The Role of NSAIDs in Impaired Osseointegration in Dental Implant Prosthodontics

Brenton Paul Lauder Coverdale Winnett

A thesis submitted in conformity with the requirements for the degree of Masters of Science (Prosthodontics)

Discipline of Prosthodontics
Department of Clinical Sciences
Faculty of Dentistry
University of Toronto

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Abstract

Objective: To appraise whether adverse events following oral implant placement may be associated with peri-operative use of non-steroidal anti-inflammatory drugs (NSAIDs).

Methods: All patients with recorded implant failures between 1979 and 2012 in the Implant Prosthodontics Unit were contacted to solicit additional information about potential peri-operative use of NSAIDs. Results: From a total of 168 patients with 292 implant failures between 1979 and 2012, 122 consented to participate and had intact records. Just over half (56.6%) reported no peri-operative NSAID usage. However, compared to patients who did not use peri-operative NSAIDs, four times as many had complicated medical histories and twice as many patients taking NSAIDs suffered multiple implant failures. Conclusions: Patients with a variety of systemic diseases may be adversely affected by the inhibitory effect of NSAIDs on bone healing. Further prospective clinical studies are warranted to clarify this potential causative relationship in humans.
Acknowledgments

This thesis – and the many hours of solitary work it’s completion represents – is dedicated first to my wife, without whom meeting the rest of life’s obligations would not be possible. Thank you for your understanding, your tireless effort raising our children, and your support.

This thesis – and the many hours of poring over dusty records in a windowless office – is dedicated to my children, without whom much of life would be like that same office. Thank you for your joy and energy, and for sharing them with us.

This thesis is dedicated to Dr. Asbjorn Jokstad, without whose guidance and dedication to academic rigor the courage to declaim the conclusions of this research would be lacking. Thank you for teaching.

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This thesis is dedicated to Mrs. Janet Dewinter, without whom the 33 year cache of data would not exist. Thank you for your dedication to the science of osseointegration; your work has been essential to the growth of this discipline in Canada.
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1 The dental implant: success and failure

1.1 Contraindications to implant placement

Osseointegrated dental implants provide prosthetic treatment options previously unknown in dentistry and have become an essential part of the modern dental armamentarium. The restorations made possible by these implants dramatically improve the edentulous and partially edentulous patient’s quality of life, and they do so predictably. This clinical success depends on the successful osseointegration of the dental implant, and in general this therapy has been proven to achieve a high rate of successful osseointegration when employed in patients with few or no known risk factors (Berglundh et al. 2002, Pjetursson et al. 2007). In fact, over the many years of research dedicated to the investigation of those risk factors, little progress has been made in identifying the essential factors leading to implant failure. The opposite is true: there are fewer risk factors believed to be associated with the failure of osseointegrated dental implants than ever before, and none of them absolute.

Yet, implant failures still occur, and with approximately the same frequency regardless of the advances in biomaterial science and medicine in general; theories abound about their putative causes (Esposito et al. 1998, Moy et al. 2005, Bornstein et al. 2009). As noted, the list of absolute contra-indications for dental implant surgery originally proposed by Brånemark and colleagues (1977) has subsequently been revised many times in recent years and now can be said to include only a patient’s exposure to high dose radiation therapy, high dose intravenous bisphosphonate therapy, psychiatric patients, and patients unable to maintain oral care for whatever reason. No other systemic disease or associated pharmacological therapy is currently believed to absolutely preclude the placement of dental implants.

Outside of the potential role of biomechanical and technical complications in the etiology of late dental implant failure, the degree to which one or more local or systemic diseases contributes to early adverse implant osseointegration outcomes remains controversial (Bornstein et al. 2009). A short list of these might include rheumatoid arthritis, osteomalacia, immune deficiency
diseases, drug abuse (alcohol, tobacco, etc.), uncontrolled diabetes, bleeding disorders, and the systematic consequences of radiation therapy (Buser et al 2000, Mombelli & Cionca 2006), but for every study demonstrating an increased incidence of failure, there is another demonstrating case success.

In addition to these potential systemic causes of implant failure, other theories suggest that surgical trauma (including overheating during site preparation), inadequate implant primary stability, and biomechanical and technical complications like inadequate interdental space, premature prosthetic loading, or excessive overall biomechanical loading also contribute to otherwise unexplained loss of implant osseointegration (Buser et al 2000, Martin et al 2009). However, shortcomings of study design make it difficult to assess the legitimacy of competing conclusions regarding these influences, and the general consensus for now is that better evidence is required (Salvi & Bragger, 2009). In general, current practice commonly limits the application of dental implants to patients with few and well-controlled systemic risk factors in an attempt to optimize clinical outcomes (Mombelli & Cionca 2006), but this is not exclusively true; many patients with one or several of these risk factors are treated successfully with dental implants, leaving the challenge of identifying individual risk unresolved.

1.2 Cluster failures

As Bornstein noted (2009), the level of evidence identifying the absolute and relative contraindications for implant placement is quite low; few studies have compared patients with and without specific risk factors in a controlled setting. Clearly, it is difficult to identify the patients that are most likely to actually experience dental implant failures (Cochran et al. 2009). As Moy and colleagues (2005) found in their retrospective study of 4,680 implants placed in 1,140 patients from 1982 to 2003, a greater percentage of implants had failed in “healthy” patients than in “medically compromised” patients. This is excluding data from patients receiving unsafe implant designs (Malmqvist & Sennerby, 1990). To date, research has been unsuccessful in finding the unidentified factors interfering with implant success rates.
Considering the progressive elimination of systemic absolute contraindications to dental implant failure, the research acknowledging the phenomenon of multiple implant failures occurring in a small subset of patients without obvious risk factors is especially troublesome. This “clustering of failures” phenomenon was first described by Weyant and Burt (1993). The persistence of occasional but problematic failure of osseointegration in the absence of other diagnosed pathologies raises the issue of what other factors may be responsible. The cluster failures may be simply the result of a combination of several things going wrong in a single patient, or it may reflect an as yet unknown alternative etiology (Sugerman & Barber 2002, Jemt & Hager 2006). The number of potential interactions between these variables makes it very difficult to explain clustered implant failures with any confidence.

1.3 Confounding factors

Recently, sudden unexplained advanced bone loss was observed in a small number of patients with no previously identified contraindications treated in the University of Toronto Faculty of Dentistry Graduate Prosthodontics Clinic. Upon scrutiny of the patient charts to identify potential associations, it was determined that one factor these patients appeared to have in common was the peri-operative use of the drug Celebrex (Celecoxib). Celecoxib belongs to the pharmaceutical class Non-Steroidal Anti-inflammatory Drugs (NSAID) and, specifically, is a selective cyclo-oxygenase isoform 2 (COX-2) inhibitor normally used in the treatment of chronic inflammatory pain in patients with conditions like arthritis.

This drug, along with all other NSAIDs, is known to reduce traumatic bone healing to varying degrees, but there is little agreement in the literature regarding the specific mechanisms of this inhibitory effect at the cellular and molecular levels (Norridin et al 1990, Chikazu et al 2007, Utvag et al 2010, Pountos et al 2012). The challenge of identifying a specific effect of NSAIDs on bone healing in humans is complicated by the diversity and prevalence of NSAID subtypes commonly used to treat different types of inflammation, the different dosing regimens, the drugs’ different mechanisms and duration of action, and their relative effectiveness or potency at inhibiting inflammation (Gilroy et al, 1998; Pountos et al, 2012). To begin to understand this complexity, and the implications it has for determining a potential interaction of NSAIDs with
implant osseointegration, some background information may elucidate the current understanding of the biological effects of the drug.

1.4 Non-Steroidal Anti-inflammatory Drugs

As a class, NSAIDs are inexpensive, widely available, prescription and non-prescription drugs used for the suppression of inflammation and/or the treatment of inflammation-induced pain. There are several different specific NSAIDs – the salicylates, antipyrines, phenacetins, phenylbutazones, propanoates, fenamates – and any one of these may be employed via more than one mechanism of action and/or via different dosages of a single drug to treat different aspects of inflammatory disease (Vane & Botting 1998).

NSAIDs universally affect the enzyme cyclo-oxygenase (COX). Cyclo-oxygenase catalyzes the conversion of arachidonic acid to prostaglandin H₂, the precursor for all subsequent prostaglandins. Figure 1 shows the current understanding of the COX cascade, and provides an example of some of the different tissues in which these prostanoids are effective (Gilron et al 2003).
Arachidonic acid (AA) is abundant in mammalian cell membranes and is cleaved by the enzyme phospholipase A\(_2\) in response to tissue damage. Once initiated, this prostanoid cascade yields several different end products (prostaglandins) that each have important roles in the inflammatory response and normal tissue healing. Although controversial, it is currently believed that the different COX isoforms (COX-1 and COX-2) have different basic roles (Gilroy et al 1998): COX-1 is believed to be primarily constitutive, be widely-distributed in many tissues, and play an essential part in tissue homeostasis; however, there is evidence that increased expression of COX-1 is induced by inflammation. Conversely, COX-2 is believed to be
primarily induced by tissue damage and act specifically to produce the prostaglandins involved in acute inflammation. Still, the fine line between constitutive and induced is difficult to define, and COX-2 isoforms clearly are present in the absence of acute inflammation. A third COX isoform, COX-3, seems isolated to the central nervous system and is sensitive to acetaminophen; little else is known about this isoform (Chandrasekharan et al, 2002; Riccioti & FitzGerald, 2011).

