

# Prostaglandins and enhanced orthodontic tooth movement: In search of the silver bullet

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**Prostaglandins are a group of chemical messengers that carry out a number of functions in the human body. One of their important functions is to enhance bone resorption. This may have a profound meaning for orthodontics, as the process of tooth movement is based on selective bone resorption and deposition around the teeth. This article reviews the literature concerning the discovery of prostaglandins, as well as the research into its applications in orthodontics for the purpose of enhancing tooth movement. Also discussed, are the various synthetic alternatives to prostaglandins, which could bestow the desirable effects of prostaglandins, while avoiding their side effects.**

**Keywords:** Arachidonic acid, cyclic AMP, eicosanoids, prostaglandins, resorption.

PROSTAGLANDINS are a group of chemical messengers belonging to a family of hormones called eicosanoids. These are paracrine hormones, i.e. they act only on cells near the point of hormone synthesis instead of being transported via blood to act on cells in other tissues or organs, and they have a variety of dramatic effects on vertebrate tissues. All eicosanoids are derived from arachidonic acid, from which they take their general name (eikosi in Greek means twenty)<sup>1</sup>.

The three major classes of eicosanoids are prostaglandins, thromboxanes and leukotrienes. Thromboxanes are produced in the human body by platelets and act in blood clot formation, while leukotrienes are involved in inflammation and their overproduction causes asthmatic attacks. Prostaglandins act in many tissues by regulating the synthesis of cyclic AMP. As cyclic AMP mediates the actions of diverse hormones, prostaglandins affect a wide range of cellular and tissue functions. Some of the effects of prostaglandins are as follows:

1. They stimulate contraction of the smooth muscle of the uterus.
2. They affect blood flow, sleep cycle and response to hormones such as adrenaline and glucagon.
3. They elevate body temperature, cause inflammation and pain.

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## Synthesis of prostaglandin in the body

Prostaglandins are formed from arachidonic acid, which is itself produced by the action of an enzyme phospholipase A2 on phospholipids containing arachidonic acid. The cyclo-oxygenase activity of enzyme cyclo-oxygenase on arachidonic acid produces PGG2. This step is inhibited by aspirin. The peroxidase activity of cyclo-oxygenase converts PGG2 to PGH2, from which other prostaglandins as well as thromboxanes are derived.

## History of prostaglandins<sup>2</sup>

Kurzrok and Lieb (1930) first observed that strips of human uterus relax or contract when exposed to human semen. A few years later, Goldblatt in England and Von Euler in Sweden independently reported smooth muscle contracting and vasodepressor action in seminal fluid. Euler identified it as a lipid-soluble substance and named it prostaglandin, as it was believed to be secreted from the prostate gland. Bergstrom and Samuelson demonstrated that prostaglandins were in fact a family of compounds. They elucidated the structure of PGE1 and PGF2 in 1962. In 1964, Bergstrom and coworkers, and van Dorp independently achieved the biosynthesis of PGE2 from arachidonic acid.

During the past 25 years, a number of important discoveries have led to the realization that the classically known prostaglandins constitute only a fraction of the physiologically active products of the arachidonate metabolism. These include the discovery of thromboxane A2 (TXA2) by Hamberg and coworkers in 1975, prostacyclin (PGI2) by Moncada and coworkers in 1976, and the leukotrienes by Samuelsson in 1983.

The discovery by Vane, Smith and Willis (1971) that aspirin and related drugs inhibit prostaglandin synthesis, provided insight into the mechanism of action of these drugs, as well as an important tool for investigation of the role of these autacoids<sup>2</sup>.

## Role of prostaglandins in bone resorption

Research into the properties of prostaglandins by Klein and Raisz<sup>3</sup>, Raisz *et al.*<sup>4</sup>, Dowsett *et al.*<sup>5</sup>, demonstrated that prostaglandins had an important role in promoting

the resorption of bone in the human body. Though the exact role of prostaglandins in bone resorption is not clear, it is thought to do so by stimulating cells to produce cyclic AMP, which is an important chemical messenger for bone resorption.

