Metabolic abnormality and the proinflammatory state following hip joint surgery

Hip surgery is one of the most commonly performed operations in adult orthopedics. A significant proportion of patients undergoing hip surgery are at considerable risk for postoperative complications secondary to age-related medical issues and the morbidity and mortality associated with hip fractures. Inflammation has been shown to play a pivotal role in the host response to total hip arthroplasty and hip fracture surgery. A newly evolved area of research aimed at investigating the complex biochemical roles of the immune system, cytokine cascades and adipose tissue in the systemic inflammatory response to hip surgery has already identified a few central players in this response, namely IL-6, leptin and cortisol. This new area of study has also begun to define the influence of the metabolic syndrome on creating an underlying, chronic state of low-grade systemic inflammation that may predispose patients to postoperative complications in the setting of hip surgery. The ultimate goal of researchers is to develop therapeutic strategies targeted at modulating and controlling postoperative inflammation. In doing so, it is believed that we can improve the biochemical environment in which hip surgery is performed, ameliorate patient outcomes in the realm of pain and function, and predict and reduce postoperative complications associated with aberrant immune and inflammatory responses.

KEYWORDS: adipokines ▪ cytokines ▪ hip arthroplasty ▪ hip replacement ▪ hip surgery ▪ inflammatory markers ▪ metabolic syndrome

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Around 25,000 total hip arthroplasties (THA) are performed in Canada each year, as compared with 300,000 in the USA annually [1,101]. By 2030, it is projected that the number of THA in North America could surpass 2–3 million [1]. The main indication for THA is osteoarthritis (OA). Over 60% of patients undergoing THA are over the age of 65 [1,101]. The global incidence of hip fractures in adults aged 50 years and older is expected to exceed 7 million in the next 30–40 years [1]. Hip fractures are associated with significant morbidity and mortality despite advances in surgery and anesthesia [2]. Hence, patients undergoing hip surgery for OA or hip fracture are at increased risk for postoperative complications given their diagnosis and underlying medical comorbidity.

Surgery evokes a series of well-characterized hormonal, metabolic and immunological changes that are often described as the 'stress response.' This physiological stress state is essential for survival and is very similar to that induced by trauma, parturition and exercise [3–8]. This stress response is characterized by acute phase proteins such as C-reactive protein (CRP), fibrinogen, IL-6, TNF-α and IL-1β [9]. The postoperative activation of cytokines and acute phase proteins has been shown to not only mediate the inflammatory host response, but also to have an association with surgical recovery. For instance, CRP has been shown to be useful in diagnosing and monitoring bacterial infection [10]. Further, chronic postsurgical pain has been linked to ongoing postoperative inflammation [11]. Postoperative inflammation activates the coagulation cascade, inhibits fibrinolysis, and plays an integral role in cardiovascular disease (CVD), with numerous studies demonstrating a consistent relationship between inflammatory markers (such as CRP, fibrinogen, IL-6 and TNF-α) and the occurrence of cardiovascular events [12–15]. IL-6 has been shown to affect the coagulation cascade at several levels in monocyte and liver cell lines [14]. In addition to IL-6, CRP, white cell count and increased blood viscosity, secondary to elevated lipids have been shown to have a graded relationship to the incidence of deep vein thrombosis (DVT), pulmonary embolism (PE), coronary thrombosis and myocardial infarction (MI) [9,14].

In the setting of hip surgery the myriad of biochemical processes that span the perioperative time frame are influenced not only by the trauma of surgery, but also by the patient's underlying comorbidity; including the metabolic syndrome (MetS) and OA. Thus, understanding the inflammatory host response to hip surgery, especially in context of these underlying pathologies, presents a tremendous opportunity to ameliorate the

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postoperative inflammatory state and improve patient outcomes by reducing the risk of chronic pain, infection and thromboembolic disease.

MetS & OA

There is not a definite consensus on the definition of MetS. The WHO defines the MetS by the following risk factors [102]:

- Insulin resistance (Type 2 diabetes, impaired fasting glucose, impaired glucose tolerance)

Plus any two of the following:

- Elevated blood pressure
- Plasma triglyceride of at least 150 mg/dl
- HDL not exceeding 35 mg/dl (men) or not exceeding 40 mg/dl (women)
- BMI of at least 30 and/or waist/hip circumference of at least 0.9 (men) or at least 0.85 (women)
- Urinary albumin of at least 20 mg/min; albumin/creatinine of at least 30 mg/g

The American Heart Association (AHA) defines the MetS as [16]: patients having three or more of the following risk factors:

- Increased waist circumference: men, at least 102 cm; women, at least 88 cm
- Elevated triglycerides of at least 150 mg/dl
- Reduced HDL cholesterol: men, less than 40 mg/dl; women, less than 50 mg/dl
- Elevated blood pressure of at least 130/85 mmHg
- Elevated fasting glucose of at least 100 mg/dl

All of these features of the MetS, including truncal obesity, have been shown to promote a baseline elevation in systemic inflammation that increases the risk for CVD, stroke and thromboembolic disease [17–19]. In fact, patients with the MetS have been shown to have a chronically elevated prothrombotic state with a 1.5-times higher risk for PE and a two-times greater risk of DVT after THA when compared with those without MetS [20–23].

The metabolic derangements and inflammatory cytokine profile (specifically IL-6, CRP, TNF-α, leptin and adiponectin) that characterize the MetS have also been found to have independent associations with the synovial joint inflammation and chondrocyte death found in OA [17]. This may be partly explained by underlying microvascular disease, secondary to obesity-induced atherosclerosis, which appears to exert effects on subchondral bone leading to poor cartilage nutrition, cartilage degeneration and direct ischemic insult [24]. OA patients undergoing THA have been shown to have increased joint pain and dysfunction, both pre- and post-operatively, when correlated to a number of MetS risk factors, especially obesity and hypertension [17]. CVD risk factor such as hypertension and hypercholesteremia were shown to have a correlation to self-reported OA among US adults according to data from the Third National Health and Nutrition Examination Survey [25]. Obesity has also been shown as an independent risk factor for the incidence and progression of OA [26]. All of these findings are best summarized by a recent article by Katz *et al.*, which places OA as part of the MetS [27].

Can we predict & improve patient outcomes by modulating systemic inflammation in hip surgery?

There is already evidence to suggest that modifying the complex prothombotic, proinflammatory state after hip surgery can improve patient outcomes. Numerous studies have shown that NSAIDs are effective analgesics for the control of postoperative pain, by principally inhibiting the inflammatory cyclooxygenase 1 and cyclooxygenase 2 pathways [28]. The clinical benefits of these medications must be balanced, however, against their increased risk for cardiac events and so judicious use must be employed to ensure patient safety [29]. It has also recently been shown that treatment with statins for hypercholesterolemia can lower plasma viscosity by altering systemic lipid levels, lowering the risk for postoperative ischemic heart disease (IHD) [14]. Additionally, the use of statins postoperatively has been shown to decrease the incidence of atrial fibrillation in cardiac surgery patients [30]. Statins have been shown to impart their own anti-inflammatory properties as well, with a few trials examining their potential use in the treatment of rheumatoid arthritis (RA) [31].

Studies have also shown that risk factors for MetS, specifically hypertension and obesity, are predictors for increased joint pain and dysfunction after THA [17]. Furthermore, high sensitivity CRP, along with fibrinogen, has been shown to be a well established predictor for the development of CVD postoperatively [12–14]. Further studies are necessary, however, to evaluate whether other inflammatory markers are also predictors for postoperative complications and diminished patient outcomes.

