skeleton. The relative impact of these general and local factors has not yet been fully elucidated.

Patients requiring orthodontic treatment can be anticipated to present variations from normal bone turnover due to metabolic disease or medication, e.g. steroid treatment of allergies. Adult patients, in addition, often present varying degrees of marginal bone loss. When planning appliance therapy for the individual patient the local and general condition of the periodontal tissues should be taken into consideration (Melsen, 1988). Adaptation of the biomechanical system to the level of the marginal bone can be carried out, but it is of equal importance to consider the local bone metabolism.

The influence of force application on bone reaction has been described (Reitan, 1967; Storey, 1973; King and Thiems, 1979; Roberts *et al.*, 1992) and several studies have indicated that general bone metabolism is an important factor in the determination of tissue reaction and thus tooth movement (Midgett *et al.*, 1981; Goldie and King, 1984; Engström *et al.*, 1988; Hellsing and Hammarström, 1991). Moreover, it has been shown that orthodontic tooth movement can be influenced by general and local pharmacological modulation (Yamasaki *et al.*, 1984; Chumbley and Tuncay, 1986; Collins and Sinclair, 1988; Mohammed *et al.*, 1989; Takano Yamamoto *et al.*, 1992). Not only the rate of turnover, but also the local structure of bone can be influenced in impaired metabolic condition. Bone structure is one of the variables determining the localization

of the centre of resistance of a tooth. It can be hypothesized that high and low bone turnover might affect not only the rate of tooth movement, but also the type of tooth movement (e.g. tipping or translation). This influence of bone metabolism on the mode of tooth movement has not previously been investigated. The aim of this study was to examine the degree to which an experimentally induced high and low turnover of bone metabolism influences both the rate and the mode of tooth movement.

Materials and methods

Fifty-two 6-month-old out-bred male Wistar rats with a body weight of 500–550 g were obtained from Møllegaards Breeding and Research Centre, Ejby, Denmark. They were housed in individual cages in a room with a 12:12-hour artificial light cycle, at room temperature and humidity according to the National Research Council's guide for the care and use of laboratory animals (Dyreforsøgstilsynet, 1990). They were divided into three groups:

Group 1: normal bone turnover and orthodontic force ($n = 19$).
Group 2: high bone turnover and orthodontic force ($n = 18$).
Group 3: low bone turnover and orthodontic force ($n = 18$).

Moreover, three external control groups (normal, high, and low bone turnover) consisting of five rats each without orthodontic treatment were included to evaluate eventual methodological bias inherent with the split-mouth design (Brunette, 1996). High and low bone turnover was obtained by the induction of hyper- and hypothyroidism, respectively. Hyperthyroidism was obtained by the administration of 0.003 per cent L-T4 (Sigma Chemical Co., St Louis, USA) added to the drinking water (stock dissolved in 0.5 mol/l NaOH and 99 per cent ethanol, 0.32:0.68), and hypothyroidism by a semi-synthetic iodine-restricted diet [<50 μg/kg, Altromin-C 1042 (Brogaarden, Gentofte, Denmark) with 2 per cent $KClO_4$ in the drinking water, according to the protocol of Gøtzsche and Ørskov (1994)]. The normal turnover group received a standard diet (Altromin, Brogaarden, Gentofte, Denmark) and tap water *ad libitum*. Under general anaesthesia, induced by subcutaneous injection of 0.1 ml/100 g body weight of Immobilon® and reversed by the same amount of Revivlon® (Pherrovet, Malmö, Sweden), blood samples were collected from the jugular vein before the administration of the drugs and at death. The level of serum total tri-iodothyronine (TT_3) and serum total thyroxin (TT_4) was determined as described by Weeke and Ørskov (1973). Body weight was checked weekly.

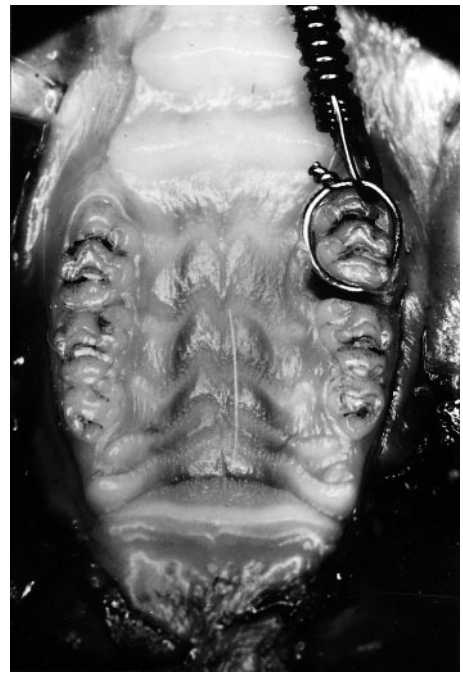

Figure 1 The orthodontic appliance at the end of treatment in a high turnover rat.

