

Medication effects on the rate of orthodontic tooth movement: A systematic literature review

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Introduction: Recently, several reviews have been published on the effects of medications on bone physiology and the clinical side effects in orthodontics. However, the effects of medications on the rate of orthodontic tooth movement have not been evaluated. **Methods:** A systematic literature review on the effects of medications and dietary supplements on the rate of experimental tooth movement was performed by using PubMed (1953–Oct 2007), Web of Science, and Biosis, complemented by a hand search. **Results:** Forty-nine articles were included in the review, but their interpretation was hindered by the variability in experimental design, magnitude of force applied during tooth movement, and medication regimens. Therapeutic administration of eicosanoids resulted in increased tooth movement, whereas their blocking led to a decrease. Nonsteroidal anti-inflammatory drugs (NSAIDs) decreased tooth movement, but non-NSAID analgesics, such as paracetamol (acetaminophen), had no effect. Corticosteroid hormones, parathyroid hormone, and thyroxin have all been shown to increase tooth movement. Estrogens probably reduce tooth movement, although no direct evidence is available. Vitamin D3 stimulates tooth movement, and dietary calcium seemed to reduce it. Bisphosphonates had a strong inhibitory effect. **Conclusions:** Medications might have an important influence on the rate of tooth movement, and information on their consumption is essential to adequately discuss treatment planning with patients. (*Am J Orthod Dentofacial Orthop* 2009;135:16–26)

Recently, several reviews have been published about the biologic processes related to orthodontic tooth movement (OTM).^{1–4} These reviews describe similar reactions of periodontal cells and extracellular matrices to orthodontic force application. Briefly, the principal trigger for OTM is probably strain of the periodontal ligament cells, bone-related cells, and the extracellular matrix.³ This strain leads to changes in gene expression in the cells by interactions between the cells and the extracellular matrix, whereby integrins play an important role.² Various cell-signaling pathways are activated, which ultimately lead to stimulation of periodontal ligament turnover, and localized bone resorption and bone deposition.^{2–4}

In addition, recent reviews by several authors have been published on the effects of systemic or local application of medications and the intake of dietary supplements, such as vitamins and minerals, during OTM.^{5–7} In most cases, these reviews distinguish 2 categories of effects: those related to general bone physiology in terms of bone density, bone mineralization, bone turnover rate, and osteoclast differentiation; and clinical side effects induced by medications, such as gingival hyperplasia, xerostomia, and external root resorption.^{5–7}

Most reviews, however, did not report experimental data on the effects of medications or dietary supplements on the rate of OTM.^{7–10} Nonetheless, such information is important for clinicians in communications with patients, because many patients use prescription and over-the-counter medications, as well as dietary supplements daily. Consequently, these substances can affect both the rate of OTM and the expected duration of treatment.^{6,7,11}

Therefore, we performed a systematic literature review based on experimental data on the sequelae of pharmaceutical interventions and the use of dietary supplements on the rate of OTM. Unfortunately, only a few human clinical trials have been published.^{12–14} As a result, this review focuses mainly on well-controlled animal studies.

Our review is organized around several regulatory systems of which disturbances might lead to pathologic

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Table I. Medline search strategy

Query	Results	New
1. (Tooth movement) and (drug-effects in SH)	140	140
2. (Tooth movement) and (Explode "Physiological-effects-of-drugs"/all subheadings in MIME, MJME, PT)	55	21
3. (Tooth movement) and (Explode "Therapeutic Uses"/all subheadings in MIME, MJME, PT)	53	7
4. (Tooth movement) and (Explode "Hormones-"/all subheadings in MIME, MJME, PT)	42	18
5. (Tooth movement) and (Explode "Pharmaceutical-preparations"/all subheadings in MIME, MJME, PT)	24	15
6. (Tooth movement) and (Explode "Steroids-"/all subheadings in MIME, MJME, PT)	29	5
7. (Tooth movement) and (Explode "Micronutrients"/all subheadings in MIME, MJME, PT)	1	0
Total		206

conditions that affect bone metabolism or cause other unwanted signs and symptoms. Most pharmaceutical interventions aim to increase the local production of regulatory factors by either stimulating their synthesis or administering synthetic analogues. On the other hand, they often try to counteract the effect of these regulatory factors by selective inhibition of their synthesis or blocking their active domains.

MATERIAL AND METHODS

Our search strategy included the Cochrane Library (October 2007) and Medline (October 2007, including OLDMEDLINE, covering the literature from 1950 to September 2007) by using the search terms and their combinations shown in Table I. We also searched Embase (EM 74) (via DIMDI)/Embase Alert (Elsevier), Web of Science (Science Citation Index Expanded), and Biosis. The references from the retrieved articles were perused to identify additional relevant publications.

Our inclusion criteria were as follows.

