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ARTICLE

The impaired healing hypothesis: a mechanism by which psychosocial stress and personal characteristics increase MSD risk?

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ABSTRACT

While the effects of physical risk factors on MSD development have been a primary focus of musculoskeletal research, psychological stressors, and certain personal characteristics (e.g. ageing, sex, and obesity) are also associated with increased MSD risk. The psychological and personal characteristics listed above share a common characteristic: all are associated with disruption of the body's neuroendocrine and immune responses resulting in an impaired healing process. An impaired healing response may result in reduced fatigue life of musculoskeletal tissues due to a diminished ability to keep pace with accumulating damage (perhaps reparable under normal circumstances), and an increased vulnerability of damaged tissue to further trauma owing to the prolonged healing process. Research in engineered self-healing materials suggests that decreased healing kinetics in the presence of mechanical loading can substantially reduce the fatigue life of materials. A model of factors influencing damage accrual and healing will be presented.

Practitioner summary: This article provides a potential reason why musculoskeletal disorder risk is affected by psychosocial stress, age, sex, and obesity. The reason is that these factors are all associated with a slower than normal healing response. This may lead to faster damage development in musculoskeletal tissues resulting in higher MSD risk.

Abbreviations: BMI: bone mass index; HPA: hypothalamic-pituitary-adrenal; IGF: 1: insulin-like growth factor; MPa: megapascal; MSD: musculoskeletal disorder; Nf: number of cycles of stress or strain of a material before failure; NIOSH: national institute of occupational safety and health; SAM: sympathetic-adrenal-medullary; SNS: sympathetic nervous system

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Musculoskeletal disorders; fatigue failure; psychological stress; age; sex; obesity healing

I. Introduction

Musculoskeletal disorders (MSDs) are comprised of a variety of inflammatory and degenerative conditions in musculoskeletal tissues, which may involve muscles, tendons, ligaments, and peripheral nerves. They are prevalent in society and result in substantial direct and indirect costs for both individuals and industry (National Research Council – Institute of Medicine 2001; Punnett et al. 2005; Deeney & O'Sullivan, 2009; Global Burden of Disease Study 2013 Collaborators 2015; Global Burden of Disease 2018; Bevan 2015; Hoy et al. 2015; Huisstede et al. 2006 Bureau of Labor Statistics 2019,). The association of physical work risk factors and MSDs has been well-studied (e.g. NIOSH 1997; National Research Council – Institute of Medicine 2001), and include factors such as high force demands, repetitive work, adoption of non-neutral postures, and/or exposure to vibration (Bongers et al. 1993; Bongers, Kremer, and ter Laak 2002; Deeney & O'Sullivan, 2009; Hauke et al. 2011). Certain personal characteristics are consistently associated with the development of MSDs, including age, sex, and obesity (National Research Council – Institute of Medicine 2001). MSDs are also associated with psychosocial stress at work, such as high psychological job demands and low job control (Deeney & O'Sullivan, 2009; Davis and Heaney 2000). Yet, specific mechanisms associated with the increased risk of MSDs from psychological (or psychosocial) stressors and personal characteristics are less well understood than their physical counterparts (Deeney & O'Sullivan, 2009).

It is apparent that musculoskeletal tissues subjected to repeated stress experience tissue damage as the result of a fatigue failure process (e.g. Andarawis-Puri and Flatow 2011; Barbe et al. 2013; Brinckmann, Biggemann, and Hilweg 1988; Carter and Hayes 1976;