After 4 weeks of pharmacological treatment, a 25 g Sentalloy® (GAC, Ctr. Iship, USA) orthodontic closed coil spring was inserted under general anaesthesia, between the upper left first molar and upper incisors (Figure 1) in groups 1, 2, and 3. It was left in place for 21 days, in order to generate a mesial movement of the first molar. To limit the influence of inter-animal variation in response to metabolic stimuli, a split-mouth design was used and the untreated contralateral side served as the control.

Tetracycline (15 mg/kg) and calceine (20 mg/kg) were administered intraperitoneally 7 and 2 days before death to the animals in all the three groups (Allain *et al.*, 1995). At the end of the observation period the animals were killed with an overdose of CO_2, and the maxillae and the left femora were excised.

During the experiment, three animals had to be excluded from the study, as two rats in group 2 died under anaesthesia, and one maxilla in group 3 showed a loose mid-palatal suture during excision. The final number of rats studied was consequently 19 animals in group 1, 17 in group 2, and 16 in group 3.

The distance between the mesial surface of the first and the distal surface of the third molar was measured bilaterally with an electronic calliper. Tooth movement was evaluated by subtracting the measured value of the treated side from that of the control side as indicated by Hong *et al.* (1992).

The error of the method based on double measurements performed on 25 randomly selected animals was estimated as:

$$S = \sqrt{\Sigma(d)^2/2n}$$

where n = number of paired measurements and d = difference between replicate measurements.

The maxillae were then embedded in methyl-methacrylate and scanned with a micro-CT scanner (Scanco Medical, Zürich, Switzerland), producing 122 35-μm thick sagittal scans per side. A three-dimensional reconstruction of each hemi-maxilla was performed (Figure 2) and for each first molar the image including the longest root was selected, and the root length measured with the scanner's built-in image analysis tools. On a hard copy of the selected scan, the occlusal plane (OP) was defined as the plane passing through the occlusal cusps of the second and third molar. The angle between the OP and the main axis of the first root of the molar was measured on both the treated and the control side. The estimated change in inclination was evaluated by subtracting the value of the treated side from the control side within the same animal (Figure 3). In 15 rats, the OP and the angle with the first root were measured twice to assess the error of the method. The validity of the method for the evaluation of tooth inclination was also evaluated by comparison with measurements carried out on the external control groups.

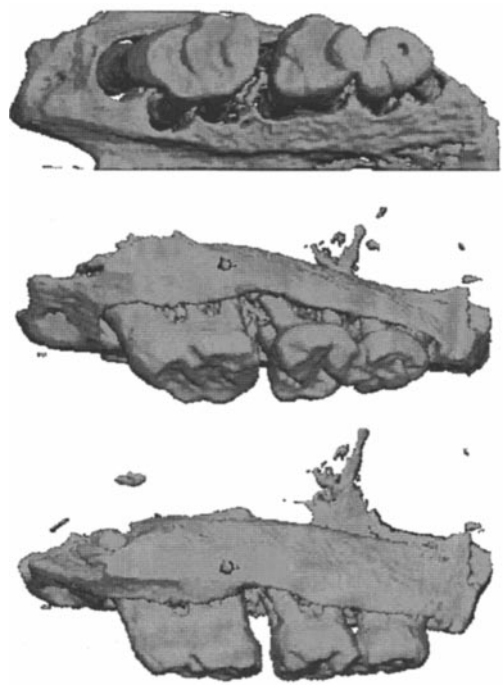

Figure 2 3D reconstruction of the whole maxilla after micro-CT scanning.

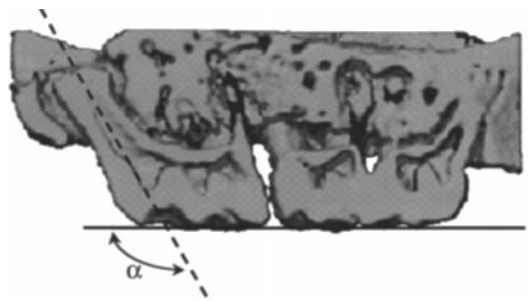

Figure 3 The definition of the occlusal plane and the main axis of the first root of the first molar and the measurement of tooth inclination (α).