These data, taken together, further support and expand the need to understand the systemic inflammatory response to hip surgery,

especially in the context of MetS and OA, and develop novel therapies targeted at modulating the occurrence of a protracted, prothrombotic, proinflammatory state. This article will attempt to discuss the complex relationship between patients' underlying medical comorbidity, specifically MetS and OA, and the systemic inflammatory state following hip surgery. We will review the key players, including the inflammatory cytokines (CRP, erythrocyte sedimentation rate [ESR], IL-6, TNF-α, IL-1β, IL-10, leptin and adiponectin) and immune mediators (macrophages), involved in regulating the global response to hip surgery and explore current concepts in modulating this response to improve patient outcomes postoperatively.

Methods

The authors completed an online search of PubMed, OVID MEDLINE (1950 to May 2010), and EMBASE (1950–2010) with the following search terms: hip arthroplasty, hip replacement, hip surgery, inflammatory markers, MetS, adipokines and cytokines.

We included articles relevant to the following:

- Patients undergoing primary THA
- Studies examining the expression of cytokines, adipokines and inflammatory markers prior to and following hip surgery
- Peer-reviewed literature reviews related to MetS, inflammatory markers and hip surgery
- Articles examining risk factors for the development of postoperative complications following THA and hip surgery
- Articles that examined the influence of modifying the inflammatory environment around the time of hip surgery on postoperative function and the development of postoperative complications

The bibliographies of included studies were also reviewed for potentially relevant studies not found in the online search.

Systemic markers of inflammation around the time of hip surgery

The majority of research has focused on catecholamines, CRP, ESR, glucose and cortisol in the systemic response to THA .

Catecholamines

The typical time course of hip surgery shows an initial systemic response similar to that seen in a flight or fight response. This response is characterized by peaking of catecholamines, adrenaline and noradrenaline levels, at 4 h postoperatively, with levels returning to baseline around 24 h compared with controls [3].

CRP & ESR

The trends of CRP and ESR post-hip surgery have been well documented in the literature, and have been shown to be very helpful in the diagnosis of postoperative infection and response to therapeutic treatment [10,32–40]. All of the literature demonstrates that detection of CRP is far more sensitive and responsive to inflammatory/infectious changes than ESR in the postoperative time period with detectable levels peaking at 2–3 days. The ESR, on the other hand, peaks at 5–7 days, declining after day 7 and returning to normal levels in the third month postoperatively [33–36,41].

As such, CRP has become a useful biomarker in the early detection of postoperative complications, namely infection. Furthermore, high sensitivity-CRP, along with fibrinogen, has been shown to be a well established predictor for the development of CVD [12–14]. This is thought to be mediated by its involvement in the systemic activation of the coagulation cascade and inhibition of fibrinolysis in response to the surgical trauma [9].

Cortisol & glucose

Of more recent interest are the trends of cortisol and glucose in the perioperative period of hip surgery, as these biochemical markers have significant relevance to MetS and obesity. Studies have shown that glucose levels peak at 4 h in THA, while cortisol levels peak at 8 h and remain elevated for 7 days [3].

In a recent study by Bjornsson *et al.* they found an inverse relationship between preoperative cortisol levels and IL-6 (a potent inflammatory cytokine) concentrations postoperatively at 6 h [42]. These findings are in keeping with *in vitro* evidence showing that inflammatory cytokines, IL-6 and IL-1β, stimulate adrenocorticotrophic hormone secretion, which is known to inhibit cytokine synthesis and hence, further IL-6 production [43–47]. Although other measured cytokines did not demonstrate the existence of a negative feedback loop (i.e., minimal production of IL-10 [an anti-inflammatory cytokine] in the wake of powerful IL-6 production) it is well known that cortisol has a powerful immunomodulating effect and that concentrations of cortisol increased after hip surgery [48,49]. Thus, cortisol presents itself as an important feedback mechanism to limit the inflammatory response to tissue damage.

In the Bjornsson *et al.* study, a positive correlation between postoperative IL-6 levels and cortisol secretion during the first 24 h was shown [42]. In fact, individuals with the highest peak in IL-6 also had the highest cortisol response, while those that did not have a distinct IL-6 peak postoperatively had higher preoperative cortisol levels than others. These findings not only point to the possibility that IL-6 drives cortisol production in the postoperative period, but that cortisol functions as part of a potent negative feedback loop in the complicated neuro-endocrino-immune inflammatory response.

Macrophages & the immune response

Surgical trauma produces alterations in the metabolic and immune response of the patient. While some elements of the immune system are stimulated excessively, others are depressed. Protective immunity following trauma is greatly dictated by an appropriate cytokine balance. Cytokines are immune mediators that direct the inflammatory response to sites of injury, playing an integral role in wound healing [50]. The initial proinflammatory immune response to surgery is mediated primarily by the innate immune system. A compensatory anti-inflammatory response follows, mediated primarily by cells of the adaptive immune system [51]. Like most physiologic responses, inflammation and immunity are dynamic processes that if disrupted may cause immune dysfunction and predispose to complications such as infection [50].

The macrophage plays a key role in innate immunity and specifically the pathogenesis of chronic inflammation both in the setting of MetS and OA [52]. In obese individuals muscle cells and adipocytes are stimulated by activated macrophages that produce inflammatory cytokines, which not only enhance acute inflammation, but also contribute to a chronic state of low-grade inflammation [27]. Activated macrophages do so through the production of TH1 cytokines that suppress the sensitivity of insulin receptors on these cells [52]. This creates a feedback loop relationship that not only induces an inflammatory reaction but also contributes to its own inciting metabolic derangement of insulin resistance. In addition to this, the adipose tissue acts as an amplifier of this inflammatory cycle because of its increased number of macrophages [53].

There are several proinflammatory TH1 cytokines produced by macrophages, such as IL-6 and IL-8 [54]. IL-6 promotes inflammation in endothelial cells and liver cells. Again, a very similar cytokine profile is evident for adipose tissue in the context of MetS, which is characterized by an increased number of activated macrophages producing IL-6 and IL-8 [54]. Interestingly, studies have shown that individuals with MetS, where central adiposity is a key feature, have higher circulating IL-6 levels than normal controls [55]. Hence, there is clear evidence that macrophages play a key role in the production of inflammatory mediators in the setting of surgical trauma, and this in turn plays an important part in the systemic response to hip surgery in the context of MetS.

Metabolic modulators of inflammation

Cytokines

The cytokine cascade consists of a complex biochemical network in which the production and regulation of cytokines are pivotal preliminary processes with diverse effects on the injured host. In the setting of surgical trauma it is these complex interactions that form the foundational pathophysiology of inflammation [50]. In general, the greater the severity of inflicted trauma, the greater the intensity of the cytokine response [8,56]. The main source of cytokine production is localized to the wound, and so systemic levels of these markers do not necessarily reflect local reactions [50]. Most cytokine cascades share similar sources of origin, for example monocytes, endothelial cells, fibroblasts, as well as T lymphocytes [42]. The role of cytokines in accidental trauma has been studied extensively, and adding to this body of knowledge are the increased levels identified in major elective surgery, namely THA [57].