The cascade of pro-inflammatory cytokines initiated by this conversion of AA to PGH$_2$ includes PGE$_2$ (brain, kidneys, vascular smooth muscle cells, platelets), PGD$_2$ (brain, airways, mast cells), PGF$_{2\alpha}$ (eyes, uterus, airways, vascular smooth muscle cells), PGI$_2$ (brain, kidneys, vascular smooth muscle cells, endothelium, platelets), and thromboxane A$_2$ (TxA$_2$; kidneys, macrophages, vascular smooth muscle cells, platelets). There are 11 subtypes of these prostanoids, and some 20 different coupled G-proteins (Gilron et al, 2003). The actions of each prostanoid vary by tissue and by relative concentration of the prostanoids present at any given time, and can change in a moment. An example of this is the vascular endothelium vs. the platelet: homeostatic levels of endothelium-derived PGI$_2$ prevent platelet aggregation, while platelet-derived TxA$_2$ remains sequestered and ineffective until triggered (by the exposed collagen of a ruptured blood vessel, perhaps), at which point the balance swings dramatically and immediately in favour of the effects of TxA$_2$ and clot initiation (Shafer, 1995). Several steps in this process are mediated by the effects of prostaglandins, and if the recent disaster of COX-2 inhibitors and cardiovascular disease is any indication, the relationships are complex and not easily therapeutically manipulated (Fosbol et al, 2009).

The effects of a specific NSAID depend on the particular COX isoform affected and to what degree, the dose, and the timing of the NSAID presentation. Even though COX inhibitors generally affect both isoforms with variable efficacy (non-specific COX inhibitors affect both isoforms, but so too do COX-2 inhibitors to a lesser degree; see Figure 2), the tissue distribution of the COX and its products allows for some selective specificity of effect even though the drugs are somewhat non-selective themselves.
As discussed, the reason for this appears to be variations in the different tissues’ expression of both COX-1 and COX-2 under different conditions, as well as the mechanism by which the NSAID inhibits the function of COX. Further, the turnover of a particular tissue similarly affects the rate at which a long-term temporary or permanent disabling of the COX enzyme can be reversed by regeneration.

1.5 NSAIDs and dental implant therapy

The potential effects of prescription drug usage concurrent with dental implant surgery, with or without bone augmentation, have received remarkably little recent attention in the dental literature. NSAIDs have been studied in a periodontal context to a limited degree; the findings of Williams and colleagues (1988) regarding the modest impact of systemic NSAIDs and a
reduction in the progression of periodontal disease in beagle dogs demonstrated significant differences in tooth loss between control and test groups. This research was continued by one of Dr. Williams’ coworkers, Dr. Jeffcoat, with investigations in humans into the effect of flurbiprofen on chronic inflammation, periodontal disease, and peri-implant bone levels (1989, 1993, 1995), with limited but positive findings in the short term. This same issue has been only sparsely investigated by others in the context of NSAIDs and dental implants, and little evidence of any quality from in vivo studies is presented (Alissa et al, 2008; Urdaneta et al 2011).

By comparison, the research associating the use of NSAIDs during orthodontic treatment and significant problems with bone remodeling seems robust (Walker & Buring, 2001; Arias & Marquez-Orozco, 2006; de Carlos et al, 2006; de Carlos et al, 2007; Bartzela et al, 2009; Retamoso et al, 2011). On the balance, the limited dental literature available regarding the topic supports the concern that the concurrent use of NSAIDs may clinically inhibit normal bone metabolism, but the clinical applicability of the data to in vivo peri-implant bone healing is difficult to judge.

Importantly, this same concern exists in the non-dental literature regarding long bone fracture healing (Simon & O’Connor 2007), and healing after other osseous surgeries involving orthopedic prosthetic implants and non-prosthetic orthopedic vertebral fusions, for example (Li et al 2011, Abdul-Hadi et al 2009, Vuolteenaho et al 2008, Radi & Khan 2005). Despite such research demonstrating clinically significant consequences of NSAIDs on bone metabolism, there are unresolved issues regarding the dose and time-course of NSAID therapy necessary to yield clinically important impediments or improvements in bone healing – especially in humans (Thomas & Puleo 2011). This same issue has been only sparsely investigated with respect to its effect on dental implants and little evidence of any quality from in vivo studies is available at all (Urdaneta et al 2011). The reason for this may be attributable to the ambiguities in our understanding of the mechanisms of action of NSAIDs under different circumstances and in different tissues because of the wide-ranging effects of the various prostaglandins during the normal time course of healing.
Without question, the prostaglandins appear to be essential in normal bone healing overall, and an abundance of data demonstrates their role in the signaling mechanism stimulating bone resorption (through an increase in osteoclastic activity) and bone formation (through an increase in differentiation of osteoblasts; Thomas & Puleo 2011), as well as angiogenesis (Jones et al, 1999). The complexity of interaction between tissue, drug, dosage, and time explains the difficulty of demonstrating conclusively the *in vivo* harmful effects of one or more NSAIDs on the osseointegration of dental implants. Worse, a large body of literature supporting the peri-operative safety and efficacy of the COX-2 inhibitors in humans has been found to be fraudulent and subsequently has been retracted (White et al. 2009, 2011). This has revealed a sizable deficit in our current understanding of the clinical consequences of the use of COX-2 inhibitors.

Hence, there is circumstantial evidence that should indicate that the role of NSAIDS on implant therapy outcomes ought to be investigated as a potential contributing factor for clustering implant failures effect.

### 1.6 Causality

Well-designed randomized controlled trials can be said to satisfy the strict demands of causality when the research is conducted in human subjects, but conducting such study with an ultimate aim to demonstrate potential negative effects of NSAIDS on dental implant healing is obviously problematic from an ethical perspective. A retrospective cohort study, by comparison, ranks low in the hierarchy of evidence indeed. Yet, many research questions are initially developed and clarified through the correlations and associations discovered by the retrospective study; such is the goal of this investigation. Causality cannot be established definitively, but it is hoped the strength of the argument will be sufficient to merit further consideration.
1.7 Hypothesis

It is the purpose of the proposed clinical study to determine whether the use of NSAIDs is associated with a higher-than-usual rate of implant osseointegration failure in the University of Toronto Faculty of Dentistry Graduate Prosthodontics clinic outpatient population. The null hypothesis is that, within the population of patients suffering implant failure, there will be no difference between those patients exposed to peri-operative NSAIDs and those not exposed.
2 Methodology

The protocol for the study was developed by the author and approved by the University of Toronto Research Ethics Board on 10 May 2012, approval #27644 (Appendix 6.1).

2.1 Subjects

The Graduate Prosthodontics Clinic strives to maintain all implant patient records – active and inactive – indefinitely. The Clinic also maintains a database (Tracker©) containing the pertinent details of all implant patients and surgeries; this includes among other things the number and location of implants placed by the surgeons/graduate residents in the Implant Prosthodontic Unit (IPU), as well as any complications or failures for patients who returned to the Clinic for dental treatment. All patients – edentulous and partially edentulous – suffering implant failure were invited to participate.

2.2 Target Data

From this pool of implant therapy patients treated in the IPU, the records of all patients having suffered at least one dental implant failure in either a partially or completely edentate jaw were compiled and reviewed. Specific investigations were made into the possibility of an association between a non-steroidal anti-inflammatory drug (NSAID) usage concurrent with implant surgery, and in addition, the following data was gathered:

- any systemic disease present at the time of implant surgery for all implants failed/present
- any medications present at the time of implant surgery for all implants failed/present
- the surgical/restorative protocols employed for all implants failed/present
- the related surgical/restorative complications associated for all implants failed/present
- the clinical course and radiographic appearance of any bone loss for all implants present.
2.3 Recruitment

All patients suffering implant failure were contacted to solicit their active participation in the study. The initial contact was by invitation letter accompanied with a description of the rationale and purpose of the study (Appendices 6.2, 6.3, 6.4, 6.5), with a follow-up call by telephone if no response was received within 14 days. If necessary, interested patients were sent another package and, in a few cases, were invited to attend in person if they requested to do so. On these infrequent occasions, the rationale and purpose of the study was presented verbally and discussed, the necessary forms were filled out cooperatively, and a brief clinical exam was completed at the patients’ request to update their records.