The application of a single force at the level of the crown produces a tipping of the tooth, which can be defined by the localization of the centre of rotation (CRot). In order to calculate the position of the CRot for the movement of the molar, the

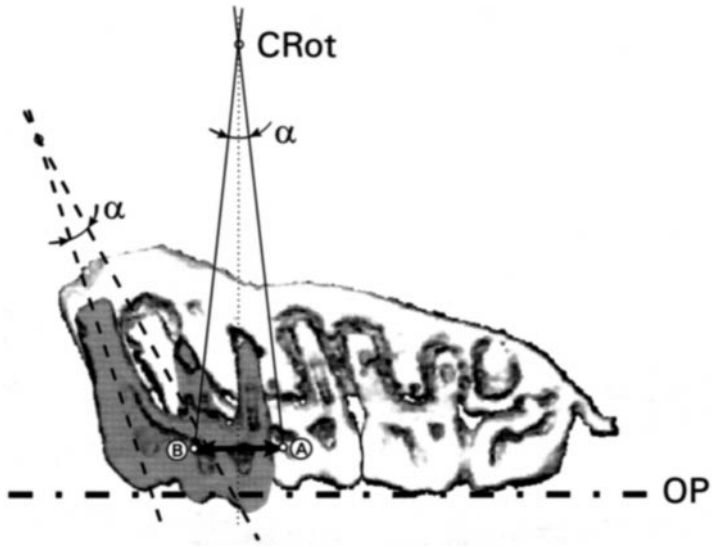

Figure 4 Drawing illustrating the principles for the calculation of the centre of rotation (CRot) as the combination of the tooth movement (A–B) and the tooth inclination (α). OP = occlusal plane.

initial and the final positions have to be known. However, as only the final position of the molar was known, the following approximation to determine the location of the CRot was made. The total movement of the molar comprises a translation and a pure rotation. Assuming that these occur simultaneously, the CRot corresponds to the intersection of the two equal sides of an isosceles triangle, whose base and opposing angle are given by the translation and pure rotational components of the movement, respectively (Figure 4).

The femora were also embedded in methylmethacrylate and mid-diaphyseal 10-μm sections were cut and left unstained for fluorescent light microscopy analysis. The mineral appositional rate (MAR; Parfitt *et al.*, 1987) of the outer periosteal surface of the cortex, indicating appositional growth, was evaluated. The surface-sampled orthogonal distance between bone labels was measured on 120 intersections with double-labelled bone at ×200 magnification. The mean inter-label distance was then used to calculate the MAR as [(mean inter-label distance) × π/4]/labelling interval. The MAR thus describes how fast the mineralization front proceeds during formation activities.

The levels of TT_3 (total tri-iodothyronine), TT_4 (total thyroxin), and body weight throughout treatment were analysed by a repeated measurement ANOVA. Tamhane test for pairwise comparison and the Student–Newman–Keuls (SNK) range test were also performed. Due to the lack of normal distribution of the data, mineral apposition rate, tooth movement, and inclination were analysed with a Kruskall–Wallis test, followed by a Mann–Whitney test for pairwise comparisons when a significant difference was found (Armitage and Berry, 1995).

Results

When the induction of the metabolic diseases was checked by measuring the serum levels of TT_3 and TT_4 in the different groups, it could be seen that a state of hyper- and hypothyroidism was successfully induced. The ANOVA analysis showed a significant difference among the three turnover groups. SNK analysis indicated that the three groups were equal at the beginning of the experiment and differed significantly at the end of treatment (Table 1).

Both the Kruskall–Wallis test, and the subsequent Mann–Whitney test showed that

Table 1 Serum TT_3 and TT_4 in mmol/l (mean ± SE) before the beginning of the pharmacological treatment and at the end of the experiment.

Bone turnover	TT_3 initial	TT_3 final	TT_4 initial	TT_4 final
Normal (n = 19)	0.825 ± 0.036	0.71 ± 0.062*	79.84 ± 3.54	80.63 ± 2.69*
High (n = 16)	0.7288 ± 0.05	2.12 ± 0.17*	79.32 ± 4.47	234.94 ± 12.08*
Low (n = 17)	0.80 ± 0.038	0.025 ± 0.0085*	77.00 ± 4.11	34.94 ± 2.29*

*Statistically different from the other groups, $P < 0.05$.

Table 2 Body weight in grams (mean ± SE) during treatment.