In the field of dentistry, Goldhaber *et al.*<sup>6</sup> reported on the association of increased levels of prostaglandins with bone loss in periodontal disease, while Harris *et al.*<sup>7</sup> reported that the bone resorption produced by dental cysts was not due to pressure on bone but by the secretion of prostaglandin-like substances. Goodson *et al.*<sup>8</sup> were able to produce resorption of calvarium bone as well as alveolar bone in rats by repeated injections of PGE1. All these studies served to show the important role of prostaglandins in the process of bone resorption.

### Prostaglandins and orthodontics

Naturally, the above findings were of interest to the orthodontic community, as orthodontic tooth movement is primarily dependent on bone resorption adjacent to the tooth to be moved. Also, the generally slow speed of orthodontic tooth movement has been the Achilles heel of the profession, delaying results and prolonging treatment time. Yamasaki and associates<sup>9</sup> were among the earliest researchers to investigate the role of prostaglandins in bone resorption associated with orthodontic tooth movement. They conducted experiments on rats to investigate whether the synthesis of prostaglandins is induced by orthodontic force, and whether exogenous prostaglandins can produce bone resorption similar to orthodontic force. They reported that the application of orthodontic force did indeed cause increased synthesis of prostaglandins, which in turn stimulated osteoclastic bone resorption. A similar study on cats by Davidovitch *et al.*<sup>10</sup> also showed increased levels of PGE2 in the alveolar bone, as a result of application of orthodontic force. The histological data were supported by the finding of Chumbley *et al.*<sup>11</sup>, that Indomethacin, an inhibitor of prostaglandin synthesis, also inhibited orthodontic tooth movement.

These indications led Yamasaki *et al.*<sup>12</sup> to attempt to clarify the effect of prostaglandins on the rate of orthodontic tooth movement in monkeys and also to examine possible side effects on gingival tissues. Another aim was to explore the possibility of local administration of prostaglandins in conjunction with orthodontic tooth movement to increase the rate of tooth movement as well as decrease the treatment time. The results of experiments on two *Macaca fuscata* monkeys showed that the local administration of PGE1 or PGE2 in gingiva near the distal area of canines to be retracted, caused double the rate of tooth movement compared to the opposite, control side. Also, no side effects were seen in the gingiva.

As a result of these favourable findings, Yamasaki *et al.*<sup>13</sup> were encouraged to study the effects of PGE1 ad-

ministration on orthodontic tooth movement in humans. This study was performed in two phases. In the first phase, buccal movement of the first premolars scheduled for extraction was examined with and without PGE1 administration. In the second stage, PGE1 was administered in canine retraction for up to three weeks in first premolar extraction cases. In both phases, the rate of tooth movement was doubled compared to control sides. The authors reported no side effects macroscopically or radiographically, except for a slight pain reaction consistent with tooth movement. This lack of pain was presumably due to the fact that the PGE1 was injected in a lidocaine vehicle, which exerted an anaesthetic effect.

In a later study, Lee<sup>14</sup> contended that the vasoconstriction produced by the lidocaine solution at the site of administration would suppress the inflammatory reaction required for bone resorption. He reported that systemic intravenous administration of PGE1 was more effective and produced more bone resorption than local injection. However, he conceded that rapid inactivation of PGE1 in the lungs, and certain side effects such as local irritation and phlebitis were associated with this method.

Leiker *et al.*<sup>15</sup>, studied the long-term effects of varying concentrations and frequencies of injectable, exogenous PGE2 on the rate of tooth movement in rats, and reported that injections of exogenous PGE2 over an extended period of time in rats did enhance the amount of tooth movement. However, there was an increase in the amount of root resorption with increasing numbers and concentrations of the PGE2 injections.