It is important to note, however, that the effect of cytokines on different organ systems is quite dependent on the timing and context of their expression (**Box 1**). A single cytokine can have both inflammatory and anti-inflammatory properties given the appropriate biochemical environment [58]. There are studies to show, for example, that depending on the time from hip fracture IL-6 can have regenerative properties, stimulating angiogenesis and promoting mesenchymal stem cell differentiation and proliferation in the initial inflammatory phase of bone healing, while subsequently demonstrating resorptive properties, promoting osteoclast formation and bone resorption in the remodeling phase of bone healing [59,60]. These elevated local levels of IL-6 post injury then correlate with decreased load-bearing capability at the injury site during patient recovery [59,60]. Hence, the influence of

time and context on cytokine expression when examining the roles of various factors on the host response to hip surgery must be considered in order to properly identify potential opportunities to improve patient outcomes through targeted therapeutic strategies. Similar findings for the dual, seemingly opposing roles of IL-6 will be discussed further in the context of hip surgery.

Box 1. Summary of host responses to hip surgery.

- Proinflammatory response characterized by:
  - Innate immunity: macrophages produce ↑ TH1 response and ↑ IL-6, ↑ IL-8 and insulin resistance
  - Metabolic: ↑ catecholamines, ↑ CRP, ↑ ESR
  - Cytokines: ↑↑ IL-6, ↑ IL-8
  - Adipokines: ↑ leptin, resistin?
- Anti-inflammatory response characterized by:
  - Adaptive immunity
  - Metabolic: ↑ cortisol
  - Cytokines: ↑ IL-10, ↑ IL-1Ra, ↓ IL-2, ↓ IL-2Ra, ↑ prostaglandin E2
  - Adipokines: ↑ adiponectin?

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IL-1Ra: IL-1 receptor antagonist.

Proinflammatory cytokines: IL-6, IL-1β, TNF-α, IL-2 & IL-2 receptor antagonist

Among the proinflammatory cytokines IL-6 has been shown to play a central role in the host response to hip surgery [8,61]. Several studies have confirmed that IL-6 is the principal regulator of most acute phase protein genes, including CRP, by triggering the activation of the JAK/STAT or MAP kinase pathways and regulating the hepatic component of the acute phase response [50]. This is demonstrated in numerous studies where a postoperative elevation of CRP is correlated with elevated serum concentration IL-6 [42,62–65].

Although IL-β and TNF-α were originally thought to be the main mediators of the response to elective surgery, numerous studies have demonstrated the opposite [42,57,62,63,66]. This assumption was initially informed by earlier literature that showed a dramatic elevation in TNF-α and IL-1β in the setting of severe trauma. It has since been clearly shown that TNF-α and IL-1β are only elevated in severe trauma and associated hypoxia and not in the setting of THA [57,60,65].

IL-6 has been found to increase 25-fold from 6–24 h after THA, peaking at 4–6 h after surgery and returning to normal levels around 24–48 h [42,57,62,63,66]. The magnitude of the IL-6 response appears to be closely related to the magnitude of inflicted injury [8]. This notion is supported by the fact that the IL-6 response is 50% greater in total knee arthroplasty patients, an operation that is theoretically more skeletally traumatic than THA because of the increased amount of bony sculpting needed to implant the prosthesis [36]. Consequently, a greater number of macrophages are released from the bone and bone marrow, resulting in an inflated acute inflammatory response [36]. Furthermore, there is a demonstrated significance to expressed local and systemic levels of IL-6 after surgery, with local levels demonstrating as high as a 1000-fold increase when measured from wound drainage fluid [57,67,68]. These findings do not appear to be influenced by gender, BMI, type of anesthetic or type of arthroplasty [69]. The same studies demonstrate no statistically significant response or change in both TNF-α and IL-1β levels, although systemic levels may be somewhat elevated [42,50,57,62,63,66,70].

Finally, IL-2 and IL-2 receptor antagonist (IL-2Ra) are known to have a pivotal regulatory role in generating the host immune response in the early phase of inflammation via T lymphocytes [50]. A recent study has, in fact, shown that IL-2 activates monocytes [50]. Although these cytokines are known to have an inflammatory role in the initial host response, their immediate postoperative values do not change significantly after THA [50]. What is interesting, however, is that the IL-2 and IL-2Ra levels decrease dramatically 24 h after hip surgery, indicating that subsequent anti-inflammatory mechanisms are likely being activated at that surgical time point to counter the host inflammatory response [50].

Proinflammatory cytokines appear to play a role in determining patient outcomes post-THA. Numerous studies have demonstrated a consistent relationship between inflammatory markers such as IL-6, CRP, fibrinogen and TNF-α and the occurrence of cardiovascular events postoperatively [12–15]. Part of the physiology underlying these findings is the activation of the coagulation cascade and inhibition of fibrinolysis by the systemic inflammatory response to surgery [9]. IL-6 has been shown to affect the coagulation cascade at several levels in monocyte and liver cell lines [14]. In fact, IL-6, CRP, white cell count and increased blood viscosity (secondary to elevated lipids) have been shown to be strong long term predictors of IHD, with a graded relationship to the incidence of postoperative DVT, PE and MI [9,14].

Chemokine: IL-8

Another possible player in the proinflammatory arm of the cytokine response to hip surgery is the release of CXCL8 (IL-8) [42]. IL-8 is an important chemotactic cytokine involved

in controlling the migration, recruitment and activation of neutrophils and leukocytes in local tissues by promoting cellular adhesion to endothelial cells [71]. It is mainly induced by proinflammatory cytokines such as IL-1β and TNF-α, but is also released by endothelial cells activated by the complement cascade or adherent platelets in damaged blood vessels [72].

The expression of IL-8 in the context of hip surgery varies in the literature. Bastian *et al.* demonstrated strong local increases in IL-8 expression that peaked 4 h after wound closure, although systemic levels remained consistently low [50]. Other studies have found changes in the expression IL-8 after THA, although they were not statistically significant [42]. It is currently unknown what may be inducing the production of IL-8. Bastian *et al.*'s study, examining the level of 25 different cytokines at the time of THA, did not show any other significant changes that could account for the increase in its production.

Anti-inflammatory cytokines: IL-10, IL-1Ra & prostaglandin E2

The purpose of anti-inflammatory cytokines is to participate in the compensatory host response to inflicted surgical trauma. Certainly, studies demonstrate that after the initial systemic proinflammatory reaction to hip surgery exists a transition to an anti-inflammatory, immunosuppressive state aimed at counterbalancing the host response [50]. This notion of direct modulation of the immune system post-hip surgery can be supported by the findings of Bastian *et al.* who showed a significant systemic and local reduction of IL-2 and IL-2Ra levels 24 h after THA [50]. Although further investigations into the actual players involved in downregulating the immune response to systemic inflammation after hip surgery are necessary, a few anti-inflammatory cytokines have been shown to potentially explain the pathophysiology of this process.

Among the anti-inflammatory cytokines IL-10 has been shown to be one of the most potent inhibitors of proinflammatory cytokine synthesis both *in vivo* and *in vitro* [57,73,74]. It is specifically known to be a potent downregulator of IL-6-induced type 2 acute phase proteins, and IL-1β and TNF-α-induced type 1 acute phase proteins [50]. However, the conditions under which IL-10 seems to exert its effects are unclear. For instance, although elevated IL-10 expression has been reported after major trauma, this does not appear to be the case after elective surgery [73,75–77]. Specifically, many studies show that levels undergo only modest changes after hip surgery [73,75–77]. This may indicate that its consumption depends on the degree of tissue injury, which would be more severe with major trauma versus elective surgery [57,74,77]. In this way the effects of IL-10 only become pronounced in the setting of severe trauma, similar to the conditions that demonstrate significant IL-1β and TNF-α activity.