Bone turnover	At drug administration	At force application	10 days after force administration	At end of treatment
Normal (n = 19)	454.10 ± 7.37	490.111 ± 8.55	474.84 ± 8.10	474.00 ± 8.00
High (n = 16)	458.69 ± 5.10	478.75 ± 5.89	461.19 ± 5.69	450.56 ± 5.56
Low (n = 17)	443.88 ± 6.03	441.76 ± 6.64*	407.06 ± 7.09*.**	400.65 ± 7.018*.**

*Statistically different from the normal, $P < 0.05$.
**Statistically different from high turnover, $P < 0.05$.

the MAR was significantly different in the three turnover groups ($P < 0.05$). The normal turnover group (group 1) had a median MAR of 0.99 µm/day (lower quartile = 0.92, upper quartile = 1.14), the high turnover group (group 2) of 1.22 µm/day (lower quartile = 1.06, upper quartile = 1.27), and the low turnover group (group 3) of 0.77 µm/day (lower quartile = 0.47, upper quartile = 0.78).

Table 2 shows body weight during the experiment. The repeated measurements ANOVA showed a difference in body weight during treatment in the three groups. Group 3 already showed a significant decrease in body weight at the application of an orthodontic appliance compared with group 1 and at the end of the experiment compared with group 2. The SNK range test indicated that, at the end of treatment, all three groups differed from each other.

Mean values and standard deviations indicating tooth movement in the three different bone turnover groups are illustrated in Figure 5. The error of the method for the tooth movement was 0.04 mm and was thus considered to be of no further importance. The rate of tooth movement in the high turnover group was higher than in the normal turnover group, while the low turnover group displayed a decrease. The Kruskall–Wallis test showed a significant difference in tooth movement among the three turnover groups. The Mann–Whitney test revealed a significant difference between both the high and low turnover groups, and the normal and high turnover groups. No significant differences were found in

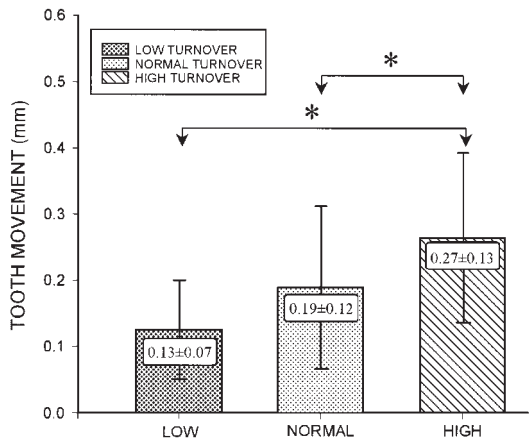

Figure 5 Bar diagram illustrating mean values and standard deviation of tooth movement. *$P < 0.05$.

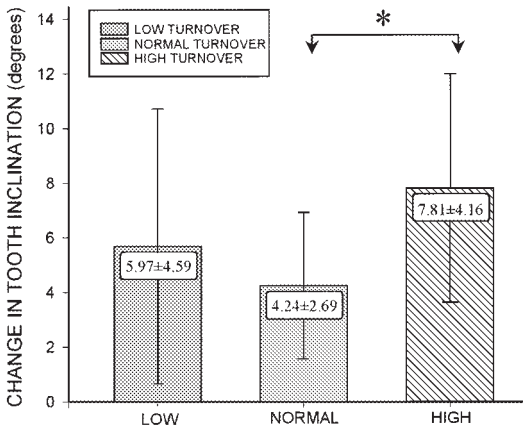

Figure 6 Bar diagram illustrating mean values and standard deviation of tooth inclination. $*P < 0.05$.

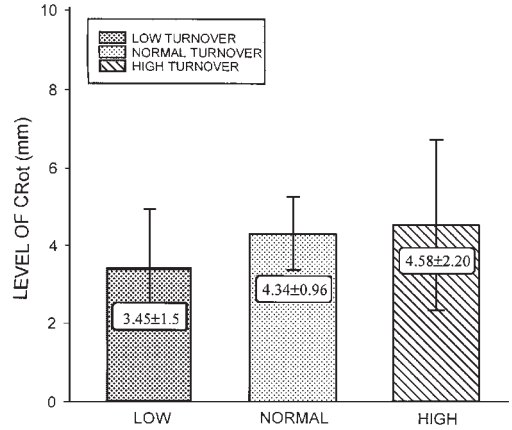

Figure 7 Bar diagram illustrating mean values and standard errors of CRot location.

root length between the treated group and the control group, or within the different groups.