1. Experimental animal study or clinical investigation that included at least 1 experimental group and a control or sham group.
2. Adequate description of the animals used in the study.
3. At least 5 animals or humans per experimental group.
4. Systemic or local administration of well-defined medications or dietary supplements that are supposed to interfere with the physiologic processes of bone, or that might have side effects related to bone physiology.
5. Adequate descriptions of dosages and administration regimens.
6. Adequate descriptions of the force magnitude and regimen.
7. Adequate description of the technique for measuring the rate of tooth movement.
8. Adequate statistical analysis.

Articles in Dutch, English, French, German, Greek, Italian, Portuguese, and Spanish were considered.

Those in other languages were included only if an English abstract was available from which the inclusion criteria could be evaluated.

General information on the medications and their effects on various mediators in this review is mainly web-based information derived from the following Internet sites (October 2007): <http://en.wikipedia.org>, www.nlm.nih.gov/medlineplus, www.rxlist.com, and www.drugs.com. References to these web sites were omitted in the text.

RESULTS

The total number of articles found through Medline was 206. Searches in the Cochrane Library, EMBASE, Web of Science, and Biosis produced no additional sources. Hand searching identified 7 more references. Application of the inclusion criteria resulted in 49 articles used for data extraction and subsequent review.

EICOSANOIDS

Eicosanoids are a group of signaling molecules involved in the regulation of many processes, regulatory pathways, and pathologic conditions, such as inflammatory and immune responses, anaphylaxis, vasodilation and vasoconstriction, blood clotting, stimulation of peripheral nerve endings, and the development of auto-immune diseases. Four families of eicosanoids can be distinguished: leukotrienes, thromboxanes, prostacyclins, and prostaglandins. They are all derived from arachidonic acid by various enzymatic conversions. Cyclo-oxygenases (COX) play a pivotal role for the conversion to thromboxanes, prostacyclins, and prostaglandins. There are at least 3 isoforms, COX-1, COX-2, and COX-3. COX-dependent eicosanoids are also called prostanoids. Depending on the pathologic condition, the action of eicosanoids might be stimulated by synthetic analogues or counteracted by direct or indirect inhibitors.

Leukotrienes

Leukotrienes are the only eicosanoids that are formed independently from COX. Their conversion from arachidonic acid is brought about by the action of lipoxygenase. Leukotrienes play an important role in inflammation, allergies, and diseases such as asthma. Their effects can be counteracted by medications such as montelukast and zafirlukast, which block leukotriene receptors. Another approach is to inhibit leukotriene synthesis by selective blocking of the essential enzyme lipoxygenase by a drug such as zileuton. This approach can also result in not only inhibition of bone resorption, but also in stimulation of bone deposition, thereby possibly influencing OTM.¹⁵

The effect of the selective inhibitor of leukotriene synthesis AA861 on OTM in a rat model was studied. After application of a force of 60 cN (1 centinewton = approximately 1 g) to mesialize the first molars, AA861 was administered in a dosage of 20 mg per kilogram per day. This led to a significant decrease in the rate of OTM.¹⁵ The net effect of the inhibition of leukotriene synthesis might be the same as the effect of blocking leukotriene receptors. Therefore, these findings suggest that pharmaceuticals such as zileuton, montelukast, and zafirlukast might also decrease the rate of OTM.

Thromboxanes

Thromboxanes act as vasoconstrictors and facilitate platelet aggregation. They are found in increased amounts in the oral cavity under inflammatory conditions, eg, in deep periodontal pockets. However, no relationship with periodontal bone loss could be established.¹⁶ The thromboxane analogue U 46619, locally administered at dosages between 2.10^{-5} and 2.10^{-3} μmol every 12 hours, significantly increased the rate of OTM evoked by a separation force of 20 cN between rat incisors.¹⁷ These data suggest that inhibition of thromboxane synthesis by, eg, nonsteroidal anti-inflammatory drugs (NSAIDs) (see below), might inhibit the rate of OTM.

Prostacyclins

The effects of prostacyclins are opposite those of thromboxanes on platelet aggregation and vasodilation. They act as vasodilators and prevent platelet aggregation. Synthetic prostacyclin (epoprostenol) or analogues such as iloprost are used for the treatment of ischemic conditions and pulmonary arterial hypertension.

Local iloprost administration at dosages from 2.10^{-5} and 2.10^{-3} μmol every 12 hours significantly increased the rate of OTM evoked by separation force of 20 cN between rat incisors.¹⁷ This indicates that the

effects of prostacyclins and thromboxanes on OTM are comparable, although their effects on platelet aggregation and vasodilation are opposite. An explanation can be found in in-vitro findings showing that stimulation of either thromboxane receptors or prostacyclin receptors leads to upregulation of COX-2 and subsequently to a positive feedback loop that also includes prostaglandin synthesis.¹⁸ Therefore, administration of the prostacyclin analogue iloprost and the thromboxane analogue U 46619 increases the synthesis of prostaglandins, thereby indirectly affecting the rate of OTM. As for thromboxanes, the synthesis of prostacyclins is inhibited by NSAIDs.

