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Does orthodontic tooth movement cause an elevation in systemic inflammatory markers?

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SUMMARY The aim of this study was to evaluate the effects of orthodontic treatment on systemic levels of the inflammatory markers, C-reactive protein (CRP), tumour necrosis factor-α (TNF-α), and interleukin-6 (IL-6). The study group comprised 11 girls and 6 boys (mean age 13.1 years) treated with fixed appliances and distalizing headgear. Venous blood samples were taken from the cubital vein of each subject before treatment (T0) and then at three further time points during treatment (T1–T3), 2 months apart. The sera from these blood samples were analysed using enzyme-linked immunosorbent assay (ELISA) assay technology for CRP, TNF-α, and IL-6 concentration levels. Data were compared between baseline and subsequent sequential time points using a Mann–Whitney test for non-normally distributed variables.

The results showed that there was no significant elevation of any of the three inflammatory markers at any of the time points. This research provides evidence that conventional orthodontic treatment is not associated with a systemic immune response in the factors investigated.

Introduction

Recently, there has been speculation that oral health may have a modulating or aetiological role in other systemic diseases (Mustapha *et al.*, 2007; Tonetti *et al.*, 2007; Parahitiyawa *et al.*, 2009). The systemic elevation of inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumour necrosis factor-α (TNF-α) as a response to an oral stimulus has been postulated as an explanatory mechanism (Danesh *et al.*, 2004). Such a stimulus could either be periodontal tissue inflammation, the systemic spread of oral bacteria and their products, or a combination of these factors. Studies have shown that orthodontic treatment can cause or facilitate the following situations.

Periodontal tissue inflammation

At the beginning of orthodontic tooth movement, the mechanical stimulus causes an acute inflammatory reaction within the periodontal tissues, which, in turn, triggers the biologic processes that result in bone resorption to accommodate movement of the tooth (Sandy *et al.*, 1993). TNF-α is a typical mediator of inflammatory response that has been shown to be involved in the process of bone resorption and to be locally elevated in response to orthodontic force (Alhashimi *et al.*, 2001; Basaran *et al.*, 2006b; Karacay *et al.*, 2007). It plays a prominent role in the mechanism controlling the appearance of osteoclasts at compression sites (Sandy *et al.*, 1993; Meikle, 2006). This inflammatory marker is produced not only by activated monocytes and macrophages but also by osteoblasts, and has been proven to be an activator of osteoclastic bone resorption (Azuma *et al.*, 2000).

CRP was the first inflammatory marker to be described. It is a marker of inflammation and tissue damage (Pepys and Baltz, 1983). It is an integral part of the acute inflammatory response with multiple activation pathways.

IL-6 regulates immune responses in inflammation sites (Okada *et al.*, 1997) and stimulates osteoclast formation and the bone-resorbing activity of osteoclasts (Uematsu *et al.*, 1996; Basaran *et al.*, 2006a). Since it is responsible for the up-regulation of CRP, an elevation of IL-6 followed by an elevation of CRP might be expected (Pajkrt and Manten, 1997). These inflammatory markers act locally and systemically with overlapping functions.

There have been no studies investigating systemic inflammatory marker levels in response to periodontal inflammation caused by orthodontic tooth movement; however, there have been many studies relating inflammatory marker levels to the oral stimulus of periodontal disease. Noack *et al.* (2001) related periodontal status in adults to circulating CRP and reported a significant relationship between the severity of periodontitis and circulating CRP.

The systemic spread of oral bacteria and their products

Bacteraemia have been reported in several studies during orthodontic procedures of banding, debanding, and placement of separators (McLaughlin *et al.*, 1996; Erverdi *et al.*, 1999, 2000; Lucas *et al.*, 2002). Plaque control in orthodontic patients is often sub-optimal and therefore mild-to-moderate gingivitis often develops during treatment. This can lead to transient bacteraemia (Silver *et al.*, 1977; Schlein *et al.*, 1991). Bacteria and their endotoxins are capable of generating a range of systemic and local host responses. As well as a non-specific activation of the immune system, circulating micro-organisms, or their products may promote atherogenesis and enhance local inflammatory changes in vessel walls, as well as adversely

influence the rheology of the blood, promoting clotting, and thrombus formation (Herzberg and Meyer, 1996; Beck *et al.*, 1998; Chiu, 1999; Libby, 2006).