To add further confusion, other studies have shown that IL-10 levels are unchanged and may even be depressed in trauma patients [75,76]. As such it cannot be utilized as a reliable parameter for monitoring the severity of trauma as of yet [42]. These contradictory findings then beg the question of what other mechanisms are responsible for activating the adaptive immune system, which may be responsible for halting IL-6 production.

Interestingly, IL-6 may exert its own anti-inflammatory effects, or least participate in its own inhibitory feedback loop, by attenuating TNF-α and IL-1β activity through the promotion of IL-Ra release and soluble TNF receptors [50,51,78]. The production of these soluble receptors allows for binding of these proinflammatory cytokines and attenuation of the proinflammatory response. This hypothesis would be supported by the numerous studies demonstrating a very modest rise in TNF-α and unchanged IL-1β levels in elective surgery [42,57,62,63,66]. Additionally, other studies have shown prostaglandin E2, a powerful endogenous immunosuppressant, to be released by IL-6 induced macrophages [79].

The hypothesized anti-inflammatory effects of IL-6 may further be supported by the work of Tilg *et al.*, who demonstrated a rise in circulating IL-1Ra, IL-10 and cortisol after administration of recombinant human IL-6 [80]. *In vitro* studies have also shown a potential induction of IL1-Ra production in human macrophages following stimulation with IL-6 [78]. It is thought that local tissue macrophages are the primary source of IL-1Ra production. Bastian *et al.*'s work supports this notion as well, by demonstrating a marked rise and peak at 24 h in local IL-1Ra levels, with a decrease in systemic levels of IL-1Ra after THA [50]. Again, this likely represents a physiological reaction aimed at countering the local proinflammatory reaction.

Adipokines

Visceral and subcutaneous truncal white adipose tissue (WAT) is a metabolically active endocrine organ that secretes a biologically active group of cytokines known as 'adipokines' [81].

By engaging through endocrine, paracrine and autocrine activity adipokines play a significant role in the pathophysiological processes of immunity and inflammation [82]. In the context of hip surgery and MetS, specific proinflammatory adipokines appear to contribute to a host of metabolic aberrations influencing cardiovascular disease, glucose metabolism, insulin sensitivity, regulation of bone turnover and autoimmune inflammatory disease [26]. Certainly, these adipokines appear to contribute significantly to the chronic, low-grade inflammatory state of obese subjects, which in turn has implications for the metabolic and inflammatory response to hip surgery, and potential postoperative complications including chronic pain, joint dysfunction, DVT, PE and MI.

Leptin

Leptin is a 16 kDa nonglycoslated peptide hormone encoded by the obese *(ob)* gene. It is mainly produced by adipocytes, with circulating levels being directly correlated with WAT mass [81]. Circulating leptin levels are gender specific, with concentrations being higher in women than men, which may be relevant to the influence of sex on the host response to hip surgery. Originally described for its role in appetite and obesity, leptin was initially investigated for its role in decreasing food intake and increasing energy consumption [82]. Subsequently, there has been immense progress in our understanding of leptin's complex contribution to numerous physiological processes, namely its key role in immunity and inflammation [26].

Leptin has been shown to have effects on both arms of the immune response. Its effect on innate immunity includes modulation of macrophages, neutrophils, eosinophils, natural killer and dendritic cells, while its role in adaptive immunity lies in its ability to drive T-cell production towards a TH1 proinflammatory response [82]. Additionally, leptin has been shown to have remarkable effects as a proinflammatory cytokine itself. First, it is produced by inflammatory cells and, second, circulating levels are stimulated by other proinflammatory cytokines such as IL-1, IL-6 and lipoolysaccharide [81]. Leptin has also been shown to induce the production of nitric oxide (NO), IL-6 and IL-8 [83].

Interestingly, leptin and its receptor Ob-Rb share common structural and functional properties with the family of IL-6 [84]. Since Ob-Rb is widely expressed in peripheral tissues, leptin possesses the ability to be pleotropic, and control various processes including lipid homeostasis, insulin secretion, reproductive functions, immune function, thermogenesis and angiogenesis [81]. In addition, lab studies have demonstrated an association between synovial fluid leptin and knee cartilage degeneration [85,86]. The leptin receptor Ob-Rb has been identified on the surface of human articular chondrocytes and is believed to induce proinflammatory, damaging effects on cartilage cells through the production of IL-1β and matrix metalloproteinase (MMP) 9 and 13 [86,87]. These inflammatory mediators potentiate the further release of local type II NO synthase (NOS2) leading to further chondrocyte death [88]. All of these findings situate leptin as a key player in the model of incorporating OA into the MetS. This, of course, has implications for our understanding of the host response to hip surgery in the context of MetS and OA.

To date, there have been few studies examining leptin levels following hip surgery. The few studies that investigated this relationship have shown that circulating leptin levels after THA are markedly elevated within the first 24 h, and subsequently drop off afterwards [89]. Hence, leptin certainly appears to be involved in the early, acute phase response to hip surgery, much in the same way as other inflammatory cytokines, namely IL-6. This has important implications for our understanding of leptin's role in the context of hip surgery, as it may well be a predictor of IHD in much the same way as IL-6, CRP and fibrinogen. Furthermore, given its association with MetS and OA, leptin may also demonstrate a relationship with postoperative complications such joint pain, infection and thromboembolic disease.

Adiponectin

Adiponectin is 244-residue protein largely produced by WAT that appears to play a protective role in obesity and cardiac disease, by increasing fatty oxidation and reducing the synthesis of glucose in the liver [81]. Adiponectin levels tend to be lower in morbidly obese patients, increasing with weight loss and/or the use of thiazolidinediones, which enhance insulin sensitivity [81]. In contrast to leptin, adiponectin appears exert an anti-inflammatory role through innate and adaptive immunity mechanisms [81]. Adiponectin interferes with macrophage activity and phagocytic function in innate immunity by inhibiting IL-1 and TNF-α production, while decreasing the T-cell response in adaptive immunity [26]. Furthermore, adiponectin induces systemic production of anti-inflammatory factors such as IL-10 and IL-1Ra

[90]. Other studies have also shown adiponectin to decrease endothelial inflammation in the setting of vascular disease, making it a potential antiatherosclerotic factor [91].

Despite the numerous studies pointing towards its anti-inflammatory properties, the role of adiponectin is not as clearly defined as that of leptin. Some studies suggest that adiponectin has an inflammatory role in skeletal joints by being involved in matrix degradation and cartilage degeneration [81]. For example, adiponectin receptors have been identified on the surface of human chondrocytes. Treatment of these chondrocytes with adiponectin *in vitro* produces lL-6, TNF-α and monocyte chemotactic protein 1, MMP3 and 9, as well as activating the inflammatory NOS2 pathway [92]. Furthermore, plasma and SF concentrations of adiponectin tend to be higher in RA patients than healthy controls or patients with OA [81].