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Cyron and Hutton 1978; Fung et al. 2010; Gallagher and Heberger 2013; Gallagher et al. 2007; Schechtman and Bader 1997; Shepherd and Screen 2013; Sun et al., 2010; Weightman 1976). Fatigue failure is the mechanism by which all materials incur cumulative damage development when exposed to repeated stress (Stephens et al. 2001). Fatigue failure methods have long been employed to evaluate the fatigue life of engineering materials, such as metals, plastics, or composite materials. However, musculoskeletal tissues are also materials, and (like other materials) would also be expected to incur fatigue damage when subjected to repeated stress. Without exception, musculoskeletal tissues tested *in vitro* or *ex vivo* display a characteristic fatigue failure response when exposed to repeated stress (e.g. Brinckmann, Biggemann, and Hilweg 1988; Schechtman and Bader 1997; Thornton and Bailey 2013; Gallagher et al. 2007; Carter and Hayes 1976; Carter et al. 1981; Weightman 1976; Shepherd et al. 2012; Shepherd and Screen 2013). Results of *in vivo* animal studies examining the effects of repetitive loading on musculoskeletal tissues also report damage accumulation characteristic of a fatigue failure failure process (e.g. Barbe et al. 2013; Barbe et al. 2020; Andarawis-Puri and Flatow 2011; Fung et al. 2009, 2010; Sun, et al., 2010). A systematic review of MSD epidemiology studies allowing assessment of a force-repetition interaction found a consistent interaction pattern predicted by fatigue failure theory (Gallagher and Heberger 2013). Additionally, three recently developed fatigue failure-based risk assessment tools have demonstrated dose-response relationships between fatigue failure damage estimates and multiple low back, upper extremity and shoulder outcomes (Gallagher et al. 2017; Gallagher et al. 2018; Bani Hani et al. 2021). Thus, several lines of evidence support the notion that a fatigue failure process is aetiologically significant in the development of MSDs.

However, fatigue failure in musculoskeletal tissues differs from the fatigue failure process of inert materials (metals, plastics, etc.) due to the presence of a healing process that can help repair damage incurred. This healing capacity is clearly extremely important to musculoskeletal health. We will examine the impacts of both damage and healing in this modified" fatigue failure process below.

II. The importance of healing on musculoskeletal tissue fatigue life

The fatigue life of a material (often designated by N_f) is defined as "the number of cycles of stress or strain of a specified character that a given specimen sustains before failure of a specified nature occurs" (Stephens et al. 2001). Failure could be defined as the initiation of damage, damage reaching a specified size, or complete material failure, for example. In non-biological materials, fatigue life is dependent on two primary factors: the strength of the material and the load stress characteristics. However, biological tissues have an additional factor that likely to influence fatigue life: the ability to repair tissues damaged due to exposure to repeated stress. The healing process referred to here is defined as the classic model of wound healing which is divided into three sequential, yet overlapping, phases that occur in parallel with hemostasis: (1) inflammatory, (2) proliferative, and (3) remodelling (Gonzalez et al. 2016). Clearly, this repair capacity would be expected to extend the fatigue life of the tissue (as compared to the absence of such capacity).

A common finding from *in vitro* or *ex vivo* material testing of musculoskeletal tissues is that the fatigue life of tissues in these conditions appear to be much lower than that necessary to maintain the health of the material throughout one's lifetime. For example, in vitro tests on the human extensor digitorum longus indicated that at a stress level of 20 MPa (20% of ultimate tensile strength), the fatigue life of these tendons in vitro was about 300,000 cycles. This is the equivalent of approximately 4 months of normal walking activity (Schechtman and Bader 1997). Similar findings have been shown with other musculoskskeletal materials (e.g. Thornton and Bailey 2013; Shepherd and Screen 2013; Carter and Hayes 1976; Brinckmann, Biggemann, and Hilweg 1988; Gallagher et al. 2007). Clearly, there must be a reason for the considerable difference between the fatigue life obtained in vitro compared to that observed in vivo. There would appear to be four possible options for this: (1) loads on the tissues are much lower than we believe to be the case, (2) tissue strength in vivo is much greater than that in vitro, (3) the body's healing process substantially increases fatigue life, or (4) some combination of these factors. There is not much in the way of evidence that the first two options are the case. However, there is evidence to suggest that the presence of a healing process can substantially increase the fatigue life of a material.

But what happens if the fatigue-life extending healing process becomes disrupted? For example, suppose that there are factors present that slow down the healing process or that impact a portion of the process in a way that reduces the effectiveness of the healing mechanism. There are several reasons to

believe that an impaired healing process may have a deleterious effect on the fatigue life of a self-healing tissue. For example, the healing process of soft tissues generally involves the cleaning out of debris from the injured area through phagocytosis and will often be associated with the development of a notch or a groove in the tissue which is gradually filled in from the edges of the wound to the centre during the healing process (Gonzalez et al. 2016). It should be noted that the notched or indented shape of the debrided wound will result in a stress concentration and would be expected to be an area vulnerable to additional damage if exposed to sufficient repeated stress. Any process that delays the kinetics of the healing process would extend the period of increased vulnerability for the damaged tissue. This increased vulnerability would be expected to have a negative impact on the fatigue life of the healing tissue.