Prostaglandins

Prostaglandins play an important role in inflammation. Furthermore, they have an effect on smooth muscle cells, platelet aggregation, peripheral nerve endings, and calcium homeostasis. Synthetic prostaglandin analogues, such as misoprostol, are used for various conditions, including prevention of peptic ulcers and induction of labor.

The effect of exogenous prostaglandins on OTM was studied in monkeys.¹⁹ In a split-mouth design, canine retraction was performed after extraction of the first premolars. The initial force was 100 cN, and, at 1 side, local injections of synthetic exogenous prostaglandin (PGE2) (dinoprostone) were given at 4-day intervals at a dosage of 40 μg . The results suggest faster OTM at the experimental sides, but there was no statistical analysis.¹⁹ Some studies in rats are more convincing.^{20,21} In these studies, incisors were separated by forces of 20 and 60 cN, respectively. It was shown that the rate of OTM increased significantly in a dose-dependent manner after single or multiple local injections of exogenous PGE2 at dosages between 0.1 and 10.0 μg . Weekly local injections of 100 μg of exogenous PGE2 also stimulated mesial molar movement in rats induced by a force of 60 cN.²²

The effects of exogenous PGE1 (alprostadil) and its synthetic analogue misoprostol on OTM have also been studied. PGE1 stimulates the synthesis and secretion of the protective mucus that lines the gastrointestinal tract. Furthermore, it increases mucosal blood flow, thereby improving mucosal integrity. It is sometimes coprescribed with NSAIDs to prevent gastric ulceration, a common adverse effect of NSAIDs.

In an experiment with guinea pigs, a separating force of 25 cN was applied to the incisors.²³ Administration of misoprostol at a dosage of 100 μg per kilogram every 12 hours resulted in a significant increase in the rate of separation.²³ The stimulatory effect of misoprostol on incisor separation was also found in a rat study in which

it was administered at various dosages by gastric lavage.²⁴ A force of 60 cN was used; dosages of 10 µg per kilogram per day and more showed significant increases in the rate of OTM.

The effect of PGE1 has also been studied in humans and monkeys. The study in monkeys yielded no convincing results because of the lack in statistical analysis.¹⁹ Two investigations in humans with a split-mouth design showed significant increases in the rate of palatal premolar movement after multiple local injections of PGE1 at a dosage of 10 µg.^{12,13}

An indirect way to influence PGE2 synthesis is a diet rich in omega-3 fatty acids. After 5 weeks of this diet, the rats showed lower arachidonic acid and PGE2 concentrations in lipids extracted from the alveolar bone than after a diet rich in omega-6 fatty acids.²⁵ Orthodontic incisor separation with a force of about 56 cN was significantly slower in animals receiving the omega-3 fatty acids diet. Similar results were shown after buccal movement of the maxillary first molars in rats with an initial force of 20 cN.²⁶

Inhibitors of prostanoid synthesis have found widespread applications in medicine. NSAIDs represent the most important class of these drugs.

NSAIDS

NSAIDs are the most important class of prostanoid-synthesis inhibitors. They have analgesic, antipyretic, and anti-inflammatory effects, and are prescribed for many conditions, such as rheumatoid arthritis, osteoarthritis, gout, dysmenorrhea, headache, migraine, and postoperative pain, as well as for the prevention of cardiovascular diseases and colorectal cancer. The prescriptions have important differences. For chronic diseases such as rheumatoid arthritis, osteoarthritis, and gout, relatively high doses are prescribed for a long period of time. For the prevention of cardiovascular problems and colorectal cancer, long-term prescriptions are also given, but at a low dose. For pain and headache, NSAIDs are taken incidentally. This should be considered in evaluating the effects of NSAIDs on OTM.

NSAIDs can be divided into different groups by their chemical composition. Well-known members of these groups are listed in Table II.