In contrast to these findings, other work has shown that perhaps adiponectin does, indeed, retain its anti-inflammatory title in skeletal joints by downregulating IL-1β and decreasing MMP13 levels [26]. In light of these conflicting findings, perhaps the supposed anti-inflammatory nature of adiponectin could explain its observed elevation in RA patients. Perhaps elevated adiponectin levels represent a host counter response to the systemic inflammatory state of RA, with the body laboring to elevate levels of anti-inflammatory adiponectin and counter elevated systemic IL-6 and TNF-α.

Clearly, the activity and effects of adiponectin remain to be fully elucidated. What is clear is that it certainly plays a role somewhere along the spectrum of the inflammatory host response in the context of OA and MetS, and as such must have some bearing on the post-traumatic response to hip surgery.

Resistin

Resistin is a dimeric protein that was initially linked to the induction of insulin resistance in mice. Although this property of resistin did not bear out in human studies, this adipokine continues to be examined as a possible player in the proinflammatory host response. Resistin has been shown to be secreted by adipose tissue, macrophages and cartilage itself [93]. Some studies have suggested that resistin acts as a powerful proinflammatory cytokine that is not only induced by, but also stimulates the production of IL-1β, TNF-α and IL-6 by mononuclear cells and articular cartilage as part of its involvement in matrix degradation [81]. In fact, some studies have proposed that an arthritis-like condition can be induced when resistin is injected into the joints of mice, stimulating a leukocyte infiltration of tissue, hypertrophy of the synovium and pannus formation [81].

Resistin's effects on hip surgery have yet to be investigated, but it would be interesting to see if it does indeed contribute to the proinflammatory response to surgical trauma.

Conclusion

Hip surgery stands as one of the most prevalent surgical interventions in orthopedics. Given the preexisting, underlying comorbity of the vast majority of THA and hip fracture patients, there exists a significant concern for morbidity and mortality after hip surgery. Although a few central players have been identified (namely IL-6, leptin, CRP and cortisol) further research is necessary to clearly delineate the intricate biochemical pathways that regulate the host response to hip surgery. This is especially true in the context of the MetS where there is a complex interplay between immunity, cytokine cascades and adipose tissue in the setting of concomitant cardiovascular aberrations, insulin insufficiency, and lipid disarray. All of these features of the MetS have been shown to promote a chronic state of low-grade, systemic inflammation that increases the risk for CVD, stroke and thromboembolic disease. These features have also been shown to predict increased pain and poorer functional outcomes after THA [17]. OA is also considered to be part of the spectrum of derangements that comprise the MetS. The parallel, underlying pathophysiologies of both of these entities are important in understanding inflammation after hip surgery, and may hold the key to identifying predictors that could help improve postoperative outcomes and complications.

Numerous studies have shown that the initial proinflammatory, prothrombotic stress response to hip surgery is inevitably responsible for tissue repair and regeneration [58]. Hence, in addition to further characterizing the host reaction to hip surgery, many authors have proposed the rationale of designing therapeutic strategies to modulate and control postoperative inflammation. By exploiting the time- and context-specific activity of inflammatory markers, scientists believe that biochemical pathways can be directed towards improved soft tissue and bone healing [58]. These novel techniques may be able to achieve the ultimate goal of reducing postoperative complications while improving patient outcomes in the realms of pain and function.

Future perspective

As research continues forward over the next 5–10 years, there are many exciting areas of interest open for investigation. With rapidly advancing assay techniques, biochemical analysis and arthroplasty database generation, future studies look to further elucidate the specific molecular pathways of each cytokine and adipokine. An interesting facet of future research should also touch on the circadian rythmicity with which many of these biomarkers are expressed [94]. Numerous studies have demonstrated this finding, hence future studies should emphasize the importance of selecting specific times for the collection of biosamples. By more clearly defining these biochemical interactions and delineating which systemic and local factors can drive the inflammatory host response towards reparative and regenerative pathways, researchers will be able to explore new and accessible therapies for OA and MetS. Already, IL-6 and leptin are promising to be key targets for pharmacologic and tissue engineering strategies aimed at improving fracture healing, soft tissue repair and reducing systemic inflammation and associated atherosclerosis. By exploring these modalities we hope to improve the biochemical environment in which hip surgery is performed, better predict who is at risk for postoperative complications and ameliorate patient outcomes after hip surgery.

Executive summary

- Total hip arthroplasty and hip fracture surgery represent the most commonly performed operations in orthopedics, with osteoarthritis (OA) being the main indication for total hip arthroplasty.
- IL-6, C-reactive protein, fibrinogen and plasma viscosity (secondary to elevated lipids) have been shown to be long-term predictors of ischemic heart disease and elevated levels have a graded relationship with postoperative deep vein thrombosis, pulmonary embolism and myocardial infarction.
- There is evidence that inhibiting inflammation with nonsteroidal anti-inflammatory drugs improves pain.
- There is evidence that lowering plasma viscosity with statins lowers postoperative ischemic heart disease and atrial fibrillation.

Metabolic syndrome & OA

- Metabolic syndrome (MetS) is defined by the risk factors of central adiposity, hypertension, elevated fasting glucose and dyslipidemia defined as high triglyceride and low high-density lipoprotein cholesterol.
- OA has taken its place among the MetS because the numerous comorbities and metabolic derangements necessary to create MetS are coincident with those that cause OA.
- MetS and obesity create a chronic state of low-grade systemic inflammation.
- In the setting of hip surgery, the MetS can result in an increased proinflammatory, prothrombotic host response with elevated risk for postoperative deep vein thrombosis, pulmonary embolism and myocardial infarction.

Systemic markers of inflammation around the time of hip surgery

- The host response to surgery has an initial proinflammatory response characterized by increased catecholamines, C-reactive protein and erythrocyte sedimentation rate.
- Subsequent anti-inflammatory counter response that consists of increased cortisol and coordination between immune, cytokine and adipokine activity.

Macrophages & the immune response

- Macrophages play a key role in the inflammatory host response to hip surgery by stimulating the innate immune system to produce an increased TH1 response with increased IL-6, increased IL-8 and insulin resistance.
- A secondary anti-inflammatory compensatory response is characterized by adaptive immunity and cortisol.

Cytokines

- IL-6 is the central cytokine mediator of the inflammatory host response with significant elevation postsurgery, specifically at the site of surgery.
- IL-10 is believed to mediate the compensatory anti-inflammatory response to hip surgery, characterized by an immunosuppressive state of increased IL-1 receptor antagonist (IL-1Ra), decreased IL-2, decreased IL-2Ra, increased prostaglandin E2, although data are not conclusive at this point.

Adipokines

- Leptin appears to play a central role in the pathophysiology of MetS, OA and the postsurgical inflammatory response.
- Adiponectin has been shown to have systemic anti-inflammatory properties, although its effects on skeletal joints continues to be inconclusive.

Conclusion

- Further research is necessary to characterize the various players in the host response to hip surgery.
- Current research is directed towards controlling the inflammatory response and directing biochemical pathways towards tissue healing and regeneration.
- The ultimate goal of current research is to identify possible predictors of poor patient outcomes after hip surgery and to develop novel therapies aimed at improving patient function, while reducing complications such as infection, pain, delirium, deep vein thrombosis, pulmonary embolism and myocardial infarction.

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Bibliography

Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

1 Kurtz S, Ong K, Lau E, Mowat F, Halpern M: Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J. Bone Joint Surg. Am.* 89(4), 780–785 (2007).