Thus, it would appear fatigue life of a tissue can be influenced by cumulative damage development due to both the traditional fatigue failure process (i.e. increased damage kinetics), but may also be influenced by the kinetics of the repair process. Things that would enhance fatigue life would include avoiding stressful, repetitive loading and/or a more rapid healing process. Factors that would reduce tissue fatigue life would include increased damage kinetics (higher stress and increased repetition) and/or decreased healing kinetics (e.g. an impaired healing response). The fact that these two processes can each influence the fatigue life of musculoskeletal materials suggests that both should be taken into consideration when evaluating MSD risk due to fatigue damage.

The fact that the tissue remodelling and repair processes are constantly at work in the body suggests a potential reason why fatigue life may be extended to such a remarkable degree in musculoskeletal tissues. Through this constant process it would be expected that relatively small areas of damage could be repaired rather quickly. Repair early in the fatigue failure process can be very effective at reducing the chances of significant damage accumulation (Stephens et al. 2001; Jones et al. 2007; Maiti et al. 2006). Thus, the turnover of old collagen with new and repair of early microfailures would be expected to lead to significant life extension of these materials. However, the greater the rate of cumulative damage, the more difficult it would be for the healing process to keep pace with damage development.

Unfortunately, we know little regarding the relationship of these competing processes. However, maintenance of musculoskeletal health must involve a dynamic balance between the amount of damage accrual due to fatigue loading versus the amount of healing that can be achieved over a given timeframe (Nash 1966). Disruption of this balance by either process (or both) will increase MSD risk. Excessive fatigue loading would increase the rate of damage development and may exceed the normal rate of damage repair (Gallagher and Schall 2017). On the other side of the ledger, factors that negatively impact repair kinetics would also enhance damage development and reduce fatigue life (Godbout and Glaser 2006; Gouin and Kiecolt-Glaser 2011; Guo and DiPietro 2010), such as from factors related to psychological stress, ageing, sex, and obesity, as discussed below. An impaired healing capacity could mean, for example, that damage previously repairable by a normal (unimpaired) healing process might instead accumulate (Gallagher and Schall 2017). An impaired healing response may also extend the time period during which a healing tissue, weakened by damage and experiencing a stress concentration in the injured area, would remain vulnerable to the development of additional damage.

III. Psychological (psychosocial) stress and MSDs

Commonly cited MSD risk factors associated with psychosocial stress include high psychological job demands, low job control, monotonous work, and low social support for the worker in the workplace (Deeney & O'Sullivan, 2009; Davis and Heaney 2000). Job demands include work that is performed under time pressure, work pressure, and/or with low workload variability (NIOSH 1997). High psychological job demands, or emotionally demanding work have been associated with increased risk of upper extremity MSD complaints in several studies (Smith et al. 2006; Van Den Heuvel et al. 2005; Bernard, Sauter, Fine, Petersen, and Hales 1994; Nicolakakis et al. 2017). Low worker job control has also been associated with increased MSD symptoms in the upper extremities (Bernard, Sauter, Fine, Petersen, and Hales 1994; Hales et al. 1994; Lagerström, Wenemark, Hagberg, and Wigaeus Hjelm, 1995). Jobs that are associated with tedium and little variety are considered monotonous work. Research has demonstrated a relationship between monotonous work and MSDs, including of the neck and shoulder (Harkness et al. 2003; Ryan and Bampton 1988; Johansson et al. 1993). Finally, social support at work is generally defined as how an individual draws support from interpersonal interactions. Examples of low social support at work includes low recognition at

work, a lack of promotion prospects, poor support from co-workers and supervisors, hostility at work, and harassment. Low social support has been associated with neck and shoulder MSDs (Aasa et al. 2005) and back pain (Skov, Borg, and Orhede 1996; Nicolakakis et al. 2017).