Inflammatory markers are recognized as surrogate measures of inflammation, acting locally, and systemically. CRP especially has gained much attention as CRP levels show greater predictive power for cardiovascular disease than conventional lipid parameters (Ridker *et al.*, 1997, 2000a; Danesh, 2000). Other chronic diseases and pathological processes associated with elevated levels of inflammatory markers are summarized in Table 1 along with lifestyle factors associated with decreased circulating levels of inflammatory markers.

There are no data available on the acute systemic host response to orthodontic treatment. The objective of this study was therefore to assess if there is a clinically significant rise in these inflammatory markers in response to conventional orthodontic forces.

Subjects and methods

Study population

Approval for the study was obtained from the Institutional Review Board of the University of Hong Kong to recruit patients who were due to receive fixed appliance orthodontic treatment in conjunction with distalizing headgear (IRB Reference Number: UW 07-109).

Seventeen subjects (11 females and 6 males) aged 11.2–15.3 years (mean 13.1 years) were recruited to the study. The sample size was derived from a similar study by Ide *et al.* (2004). Among children in this age range, third molars have not erupted, and growth potential facilitates molar distalization. Ineligible patients were those with persistent or recurrent upper respiratory tract infections, asthma, generalized gingivitis, localized or generalized periodontitis or obesity. Also ineligible were patients who were routinely taking medication and those who had poor oral hygiene. Children were only included if a parent/guardian agreed to accompany them to each study visit. None of the patients were smokers.

Baseline 3 ml blood samples (T0) were taken from each subject from the cubital vein before any orthodontic therapy was started. EMLA (eutectic mixture of lidocaine and prilocaine) topical anaesthetic cream was applied to the cubital fossa area of each subject and left for 40 minutes. The area was then cleaned with an alcohol wipe before each blood sample was drawn. Baseline data were collected for all subjects by questionnaire. This considered factors that may possibly influence immune system status.

Three further 3 ml blood samples were taken during treatment: 2 (T1), 4 (T2), and 6 months (T3) into treatment. These blood samples were obtained 1 week following the subject's routine orthodontic appointment. None of the blood taken was discarded.

Compliance with headgear wear was assessed using self-reporting time charts.

Further health questionnaires were issued at the T1, T2, and T3 time points to check for any recent health changes.

Table 1 Association of inflammatory marker concentrations and non-cardiovascular medical conditions/lifestyle factors.

Association of medical condition/lifestyle factors with increased circulating inflammatory marker levels	Authors
Periodontal disease	Mustapha *et al.* (2007)
Depression	Lanquillon *et al.* (2000)
Rheumatoid arthritis before onset of symptoms	Masi *et al.* (2001)
Diabetes mellitus	Ford (1999)
Chronic fatigue	Buchwald *et al.* (1997)
Obesity	Lyon *et al.* (2003)
Decreased physical performance	Geffken *et al.* (2001)
High level of alcohol consumption	Imhof *et al.* (2001)
Obstructive sleep apnoea	Yokoe *et al.* (2003)
Coffee consumption	Zampelas *et al.* (2004)
Association of medical condition/lifestyle factor with decreased circulating inflammatory marker levels	
Regular exercise	Mattusch *et al.* (2000)
Eating fish regularly	Zampelas *et al.* (2005)
Low level of alcohol consumption	Imhof *et al.* (2001)

Laboratory analysis

The laboratory protocol followed the instructions of the various manufacturers of the enzyme-linked immunosorbent assay (ELISA) assay kits for CRP, IL-6, and TNF-α. The following is a brief summary.