2 Cummings SR, Rubin SM, Black D: The future of hip fractures in the United States. Numbers, costs, and potential effects of postmenopausal estrogen. *Clin. Orthop. Relat. Res.* 252, 163–166 (1990).

3 Hall GM, Peerbhoy D, Shenkin A, Parker CJR, Salmon P: Hip and knee arthroplasty: a comparison and the endocrine, metabolic and inflammatory responses. *Clin. Sci.* 98, 71–79 (2000).

4 Wilmore DW, Long JM, Mason AD, Pruitt BA Jr: Stress in surgical patients as a neurophysiologic reflex response. *Surg. Gynecol. Obstet.* 142, 257–269 (1976).

5 Traynor C, Hall GM: Endocrine and metabolic changes during surgery: anaesethtic implications. *Br. J. Anaesth.* 53, 153–161 (1981).

6 Chernow B, Alexander HR, Smallridge RC *et al.*: Hormonal responses to graded surgical stress. *Arch. Intern. Med.* 147, 1273–1277 (1987).

7 Weissman C: The metabolic response to stress: an overview and update. *Anesthesiology* 73, 308–327 (1990).

8 Cruickshank AM, Fraser WD, Burns HJG, Van Damme J, Shenkin A: Response of serum interleukin-6 in patients undergoing elective surgery of varying severity. *Clin. Sci.* 79, 161–165 (1990).

9 Parolari A, Camera M, Alamanni F *et al.*: Systemic inflammation after on-pump and off-pump coronary bypass surgery: a one-month follow-up. *Ann. Thorac. Surg.* 84(3), 823–828 (2007).

▪▪ **Important study that discusses inflammatory markers after surgery, and how IL-6, C-reactive protein, fibrinogen, white cell count and plasma viscosity are predictors of ischemic heart disease and postoperative complications.**

10 White J, Kelly M, Dunsmuir R: C-reactive protein level after total hip and total knee replacement. *J. Bone Joint Surg. Br.* 80(5), 909–911 (1998).

11 Kehlet H, Jensen TS, Woolf CJ: Persistent postsurgical pain: risk factors and prevention. *Lancet* 367(9522), 1618–1625 (2006).

12 Ernst E, Resch KL: Fibrinogen as a cardiovascular risk factor: a meta-analysis and review of the literature. *Ann. Intern. Med.* 118, 956–963 (1993).

13 Danesh J, Collins R, Appleby P, Peto R: Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease. *JAMA* 279, 1477–1482 (1998).

14 Yarnell J: Haemostatic/inflammatory markers predict 10-year risk of IHD at least as well as lipids: the Caerphilly collaborative studies. *Eur. Heart J.* 25(12), 1049–1056 (2004).

15 Blake GJ, Ridker PM: Novel clinical markers of vascular wall inflammation. *Circ. Res.* 89 763–771 (2001).

16 Grundy SM: Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Arterioscler. Thromb. Vasc. Biol.* 24(2), e13–e18 (2003).

17 Gandhi R, Razak F, Davey JR, Mahomed NN: Metabolic syndrome and the functional outcomes of hip and knee arthroplasty. *J. Rheumatol.* 37(9), 1917–1922 (2010).

▪▪ **Demonstrates a functional outcome correlation with risk factors for metabolic syndrome after total hip arthroplasty.**

18 Bray GA, Bellanger T: Epidemiology, trends, and morbidities of obesity and the metabolic syndrome. *Endocrine* 29(1), 109–117 (2006).

19 Grundy SM: Obesity, metabolic syndrome, and cardiovascular disease. *J. Clin. Endocrinol. Metabol.* 89, 2595–2600 (2004).

20 Gandhi R, Razak F, Tso P, Davey JR, Mahomed NN: Asian ethnicity and the prevalence of metabolic syndrome in the osteoarthritic total knee arthroplasty population. *J. Arthroplasty* 25(3), 416–419 (2010).

21 Ay C, Tengler T, Vormittag R: Venous thromboembolism – a manifestation of the metabolic syndrome. *Haematologica* 92, 374–380 (2007).

22 Ageno W, Prandoni P, Romualdi E *et al.*: The metabolic syndrome and the risk of venous thrombosis: a case–control study. *J. Thromb. Haemost.* 4, 1914 (2006).

23 Durina J, Remkova A: Prothrombotic state in metabolic syndrome. *Bratisl. Lek. Listy.* 108, 279 (2007).

24 Conaghan PG: Is progressive osteoarthritis an atheromatous vascular disease? *Ann. Rheum. Dis.* 64(11), 1539–1541 (2005).

25 Singh G, Miller JD, Lee FH, Pettitt D, Russell MW: Prevalence of cardiovascular disease risk factors among US adults with self-reported osteoarthritis: data from the Third National Health and Nutrition Examination Survery. *Am. J. Manag. Care* 8(Suppl. 15), S383–S391 (2002).

26 Gandhi R, Takahashi M, Syed K, Davey JR, Mahomed NN: Relationship between body habitus and joint leptin levels in a knee osteoarthritis population. *J. Orthop. Res.* 28(3), 329–333 (2010).

▪ **Shows a correlation between BMI/waist circumference and leptin levels in the knee.**

27 Katz JD, Agrawal S, Velasquez M: Getting to the heart of the matter: osteoarthritis takes its place as part of the metabolic syndrome. *Curr. Opin. Rheum.* 22(5), 512–519 (2010).

▪▪ **Very important article that takes the most recent literature about metabolic syndrome and osteoarthritis, and discusses the many reasons why osteoarthritis warrants consideration as part of the metabolic syndrome.**

28 Romsing J, Moiniche S: A systematic review of COX-2 inhibitors compared with traditional NSAIDs, or different COX-2 inhibitors for postoperative pain. *Acta Anaesthesiol. Scand.* 48, 525–546 (2004).

29 Trelle S, Reichenbach S, Wandel S *et al.*: Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* 342(1), C7086–C7086 (2011).

30 Chen WT, Krishnan GM, Sood N, Kluger J, Coleman CI: Effect of statins on atrial fibrillation after cardiac surgery: a duration- and dose-response meta-analysis. *J. Thorac. Cardiovasc. Surg.* 140(2), 364–372 (2010).

31 Mccarey DW, Sattar N, Mcinnes IB: Do the pleiotropic effects of statins in the vasculature predict a role in inflammatory diseases? *Arthritis Res. Ther.* 7(2), 55 (2005).

32 Niskanen RO, Korkala O, Pammo H: Serum C-reactive protein levels after total hip and knee arthroplasty. *J. Bone Joint Surg. Br.* 78(3), 431–433 (1996).

33 Bilgen Ö, Atici T, Durak K, Karaeminogullari O, Bilgen M: C-reactive protein values and erythrocyte sedimentation rates after total hip and total knee arthroplasty. *J. Int. Med. Res.* 29, 7–12 (2001).

34 Aalto K, Osterman K, Peltola H, Räsänen J: Changes in erythrocyte sedimentation rate and C-reactive protein after total hip arthroplasty. *Clin. Orthop. Relat. Res.* 184, 118–120 (1984).

35 Shih LY, Wu JJ, Tang DJ: Erythrocyte sedimentation rate and C-reactive protein values in patients with total hip arthroplasty. *Clin. Orthop.* 225, 238–246 (1987).

36 Larsson S, Thelander U, Friberg S: C-reactive protein (CRP) levels after elective orthopedic surgery. *Clin. Orthop.* 275, 237–242 (1992).