2.4 Recording of complications

The following information was be obtained from the patients’ charts and phone interviews: age; medical history; medication intake; smoking history; reason for tooth loss; type, number, and distribution of implants; surgeon; grafting; timing of failure; the date of prosthesis insertion (if any); and periapical/panoramic radiographs taken immediately post-operatively and all subsequent radiographs pertaining to the implants suffering biological complications. Clinical data entered into the patients’ charts during the surgical and restorative procedures (signs and symptoms of peri-implant mucositis and/or -osteitis, restorative technical complications, etc.), as well as those entered through hygiene recall, was similarly collected to assist with determination of true failure timing, as well as the clinical presentation of other implants present in the event of coincident biological complications.

For the purposes of this study, biological complications were defined as implant failure (defined by the removal of the implant prior to the present date), or peri-implant osteitis (defined by the failure to meet any of the following criteria from Albrektsson 1989, Buser et al 1990, Salvi & Lang 2004):

- Absence of mobility
• Absence of persistent subjective complaints (pain, foreign body sensation and/or dysesthesia)
• No PPD > 5 mm
• No PPD = 5 mm and exhibiting bleeding-on-probing
• Absence of a continuous radiolucency around the implant
• After the first year of service, the annual crestal bone loss should not exceed 0.2 mm

Cases with a chart documentation of biological complications had the following details recorded:
• The amount of time, in months, before failure of the implant or diagnosed onset of peri-implantitis
• The timeframe of the failure will be categorized according to the following criteria:
  • Early Failure: implants lost before the insertion of the definitive prosthesis
  • One-year Failure: implants failed within the one year of loading with the definitive prosthesis
  • Late Failure: implants lost after one year following the insertion of the definitive prosthesis (Roos-Jansaker et al 2006).
• History of peri-implant mucositis or peri-implant osteitis (biological complication)

According to this threshold, the implant would be characterized as a failure (i.e. implant with a biological complication) if mesial or distal annual bone loss was > 0.2 mm, or PPD > 5 mm or PPD = 5 mm and exhibiting bleeding-on-probing. Since the time-course of the putative effect of NSAID usage concurrent with implant surgery could not be defined pre-hoc, descriptive statistics were used to characterize patients identified according to the preceding criteria that prove positive for concurrent NSAID usage at the time of implant surgery and thereafter who suffer peri-implant osteitis or implant failure.

Finally, the patients’ medical histories were carefully scrutinized for patterns related to either implant failure or NSAID usage or both, and descriptive statistics of the relationships were
calculated. The criteria applied would attempt to separate patients into two groups: those with complicated medical histories and those without. Complicated would be defined as containing any local or systemic disease or medication known to interfere with the autoimmune system or bone healing directly. These diseases were deemed initially to include: osteoarthritis with medication, rheumatoid arthritis with medication, osteomalacia, immune deficiency diseases (including hepatic diseases), drug abuse (alcohol, tobacco, etc.), diabetes mellitus, bleeding disorders, and radiation therapy (Buser et al. 2000, Mombelli & Cionca 2006), renal disease (Lee et al. 2008), and thyroid disorders with or without medication (Hodkinson et al. 2009).

2.5 Statistical analyses

Potential associations between peri-operative NSAID usage and the incidence of biological complications were explored by the use of 2x2 tables and Fisher's exact test with two-tailed P values.
3 Results

3.1 Survival

During the period of 1979 to 2012, 5829 implants have been placed in the Faculty of Dentistry Implant Prosthodontic Unit. There are 168 patients recorded in the Tracker database as having suffered implant failure. Of these, 122 patient charts were located and contained sufficient information to at least determine peri-operative analgesic prescription. In these patients, a total of 537 implants were placed in the IPU, and from that 238 implants were recorded in tracker as being failed and removed.

3.2 Failure and analgesic history

Of the 122 patients that experienced 238 implant failures, 69 (57%) patients with 108 failed implants (45%) had no peri-operative use of NSAIDs, while the remaining 53 (43%) patients with 130 failed implants (55%) had a history of peri-operative use of NSAIDs. In this patient group, the association between NSAID use and failed versus non-failed implants was judged to not be statistically significant according to a two-tailed Fisher's exact test (P = 0.1384) (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>Failed Implants</th>
<th>Non-failed implants</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-NSAIDs</td>
<td>108</td>
<td>154</td>
<td>262</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>130</td>
<td>141</td>
<td>271</td>
</tr>
<tr>
<td>Total</td>
<td>238</td>
<td>271 (51)</td>
<td>533</td>
</tr>
</tbody>
</table>

*Table 1: Distribution of failed and non-failed implants within the patient failure population by usage of peri-operative use of NSAIDs.*
Moreover, of the 130 failed implants in the NSAID-use group, 5 were attributable to the following credible etiological factors: Implant fracture (1), late failure due to repeated technical complications (1), periapical infection (1), occlusion on cover-screw prior to Stage 2 (1) and displacement into maxillary sinus (1). Hence 125 failed implants could not be attributed to a particular etiological factor, increasing the two-tailed test to $P = 0.1895$.

### 3.3 Cluster failure

The term “cluster failure” was defined as the loss of 50% or more of implants when 3 or more implants were placed. As noted, the non-NSAID (“other” analgesics) group, representing 57% of patients but only 45% of the failed implants, contained 17 non-NSAID patients that met the criteria for suffering cluster failure. The NSAID group, representing 43% of the patients but 55% of the failed implants, contained 32 patients meeting the criteria for suffering cluster failure (see Table 2). Fisher's exact tests indicated significant associations between NSAID use and cluster failure history when based on using the patient as the statistical unit (Table 2, $p < 0.0001$), but not when implants formed the statistical unit (Table 3, $p = 0.15$).

<table>
<thead>
<tr>
<th></th>
<th>Cluster Failure</th>
<th>No Cluster Failure</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-NSAIDs</strong></td>
<td>17</td>
<td>52</td>
<td>69</td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
<td>32</td>
<td>21</td>
<td>53</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>49</td>
<td>73</td>
<td>122</td>
</tr>
</tbody>
</table>

*Table 2: Patients dichotomized by cluster failure, i.e., suffering failure of 50% or more of the implant(s) placed, $n=122$ patients*
Fisher's exact test indicated a two-tailed P value of less than 0.0001, which indicates that the association between NSAID use and cluster failure when based on the patient as the statistical unit is extremely statistically significant.

3.4 Biological complications

Evaluation of the patient records for evidence of complications associated with the patient’s remaining implants when placed coincident with the failure revealed a population of implants suffering significant bone loss. Based on related human physiologic research demonstrating a conservative estimate of meaningful differences (Grossi et al, 2001; Todd, et al, 1996), an arbitrary threshold for clinically significant bone loss was set at 30% radiographic, and the following categorization was made: The non-NSAID group, representing 56.6% of patients and 45.4% of the failed implants, presented an additional 17 implants with greater than 30% radiographic bone loss at the time of the last radiograph present (see Table 3). The NSAID group, representing 43.4% of the patients but 54.6% of the failed implants, presented an additional 65 implants with greater than 30% radiographic bone loss at the time of the last radiograph present (see Table 3).
Failed Implants | Remaining Implants with Bone Loss > 30% | Remaining Implants with Bone Loss < 30% | Total
---|---|---|---
Non-NSAIDs | 108 | 17 | 137 | 262
NSAIDs | 130 | 65 | 76 | 271
Total Implants Placed | 238 | 82 | 213 | 533

**Table 3**: Patients with received implants dichotomized by failure or remaining implants suffering from greater than 30% radiographic bone loss (n=320) versus remaining implants with bone loss < 30% (n=213).

Fisher's exact test indicated a two-tailed P value of less than 0.0001, which indicates that the association between NSAID use and remaining implants with severe bone loss when based on the implants as the statistical unit is extremely statistically significant.

### 3.5 Complicated medical histories

The chart review revealed a consistent trend with the distribution of patients between groups: the presence of a complicated medical history that included diseases known or suspected to affect bone healing or overall healing in general. The non-NSAID group included 6 patients with complicated medical histories at the time of Stage 1 surgery (see Table 4). These complicated medical histories included: one patient with a history of radiotherapy; two patients with diabetes mellitus type II; two patients with a history of hepatitis, and one patient was concurrently on Coumadin anticoagulant therapy. The NSAID group included 22 with complicated medical
histories at the time of Stage 1 surgery (see Table 4). The complicated medical histories included: seven patients with diabetes mellitus type II; five patients with osteoporosis and prescription medications; four patients with thyroid disease; three patients with a history of renal failure; one patient with fibromyalgia, depression, and asthma with several prescription medications; one patient with a history of hepatitis; and one patient with a symptomatic history of tuberculosis and syphilis.