The blood was collected in serum separator tubes and left to clot for 30 minutes. The tube was then centrifuged at 2300 rpm for 15 minutes to separate the serum. The serum was then decanted into 0.2 ml aliquots and stored at −70°C until all specimens had been collected.

Samples were assayed for CRP (DSL-10-42100 Ultra Sensitive (US), Diagnostic Systems Laboratories Inc., Webster, Texas, USA), TNF-α (Quantikine HSTA00D, R & D Systems, Inc., Minneapolis, Minnesota, USA), and IL-6 (Quantikine HS600B, R & D Systems, Inc.) using quantitative enzyme immunoassays. These have a lower detection limit for CRP of approximately 1.6 ng/ml, for TNF-α of 0.106 pg/ml, and for IL-6 of 0.039 pg/ml.

The DSL-10-42100 US CRP ELISA is an enzymatically amplified sandwich-type immunoassay. In the assay, standards, controls, and unknown samples were incubated in microtitration wells that had been coated with anti-US CRP antibody. After incubation and washing, the wells were treated with another enzyme-linked anti-US CRP detection antibody. After a second incubation and washing, the wells were incubated with the substrate amplifier. An acidic stopping solution was then added and the degree of enzymatic turnover of the substrate was determined by dual wavelength absorbance measurement at 450 and 620 nm.

The absorbance measured was directly proportional to the concentration of US CRP present. A set of US CRP standards was used to plot a standard curve of absorbance versus US CRP concentration from which the US CRP concentrations in the unknowns can be calculated.

The IL-6 assay employed the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for IL-6 was pre-coated onto a microplate. Standards and samples were pipetted into the wells and any IL-6 present was bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for IL-6 was added to the wells. Following washing to remove any unbound antibody–enzyme reagent, a substrate solution was added to the wells. After an incubation period of 2 hours, an amplifier solution was added to the wells and colour developed in proportion to the amount of IL-6 bound in the initial step. The colour development was stopped and the intensity of the colour was measured by dual wavelength absorbance at 490 and 650 nm.

A similar process was used for TNF-α assay. This assay also employed the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for TNF-α was pre-coated onto a microplate. Standards and samples were pipetted into the wells and any TNF-α present was bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for TNF-α was added to the wells. Following washing to remove any unbound antibody–enzyme reagent, a substrate solution was added to the wells. After an incubation period of 2 hours, an amplifier solution was added to the wells and colour developed in proportion to the amount of TNF-α bound in the initial step. The colour development was stopped and the intensity of the colour was measured by dual wavelength absorbance measurement at 490 and 650 nm.

Statistical analysis

Data were analysed using the Statistical Package for Social Sciences (Windows version 15.0, SPSS Inc., Chicago, Illinois, USA). Frequency distributions were determined for all variables. It was not possible to transform the data for any of the inflammatory markers to a normal distribution by simple arithmetic functions. Data were compared between baseline and subsequent sequential time points using a Mann–Whitney test for non-normally distributed variables.

Results

A complete set of samples was taken from the 17 subjects.

Good general health was reported by all the subjects during the experimental period. All patients reported wearing the headgear for at least 8 hours/day (range 8–14 hours) during the experimental period.

Table 2 shows the findings at each recorded time point for the inflammatory molecules CRP, TNF-α, and IL-6,

Table 2 Levels of C-reactive protein (CRP), tumour necrosis factor-α (TNF-α), and interleukin-6 (IL-6) at baseline (T0) and after 2 (T1), 4 (T2), and 6 months (T3) for the 17 subjects.