All NSAIDs have more or less similar effects and mechanisms of action. They suppress the production of all prostanoids (thromboxanes, prostacyclins, and prostaglandins) because of their inhibition of COX-1 and COX-2, which are essential enzymes in the synthetic pathways of the prostanoids. COX-1 is a constitutive form, whereas COX-2 is inducible. Acetylsalicylic acid, for example, inhibits both types of COX in a

Table II. Groups and subgroups of NSAIDs, and some well-known brand names

Group	Subgroup	Brand names
Salicylates	Aspirin	Aspirin, Acetal, Acetophen, Acetosal, Aspro, and over 100 more
	Diflunisal	Dolobid
Arylalkanoic acids	Diclofenac	Voltaren, Voltarol, Diclon, Dicloflex, Difen, Difene, Cataflam, Pennsaid, Rhumalgan, Abitren
	Indometacin	Indocin, Indocid, Indochron
Arylpropionic acids (profens)	Ibuprofen	Nurofen, Advil, Brufen, Dorival, Panafen, Ibumetin, Ibuprom
	Flurbiprofen	ANSAID
	Naproxen	Aleve, Anaprox, Naprogesic, Naprosyn, Naprelan
Oxicams	Piroxicam	Feldene
	Meloxicam	Movalis, Melox, Recoxa, Mobic
Coxibs	Celecoxib	Celebrex, Celebra
	Rofecoxib	Vioxx, Ceoxx, Ceeoxx
	Valdecocixib	Bextra

noncompetitive and irreversible way²⁷; thus, it effectively inhibits prostaglandin synthesis. In the early 1990s, it became apparent that COX-1 mediates the synthesis of prostaglandins responsible for the protection of the stomach lining, whereas COX-2 is induced during inflammatory reactions, thereby mediating the synthesis of prostaglandins responsible for pain.²⁸⁻³⁰

A special category of NSAIDs is the so-called coxibs. These are specific COX-2 inhibitors developed for the management of osteoarthritis, but they are also used in the therapy of acute or chronic pain and dysmenorrhea. Concerns about the increased risk of cardiac attack and stroke associated with long-term, high-dosage use has led to either a complete withdrawal from the market or a more stringent prescription policy.

Studies on the effects of NSAIDs during experimental OTM in animals all evaluate the effects of relatively short administrations. They showed decreases in the number of osteoclasts, since prostaglandins are involved either directly or indirectly in osteoclast differentiation or in stimulating their activity. This has been shown for acetylsalicylic acid and flurbiprofen,⁸ indometacin (indomethacin),⁹ and ibuprofen.¹⁰ Whether this also leads to a reduction in the rate of OTM is less clear.

Salicylates

Acetylsalicylic acid is the first discovered and most widely used NSAID.

Acetylsalicylic acid administration of 65 mg per kilogram per day in guinea pigs did not reduce the rate of lateral incisor movement with mild forces of 8 cN.²⁷ On the other hand, the rate of lateral incisor movement in rats, evoked by a force of 35 cN, significantly decreased after administration of acetylsalicylic acid at a dosage of 100 mg per kilogram twice a day.¹⁰ Also, local injections of 17.5 to 35 mg per kilogram per day of copper salicylate led to significant reductions in mesial molar movement in rats after a force of 50 or 100 cN.³¹ The differences in outcome might be related to differences in study design.

Arylalkanoic acids

Administration of a single dose of indometacin (4 mg per kilogram) in rats resulted in a significant short-lasting inhibitory effect on the mesial movement of molars induced by a force of 40 cN.³² Other authors used forces of 60 cN, and 50 or 100 cN, respectively, with indometacin administered at 2.5 to 5 mg per kilogram per day.^{15,31} A significant reduction in the rate of molar movement was found during the experimental periods of 14 and 28 days, respectively, regardless of the force level. The effect of indometacin on OTM has also been studied in cats and miniature pigs. In cats, the third premolars were moved mesially by a force of 250 cN. Indometacin was administered orally at 5 mg per kilogram per day, and a significant reduction in the rate of OTM was found.^{15,33} In miniature pigs, the incisors were separated by a force of 100 cN. Initially, a dosage of 20 mg per kilogram per day of indometacin was given, but this had to be changed during the study to 10 mg per kilogram per day because of peptic ulcer problems.⁹ Although no direct tooth movement was measured, the reduced bone turnover strongly suggested a decrease in OTM rate.⁹

The effect of diclofenac was studied in a rat model in which mesial tipping of the first molars was induced by a force of 50 or 100 cN. Injections of diclofenac (10 mg per kilogram at days 1 and 3) stopped OTM completely.³⁴

Arylpropionic acids

Administration of ibuprofen at an unknown dose for 5 days resulted in a significant reduction of tipping molar movement induced in rats by a mesial force of 50 cN over 21 days.³⁵ Also, studies in which rat incisors were moved laterally by a force of 25 or 35 cN, point in the same direction. After ibuprofen administration of 30 mg per kilogram twice a day, the rate of OTM decreased significantly.¹⁰ On the other hand, no inhibitory effect was found at a low dose (10 mg per kilogram per day) of flurbiprofen on the mesial movement of rabbit first molars with a force of 100 cN.⁸

Oxicams

No experimental data are available from the literature on the effects of oxicams on the rate of OTM.