<table>
<thead>
<tr>
<th></th>
<th>Patients with a Complicated Medical History</th>
<th>Patients with no Complicated Medical History</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-NSAIDs</td>
<td>6</td>
<td>63</td>
<td>69</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>22</td>
<td>31</td>
<td>53</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>94</td>
<td>122</td>
</tr>
</tbody>
</table>

Table 4: Patients presenting with complicated medical histories at the time of Stage 1

Fisher's exact test indicated a two-tailed P value of less than 0.0001, which indicates that the association between NSAID use and complicated medical history is extremely statistically significant.
3.6 Smoking history

Similar categorization was completed regarding the smoking habits of the patients suffering failures: the non-NSAID group included 8 patients who acknowledged smoking at the time of Stage 1 surgery (see Table 5); the NSAID group included 9 patients who acknowledged smoking at the time of Stage 1 surgery (see Table 5).

<table>
<thead>
<tr>
<th></th>
<th>Smokers</th>
<th>Non-smokers</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-NSAIDs</td>
<td>8</td>
<td>61</td>
<td>69</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>9</td>
<td>44</td>
<td>53</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>17</td>
<td>105</td>
<td>122</td>
</tr>
</tbody>
</table>

Table 5: Patient distributing according to self-reported smoking habit

The Fisher's exact test indicated that there were no association between NSAID use and smoking (p= 0.4371).

3.7 Surgeon

Distribution of failures between surgeons was approximately even, taking into account the variable durations of the different surgeon’s tenures with the IPU and the total number of implants placed by the surgeon (or, more specifically, the residents under the surgeon’s supervision (Table 6).
## Table 6: Implant failures by implant surgeon

<table>
<thead>
<tr>
<th>Surgeon</th>
<th>Tenure</th>
<th>Implants Placed</th>
<th>Implants Failed</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>1986-2011</td>
<td>1379</td>
<td>76</td>
<td>5.5</td>
</tr>
<tr>
<td>#2</td>
<td>1999-2009</td>
<td>376</td>
<td>19</td>
<td>5.1</td>
</tr>
<tr>
<td>#3</td>
<td>1979-1984</td>
<td>211</td>
<td>16</td>
<td>7.6</td>
</tr>
<tr>
<td>#4</td>
<td>1986-2011</td>
<td>464</td>
<td>19</td>
<td>4.1</td>
</tr>
<tr>
<td>#5</td>
<td>1988-1991</td>
<td>82</td>
<td>5</td>
<td>6.1</td>
</tr>
<tr>
<td>#6</td>
<td>2000-2010</td>
<td>578</td>
<td>15</td>
<td>2.6</td>
</tr>
<tr>
<td>#7</td>
<td>1985-2004</td>
<td>431</td>
<td>16</td>
<td>3.7</td>
</tr>
<tr>
<td>#8</td>
<td>1982-2011</td>
<td>661</td>
<td>33</td>
<td>5.0</td>
</tr>
<tr>
<td>#9</td>
<td>2009-2013</td>
<td>184</td>
<td>9</td>
<td>4.9</td>
</tr>
<tr>
<td>#10</td>
<td>1988-2011</td>
<td>207</td>
<td>10</td>
<td>4.8</td>
</tr>
<tr>
<td>#11</td>
<td>2005-2011</td>
<td>236</td>
<td>12</td>
<td>5.1</td>
</tr>
<tr>
<td>#12</td>
<td>1992-2011</td>
<td>235</td>
<td>7</td>
<td>3.0</td>
</tr>
<tr>
<td>#13</td>
<td>1982-1986</td>
<td>9</td>
<td>1</td>
<td>11.1</td>
</tr>
<tr>
<td>#14</td>
<td>2009-2013</td>
<td>100</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>#15</td>
<td>2002-2004</td>
<td>92</td>
<td>4</td>
<td>4.3</td>
</tr>
<tr>
<td>#16</td>
<td>1997-2013</td>
<td>184</td>
<td>3</td>
<td>1.6</td>
</tr>
</tbody>
</table>

### 3.8 Timing of failure

The distribution of failure timing was different between the NSAID-usage versus the non-NSAID-usage groups. Early failures were considered to be failures that occurred prior to the restoration and loading of the implant. Suspected early failures were those that occurred within one year of restoration and loading and which had associated clinical notes indicating a steady progression of symptoms associated with the failed implant. Late failures were those that occurred more than one year after restoration and loading. The distribution of failures between
these categories is detailed in Table 7. Between groups, the NSAID group showed 1.6x as many early failures when compared with the non-NSAID group. The NSAID group showed 5.5x as many suspected early failures when compared with the non-NSAID group. Finally, the non-NSAID group showed 1.5x as many late failures when compared with the NSAID group. Within groups, the non-NSAID group had 1.5x as many early and suspected early failures as late failures. The NSAID group had 4.1x as many early and suspected early failures as late failures.

<table>
<thead>
<tr>
<th></th>
<th>Early</th>
<th>Suspected Early</th>
<th>Late</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-NSAIDs</td>
<td>60</td>
<td>2</td>
<td>40</td>
<td>102</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>96</td>
<td>11</td>
<td>26</td>
<td>133</td>
</tr>
<tr>
<td>Total</td>
<td>156</td>
<td>13</td>
<td>66</td>
<td>235</td>
</tr>
</tbody>
</table>

**Table 7: Distribution of implant failure timing**

Fisher's exact test demonstrated a two-tailed $P=0.0012$, i.e., the association between NSAID use and early and suspected early failures versus late failures is considered to be very statistically significant.
4 Discussion

4.1 Success and Failure

Implants do not fail for no reason, but they often fail for unknown reasons. One of the suggestive results of this study is the relative frequency of failures with no known etiology. There is no reason to believe that this implant failure is a random event, yet historical and modern literature on factors affecting implant success and survival are finding statistically convincing evidence of contraindications more difficult to find as time goes by. Some believe this trend provides evidence that modern dental implants now work regardless of the presence of systemic disease, and indeed there is little doubt more patients with a greater variety of disease are being treated successfully with implants than ever before. The obvious problem with this interpretation, however, is that implants do not always survive, and they certainly do not always achieve clinical success. The persistent phenomenon of early failure epitomizes the unknown nature of the etiology of this lack of success and survival.

It is the author’s belief that the lack of evidence for a clear causal relationship between one or more systemic diseases is not evidence that no relationship exists. If a variable could be identified that affects the relationship between one or more diseases and implant failure that has not previously been accounted for, then reinterpretation of the existing literature may lead to different findings. The prevalence of non-steroidal anti-inflammatory drugs (NSAIDs) in patients’ acute and chronic peri-operative milieu makes them a strong candidate for just such a variable.

4.2 Underlying assumptions and categorization of patients

4.2.1 Distribution of NSAIDs within the patient population

In 1986, the World Health Organization proposed a set of guidelines regarding the recommended use of analgesics in the management of cancer pain. These guidelines became known as the “analgesic ladder,” which, simply stated, advocated the use of non-opioids as the first line of
analgesia. These non-opioids were, specifically, aspirin, paracetamol (acetaminophen), and NSAIDs (Vargas-Shaffner 2012). This concept has been applied generally in all areas of medicine, since in addition to their role in the management of cancer pain NSAIDs have long been known to be very effective at controlling post-operative pain and swelling; their use has been recommended as a way of reducing the quantity and duration of post-operative narcotics for pain control (Smith 2011, Derry et al 2012). There are many studies demonstrating the efficacy of both acetaminophen post-operatively and NSAIDs post-operatively (Weil et al 2007, Derry et al 2012).

The degree to which these recommendations are observed in Canada, however, is unknown. As a result of these recommendations specifying aspirin, acetaminophen, or NSAIDs as the first step in post-operative analgesia, however, certain assumptions may be made: first line non-opioids are prescribed according primarily to the surgeon’s preference, and that this preference is randomly distributed amongst surgeons practicing in the IPU. It is certain that NSAID usage was not deliberately screened for pre-operatively, so the distribution of chronic NSAID use in the patient population should also be normally distributed between surgeons and residents practicing in the IPU. Further, the relative contraindications to prescription of NSAIDs include advanced patient age, any history of renal, hepatic, or gastrointestinal disease, and hypertension. The presence of exactly these factors in the population of patients treated with NSAIDs indicates that, although some patients may not have been prescribed NSAIDs because of one or more of these pre-existing conditions, many were. The assumption that NSAIDs were prescribed primarily according to surgeon preference at the time appears to be substantiated.