Several theories have been put forth to explain the links between psychosocial factors and MSDs. These include the Biopsychosocial model (Engel 1977), Hyperventilation theory (Schleifer, Ley, and Spalding 2002), the Migraine theory (Knardahl 2002), the Muscle Spindle theory (Johansson and Sojka 1991), the Cinderella hypothesis (Hagg 1991), and the Nitric Oxide/Oxygen Ratio hypothesis (Eriksen 2004). Most of these theories concentrate on effects such as increased muscle tension and pain (Johansson and Sojka 1991), decreased blood flow, factors inhibiting the repair of muscle tissue, and prolonged activation of low-threshold motor units (Hauke et al. 2011). While most of these explanations primarily focus on possible psychosocial effects on muscle physiology (Deeney & O'Sullivan 2009; Hauke et al. 2011), psychosocial factors have also been associated with a number of MSDs involving tendon damage, damage to other musculoskeletal tissues, and/or peripheral nerves (e.g. lateral/medial epicondylitis, low back pain, and carpal tunnel syndrome) (Bugajska et al. 2013; Thiese et al. 2020).

Another theory that has been increasingly used to understand how psychological stressors lead to pathophysiological responses in workers is Allostatic Load (i.e. the cost of maintaining Allostasis), proposed by McEwen in 1998 (McEwan 1998). Allostasis (literally "maintaining stability, or homeostasis, through change") refers the process of adaptation of an organism to acute stress across all biological systems, as a means to restore homeostasis after a challenge (McEwen 2000). Biological systems promote and coordinate adaptation using systemic mediators (cortisol, sympathetic and parasympathetic mediators, pro- and anti-inflammatory cytokines, metabolic mediators, and hormones), via a non-linear network in which each mediator regulates other mediators, often in a reciprocal fashion, with the brain typically coordinating these efforts (Karatsoreos and McEwen 2011; Sterling 2012). While adaptive acutely, chronic overactivity of a system, such as, cardiovascular, metabolic, immune, hypothalamus-pituitary-adrenal (HPA) axis, sympathetic-adrenal-medullary (SAM) system, and cognitive centres of the brain, in response to chronic or severe stressors (McEwen 1998; Karatsoreos and McEwen 2011) can induce a domino effect on the interconnected systems, leading one or more to overcompensate or become dysregulated, and can lead to the eventual disruption of a system, leaving the organism open to stress-related diseases (McEwen and Gianaros 2011; Juster, McEwen, and Lupien 2010). For example, pro-inflammatory cytokines released from injured cells or macrophages can enter the blood stream and become systemic. This can stimulate production of corticosteroids by the brain that then, in turn, reduce inflammatory cytokine production, as seen in Figure 1. Sympathetic and parasympathetic nervous systems (fight or flight systems) exert differential effects on pro-inflammatory cytokines, with the former stimulating production and the latter inhibiting them. When these responses are unbalanced, appropriate inflammatory responses may be inhibited, or vice versa. Allostatic Load is the accumulated burden ("wear and tear") on the brain and other systems from trying to re-establish allostasis after exposure to repeated or chronic stressors (McEwen 1998; McEwen 2000), while Allostatic Overload occurs when the demands of the stressor exceed the body's ability to repeatedly adapt, leading to disordered and diseased endpoints (Juster, McEwen, and Lupien 2010). In the current context, an allostatic overload due to psychological stress may result in a diminished healing capacity, which when paired with the physical process of tissue damage (fatigue failure) may result in increased MSD risk. The following sections will examine the effects of psychological stress and certain personal characteristics on healing kinetics and how these factors might influence the development of MSDs.

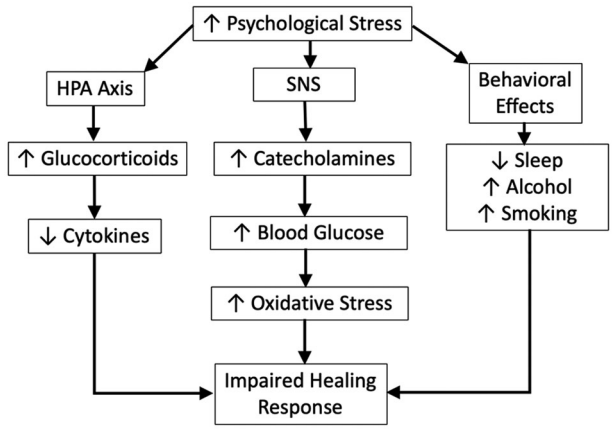

Figure 1. Mechanisms associated with the impaired healing response resulting from psychological stress.