Coxibs

Only 1 study is available on the effects of selective COX-2 inhibitors on the rate of OTM.³⁴ The effect of local injections of rofecoxib (1 mg per kilogram at days 1 and 3) was studied in a rat model in which mesial movement of the first molars was induced by a force of 50 or 100 cN. It appeared that no OTM occurred with a force of 50 cN, but 100 cN induced OTM, although it was significantly less than in the controls without medication.

OTHER ANALGESICS

Paracetamol

Paracetamol (acetaminophen) is a commonly used analgesic. It lacks anti-inflammatory properties. Therefore, it does not belong with NSAIDs, although their chemical structures are comparable. Other important differences are that paracetamol has almost no effect on blood clotting and no detrimental effects on the stomach lining. These differences are related to its mode of action. Whereas NSAIDs block COX-1 and/or COX-2, paracetamol blocks a third isoform, COX-3, which is expressed only in the brain and the spinal cord. As a consequence, paracetamol has minimal effects on prostaglandin synthesis.

The effect of paracetamol on OTM in rabbits was studied with the administration of 500 mg per kilogram per day. With a force of 100 cN, no effect on the rate of mesial molar movement was found.³⁶ Likewise, a dosage of 400 mg per kilogram per day for 10 days in rats did not influence the rate of lateral displacement of the incisors with a force 35 cN.¹⁰ Because paracetamol does not affect the rate of OTM with those dosages, both studies suggest that it should be the analgesic of choice for managing pain associated with orthodontic therapy.^{10,36}

CORTICOSTEROIDS

Corticosteroids are a class of steroid hormones, produced in the adrenal cortex. They are involved in many physiologic systems, such as stress response, inflammatory and immune responses, carbohydrate metabolism, protein catabolism, and blood electrolyte levels.

Some corticosteroids such as cortisol are called glucocorticoids. They are mainly involved in the control of carbohydrate, fat, and protein metabolism, but they also have anti-inflammatory properties. Other corticosteroids (mineralocorticoids), such as aldoste-

rone, control mainly electrolyte and water levels by promoting sodium retention in the kidneys. The glucocorticoids are also involved in bone physiology, but their mode of action is not yet completely elucidated. It was recognized that osteoblasts and osteoclasts can express glucocorticoid receptors; this expression is influenced by proinflammatory factors, such as IL-6 and IL-11.³⁷

Glucocorticoids are prescribed for various inflammatory and autoimmune conditions, including rheumatoid arthritis, dermatitis, allergies, and asthma. They are also used as immunosuppressive medications after organ transplantation.

Their anti-inflammatory effect is based on the indirect blocking of phospholipase A2 and the suppression of the synthesis of both COX-1 and COX-2. This leads to inhibition of the synthesis of prostaglandins and leukotrienes. Their immunosuppressive action is due to the inhibition of interleukins and IFN- γ .

Only a few authors have examined the effects of glucocorticoids on OTM, and no study was found dealing with mineralocorticoids. The glucocorticoids that have been studied are cortisone, prednisolone, and methylprednisolone.

The effect of cortisone on OTM was investigated in rabbits. Cortisone acetate was injected at a dosage of 15 mg per kilogram per day for 4 days before and during the application of an orthodontic force of approximately 100 cN for 14 days. Compared with the controls, this regimen led to a significant increase in the rate of OTM. Also, the relapse rate was faster in the experimental group than in the control animals.³⁸

Prednisolone was administered at 1 mg per kilogram per day in rats for an induction period of 12 days, followed by an experimental period of 12 days. During the latter phase of the study, the first molar was moved mesially with a force of 30 cN. This therapy had no significant effect on the rate of OTM.³⁹ The same experimental design was used in another study in which methylprednisolone was given at a dosage of 8 mg per kilogram per day.⁴⁰ In 1 experimental group, an induction period of 7 weeks was used; then OTM was performed for 3 weeks with a force of 25 cN. This led to an increase in the rate of OTM. However, in another experimental group without an induction period, methylprednisolone had no effect on the rate of OTM.⁴⁰

The differences in the results of these studies probably reflect the combined effects of the dosages, the induction periods, and the relative anti-inflammatory activity of the glucocorticoids tested.

CALCIUM AND CALCIUM REGULATORS

Calcium is essential in various physiologic processes, such as muscle contraction, regulation of the heartbeat, fluid balance, and enzyme activities. Hormones, such as parathyroid hormone (PTH), thyroid hormones (thyroxine, calcitonin), sex hormones (estrogens), and vitamins (eg, vitamin D3) are important regulators of calcium homeostasis. Dietary intake of calcium is also important. A separate class of drugs that affects calcium homeostasis is the bisphosphonates.

Parathyroid hormone

PTH is secreted by the parathyroid glands. Its main effect is an increase in the concentration of calcium in the blood; consequently, it stimulates bone resorption. It consists of 84 amino acids, but the active fragment contains only amino acids 1 through 34.