Further, NSAIDs generally are believed to be innocuous drugs and, as a result, non-prescription usage is relatively common in the self-medication of transient aches and pains. This non-prescription habitual intake of NSAIDs suggests that these drugs may be present during the healing phase of implant surgery regardless of the surgeon’s prescription. The inability to retrospectively determine this raises the issue of whether, perhaps, even more of the cluster failures may be categorized under the NSAID grouping.
4.2.2 Categorization of additional complications

Data was collected according to the procedures defined in the Methodology. As the chart review progressed, however, it became clear that the clinical records often failed to provide all of the data desired to allow determination of clinical success according to the standards initially proposed (Salvi & Lang 2004; Roos-Jansaker 2006). For the purposes of this retrospective study, an alternative categorization system was required; attempting to rationalize the proposed evaluation system requiring consistently recorded measurements of probing depth, bleeding, and recession with the reality of inconsistent charting was impossible. To do otherwise would require making assumptions difficult to substantiate.

In the absence of consistent and adequate data, then, application of the aforementioned clinical criteria – although accepted as a general measure of success suitable for research purposes – could not yield an accurate estimation of individual remaining implant success. Further, these research definitions of success by themselves gave no consideration to the length of the implant being evaluated. The lack of this last variable meant that, even in cases where the data was present, it was complex to quantify the severity of defects. For example, comparing the case of a 5mm probing depth on a 10mm implant in the anterior maxilla to a different case showing the same 5mm probing depth on a 15mm implant in the anterior mandible is misleading. It is not the absolute depth alone that matters in terms of survival, but also the relative length of remaining osseointegration. Attempts to track this data proved so cumbersome as to be unusable, and, as noted, could not be consistently applied due to lack of probing depth data.

A simple alternative evaluation was devised that was dependent only upon the latest available radiographs and which took into account the relative severity of the lost osseointegration. Radiographic bone loss in excess of 30% of the length of the implant would provide an estimate of severity of the clinical presentation, and even in cases of controlled or quiescent disease, could provide a sense of the problems encountered during osseous healing. While arbitrary, this measurement of bone loss is suggestive of a series of complications the patient was likely to have
experienced as clinically significant symptoms: difficulty accessing the implant for hygiene, inflammation, bleeding, recession, and, on occasion, exudate. This assumption proved to be corroborated by the chart entries of the patients’ clinical signs and symptoms that prompted the taking of the radiographs in the first place.

This measure of bone loss relative to the length of the implant proved almost uniformly useful. Circumstances in which no follow-up was performed prevented its universal application, but in most cases some standardized periapical radiograph or panoramic radiograph was present to allow evaluation of other implants placed simultaneously with the failed implant in question. These radiographs, in conjunction with clinical notes providing additional details, formed the standard for the advanced bone loss categorization.

4.2.3 Categorization of Medical History

As noted previously, there is no consensus regarding the adequacy of evidence supporting or refuting the importance of a given systemic disease with respect to its effect on osseointegration of dental implants. The literature available on the topic ranges from the extremely cautious regarding pre-existing systemic disease (Sugerman & Barber, 2002) to the extremely unconcerned (Baqain et al, 2011); without better evidence to work from, it was decided that a difference reference point for what constituted significant systemic disease was needed.

A middle-ground approach was used, similar to the categorization of disease used by Alsaadi and colleagues in 2007; “health factors” were simply categorized into systemic or non-systemic. Any disease known to affect/involve bone metabolism or compromise immune function was categorized as systemic (i.e. involving an entire organ system) and therefore the patient was categorized as having a complicated medical history. In most cases patients suffering from these conditions were suffering from other diseases as well, bolstering the categorization rather than contradicting it. These systemic diseases included thyroid disease, renal failure, hepatic disease, osteoporosis, diabetes, complicated fibromyalgia, and tuberculosis and syphilis. Cardiovascular
disease itself was not included, nor was arthritis, but anti-coagulant therapy with Coumadin or Warfarin was.

4.2.4 Categorization of smoking history

Recent literature has been inconclusive regarding the importance of current or past smoking history on both bone metabolism and osseointegration. The chart review revealed a notable lack of consistency in the number of cigarettes smoked by a given patient, whether the patient had intended to reduce the habit during the peri-operative period, the apparent success or failure of a given patient’s efforts at that reduction in smoking, and particularly the duration of the habit. These limitations, in conjunction with the self-reported nature of the data, make conclusions regarding any potential effects of smoking habit on osseointegration outcome suspect. As a result, patients were categorized simply as current smokers or non-smokers.

4.3 Association and causality

The analysis detailed has found three parallel and independent correlations between the peri-operative presence of NSAIDs and implant failure: while NSAIDs were known to be used by fewer than half of all patients suffering implant failure, the NSAID-associated failures included twice as many cluster failures, three times as many cases of severe bone loss in remaining implants, and four times as many patients with complicated medical histories. While it remains possible that these findings are coincidental, it is highly improbable. These findings are not clear evidence of a causal relationship, however, so the challenge is deciding how much weight to give them.

It is the position of the author that the primary reason for these correlations is the underlying presence of impaired bone healing made worse by the peri-operative presence of NSAIDs. It is difficult under any circumstances to obtain an accurate and precise estimation of a patient’s health status; this goal becomes infinitely complicated when confounded by the difficulty of obtaining recent and accurate medical history information from the patient in combination with
the patient’s desire for the treatment modality proposed. This difficulty underlies all scientific research with humans as subjects; dental implant clinical research simply struggles with this challenge more than some. The author’s conclusion is that these results represent the cumulative consequence of a variety of factors impairing bone healing – some known, and some not – where the peri-operative presence of NSAIDs overwhelmed the patient’s bone healing capacity. The biological basis for this conclusion has been introduced previously, and will be discussed with respect to causality in the following sections.

Sir Austin Bradford Hill addressed this issue of correlation versus causality in 1964 by identifying nine considerations relevant to the question of evidence sufficiency. His purpose was to provide a framework for the consideration of potential environmental causes of occupational harm, and by doing so to help focus the decision-making in risk mitigation or avoidance in the absence of clear causality. His rationale for this was simple: in cases where harm is suspected, the severity of the harm is inversely related to the quality of the evidence necessary to justify action to avoid or prevent it.

“…the decisive question is whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A. How such a change exerts that influence may call for a great deal of research. However, before deducing 'causation' and taking action we shall not invariably have to sit around awaiting the results of that research. The whole chain may have to be unraveled or a few links may suffice. It will depend upon circumstances (Hill, 1964).”

The issues he proposed for consideration were: strength of the association; consistency of the association; specificity of the association; temporality of the association; biological plausibility of the association; biological gradient of the association (dose response); coherence of the association; experimental evidence of the association; and, analogy to other causative relationships.
4.3.1 Strength of the association
When weighing measured outcomes, Hill argued that the best measure of outcome might often be the relative incidence of the outcome within specific populations. Absolute measures of outcome (and statistical evaluation relative to the total population) may mask the severity of the outcome within a given population. He used the example of cigarette smokers’ mortality from lung cancer to illustrate that while the absolute number of deaths in all populations from lung cancer were (at the time) somewhat similar, in smokers the relative incidence is dramatic and proportional to the number of cigarettes smoked daily; the absolute numbers of deaths do not provide the same dramatic evidence of the positive correlation that the ratios do.

The potential presence of another confounding co-variable is possible, of course, and this issue is doubly relevant to this discussion of the presence of NSAIDs during osseointegration: does the presence of NSAIDs used for post-operative pain control in one study complicate the comparison of outcome measures with another study in which NSAIDs were not used; and, do all or many of the patients taking NSAIDs in this study have some common comorbidity that is in fact causing the association with cluster failure and advanced bone loss? Either is possible, of course, but the former seems more likely. Hill acknowledges this but returns to the issue of probability when the strength of the association is great: if twice as many cluster failures occur in patients taking NSAIDs peri-operatively, and if this appears to be the only thing in common between patients, then we should consider the probability that NSAIDs are the etiology for this outcome.

4.3.2 Consistency of the association
“Has [the association] been repeatedly observed by different persons, in different places, circumstances and times?” Hill was speaking of multiple observers of the same phenomenon, and the consideration is relevant to the concerns other disciplines have raised regarding the demonstrated effects of NSAIDs on bone metabolism. As discussed, the phenomenon has been demonstrated both in vitro and in vivo in multiple areas of medicine; bone metabolism is altered by the NSAID inhibition of prostaglandin synthesis (Geusens et al, 2013). In terms of the effects of NSAIDs on peri-implant bone healing, there is no reason to presume that the process of osseointegration is meaningfully different from bone remodeling or fracture healing, and no
evidence to support that presumption. Quite the opposite is true, as recent research focuses more and more on the intracellular signaling necessary for the complex cascade of osteogenic metabolism using the paradigms of fracture healing (Terheyden et al, 2012).