IV. Psychological (psychosocial) stress and healing

The model provided in Figure 1 suggests possible mechanisms by which psychosocial stress may directly

impact the development of MSDs through changes in healing responses. Specifically, psychological stress is known to negatively impact the healing of tissues through well-established mechanisms (Chrousos and Gold 1992; Guo and DiPietro 2010). These mechanisms involve the secretion of various glucocorticoids and catecholamines (e.g. norepinephrine and epinephrine) that inhibit the healing response, as well as reducing sleep time and quality (also known to negatively impact healing). Certain unhealthy behaviours can lead to additional mechanisms that reduce the effectiveness of healing (such as smoking and alcohol use) (Guo and DiPietro 2010).

Psychological stress has been shown in many studies to have a significant impact in terms of inhibiting the healing response of tissues (Godbout and Glaser 2006; Chrousos and Gold 1992). This has been demonstrated in both animal and human studies. For example, one study found that students facing examination stress during the academic year demonstrated a 40% increase in the time it took to heal a 3.5 mm biopsy punch wound on the hard palate compared to an identical wound placed on the contralateral side during a period of vacation (Marucha, Kiecolt-Glaser, and Favagehi 1998). All 11 subjects demonstrated a slowed healing response under stress and averaged a 3-day increase in the time to heal. In other research, caregivers operating in stressful situations demonstrated a similar response (Kiecolt-Glaser et al. 1995). Compared with controls, stressed caregivers experienced wound healing averaging 9 days longer (48 versus 39 days). Similarly, individuals living in hostile marital relationships showed a 60% decrease in the rate of wound healing, which was associated with a decrease in IL-1beta, IL-6 and TNF-alpha levels at the wound site (Kiecolt-Glaser et al. 2005).

A systematic review and meta-analysis examined psychological stress and wound healing in humans (Walburn et al. 2009). Of 22 studies accepted for inclusion in the review, 17 found that psychological stress was associated with impaired wound healing or dysregulation of biomarkers associated with wound healing across a variety of experimentally induced wounds and different conceptualizations of psychological stressors. Results of the meta-analysis (involving 12 studies) demonstrated a pooled effect size of $r = -0.42$ (95% CI $= -0.51, -0.32$), indicating that greater levels of psychological stress are associated with impaired wound healing.

The delay in healing resulting from stress is partly due to the HPA axis secretion of glucocorticoid hormones. A significant impact of GC compounds is the decreased proliferation and differentiation of immune cells, along with a decrease in gene transcription, and reduce cell adhesion activity vital in the immune healing response (Sternberg 2006). One potent glucocorticoid (cortisol) acts as a strong anti-inflammatory agent which counters the immune responses involved in the initial phase of healing (Guo and DiPietro 2010). In this manner, psychological stress can impair the initiation of a normal healing response, resulting in a significant delay in the healing process.

Many of the studies on impaired healing due to psychological stress have dealt with healing of skin or mucosal biopsies. However, it is well-documented that glucocorticoids (such as those secreted as a result of psychological stress) decrease proinflammatory cytokine response in tendons and impair local collagen synthesis (Gouin and Kiecolt-Glaser 2011). This can lead to tendon atrophy, reduction of tensile strength and decreased load to failure (Balasubramaniam and Prathap 1972; Dean et al. 2014). A systematic review of the effects of local glucocorticoid administration as a treatment for tendinopathy showed mostly detrimental effects (Dean et al. 2014). Local glucocorticoid administration reduced collagen synthesis in tendon, and was associated with collagen disorganisation and necrosis, all of which adversely affected mechanical properties (including yield stress, yield load and stiffness) (Dean et al. 2014). This in turn may lead to the development of increased damage accumulation with loading. It may be noted that some research has shown a beneficial healing effect of systemically delivered steroids; however, it appears that this result is dependent on the timing of the administration (it is most effective when administered during the early inflammatory stage) (Blomgran, Hammerman, and Aspenberg 2017). Unfortunately, the cortisol response to psychosocial stress is not likely to be so carefully timed.