The change in inclination of the molars in the three groups is illustrated in Figure 6. The error of the method in determining the angles was 1.1 degrees. The change in inclination was larger in groups 2 and 3 than in group 1. The Kruskall–Wallis test showed a significant difference among the three turnover groups, but the Mann–Whitney test demonstrated a significant difference only between groups 1 and 2. The paired differences between two sides in the external control groups were not statistically significant, supporting the specificity of the method.

The localization of the CRot varied between the groups. It was located closer to the crown in the low turnover group, while in the control group and the high turnover groups it was positioned more apically (Figure 7).

Discussion

The results of this study show an influence of different bone turnover rates on the quantity and quality of orthodontic tooth movement.

The experimental model for mesial movement of the rat molar has been repeatedly used in previous studies (Rygh *et al.*, 1986; King *et al.*, 1991b; Roberts *et al.*, 1992; Verna *et al.*, 1999). The rat is considered suitable for the study of skeletal adaptation to mechanical usage (Jee *et al.*, 1991) and to impaired metabolic conditions (Baron *et al.*, 1984; Frost and Jee, 1992; Allain *et al.*, 1995). The model on experimentally induced hypo- and hyperthyroidism in rats has been described by Gøtzsche and Ørskov (1994), and the high and low turnover state in this study was confirmed by the serum levels of TT_3 and TT_4.

The MAR measured on femoral bone in the normal, hyper- and hypothyroid groups confirmed different bone turnover rates, as previously shown in humans (Melsen and Mosekilde, 1977; Mosekilde and Melsen, 1978). In this study, the MAR was significantly increased in the hyper- and decreased in the hypothyroid rats, thus confirming the validity of the model used and the results obtained by Allain *et al.* (1995).

The body weight in both metabolic groups in this investigation decreased more than described by the above-mentioned authors. This could be ascribed to the orthodontic device, as confirmed by the repeated measurements analysis. Before positioning the appliance the difference was significant only between the low turnover and control groups (Table 2). Allain *et al.* (1995) used a different pharmacological treatment in growing animals and their results could thus not be compared with the present study. Because of this high inter-animal variability in response to a metabolic stimulus, the use of the split-mouth design seems highly justified.

The total treatment duration of 7 weeks (four of pharmacological treatment, and three of orthodontic treatment) was chosen in order to interfere with bone metabolism for a minimum of one remodelling cycle (sigma), ranging according to various authors between 10 and 31 days (Vignery and Baron, 1980; Tran Van *et al.*, 1982; Baron *et al.*, 1984). According to Li *et al.* (1991) the sigma of a rat changes as a function of age and at 6 months it is considered to be approximately 21 days.

The determination of the type and rate of tooth movement is critical due to the small size of the animals and the lack of reference points. The implantation of amalgam indicators has been used by Tuncay and Killiany (1986), but it cannot be ruled out to what extent the reaction of the bone due to the trauma related to the insertion of the implants can influence the bone turnover in the region (Frost, 1983). The metallic markers positioned submucosally by King *et al.* (1991a) could, on the other hand, act as a potential focus of inflammatory cells that could interfere with tissue reaction. When measurements are carried out on cephalograms taken with the rat in a special cephalostat the error related to the determination of bilateral structures is considerable (Rönning, 1971) and the inclination of the molars cannot be determined on occlusal films. In the present study the tooth movement was measured as described by Hong *et al.* (1992). This method has a high reproducibility, but most likely underestimates the true movement as the transeptal fibres can be anticipated to cause some displacement also of the second and third molar. Since the aim was to study the interaction between the metabolic state of the bone and a standardized mechanical perturbation, the under-estimation related to the tooth movement *per se* was considered acceptable.

The rate of tooth movement was higher in cases of high bone turnover and smaller in the rats with low bone turnover than in normal animals. This finding is consistent with a more rapid tooth movement found in animals with high turnover caused by secondary hyperparathyroidism (Midgett *et al.*, 1981; Goldie and King, 1984; Engström *et al.*, 1988). This was also the case during orthodontic tooth movement in the acute phase of corticosteroid treatment (Ashcraft *et al.*, 1992).