It is unlikely that diverse experimentation successfully measuring the inhibitory effect of NSAIDs on bone metabolism is all subject to the same systematic error negating its validity. Rather, the diversity of study from other areas of medicine all coming to similar conclusions is itself a strong argument in favour of the probable relationship between peri-operative NSAID usage and impairment of implant osseointegration:

“We have, therefore, the somewhat paradoxical position that the different results of a different inquiry certainly cannot be held to refute the original evidence; yet the same results from precisely the same form of inquiry will not invariably greatly strengthen the original evidence. I would myself put a good deal of weight upon similar results reached in quite different ways, e.g. prospectively and retrospectively (Hill, 1964).”

4.3.3 Specificity of the association
By itself, specificity is very important in establishing causation. In the case of the peri-operative use of NSAIDs there is a clear lack of specificity of direct effect. The multiplicity of intracellular signaling mechanisms affected and the apparently minimal direct effect of NSAIDs in absolute terms makes any claim of specificity unlikely. However, in the absence of that kind of direct and unequivocal specificity of effect, there may be other types of specificity to consider. Hill (1964) again uses the example of cigarette smoking, noting that although cigarette smokers are at an increased risk of death from many causes, when it comes to lung cancer, there is “a specificity in the magnitude of the association.”

“Indeed I believe that multi-causation is generally more likely than single causation though possibly if we knew all the answers we might get back to a single factor. In short, if specificity exists we may be able to draw conclusions without hesitation; if it is not apparent, we are not thereby necessarily left sitting irresolutely on the fence.”
This same reasoning is patently true regarding the findings of the current study: within the population of patients suffering outright implant failure, the subpopulation of patients taking peri-operative NSAIDs contains three times as many patients with complicated medical histories than the subpopulation of patients using other analgesics. Compromised bone healing may be the result of a single severe dysfunction or the summation of several, less severe insults to the overall maintenance or repair of homeostasis. These findings suggest that the peri-operative use of NSAIDs is a complicating factor that interacts with marginal bone healing in vulnerable patients; the absence of specificity of effect does not seem to outweigh the specificity of association.

4.3.4 Temporality of the association
It seems apparent that the greatest effect of peri-operative NSAID usage on bone repair would be most evident when the drugs were present prior to and immediately following implant placement. This may be the case, but the true effect may be more complicated.

The most likely rationale for the observed effect of NSAIDs on peri-implant bone healing is the immediate effect of the drugs on blood clot formation and maturation. These steps are critical to the migration of osteogenic cells to the immediate wound (Davies, 2003), and it is proposed that interference in this initial inflammatory response is responsible for the results observed in this study. However, bone healing is a dynamic process that demonstrates redundancy and flexibility; in the absence of a clot, excellent initial primary stability may mitigate the loss of primary intention healing and permit a more gradual healing by secondary intention, similar to that observed in fibrinolytic alveolar osteitis (“dry socket”) following tooth extraction. This process is dependent upon many factors – perhaps most importantly a submerged healing protocol – including the timing, duration, dose, and strength of the NSAID usage.

“Does a particular occupation or occupational environment promote infection by the tubercle bacillus or are the men and women who select that kind of work more liable to contract tuberculosis whatever the environment - or, indeed, have they already contracted it (Hill, 1964)?”
There may be many scenarios in which peri-operative or chronic NSAID usage would negatively affect osseointegration, and this study model is inadequate to provide more information regarding the temporal component of the effect: all patients identified as part of the NSAID subpopulation were simply either already taking NSAIDs or were prescribed NSAIDs during Stage 1 surgery.

4.3.5 Biological gradient of the association

Similar to the preceding discussion of the temporality of the association, the biological gradient of the association is obscured by many factors. Animal models long ago demonstrated the dose-response relationship between either the dose itself and the degree of impairment of bone healing (Ro et al, 1976), the degree of COX inhibition achieved by a particular NSAID and the impairment of bone healing (Törnkvist et al, 1984), as well as the relationship between the timing and duration of the administration of the NSAID post-operatively (Endo et al, 2005). These relationships have been demonstrated repeatedly, but not universally. Variations in each can and have led to conflicting results, as a review of just the last decade of research illustrates (Geusens et al, 2013), and the reasons for this are not definitively understood. In humans, the complexity of the absorption-metabolism-excretion cycle of pharmacotherapy in the presence of various systemic diseases or occult dysfunctions makes determining this relationship even more difficult. Nonetheless, there is substantial prior evidence that this biological gradient does exist – at least with respect to the effect of increasing doses of NSAIDs on the initial inflammatory cascade – and there is no evidence this author is aware of that specifically contradicts it (Brooks & Day, 1991; Vuolteenaho et al, 2008).

4.3.6 Biological plausibility of the association

Interestingly, Hill placed relatively little emphasis on this aspect of causation because it was dependent on the scientific knowledge of the moment (1964). In the context of the biological effect of COX inhibition on bone metabolism, however, there can be no disagreement: it is the express purpose of the therapeutic use of these drugs to specifically inhibit the production of
prostaglandins long known to be an essential part of tissue inflammation and, ultimately, repair. That there will be future discovery of compensatory mechanisms in the presence of COX inhibition there is no doubt, and even at the current time the challenges discussed regarding the temporality of the effect are significant. At the present time, however, there is abundant evidence that NSAIDs do inhibit the normal course of bone healing (Pountos et al 2012). There is much more to be understood of the complex interaction between this effect and the overall bone physiology in humans, though.

4.3.7 Coherence of the association
In light of the aforementioned factors, Hill reiterates the importance of weighing the balance of the evidence; if most or all of the evidence is suggestive of a causal relationship, it is important to consider the reality of a causal relationship. In the case of the peri-operative effect of NSAIDs on dental implant osseointegration, there seems to be good reason to consider the possibility of an interaction with patient vulnerability seriously. As Hill pointed out, "the cause-and-effect interpretation of [the] data should not seriously conflict with the generally known facts of the natural history and biology of the disease," and, although there is much more to be discovered about the nature of patient vulnerability, the preponderance of evidence does suggest the plausibility of a direct relationship between NSAIDs and impaired bone healing. This is inclusive of experimental evidence showing no effect.

4.3.8 Experimental evidence of the association
If there were clear experimental evidence demonstrating the contrary, there would be no reason to engage in the exercise of the Hill criteria. To date, there is no experimental evidence directly addressing this issue of patient vulnerability to NSAID impairment of bone healing in the context of dental implant osseointegration. In the absence of this clear evidence, then, the next best evidence must suffice.
“None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question - is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect (Hill 1964)?”

Consider the following: the predominance of current literature is unable to prove strong correlations between the presence of systemic disease and implant survival. Is this because there is no correlation between systemic disease and healing, or is it that there are unknown and uncontrolled variables involved in these study designs/patient populations? As discussed previously, the potential effects of prescription pharmaceuticals on the efficacy of osseointegration of dental implants has essentially never been adequately explored in the literature. One notable exception was the effect of the drug class bisphosphonates, and it should be pointed out that it took several years for the phenomenon of bisphosphonate-related osteonecrosis of the jaws to be taken seriously. If the issue of drugs and osseointegration is extended to the over-the-counter range of pharmaceuticals, the opportunity for interaction grows even greater.

It is not that the issue of drug effects on osseointegration has been entirely ignored. Relevant to the current investigation, NSAIDs have been studied as an adjunct to conventional periodontal therapy. Like most adjunctive periodontal therapies, the findings were of debatable clinical significance. The work of Williams and colleagues (1988) regarding the limited impact of systemic NSAIDs in the reduction of the severity periodontal disease in beagle dogs is one example. This research was continued by one of Dr. Williams’ coworkers, Dr. Jeffcoat (Jeffcoat et al, 1996), with investigations in humans into the effect of flurbiprofen on chronic inflammation, periodontal disease, and peri-implant bone levels (1993, 1989, 1995). The challenge that confronts academia in evaluating the quality of this research stems from a fairly typical theme: the only research demonstrating this effect was generated by this single research group out of the University of Alabama School of Dentistry, and this group openly
acknowledged its close affiliation with the Upjohn pharmaceutical company funding the research. Subsequent research from other groups found contrary results, and while differences in dosing regimens and subject populations were acknowledged to exist between study designs, the clinical applicability of these findings to humans overall was deemed to be uncertain; tenths of a millimeter of alveolar bone preservation between groups may not be justifiable, considering the potential side-effects and complications of long-term NSAID usage (Bragger et al, 1997). Although others have recently found encouraging in vitro results by varying the dose of NSAID used, these studies could be interpreted to illustrate the difficulty of applying the findings in vivo in the presence of comorbidity (Dean et al, 2008; Fracon et al, 2008). Is inhibition of bone resorption in the presence of chronic periodontal disease really a valid model for inference into altered peri-operative bone healing around dental implants?

The orthodontic literature provides an alternative perspective on the effects of NSAIDs on bone metabolism. Bartzela and colleagues (2009) illustrate this problem perfectly with their review of the various studies investigating the effect of one or more medications on orthodontic tooth movement. All findings are consistent with an interpretation of biological plausibility, but the quality of the evidence is poor and almost entirely in vitro using animal models. Not surprisingly, NSAIDs decrease orthodontic tooth movement in general, but this effect seems to be dose- and timing-dependent.