In addition to the effects of stress on glucocorticoids, psychological stress is also known to adversely impact various behavioural mechanisms that can impair healing, including disturbed sleep, alcohol use, and smoking. Sleep is considered important in the healing process of tissues due in part to the bolus of growth factors secreted during deep sleep (Veldhuis and Iranmanesh 1996). Disturbed sleep has been shown to negatively impact skin wound healing (Altemus, Rao, Dhabar, Ding, and Granstein 2001; Guo and DiPietro 2010) as well as muscle repair (Schwarz et al. 2013). This may be because disturbed sleep results in elevated serum and tissue levels of glucocorticoids (Guo and DiPietro 2010). In addition,

psychological stress is associated with unhealthy habits, such as increased alcohol use, cigarette smoking, and use of other drugs that can affect healing (Guo and DiPietro 2010). Heavy alcohol use is associated with decreased cell migration and collagen deposition at the wound site, leading to an impaired healing response (Benveniste and Thut 1981), similar to smoking (Silverstein 1992).

Finally, increased catecholamine production, another by-product of psychological stress, is also thought to play a role in inhibiting the rate of wound healing. Studies in mice exposed to various psychological stress modalities have shown that treatment with adrenergic receptor antagonists attenuate the stress-induced impairment of wound healing (Gouin and Kiecolt-Glaser 2011). These results suggest that catecholamines may play a role in slowing the healing response due to psychological stress (Gouin and Kiecolt-Glaser 2011).

In summary, there is a substantial amount of research suggesting that increased psychological stress disrupts the body's healing process, and results in an extended healing process. This would be expected to decrease the fatigue life of musculoskeletal tissues injured due to repeated stress. However, there are several personal characteristics that may also lead to an impaired healing response, which will be discussed in the following section.

V. Effects of personal characteristics on wound healing

V.1. Age

It is commonly recognised that individuals of increased age have a healing response that takes significantly longer than individuals of a younger age (Guo and DiPietro 2010). However, while the healing process takes longer, in healthy aged individuals, the quality of healing is not necessarily impaired (Gosain and DiPietro 2004). The extended wound healing time appears to be due in part to a delayed inflammatory response (Figure 2). For example, some of the altered wound healing activity in peripheral tissues includes changes in the inflammatory phase, such as, reduced vascular permeability, reduced macrophage infiltration and function, delayed T-cell infiltration, increased pro-inflammatory cytokine and chemokine production, and reduced growth factor production (Swift et al. 2001). The proliferative and remodelling phases are also affected by age-related changes, including slower collagen deposition and decreased remodelling (Figure 2) (Guo and DiPietro 2010). At the end of the process, decreased wound strength will often result (Gosain and DiPietro 2004).

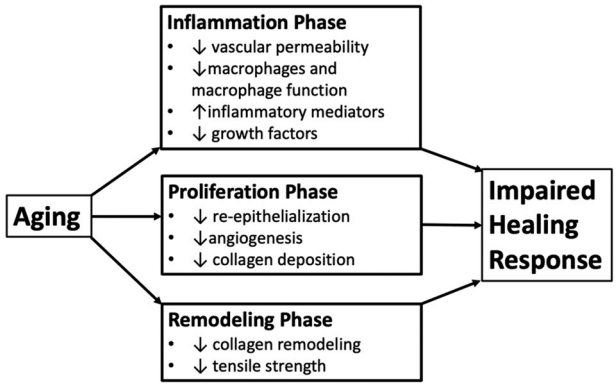

Figure 2. Effect of ageing on the healing process (Toy 2005).

V.2. Sex

The rate of collagen synthesis is a critical factor in the healing of musculoskeletal tissues. Research over the past two decades has demonstrated that a sex difference exists with respect to the rate of collagen synthesis between males and females, with decreased collagen synthesis in the latter (Kjaer et al. 2009). Females have a lower rate of basal collagen synthesis compared to males and demonstrate a decreased collagen synthesis rate compared to males after exposure to exercise (Miller et al. 2006a, 2006b). This decreased collagen synthesis rate has been linked with oestrogen levels, as varying levels of oestradiol (one of the three oestrogen hormones produced by the body) have been associated with a diminished rate of collagen synthesis in females (Hansen et al. 2008). These findings are supported by *in vitro* studies in which oestradiol receptors have been identified in ligaments (Sciore, Frank, and Hart 1998), and that oestradiol itself can inhibit collagen synthesis in ligaments and tendons (Liu et al. 1996; Yu et al. 2001). The influence of oestradiol levels on collagen synthesis may not be direct but instead be the result of the effect that oestradiol has on circulating insulin-like growth factor (IGF-I), a substance directly related with the rate of collagen synthesis (Kjaer et al. 2009).