Pathologic PTH conditions might involve hypoparathyroidism and hyperparathyroidism. Hypoparathyroidism leads to a shortage of active PTH. The most commonly used therapy is the administration of vitamin D or calcium supplementation. In primary hyperparathyroidism, overproduction of the hormone stimulates bone resorption, reduces renal clearance of calcium, and increases intestinal calcium absorption; these result in increased serum calcium levels. The therapy involves surgical removal of the glands or medication with bisphosphonates. In secondary hyperparathyroidism, the secretion of PTH is increased because of hypocalcemia, and its treatment involves vitamin D3 supplementation or phosphate binders.

Although continuous elevation of PTH leads to bone loss, intermittent short elevations of the hormone level can be anabolic for bone.⁴¹ Many experimental and clinical data show that such daily applications of short duration led to increases in bone mass, density, and strength.⁴² Teriparatide is a recombinant form of the active (1 through 34) fragment of PTH, used to treat advanced osteoporosis. Daily injections of teriparatide stimulate new bone formation, leading to increased bone mineral density.⁴³

The effect of PTH on OTM was studied in rats.^{44,45} A significant stimulation of the rate of OTM by exogenous PTH appeared to occur in a dose-dependent manner, but only when it was more or less continuously applied, by either systemic infusion⁴⁵ or local delivery every other day in a slow-release formulation.⁴⁴ The dosages ranged from 0.1 to 1.0 μg per kilogram per day, and total (1-84) PTH was as effective as the fragment (1-34). In 1 experimental group, the PTH was dissolved in physiologic saline solution. This can be considered an intermittent short application. However,

no inhibitory effect on OTM was found, probably because osteoblastic activity was stimulated, but osteoclastic activity was not affected.⁴⁴

Indirect evidence for the effect of PTH on the rate of OTM can be derived from studies dealing with the effects of a low-calcium diet, which increases PTH release in animals.^{46,47}

Thyroid hormones

The thyroid produces 2 hormones: thyroxine and calcitonin.

Thyroxine (T4) is a prohormone that can be converted to its active form tri-iodothyronine (T3). This active hormone influences the activity and metabolism of all cells, and it plays an important role in physical development and growth. Furthermore, T4 affects intestinal calcium absorption; thus, it is indirectly involved in bone turnover. Hyperthyroidism or thyroxine medication can lead to osteoporosis.

The effect of exogenous thyroxine on OTM has been studied in a rat model in which an orthodontic force of 25 cN was applied on the first molar for 21 days. After an induction period of 4 weeks, in which 0.003% thyroxine was added to the drinking water, a significant increase in the rate of OTM was found.⁴⁸ Intraperitoneal administration of dosages of 5, 10, and 20 mg per kilogram per day of thyroxine resulted in a dose-dependent stimulation of mesial molar movement in rats induced by a force of 60 cN.⁴⁹

In many ways, calcitonin has the opposite effects of those inherent to PTH; calcitonin decreases intestinal calcium absorption, osteoclast activity in bone, and renal calcium reabsorption. It is used to treat postmenopausal osteoporosis, hypocalcemia, and Paget's disease. Furthermore, it might be beneficial in osteoarthritis.

Although calcitonin is involved in bone remodeling and calcium homeostasis, no experimental data are available on the effect of the administration of exogenous calcitonin on the rate of OTM.

Estrogens

Estrogens are female sex hormones that occur naturally in 3 forms. The first and most prominent form of estrogen is estradiol, which is produced from menarche to menopause and is important in the regulation of the estrous cycle. The second form is estrone, produced after menopause, when the total amount of estrogens has decreased. The third form, estril, is expressed primarily during pregnancy. The relationship between the decrease of estrogens after menopause and the development of osteoporosis is well established. For a long time, estrogen supplementation was used to over-

come postmenopausal problems. However, it has become clear that this treatment increases the risk of breast cancer, strokes, and possibly other cardiac issues. This has led to the development of specific estrogen receptor modulators such as raloxifene, which has an estrogenic effect in bone, but reduces the risk for breast cancer. Therefore, it is considered a good alternative for hormone replacement therapy for the treatment of osteoporosis.

Only 2 investigations are available on the effect of estrogens on OTM. One study focused on the rate of buccal movement of molars evoked by a force of 12.5 cN during the normal estrous cycle in rats. It was found that the rate of OTM was inversely related to the estrogen serum level.⁵⁰ The second study looked into the effect of ovariectomy on buccal movement of rat molars evoked by a force of 10 cN. A significant increase in the rate of OTM was established.⁵¹ Both studies suggest that estrogen supplementation might slow OTM.

No experimental studies are available in which exogenous estrogens were administered to evaluate their effect on OTM. The same is true for raloxifene. Like estrogen supplementation, it might slow OTM, but experimental studies are lacking.