Finally, the single RCT specifically addressing the effect of ibuprofen (a non-selective NSAID) on bone healing around dental implants (Alissa et al 2009) provides no meaningful insight into what this author believes are the real issues: when Alissa excluded any patient with any disease or history of disease of any kind, and then found that a short course of NSAIDs caused no statistically significant worsening of crestal bone loss, they only proved that any healthy human subject treated with a two-stage surgical procedure would demonstrate the typically expected minimal crestal bone loss during the period of submerged healing. There are two major issues present: by not publishing measurements of implant stability at the time of healing abutment connection and definitive abutment connection, the authors neglect the single most important piece of information relevant to the question of altered bone-healing; and, by not following up on
the subject population beyond a maximum of 3 months post-Stage 2 they are missing observation of over much of what is considered to be the early failure period and therefore the time span most likely to demonstrate the effects of altered bone healing.

Otherwise, only one other study of peri-implant bone healing and the effect of NSAIDs has been published in English recently: Urdaneta and colleagues published data from a retrospective 81-patient case series of Bicon implants placed between 2001 and 2003 at a single centre that included information on the patient’s reported NSAID use (2011). Unfortunately, the study design seems calculated to demonstrate the imperviousness of the Bicon hydroxy-apatite coating to any negative influence of systemic disease or medication rather than provide convincing evidence of any believable correlation with bone loss or gain at the crest of the implant. There were no inclusion/exclusion criteria, the subject population was not even “consecutively treated,” and a series of multivariate analyses was required to find the two correlations presented regarding the value of the HA coating and the concurrent NSAID usage of some patients. There is no data published sufficient to justify even the title; the only bone gain observed in the group of patients taking NSAIDs was in the mandible, and the average gain measured was 0.05mm vs. -0.51mm for those not taking NSAIDs. The average bone loss in the maxilla ranged from 0.17-0.35mm for those taking and not taking NSAIDs respectively (not significant). The thin margin between +0.05mm and -0.51mm yielded the statistically significant finding alluded to in the abstract, but it is this author’s opinion that the quality of the evidence is highly suspect for the aforementioned reasons. These results provide more insight into the motives of the authors than any understanding of the effects of NSAIDs on peri-implant bone healing.

In summary, then, the volumes of data from animal models and human orthopedic models largely supports the concern that the biological process of bone healing is dependent on the prostaglandin chemical signally mechanisms. The variability in the findings seems primarily to stem from issues concerning dose, timing, and duration of NSAID prescription rather than from any overall lack of effect. There is therefore abundant evidence to support the previous declaration of biological plausibility with sound experimental evidence, and the available evidence to the contrary is – at a minimum – more severely limited than the evidence in favour.
4.4 Significance and conclusion

The implications of a positive correlation between sudden unexplained osseointegration failure and the peri-operative use of NSAIDs are clinically significant. The prescription of NSAIDs is a commonly employed technique to reduce patient dependence on opioid analgesia and is currently believed to be safe in most patients. The demonstration of an association between the use of these drugs and complications with osseointegration would be an important first step in developing an evidence-based protocol for peri-operative analgesia that does not promote the irreversible complication of implant loss or, at best, peri-implant bone loss.

The conclusion that one or more medications affect peri-implant bone healing in vulnerable populations should be obvious. The intention of this thesis is to provide substantiation to that clinical hypothesis and, hopefully, to spur more rigorous prospective experimental investigation of the problem.
5 References


6 Appendices

6.1 Research Ethics Board approval letter

PROTOCOL REFERENCE # 27644

May 10, 2012

Dr. Asbjorn Jokstad
FACULTY OF DENTISTRY

Dr. Brent Winnett
FACULTY OF DENTISTRY

Dear Dr. Jokstad and Dr. Brent Winnett,

Re: Your research protocol entitled, “The role of NSAIDs in impaired bone healing in implant prosthodontics”

ETHICS APPROVAL

Original Approval Date: May 10, 2012
Expiry Date: May 9, 2013
Continuing Review Level: 1

We are writing to advise you that the Health Sciences Research Ethics Board (REB) has granted approval to the above-named research protocol under the REB's delegated review process. Your protocol has been approved for a period of one year and ongoing research under this protocol must be renewed prior to the expiry date.

Any changes to the approved protocol or consent materials must be reviewed and approved through the amendment process prior to its implementation. Any adverse or unanticipated events in the research should be reported to the Office of Research Ethics as soon as possible.

Please ensure that you submit an Annual Renewal Form or a Study Completion Report 15 to 30 days prior to the expiry date of your current ethics approval. Note that annual renewals for studies cannot be accepted more than 30 days prior to the date of expiry.

If your research is funded by a third party, please contact the assigned Research Funding Officer in Research Services to ensure that your funds are released.

Best wishes for the successful completion of your research.

Yours sincerely,

Judith Friedland, Ph.D.
REB Chair

Daniel Gyewu
REB Manager
6.2 Invitation letter

Faculty of Dentistry, University of Toronto
124 Edward Street, Toronto, Ontario M5G 1G6

THE ROLE OF NSAIDS IN IMPAIRED BONE HEALING IN IMPLANT PROSTHODONTICS
Investigator: Dr. Brent Winnett

Dear patient,

You are invited to participate in a clinical research study being conducted at the Faculty of Dentistry, University of Toronto. You are potentially eligible to participate in this study if you have experienced a transient or persistent inflammation around a dental implant. The aim of this research study is to investigate whether transient or persistent inflammation around dental implants can be related to intake of everyday painkillers or other medications.

This letter has been sent to all former and current patients of the prosthodontics graduate clinic who, according to our records, experienced some form of transient or persistent inflammation around one or more dental implants.

If you agree to actively participate in this study, you will be contacted by phone for a brief interview to help us update your medical history. This should require about 15 minutes of your time. We will answer any questions you may have, regarding the study or otherwise related to your dental implant treatment.

You may withdraw your consent to participate and if you choose to do so your decision in any way whatsoever will not impact your ongoing or future treatment at the Faculty of Dentistry.

Your participation in this study will provide very valuable information that will be useful for treating future patients. If you agree to participate in this research study please contact the study coordinator, Mrs. Janet deWinter at 416-979-4930 ext. 4309, alternatively Ms. Heather Hyslop at ext 4423. If we do not receive a response from you in one week, we attempt to contact you by telephone.
The principal investigator of the study is Dr. Brent Winnett under supervision of Dr Asbjorn Jokstad, Professor and Head of Discipline of Prosthodontics. Feel free to contact us with any questions or concerns by telephone at 416-979-4930 ext. 4309 /4423 / 4424 or in writing to Prosthodontics, Faculty of Dentistry, University of Toronto, 124 Edward Street, Toronto M5G 1G6.

Thank you in advance for your participation in the study.

Sincerely;

Dr. Brent Winnett, M.Sc., D.D.S.
Resident, Dept. of Prosthodontics
Faculty of Dentistry
University of Toronto
(416) 979-4900 x4512
brent.winnett@utoronto.ca
6.3 Informed consent

Faculty of Dentistry, University of Toronto
124 Edward Street, Toronto, Ontario M5G 1G6

PAINKILLER MEDICATIONS AND DRUGS in implant prosthodontics
Investigator: Dr. Brent Winnett

The Faculty of Dentistry appreciates your willingness to participate in the subject study. This study will be conducted by Dr. Brent Winnett as part of his Master of Science graduate thesis and will be supervised by Dr. Asbjorn Jokstad, Professor and Head of the Discipline of Prosthodontics, Faculty of Dentistry, University of Toronto. The aim of this research study is to investigate whether transient or persistent inflammation around dental implants can be related to intake of everyday painkillers or other medications.

CONFIDENTIALITY
Any additional clinical and radiographic documentation obtained will be entered into the patient’s records. The data will remain in the Faculty of Dentistry electronic patient management system, Axium, according to regulations from the Royal College of Dentistry of Ontario (RCDSO). The Ontario's Personal Health Information Protection Act, 2004 (PHIPA) regulates how we can collect, use and disclose personal health information to provide you privacy protection. Results of this study may be presented at scientific conferences, and/or published in scientific journals but will not include any names or identifying individual information.

RISKS
There are no known risks from participating in this study.

RIGHT TO WITHDRAW FROM THE STUDY
Your participation in this study is voluntary. If you do not want to participate in the study you are free to do so. The decision you make will have no effect on your current or potential future care at the Faculty of Dentistry, University of Toronto.