The interaction between the rate of tooth movement and bone metabolic conditions has been utilized with the purpose of clinically influencing the tooth movement or to avoid unpleasant side-effects by the administration of various compounds (Davidovitch *et al.*, 1972; Yamasaki *et al.*, 1984; Collins and Sinclair, 1988; Leiker *et al.*, 1995; Igarashi *et al.*, 1996; Kehoe *et al.*, 1996; Roche *et al.*, 1997). However, whether the administration of such compounds also influences the type of tooth movement has not yet been studied. In this investigation, a controlled tipping of the first molar occurred in all bone turnover groups, but the location of the movement's CRot varied according to bone turnover, although it was not statistically significant. In the high turnover group, which exhibited the larger displacement, the CRot was positioned at the level of the root apices or above. In the low turnover group, on the other hand, less tooth movement and relatively more tipping resulted in a CRot in a more coronal position. A rotation around a centre close to the apex is consistent with the findings of Macapanpan *et al.* (1954) and Gibson *et al.* (1992). Katona *et al.* (1995), on the other hand, identified the CRot of the first molar, following the application of a single force, around the furcation area. Their results were obtained by a finite element model simulating the initial movement in two dimensions. Difference in the studied period and the boundary conditions used may explain the discrepancy between the studies. The centre of resistance of a tooth is determined by the width of the periodontal ligament (i.e. the play the root has in the alveolus) and the mechanical properties of the alveolar bone (Burstone and Pryputniewicz, 1980). The latter is given by the overall quality of bone and by the local mechanical properties of the alveolar bone. Hyperthyroidism is known to result in secondary osteopenia, even on a sub-clinical level, where not only the dynamics, but also the density and structure of cortical and cancellous bone will be influenced (Mosekilde *et al.*, 1990). It is therefore likely that the location of the centre of resistance in the

high turnover group is influenced by both a larger width of the periodontal ligament and a reduced strength of the surrounding supporting tissues. Decreased bone turnover is seen in hypothyroidism (Melsen and Mosekilde, 1977; Mosekilde and Melsen, 1978) and the reduced rate of crown movement might be explained by the reduced activation frequency of the remodelling cycles in the alveolar bone. The change in root inclination was slightly more pronounced than in the normal turnover rats. This, together with the lower rate of tooth movement, resulted in a more coronal location of the CRot. This apparent contradiction may be explained by the initial bending of the alveolar bone. The delayed onset of bone response makes the alveolar bone bending component of orthodontic tooth movement the most likely explanation of the observed root inclination in the low turnover group. An increased bone strength could also be responsible for this phenomenon. It has been suggested that the positive balance typical of hypothyroidism could increase bone mass and reduce fracture risk (Mosekilde *et al.*, 1990), but it is unlikely that this was the case in the present study, as the total observation period, with the low activation frequency, was too short to allow for any evidence of this effect.

The influence of a systemic alteration in bone metabolism has been shown in the present study and should be taken into consideration when selecting the force system needed for a certain tooth movement. The variation in bone metabolism may be a reflection of an underlying systemic disease or a result of medication such as e.g. indomethacin (Giunta *et al.*, 1995) and steroid treatment (Ashcraft *et al.*, 1992). Clinical observation of variation from normal tissue reaction has been described. In pregnant women, orthodontic tooth movement is faster, as demonstrated by Hellsing and Hammarström (1991). In a rat model, a low-calcium diet and lactation lead to an increased amount of tooth movement related to secondary hyperparathyroidism (Goldie and King, 1984) as did local administration of vitamin-D (Collins and Sinclair, 1988). Topical administration of bisphosphonates, on the other hand, reduces the occurrence of both tooth movement rate and relapse in rats (Igarashi *et al.*, 1994). Apart from pathological conditions, the age of the orthodontic patient should also be considered in relation to orthodontics. Tooth movement is delayed in adult patients (Reitan, 1954; Bridges *et al.*, 1988) due to decreased proliferative activity in the periodontal ligament (Kyomen and Tanne, 1997) and in the alveolar bone (Jäger, 1996).

Conclusions

The present study demonstrated an interaction between mechanical load and metabolic condition. An alteration of the metabolic state of bone can result in a different rate of tooth movement and in a different location of the CRot. Although a thorough planning of the biomechanical system is an efficient tool to control tooth movement, the rate of the alveolar bone remodelling could interfere with the planned result.

These results suggest that a thorough case history regarding possible pathophysiological conditions influencing bone metabolism should be performed. In subjects on medication, possible interactions with the reaction to treatment should be considered. The re-activation of the appliance in subjects with a high metabolic rate can be performed more frequently than in patients with a normal metabolic rate. In low turnover subjects, on the other hand, less frequent re-activation of the appliance should be undertaken, but in these patients a longer retention time is required, due to the prolonged bone formation period.

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