V.3. Obesity

Health issues associated with obesity are numerous, and include increased risk of type II diabetes, heart disease, high blood pressure, stroke, sleep apnoea, and respiratory problems (Guo and DiPietro 2010). In addition to these health problems, obese individuals demonstrate an impaired wound healing capability,

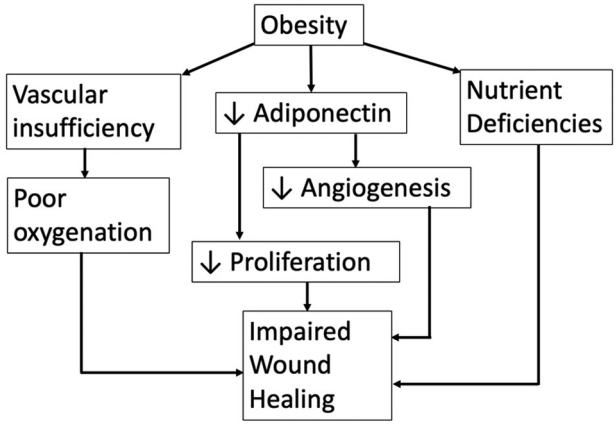

Figure 3. Pathways to impaired wound healing due to obesity.

along with an increased number of complications during the wound healing process (Guo and DiPietro 2010). Many of these problems stem from a decrease in blood perfusion and resultant ischaemia in adipose tissue. The same tension that causes a wound to experience dehiscence (bursting open) may also contribute to reduced perfusion at the wound site, leading to decreased delivery of oxygen and reducing availability of biochemical compounds necessary to heal the wound (Anaya and Dellinger 2006; Wilson and Clark 2004).

Type II Diabetes is strongly associated with obesity and can negatively impact healing kinetics to a great degree (Brem and Tomic-Canic 2007; Lin et al. 2017). Hypoxia is often observed in diabetic wounds and can prolong the injury healing time of wounds by increasing the levels of oxygen radicals in diabetics (Guo and DiPietro 2010). A decrease in the amount of angiogenesis is also commonly observed in diabetics (Brem and Tomic-Canic 2007). The neuropathy attendant to diabetes probably also increases wound healing times (Guo and DiPietro 2010). Tendinopathy, tendon ruptures, and impaired tendon healing are all more prevalent among those with diabetes (Maffulli et al. 2011). High blood glucose levels appear to inhibit proliferation of tendon derived stem cells and increase the rate of cell apoptosis (Lin et al. 2017). Thus, healing of tendons appears to be significantly delayed in a hyperglycaemic environment (Lin et al. 2017). Figure 3 shows some of the factors that may lead to impaired wound healing in obesity (Guo and DiPietro 2010).

VI. The impact of healing rate on tissue fatigue life

The evidence presented above suggests that there are several mechanisms that may lead to an impaired healing response when exposed to psychological stress, ageing, sex, and/or obesity. Certainly, combinations of these factors may have additive or multiplicative effects in this regard. The question that arises is, "What happens when a biological tissue (exposed to repeated loading and damage accrual) experiences a decrease in healing kinetics?" Unfortunately, the relationship of damage accumulation to healing is exceedingly difficult to ascertain in vivo. In a search of the literature, we found no research that assessed concurrent fatigue damage development and healing rates in musculoskeletal tissues.

However, there is some data that may be relevant to this question from the field of engineered self-healing materials. These are materials that have been inspired by (and designed to mimic) the healing process of biological materials and provide a method of repairing damage accumulated in the material due to fatigue failure. Such studies can provide some insight (clearly with caveats) into the benefits of having a self-healing process on material fatigue life, as well as how the degree of benefit may vary as the result of the rate at which healing occurs.

A fascinating study by Jones and colleagues (2007) provides data on the extension of fatigue life provided by three different rates of healing in a self-healing viscoelastic polymer. When the material experienced damage (crack formation), microcapsules containing dicyclopentadiene (DCPD) would rupture and fill the crack. This compound was then acted upon by one of three catalyst treatments (each catalyst having different healing rates). The slowest healing treatment used the catalyst as received, the moderate healing condition used the catalyst but in recrystalised form, and the fastest healing process use the catalyst in a freeze-dried state. All specimens were loaded identically using a K_{max} of 0676 MPa/m^2, $R = 0.1$ and a loading frequency of 5 Hz.