1,25 dihydroxycholecalciferol (vitamin D3)

1,25 dihydroxycholecalciferol (1,25[OH]₂D₃) is the most active hormonal form of vitamin D. It regulates calcium and phosphate serum levels by promoting their intestinal absorption and reabsorption in the kidneys. Furthermore, it promotes bone deposition and inhibits PTH release. It also plays a role in the immune response by promoting immunosuppression.

1,25(OH)₂D₃ deficiency can result from inadequate intake combined with inadequate sunlight exposure, eventually leading to impaired bone mineralization, rickets, and osteoporosis. Furthermore, it can lead to increased susceptibility to high blood pressure, periodontal disease, affective disorders, and auto-immune diseases. Therapy for 1,25(OH)₂D₃ deficiency involves diet changes or taking 1,25(OH)₂D₃ as a supplement.

Hypervitaminosis D causes hypocalcemia and might cause anorexia, nausea, polyuria, and eventually renal failure. It can be treated with a low-calcium diet and corticosteroids.

The effect of 1,25(OH)₂D₃ on OTM has been studied in rats by several authors.^{21,52,53} In 1 investigation, injections with 2.10⁻⁹ or 2.10⁻⁷ mol 1,25(OH)₂D₃ were given every third day in the submucosal palatal area of the root bifurcation of first molars, and the molars were subsequently moved buccally with forces of 5 to 20 cN.⁵² In another study, 2.10⁻⁹ mol 1,25(OH)₂D₃ was injected

every third day adjacent to the incisors, which were subsequently moved distally with forces of 20 cN.²¹ Both studies showed that $1,25(\text{OH})_2\text{D}_3$ stimulated the rate of OTM in a dose-dependent manner.^{21,52} A similar effect was found for canine retraction in cats after local administration of $1,25(\text{OH})_2\text{D}_3$ in dosages as low as 0.25×10^{-13} mol and an applied force of 60 cN.⁵³ Physiologic doses of $1,25(\text{OH})_2\text{D}_3$ do not stimulate bone resorption; conversely, low supplemental administration does, possibly by upregulation of RANKL (receptor activator for nuclear factor κB ligand) expression in osteoblasts, leading ultimately to osteoclast differentiation through the RANK/RANKL system.⁵⁴

Dietary calcium

Adults require 1000 to 1300 mg of calcium in their daily diet.⁵⁵ It is often prescribed as a dietary supplement for the prevention of osteoporosis in postmenopausal women. The effect of dietary calcium on OTM was studied in dogs that were fed low- or high-calcium diets for 10 weeks before orthodontic premolar movement was induced with a force of 100 cN for 12 weeks. From 8 weeks on, the low-calcium regimen led to a significantly higher rate of OTM than did the high-calcium diet.⁴⁶ These results agree with a comparable study in rats,⁴⁷ in which lactating rats were fed a low-calcium diet for 1 week before orthodontic molar movement with a force of 60 cN. This regimen led to faster OTM than in the control animals.⁴⁷ These data support bone turnover studies showing increases in the number of osteoclasts and osteoblasts in rats with a low-calcium diet.⁵⁶ The final outcome was increased bone remodeling phenotype in which excessive bone resorption prevailed over deposition.⁵⁶

Bisphosphonates

There are 2 classes of bisphosphonates: nitrogen-containing and non-nitrogen-containing bisphosphonates. They act on different pathways, but their final effect is the same. They all inhibit bone resorption, although their effectiveness differs considerably. They are used primarily for the prevention and therapy of osteoporosis, Paget's disease, bone metastases, and bone pain from some types of cancer.^{57,58}

Bisphosphonates are incorporated in the bone matrix, and they are unique in having an extremely long half-life of 10 years or more. Therefore, they can affect bone metabolism for many years after the patient has completed therapy.⁵⁸

Most studies on the effect of bisphosphonates on the rate of OTM have been performed by a group of Japanese researchers.⁵⁹⁻⁶¹ A similar model and protocol were used consistently during their experiments. They

induced lateral or medial movement in rat molars with a force of approximately 15 cN. All studies showed a dose-dependent decrease in the rate of OTM, with either topical or systemic administration of bisphosphonates. AHBuBP (a nitrogen-containing bisphosphonate) appeared to be more effective than clodronate, whereas risedronate was the most effective in inhibiting OTM.⁵⁹⁻⁶¹ A mouse model in which the first molar was moved in a palatal direction by a force of approximately 20 cN also showed a significant decrease in the rate of OTM by injections of pamidronate at a dosage of 5 mg per kilogram per day over 8 days.⁶² A serious drawback of long-term use of bisphosphonates is that they can cause osteonecrosis, especially in the alveolar bones of the maxilla and the mandible.⁵⁸

DISCUSSION AND CONCLUSIONS

The reviewed literature comprised almost exclusively animal studies; well-designed clinical studies were scarce. Comparison of the data from these studies was hampered by the great variability in experimental design, animal models, administration regimens, and force characteristics. Another problem was that direct extrapolation of experimental animal studies to the clinical situation is impossible. However, the effects of medication most likely point in the same direction in the experimental animals as in the clinical situation.