In India, Bhalajhi and Shetty<sup>16</sup> studied the effect of exogenous administration of PGE2 in young rabbits and reported an increase in the rate of tooth movement clinically and an increase in the number of osteoclasts and resorption lacunae, microscopically. Their results supported the theory that PGE2 increases tooth movement. The two major drawbacks associated with the use of prostaglandins as reported by them are: pain reaction and the need for frequent administration because of rapid metabolism of PGE2 in the lungs.

### Synthetic alternatives

The myriad disadvantages associated with the use of prostaglandins led researchers to test the applicability of Misoprostol, a synthetic PGE1 analogue, in enhancing orthodontic tooth movement. Kehoe *et al.*<sup>17</sup> administered Misoprostol (100 µg/kg) twice daily in guinea pigs and noted a significant increase in the degree and rate of orthodontic tooth movement. In a later study by Sekhvat *et al.*<sup>18</sup>, it was reported that Misoprostol was effective in enhancing tooth movement in doses as low as 10–25 µg/kg, twice daily, and also that Misoprostol did not significantly increase the amount of root resorption. They suggested that oral Misoprostol could be used to enhance orthodontic tooth

movement with minimal root resorption. Other attempts to reduce the amount of root resorption have included the concomitant injection of calcium gluconate with PGE<sub>2</sub>, by Seifi *et al.*<sup>19</sup>, who reported that the calcium ions provided by calcium gluconate prevented parathormone-induced root resorption in rats.

The role of vitamin D in the maintenance of calcium homeostasis in human beings has been well documented. It is a steroid hormone that has specific receptors in many target organs and tissues. It exerts its action by activating DNA and RNA within the target cell to produce proteins and enzymes that can be used in the bone resorption process. In particular, the active form of vitamin D, 1,25-dihydroxycholecalciferol (hence referred to as 1,25 DHC), is one of the most potent stimulators of osteoclastic activity known. It has been found to have a half-life in plasma of 2 to 3 h, but its cellular activation effects may last for several days. It is also involved in the formation of osteoclasts from precursor monocytes and may produce these effects at much lower doses than other hormones such as prostaglandins. Collins and Sinclair<sup>20</sup> as well as Kale *et al.*<sup>21</sup> have reported that the local administration of vitamin D increases the rate of tooth movement in cats and rats respectively. Kale *et al.* have emphasized that administration of vitamin D results in a good balance between deposition and resorption of bone and well-modulated bone turnover compared to prostaglandin administration.

## Conclusion

It stands to reason that if orthodontists could obtain the advantages of prostaglandins without the disadvantages of pain and root resorption, it would be a breakthrough of sorts which would change the way the profession is practiced. It would not only enable orthodontists attend to patients faster, but also allow them to offer their services to a larger segment of the population. It should not be regarded as too unrealistic an expectation that one day such chemical enhancers of tooth movement will become a clinical reality, and a part of everyday orthodontics. With India emerging as a global leader in biotechnology, it is incumbent upon us to take the lead in developing a safe and efficient prostaglandin substitute for orthodontic use, and make the job of the orthodontist a little easier.

1. Nelson, D. and Cox, M., *Lehninger's Principles of Biochemistry*, W.H. Freeman and Co, New York, 2004, 4th edn, p. 358.
2. Goodman Gilman, A., Rall, T., Nies, A. and Taylor, P., *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, Pergamon Press, New York, 1991, vol. 1, 8th edn, p. 600.
3. Klein, D. C. and Raisz, L. G., Prostaglandins: stimulation of bone resorption in tissue culture. *Endocrinology*, 1970, **86**, 1436–1440.