Time point	CRP				TNF-α				IL-6			
	Mean (mg/ml)	Range	Median (mg/ml)	Change from T0, Mann–Whitney test, *P*	Mean (pg/ml)	Range	Median (pg/ml)	Change from T0, Mann–Whitney test, *P*	Mean (pg/ml)	Range	Median (pg/ml)	Change from T0, Mann–Whitney test, *P*
T0	0.260	0.039–1.503	0.069		1.015	0.696–3.268	1.084		1.087	0.487–2.140	0.917	
T1	0.153	0.039–0.824	0.069	0.959 (ns)	1.439	0.313–3.056	1.405	0.125 (ns)	1.246	0.214–3.991	0.973	0.959 (ns)
T2	0.258	0.042–1.618	0.073	0.986 (ns)	1.680	0.367–7.989	1.019	0.310 (ns)	2.150	0.453–11.22	0.906	0.959 (ns)
T3	0.182	0.041–0.730	0.129	0.692 (ns)	1.727	0.256–6.156	1.220	0.117 (ns)	1.075	0.283–1.983	0.825	0.744 (ns)

ns, not significant.

respectively. Data are reported as the median and mean for the Mann–Whitney test. Figure 1 summarizes the data. The results show that there was no significant increase in concentration of any of the inflammatory markers at any of the time periods.

Discussion

This study was undertaken to assess whether the immune system was stimulated by orthodontic force, a result that could have significant long-term health implications for orthodontic patients. It was theorized that this could be caused either by local inflammatory damage of periodontal tissue having a systemic overlap or by the systemic spread of bacteria or their toxins and products, or a combination of both these factors. These situations could conceivably occur during orthodontic treatment.

In adults, it is well documented that elevated CRP is an independent predictor of adverse cardiovascular events (DeFerranti and Rifai, 2007). Increasing levels of CRP are associated with up to a 3-fold increase in the risk of myocardial infarction and a 2-fold increase in the risk of ischaemic stroke (Ridker *et al.*, 1997). CRP has proven to be the single strongest predictor of cardiovascular disease in apparently healthy subjects, more so that standard lipid measures (Ridker *et al.*, 2000a). Elevated TNF-α and IL-6 have also been shown by the same authors to be associated with cardiovascular events (Ridker *et al.*, 2000b, c).

Atheromatous plaques are acknowledged to be present in all humans from the second decade of life onwards, and CRP, TNF-α, and IL-6 are regarded as being intimately involved at various stages in atheromatous plaque formation (Libby, 2006).

Because of the commonality of elevated CRP in both periodontal and cardiovascular disease, there has been much research into this relationship, adding to the debate that an oral problem can have a systemic effect. In a recent meta-analysis, Bahekar *et al.* (2007) reported an increase in cardiovascular disease risk of between 1.14 and 1.59 times among patients with periodontal disease.

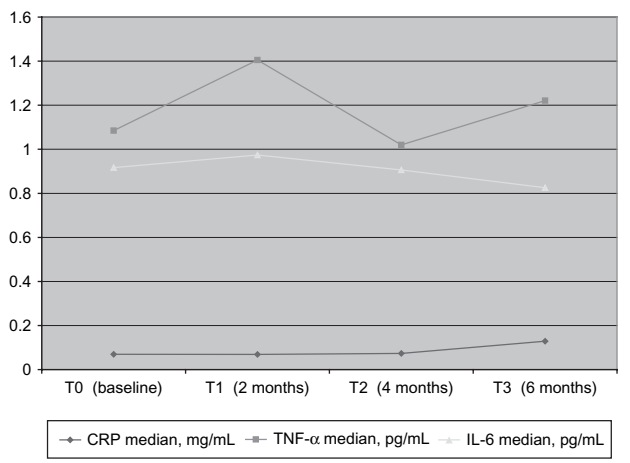

Figure 1 Levels of C-reactive protein (CRP), tumour necrosis factor-α (TNF-α), and interleukin-6 (IL-6) at baseline and during treatment.

Although the main research has been focused on the relationship between inflammatory markers and cardiovascular disease, there is a growing body of evidence that associates inflammatory markers with a wide variety of non-cardiovascular diseases and lifestyle factors, adding to the speculation that a low grade chronic inflammatory state is intrinsic to many pathological pathways (Table 1).