The most prescribed classes of medications—anti-depressants, antiulcerants, cholesterol reducers, and broad-spectrum antibiotics—might be involved in unwanted orthodontic side effects, as reviewed by Krishnan and Davidovitch,⁷ but no effect on the rate of OTM is known from these medications. Therefore, we focused on other classes of medications, such as anti-inflammatory and anti-asthmatic medications, anti-arthritis, analgesics, corticosteroids, estrogens and other hormones, and calcium regulators, all of which might affect the rate of OTM. Some of these groups of medications stimulate the rate of OTM, but others have an inhibitory effect.

Topical administration of synthetic analogues of eicosanoids increase the rate of OTM, whereas their inhibitors might decrease it. The most important inhibitors are the NSAIDs, which have both analgesic and anti-inflammatory effects. Although they all show a similar action, their effect on the rate of OTM is not uniform. The studies on the effects of NSAIDs on OTM were all performed over relatively short experimental periods. The effects found in these studies, therefore, might underestimate the effects of prolonged administration—eg, in rheumatoid arthritis patients.

Of the other analgesics, only paracetamol has been studied in relation to orthodontics, and no effect on the

rate of OTM could be established. No experimental data are available on the effect of opioid analgesics in this respect.

Corticosteroids, and especially glucocorticoids, stimulate OTM, but this depends on the relative anti-inflammatory activity of the corticosteroid and the administration protocol. Local or systemic application of PTH also increases the rate of OTM. The same effect is seen when endogenous PTH synthesis is stimulated by, for example, a low-calcium diet. Intermittent short administration of PTH or its active fragment (1-36) (teriparatide), on the other hand, has an anabolic effect on bone. However, no data are available to show that such an administration regimen inhibits OTM.⁴³

Administration of exogenous thyroxine increases the rate of OTM in a dose-dependent manner. Likewise, calcitonin is involved in bone remodeling and calcium homeostasis, although no experimental data on its effect on the rate of OTM are available.

The same applies to estrogen supplementation, specific estrogen receptor modulators (such as raloxifene), and oral contraceptives. Although an inverse relationship between estrogens and OTM was suggested, direct evidence for this effect is not available from the literature.

Administration of vitamin D3 increases the rate of OTM in a dose-dependent manner, whereas bisphosphonate administration decreases the rate of OTM in a dose-dependent manner. The use of bisphosphonates is complicated by serious osteonecrosis in the maxilla and the mandible.⁵⁸ This threat is greatest in patients with prolonged bisphosphonate use, and, because of the extremely long half-life of these drugs, patients can experience problems years after they discontinue therapy. In orthodontic patients, bisphosphonates can be used to prevent relapse, but they should be used with great caution.⁵⁸

This review shows that experimental evidence for the effects of many prescription and over-the-counter drugs on OTM is still lacking. For many years, the rate of OTM and the medication consumed by orthodontic patients apparently were not considered issues. In the clinical orthodontic literature, only isolated case reports have been mentioned.⁶³⁻⁶⁵

A case report of a postmenopausal orthodontic patient suggested that the estrogens used to treat osteoporosis might have delayed OTM.⁶⁴ It also might have inhibited alveolar bone loss in the chronic, stable phase of this patient's periodontitis.

Two case reports are available on the effects of bisphosphonate (zoledronate). In 1 patient, complete cessation of OTM was reported as a side effect of treat-

ment.⁶⁵ In the other study, slow OTM and osteopetrosis or osteonecrosis were reported.⁶⁶

Perhaps the clinician's attention should now become more focused on this matter because more patients of all ages seek orthodontic treatment, and, at the same time, prescription drug consumption has increased. Orthodontists increasingly see patients who use medications regularly; prescription and over-the-counter drug use is ever expanding in advanced societies. In addition, medications are also more often prescribed to children and adolescents. In the United States, the number of retail prescriptions increased from about 2 billion in 1992 to approximately 3.3 billion in 2001. Thus, the average American receives more than 10 prescriptions per year. The increase is supposedly caused by 3 factors: the number of first-time users has increased, more current users take their medications for longer times, and more people take more than 1 medication.⁶⁶

Consequently, orthodontists should assume that many patients are taking prescription or over-the-counter medications regularly. The orthodontist must identify these patients by carefully questioning them about their medication history and their consumption of food supplements. We recommend that such an inquiry should be part of every orthodontic diagnosis.

Furthermore, there is a need for more well-designed studies on the effects of various medications on OTM.

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