4. Raisz, L. G., Sandberg, A. L., Goodson, J. M., Simmons, H. A. and Mergenhagen, S. E., Complement-dependent stimulation of prostaglandin synthesis and bone resorption. *Science*, 1974, **185**, 789–791.
5. Dowsett, M., Eastman, A. R., Easty, D. M., Easty, G. C., Powles, T. J. and Neville, A. M., Prostaglandin mediation of collagenase induced bone resorption. *Nature*, 1976, **263**, 72–74.
6. Goldhaber, P., Rabadjija, L., Beyer, W. R. and Kornhauser, A., Bone resorption in tissue culture and its relevance to periodontal disease. *J. Am. Dent. Assoc.*, 1973, **87**, 1027–1033.
7. Harris, M., Jenkins, M. V., Bennet, A. and Wills, M. R., Prostaglandin production and bone resorption by dental cysts. *Nature*, 1973, **245**, 213–215.
8. Goodson, J. M., McClatchy, K. and Revell, C., Prostaglandin-induced resorption of adult rat calvarium. *J. Dent. Res.*, 1974, **53**, 670–677.
9. Yamasaki, K., Miura, F. and Suda, T., Prostaglandin as a mediator of bone resorption induced by experimental tooth movement in rats. *J. Dent. Res.*, 1980, **59**, 1635–1642.
10. Davidovitch, Z., Nicolay, O. F., Ngan, P. W. and Shanfeld, J. L., Neurotransmitters, cytokines, and the control of alveolar bone remodeling in orthodontics. *Dent. Clin. North Am.*, 1988, **32**, 411–435.
11. Chumbley, A. B. and Tunca, O. C., The effects of Indomethacin (an aspirin-like drug) on the rate of tooth movement in cats. *Am. J. Orthod.*, 1986, **89**, 312–314.
12. Yamasaki, K., Shibata, Y. and Fukuhara, T., The effect of prostaglandins on experimental tooth movement in monkeys (*Macaca fuscata*). *J. Dent. Res.*, 1982, **61**, 1444–1446.
13. Yamasaki, K., Shibata, Y., Imai, S., Tani, Y., Shibasaki, Y. and Fukuhara, T., Clinical application of prostaglandin E<sub>1</sub> (PGE<sub>1</sub>) upon orthodontic tooth movement. *Am. J. Orthod.*, 1984, **85**, 508–518.
14. Lee, W., Effect of prostaglandins on tooth movement. *Am. J. Orthod. Dentofac. Orthop.*, 1990, **98**, 231–241.
15. Leiker, B. J., Nanda, R. S., Currier, G. F., Howes, R. I. and Sinha, P. K., The effects of exogenous prostaglandins on orthodontic tooth movement in rats. *Am. J. Orthod. Dentofac. Orthop.*, 1995, **108**, 380–388.
16. Bhalajhi, S. I. and Shetty, V. S., The effect of prostaglandin E<sub>2</sub> on tooth movement in young rabbits. *J. Indian Orthod. Soc.*, 1996, **27**, 85–92.
17. Kehoe, M. J., Cohen, S. M., Zarrinnia, K. and Cowan, A., The effect of acetaminophen, ibuprofen and misoprostol on prostaglandin E<sub>2</sub> synthesis and the degree and rate of orthodontic tooth movement. *Angle Orthod.*, 1996, **66**, 339–350.
18. Sekhvat, A. R., Mousavizadeh, K., Pakshir, H. R. and Aslani, F. S., Effect of misoprostol, a prostaglandin E<sub>1</sub> analog, on orthodontic tooth movement in rats. *Am. J. Orthod. Dentofac. Orthop.*, 2002, **122**, 542–547.
19. Seifi, M., Eslami, B. and Saffar, A. S., The effect of prostaglandin E<sub>2</sub> and calcium gluconate on orthodontic tooth movement and root resorption in rats. *Eur. J. Orthod.*, 2003, **25**, 199–204.
20. Collins, M. K. and Sinclair, P. M., The local use of vitamin D to increase the rate of orthodontic tooth movement. *Am. J. Orthod. Dentofac. Orthop.*, 1988, **94**, 278–284.
21. Kale, S., Kocadereli, I., Atilla, P. and Asan, E., Comparison of the effects of 1,25-dihydroxycholecalciferol and prostaglandin E<sub>2</sub> on orthodontic tooth movement. *Am. J. Orthod. Dentofac. Orthop.*, 2004, **125**, 607–614.

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