Drawing a precise boundary between 'normal' and 'abnormal' CRP, TNF-α or IL-6 levels is difficult. For CRP, however, population research has shown CRP levels of roughly 3 mg/ml or less to represent truly normal, or innocuous, values, and CRP levels over 10 mg/ml to reflect clinically significant inflammatory states (Macy *et al.*, 1997). Both circulating IL-6 and TNF-α can be found in the blood of normal individuals in the 1 pg/ml range (Vassalli, 1992; D'Auria *et al.*, 1997). The results of the present study for CRP, TNF-α, and IL-6 concentrations at all time points were around the normal values, indicating a lack of systemic immune activation.

In this study, subjects undergoing fixed appliance therapy in conjunction with distalizing headgear were analysed, reasoning that this patient group would undergo a higher than average mechanical force burden which would reduce the possibility of a false-negative result.

The experimental blood samples were taken 1 week following the patients' routine orthodontic appointments. It was considered that this time lag was necessary to allow any potential immune response to develop and also to make the results more clinically relevant. D'Aiuto *et al.* (2005) assessed circulating inflammatory marker levels in a time period extending 30 days following intensive periodontal therapy. In their subjects, they found that this induced a moderate inflammatory response lasting 1 week but that inflammatory marker levels had returned to normal after 30 days. In the present experiment, the potential insult to the tissues was more subtle than intensive periodontal therapy. If there was to be an immune response, it might be expected after an initial delay to allow local inflammatory changes to be induced by the pressure/tension scenario that develops. By taking the blood samples 1 week following the subject's routine appointment, it was hoped to be safely within the window of activation, if there was to be any.

Ide *et al.* (2004) assessed CRP, IL-6, and TNF-α immediately following periodontal therapy with a sample size similar to the present study. They found a significant elevation of IL-6 and TNF-α in the hours following sub-gingival scaling. However, it is a low-level chronic inflammatory state that seems associated with many disease pathways not transient elevations (Kushner *et al.*, 2006). So, again, for the current study, taking blood samples following a time lag from the treatment date would have more systemic significance.

For further follow-up, it may be worth expanding this research to enable a more sensitive determination of difference in means. Also, different time points could be assessed, both in terms of the relationship to routine orthodontic appointments and with regard to the overall length of therapy, as treatment can last for several years.

The present findings are important as they are the first to provide evidence that orthodontic treatment is not associated with a systemic immune response. Raised levels of circulating inflammatory markers are associated with a wide variety of chronic health problems as previously described, with special emphasis on cardiovascular disease. Although orthodontic treatment would not be the immediate cause of any cardiovascular event for young healthy patients, the systemic stresses caused by orthodontic treatment over an average treatment period could possibly initiate or accelerate atheromatous plaque development with associated sequelae later in life. For adult patients, if orthodontic treatment caused levels of inflammatory markers to elevate, then one could speculate that orthodontic treatment may be a risk factor for cardiovascular disease. More immediately relevant for younger patients would be the association of raised inflammatory markers with depression and obesity, conditions that affect a significant proportion of the adolescent population: around 5 and 16 per cent, respectively (Essau and Dobson, 1999; Ogden *et al.*, 2008).

From a medico-legal point of view, it is important to establish the immunological safety of orthodontic treatment. Patients who develop medical problems during orthodontic treatment or those with chronically debilitating conditions developed later in life may attempt to rationalize life events relevant to them and perhaps apportion blame.

The findings of this study also add weight to the argument that orthodontic tooth movement is not a pathological event so much as an exaggerated form of normal physiological turnover combined with foci of tissue repair as proposed by Meikle (2006).

Conclusion

This study is the first to show that there is no activation of the immune system (as indicated by normal levels of various inflammatory markers) during active therapy, and orthodontic treatment is therefore immunologically safe.

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