QUESTIONS ABOUT THE STUDY
If you have any questions about this study, please contact Dr. Brent Winnett or Ms. Heather Hyslop by telephone at: 416-979-4930 ext. 4423, alternatively Janet deWinter ext. 4309 or by e-mail at brent.winnett@dentistry.utoronto.ca or heather.hyslop@utoronto.ca; or janet.Dewinter@dentistry.utoronto.ca
If you have questions about your rights as a research participant, please contact the Office of Research Ethics by telephone 416-946-3273 or via e-mail: ethics.review@utoronto.ca.

I have read, or have been explained to me, the above information regarding the purposes of this study and my individual rights as a potential participant. I have had the opportunity to ask questions regarding this study and have had them answered to my satisfaction. I know that I can refuse participation in this study, and may withdraw from the study at any time without affecting ongoing or future dental treatment at the Faculty of Dentistry, University of Toronto.

I have signed my name below that I have agreed to participate in the above and to permit the gathering and analysis of my personal information with the understanding that my confidentiality will be maintained and my identity will not be disclosed. I have received a copy of this consent form.

____________________  _______________  _______
Participant Name     Signature          Date
6.4 Medical history form

Medical Questionnaire
University of Toronto
Faculty of Dentistry

For office use only. Date: __________________________

Perio ________ Surgery ________ Endo ________
Crown ________ Bridge ________ Amal/Resin ________
P/Dent ________ F/Dent ________ Implants ________
Other ________ C/D 1-2-3-4 ________ MHO ________

Comments: ____________________________________________

Radiographs: Pt to obtain x-rays; reassess
P/M ________ Pan ________ Special procedures ________
Pan + B/W ________ Pan + selected periapicals ________
Other ________

Screening signature: _______________________________________

Have you ever been a patient at this Faculty? Yes ________ No ________

To provide the best possible care for our patients, all patients must fill out this questionnaire completely. Please answer the following questions as accurately as possible. If you have any questions or doubts, please check (✓) the "Not sure/Maybe" choice.

1. Are you being treated for any medical condition at the present or have you been treated within the past year? If so, why? ____________________________________________________________ Yes ________ No ________ Not sure/Maybe ________

2. Was your last medical check-up within the past one year? ____________________________ Yes ________ No ________ Not sure/Maybe ________

3. Has there been any change in your general health in the past year? ____________________________ Yes ________ No ________ Not sure/Maybe ________

4. Are you taking any medications or non-prescription drugs of any kind? If so, please list: ____________________________________________________________ Yes ________ No ________ Not sure/Maybe ________

5. Do you have any allergies? (e.g. Hayfever, Latex/Rubber) ____________________________ Yes ________ No ________ Not sure/Maybe ________

6. Have you ever had peculiar or adverse reaction to any medicines or injections? (e.g. penicillin, aspirin, local anaesthetics, "dental freezing")________ Yes ________ No ________ Not sure/Maybe ________

7. Do you have or do you have ever had any of the following? Please check off (✓) all that apply.

   __ Any heart problem __ Heart murmur __ Blood pressure problem
   __ Chest pain __ Heart transplant __ Rheumatic fever
   __ Angina __ Heart surgery __ Mitral valve problems
   __ Heart attack __ Artificial heart valve __ Congenital heart disease
   __ Stroke __ Infection of the heart (endocarditis) (from birth or early childhood)
   __ Shortness of breath __ Heart failure
   ☐ None of the above

8. Do you have any condition that could affect your immune system, e.g. Leukemia, AIDS, HIV infection? ____________________________ Yes ________ No ________ Not sure/Maybe ________

9. Do you have any tendency to bruise easily or bleed for a prolonged period of time after a cut? ____________________________ Yes ________ No ________ Not sure/Maybe ________

10. Have you ever been hospitalized for any illnesses or operations? ____________________________ Yes ________ No ________ Not sure/Maybe ________

Please explain: ______________________________________________________

PLEASE TURN OVER
Chart # 

11. Do you have, or have you ever had, any of the following? Please check off (✓) all that apply.
   - hepatitis
   - lung disease
   - steroid therapy
   - arthritis, type
   - jaundice
   - tuberculosis
   - diabetes
   - seizures
   - liver disease
   - asthma
   - stomach ulcers
   - kidney disease
   - bone strengthening pills e.g. Fosamax, Actonel
   - prosthetic joint
   - cancer
   □ NONE OF THE ABOVE
   (type)
   (how long)

Yes  No  Not sure/ Maybe

12. Are there any conditions or diseases not listed above that you have or have had?

If so, what?

13. Are there any diseases or medical problems that run in your family? (e.g. diabetes, cancer or heart disease?)

14. Do you or did you smoke? If so, how much?

15. Do you drink alcoholic beverages on a regular basis?

16. Do you use recreational drugs (such as cocaine or amphetamines)?

17. Are you nervous during dental treatment?

18. How nervous are you? (Indicate by marking the scale below).
   NOT AT ALL - 1 - 2 - 3 - 4 - 5 - VERY ANXIOUS

19. If you are nervous, would you like us to consider additional techniques, along with "freezing", to help you?

20. Have you ever had any serious trouble with any previous dental treatment?...

21. For women only, are you pregnant?

If so, what is the expected delivery date?

<table>
<thead>
<tr>
<th>Date</th>
<th>Diagnosis Appointment</th>
</tr>
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<tr>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Date</th>
<th>Emergency Appointment</th>
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</thead>
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</table>

CONSENT FORM: I ACKNOWLEDGE that the information given above is true to the best of my knowledge and that the questions have been reviewed with me. Should there be any change to my present health status in the future, I will advise the Faculty. I have been informed that my physician may be contacted by letter, fax or telephone in order to complete details of my medical history. I hereby consent to my physician providing the Faculty of Dentistry, University of Toronto with any information in this regard which may help ensure safe dental treatment. Finally, I hereby acknowledge that dental treatment may be delayed until all medical information required by the Faculty of Dentistry is received.

Date: Patient Signature: Witness Signature:

Medical Doctor’s Name: Medical Doctor’s Phone #:

Medical Doctor’s Address:

Specialist Doctor’s Name: Specialist Doctor’s Phone #:

Specialist Doctor’s Address:
6.5 Analgesic history form

<table>
<thead>
<tr>
<th>Medication Type</th>
<th>Example Brands</th>
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<tbody>
<tr>
<td>Acetaminophen</td>
<td>Abenol, Asstol, Midol, Novo-Geesic, Pamprin, Percocet, Tylenol</td>
</tr>
<tr>
<td>Acetylsalicylic Acid</td>
<td>ASA, Aspirin, Asaphen EC, Entrophen, Novasen, Percodan, Praxis ASA</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Celebrex</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Cataflam, Voltaren</td>
</tr>
<tr>
<td>Diflunisal</td>
<td>Dolobid, Apo-Diflunisol, Novo-Diflunisal, Nu-Diflunisal</td>
</tr>
<tr>
<td>Etodolac</td>
<td>Ultradol, Apo-Etodolac, Lodine</td>
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<tr>
<td>Floctafenine</td>
<td>Idarac, Apo-Floctafenine</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>Ansaid, Alti-Flurbiprofen Ansaid, Apo-Flurbiprofen, Froben-Sr, Froben, Novo-Flurprofen, Nu-Flurprofen</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Advil, Motrin, Apo-Ibuprofen, Novo-Profen, Nu-Ibuprofen</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Indocin</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Orudis Apo-Keto Sr, Apo-Keto E, Apo-Keto, Nu Ketoprofen, Nu-Ketoprofen E, Pms-Ketoprofen, Pms-Ketoprofen</td>
</tr>
<tr>
<td>Ketonolac</td>
<td>Toradol, Apo-Ketorolac, Novo-Ketorolac, Nu-Ketorolac</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>Apo-Meloxicam, Mobicox, Mobic, Mylan-Meloxicam, Novo-Meloxicam, Phil Meloxicam Pms Meloxicam, Ratio-Meloxicam Teva-Meloxicam</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>Feldene</td>
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</table>

**OTHER (NAME):**

<table>
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<tr>
<th>Approx. Duration / Strength</th>
<th></th>
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<td>1.</td>
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<td>6.</td>
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</tbody>
</table>

Signature: ____________________________  Reviewed by Dr. ________________________  Date: __/__/____

Ver. 17/2/2011. A.J.
Copyright Acknowledgements

**Figure 1:** Prostaglandin Synthesis modified from “Fig. 1. The role of cyclooxygenase (COX) in prostaglandin (PG) synthesis,” in Gilron, I., Milne, B., & Hong, M. (2003). Cyclooxygenase-2 Inhibitors in Postoperative Pain. *Anesthesiology, 99*(5), 1199.

**Figure 2:** Relative selectivity of COX inhibitors modified from “Figure 2 Degree of inhibition of COX-1 in the whole blood assay plotted at concentrations of the drugs that give an inhibition of 80% of COX-2,” in Vane, S. J. (2000). Aspirin and other anti-inflammatory drugs. *Thorax, 55 Suppl 2*(Suppl 2), S6.