37 Choudhry RR, Rice RPO, Triffitt PD, Harper WM, Gregg PJ: Plasma viscosity and C-reactive protein after total hip and knee arthroplasty. *J. Bone Joint Surg. Br.* 74(4), 523–524 (1994).

38 Maury CPJ, Teppo AM, Raunio P: Control of acute phase serum amyloid A and C-reactive protein response: comparison of total placement of the hip and knee. *Eur. J. Clin. Invest.* 14, 323–328 (1984).

39 Richards NP, Elliott TS, Powell RJ: Can the rapid semi-quanitative estimation of serum C reactive protein be adaopted for the management of bacterial infection? *J. Clin. Pathol.* 38, 464–467 (1985).

40 Sanzen L, Carlsson AS: The diagnostic value of C-reactive protein in infected total hip arthroplasties. *J. Bone Joint Surg. Br.* 71(4), 638–641 (1989).

41 Carlsson AS: Erythrocyte sedimentation rate in infected and non-infected total hip arthroplasties. *Acta Orthop. Scand.* 49, 287–290 (1978).

42 Bjornsson GL, Thorsteinsson L, Gudmundsson KO, Jonsson H, Gudmundsson S, Gudbjornsson B: Inflammatory cytokines in relation to adrenal response following total hip replacement. *Scand. J. Immunol.* 65(1), 99–105 (2007).

43 Naito Y, Fukata J, Tominaga T *et al.*: Interluekin-6 stimulates the secretion of adrenocorticotropic hormone in conscious, freely moving rats. *Biochem. Bipohy. Res. Commun.* 155, 1459–1463 (1991).

44 Lyson K, Mccann SM: The effect of interleukin-6 on pituitary hormone release *in vivo* and *in vitro*. *Neuroendocrinology* 54, 262–266 (1991).

45 Harbuz MS, Stephanou A, Sarlis N, Lightman SL: The effects of recombinant human interleukin (IL)-1a, IL-1B or IL-6 on hypothalamo-pituitary-adrenal axis activation. *J. Endocrinol.* 133, 349–355 (1992).

46 Heinrich PC, Castell JV, Andus T: Interluekin-6 and the acute phase response. *Biochem. J.* 265, 621–636 (1990).

47 Schleimer RP: An overview of glucocorticoid anti-inflammatory actions. *Eur. J. Clin. Pharmacol.* 45(Suppl. 1), 3–7 (1993).

48 Boumpas DT, Chrousos GP, Wilder RL, Cupps TR, Balow JE: Glucocorticoid therapy for immune-mediated disease: basic and clinical correlates. *Ann. Intern. Med.* 119, 1198–1208 (1993).

49 Calcagni E, Elenkov I: Stress system activity, innate and T helper cytokines, and susceptibility to immune-related diseases. *Ann. NY Acad. Sci.* 1069, 62–76 (2006).

50 Bastian D, Tambursteun MV, Lyngstadaas SP, Reikerås O: Systemic and local cytokine kinetics after total hip replacement surgery. *Eur. Surg. Res.* 41, 334–340 (2008).

▪▪ **Excellent study that demonstrates elevated IL-6 and IL-8 after total hip arthroplasty, while being the first study to show these changes were significantly pronounced at the local level.**

51 Bastian D, Shegarfi H, Rolstad B, Naper C, Lyngstadaas SP, Reikeras O: Investigation of lipolysacchride receptor expression on human moncytes after major orthopedic surgery. *Eur. Surg. Res.* 40, 239–245 (2007).

52 Bondeson J, Blom AB, Wainwright S, Hughes C, Caterson B, Van Den Berg WB: The role of synovial macrophages and macrophage-produced mediators in driving inflammatory and destructive responses in osteoarthritis. *Arthritis Rhuem.* 62, 647–657 (2010).

53 Rojas-Rodrigeuz J, Escobar-Linares L, Garcia-Carrasco M, Escárcega RO, Fuentes-Alexandro S, Zamora-Ustaran A: The relationship between metabolic syndrome and energy utilization deficit in the pathogensis of obesity-induced osteoarthritis. *Med. Hypotheses* 69, 860–868 (2007).

54 Gustafson B: Adipose tissue, inflammation and artherscerosis. *J. Atheroscler. Thromb.* 17, 1–10 (2010).

55 Kirilmaz B, Asgun F, Alioglu E *et al.*: High inflammatory activity related to the number of metabolic syndrome components. *J. Clin. Hypertens. (Greenwich)* 12, 136–144 (2010).

56 Baigrie RJ, Lamont PM, Kwiatkowski D, Dallman MJ, Morris PJ: Systemic cytokine response after major surgery. *Br. J. Surg.* 79, 757–760 (1992).

57 Clementsen T, Krohn CD, Reikerås O: Systemic and local cytokine patterns during total hip surgery. *Scand. J. Clin. Lab. Invest.* 66(6), 535–542 (2006).

58 Mountziaris PM, Mikos AG: Modulation of the inflammatory response for enhanced bone tissue regeneration. *Tissue Eng. B Rev.* 14(2), 179–186 (2008).

▪▪ **Very interesting article that discusses how novel tissue engineering strategies aimed at improving bone healing after fracture are attempting to exploit the context and time dependent activity of inflammatory markers in an effort to control inflammation and promote regenerative pathways.**

59 Miller RR, Cappol AR, Shardell MD *et al.*: Persistent changes in interleukin-6 and lower extremity function following hip fracture. *J. Gerontol. A Biol. Sci. Med. Sci.* 61, 1053 (2006).

60 Pape HC, Schmidt RE, Rice J *et al.*: Biochemical changesafter trauma and skeletal surgery of the lower extremity: quantification of the operative burden. *Crit. Care. Med.* 28 3441–3448 (2000).

61 Roumen RM, Hendriks T, Van Der Ven-Jongekrijg J *et al.*: Cytokine patterns in patients after major vascular surgery, hemorrhagic shock, and severe blunt trauma: relation with subsequent adult respiratory distress syndrome and multiple organ failure. *Ann. Surg.* 218, 769–776 (1993).

62 Hall GM, Peerbhoy D, Shenkin A, Parker CJ, Salmon P: Relationship of the functional recovery after hip arthroplasty to the neuroendocrine and inflammatory responses. *Br. J. Anaseth.* 87, 537–542 (2001).

63 Bunescu A, Widman J, Lenkei R, Menyes P, Levin K, Egberg N: Increases in circulating levels of monctye-platelet and neutrophil-platelet complexes following hip arthroplasty. *Clin. Sci. (Lond)* 102, 279–286 (2002).

64 Hodge G, Hodge S, Reynolds PN *et al.*: Up-regulation of interleukin-8, interleukin-10, monocyte chemotactic protein-1, and mooncyte chemotactic protein-2 in peripheral blood monocytes in stable lung transplant recipients are immunosuppreession regimens working. *Transplantation* 79, 287–291 (2005).

65 Wirtz DC, Heller KD, Miltner O, Zilkens KW, Wolff JM: Interleukin-6: a potential inflammatory marker after total joint replacement. *Int. Orthop.* 24, 194–196 (2000).

66 Van Deuren M, Twicklet TB, De Waal Malefyt MC *et al.*: Elective orthopedic surgery: a model for the study of cytokine activation and regulation. *Cytokine* 10, 897–903 (1998).

67 Arnold JP, Haeger M, Bengtson JP, Bengtsson A, Lisander B: Release of inflammatory mediators in association with collection of wound drainage blood during orthopedic surgery. *Anaesth. Intensive Care* 23, 683–686 (1998).

▪ **Excellent study that examines the profile of 25 cytokines post-total hip arthroplasty and adds to the most recent literature regarding IL-6, C-reactive protein, TNF-α and IL-1β reponses after hip surgery.**

68 Krohn Cd RO, Mollnes TE, Aasen AO: Complement activation and release of interleukin-6 and tumor necrosis factor-α in drained and systemic blood after major orthopedic surgery. *Eur. J. Sug.* 164, 103–108 (1998).

69 Shah K, Mohammed A, Patil S, Mcfadyen A, Meek RMD: Circulating cytokines after hip and knee arthroplasty: a preliminary study. *Clin. Orthop. Relat. Res.* 467(4), 946–951 (2008).

70 Hogevold HE, Lyberg T, Kahler H *et al.*: Changes in plasma IL-1b, TNF-a and IL-6 after total hip replacement in surgery in general or regional anasethesia. *Cytokine* 12, 1156–1159 (2000).

71 Mcgettrick HM, Lord JM, Wang KQ, Rainger GE, Buckley CD, Nash GBV: Chemokine and adhesion-dependent survival of neutrophils after transmigration through cytokine-stimulated endothellium. *J. Leukoc. Biol.* 79, 779–788 (2006).

72 Chaly YV, Selvan RS, Fegeding KV, Kolesnikova TS, Voitenok NN: Expression of *IL-8* gene in human monocytes and lymphocytes: differential regulation by TNF and IL-1. *Cytokine* 12, 636–643 (2000).

73 Giannoudis PV, Smith RM, Perry SL, Windsor AJ, Dickson RA, Bellamy MC: Immediate IL-10 expression following major orthopedic trauma: relationship to anti0inflammatory response and subsequent development of sepsis. *Intensive Care Med.* 26, 1076–1081 (2000).

74 Lyons A, Kelly JL, Rodrick ML, Mannick JA, Lederer JA: Major injury induces increased production of interleukin-19 by cells of the immune ssstem with negative impact on resistance to infection. *Ann. Surg.* 226, 450–458 (1997).

75 Brune IB, Wilke W, Hensler T, Holzmann B, Siewert JR: Downregualtion of T helper type 1 immune response and altered pro-inflammatory and anti-inflammatory T cell cytokine balance following conventional but not laparoscopic surgery. *Am. J. Surg.* 177, 55–60 (1999).

76 Hensler T, Hecker H, Heeg K *et al.*: Distinct mechanisms of immunosuppression as a consequence of major surgery. *Infect. Immun.* 65, 2283–2291 (1997).

77 Neidhardt R, Keel M, Steckholzer U *et al.*: Relationship of interleukin-10 plasma levels to severity of injury and clinical outcome in injured patients. *J. Trauma* 42, 863–871 (1997).

78 Tilg H, Dinarello CA, Mier JW: IL-6 and APPS: anti-inflammatory and immunosuppressive mediators. *Immunol. Today* 18, 428–432 (1997).

79 Sheeran P, Hall GM: Cytokines in anasethesia. *Br. J. Anaseth.* 78, 201–219 (1997).

80 Tilg H, Trehu E, Atkins MB, Dinarello CA, Mier JW: Interleukin-6 (IL-6) as an anti inflammatory cytokine: induction of circulating IL-1 receptor antagonist and soluable tumor necrosis factor receptor P55. *Blood* 83, 11–118 (1994).

81 Lago F, Dieguez C, Gómez-Reino J, Gualillo O: Adipokines as emerging mediators of immune response and inflammation. *Nat. Clin. Pract. Rheumatol.* 3(12), 716–724 (2007).

▪▪ **Excellent review of adipokines and the role they play in inflammation.**

82 Tatemoto K, Hosoya M, Habata Y *et al.*: Isolation and characterization of novel endogenous peptide ligand for the human APJ receptor. *Biochem. Bipophys. Res. Commun.* 251, 471–476 (1998).

83 Ku JH, Lee CK, Joo BS *et al.*: Correlation of synovial fluid leptin concentrations with the severity of osteoarthritis. *Clin. Rheumatol.* 28(12), 1431–1435 (2009).

84 Baumann H, Morella KK, White DW *et al.*: The full length leptin receptor has signaling capabilities of interleukin-6 type cytokine receptors. *Proc. Natl. Acad. Sci. USA* 93, 8374–8378 (1996).

85 Dummond H, Presle N, Terlain B *et al.*: Evidence for a key role of leptin in osteoarthritis. *Arthritis Rheum.* 48, 3118–3129 (2003).

▪▪ **Excellent review of leptin's role in inflammation and metabolic disease, and its correlation to severity of osteoarthritis.**

86 Simopoulou T, Malizos K, Iliopoulos D *et al.*: Differential expression of leptin and leptin's receptor isoform (Ob-Rb) mRNA between advanced and minimally affected osteoarthritic cartilage; effect on cartilage metabolism. *Osteoarthritis Cartilage* 15(8), 872–883 (2007).

87 Figenschau Y, Knutsen G, Shahazeydi S, Johansen O, Sveinbjörnsson B: Human articular chondrocytes express functional leptin receptors. *Biochem. Biophy. Res. Commun.* 287 190–197 (2001).

88 Otero M, Lago R, Lago F, Reino JJ, Gualillo O: Signaling pathway involved in nitric oxide synthase type II activation in chondrocytes: synergistic effect of leptin with interleukin-1. *Arthritis Res. Ther.* 7, 581–591 (2005).

89 Stratton RJ, Dewit O, Crowe E, Jennings G, Villar RN, Elia M: Plasma leptin, energy intake and hunger following total hip replacement surgery. *Clin. Sci. (Lond)* 2, 113–117 (1993).

90 Tilg H, Moschen AR: Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nature Rev. Immunol.* 6, 772–783 (2006).

91 Gualillo O, Gonzalez-Jaunatey JR, Lago F: The merging role of adipokines as mediators of cardiovascular diseases: physiological and clinical perspectives. *Trends Cardiovasc. Med.* 17, 277–285 (2007).

92 Lago R, Gomez R, Otero M *et al.*: A new player in cartilage homeostasis: adiponectin induces nitric oxide synthase type II and pro-inflammatory cytokines in chondrocytes. *Osteoarthrits Cartilage* 16, 1101–1109 (2008).

93 Sandell LJ: Obesity and osteoarthritis: is leptin the link? *Arthritis Rheum.* 60(10), 2858–2860 (2009).

94 Gomez-Abellan P, Gomez-Santos C, Madrid JA *et al.*: Circadian expression of adiponectin and its receptors in human adipose tissue. *Endocrinology* 151(1), 115–122 (2009).

Websites

101 Canadian Institute for Health Information: Hip and Knee Replacements in Canada – Canadian Joint Replacement Registry (CJRR) 2008–2009 annual report. CIHI, Ottawa, ON, Canada (2009) http://secure.cihi.ca/cihiweb/products/2008_cjrr_annual_report_en.pdf

102 WHO. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. WHO, Geneva, Switzerland (1999) http://whqlibdoc.who.int/hq/1999/who_ncd_ncs_99.2.pdf