Results of this study demonstrated that the presence of a self-healing process significantly increased fatigue life of the material compared to the control condition (which had no healing capability), even when healing kinetics were relatively slow. Compared with the control condition, the condition with slow healing kinetics exhibited a fatigue life extension of approximately 17 times that of the control condition (1.5 million versus 86,000 cycles). The life extension multipliers of the moderate and fast healing kinetics conditions were 25 (2.2 million cycles) and 32 (2.8 million cycles) times the fatigue life of the control condition, respectively. These data suggest that the ability

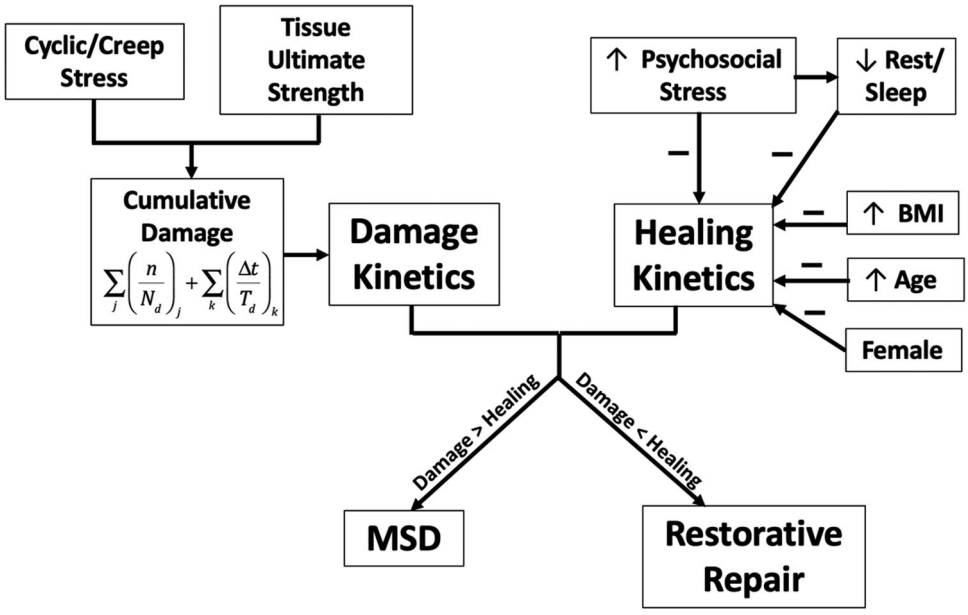

Figure 4. An individual-level model of the relationship of damage versus healing kinetics and selected MSD risk factors. In the cumulative damage box, the first term refers to tissue damage resulting from cyclic loading (fatigue damage), while the second term represents tissue damage due to static loading (creep damage).

of a material to self-heal can confer impressive benefits in terms of extending a material's fatigue life.

However, these data also demonstrate that the degree to which material fatigue life is extended is highly dependent on the rate of healing. In this example, the slowest healing process exhibited a fatigue life extension that was only 54% that of the fast-healing condition. Moderate healing kinetics demonstrated about 80% of the fatigue life extension compared to the fast-healing condition (Jones et al. 2007). Thus, a dose-response relationship was observed between the rate of healing and the degree to which fatigue life was extended in this self-healing material.

The fatigue life of musculoskeletal tissues may be primarily a function of three parameters: the strength of the material, the load to which it is exposed, and the rate at which damage can be healed. Our "Impaired Healing" hypothesis deals with factors that negatively impact the healing process (psychological stress, ageing, sex, and obesity), while the fatigue failure process explains the development of cumulative loading due to repeated stress. It is the combination of these two processes that are expected to control the fatigue life of musculoskeletal tissues, according to this model. Changes in any of the parameters above may have a significant impact on musculoskeletal health.

In prior models of the effects of psychosocial stress, emphasis has generally been placed on the loading (damage development) side of the equation, but there are certainly indications that psychological stress may play a very influential role in healing kinetics, and this may be a significant reason for the relationship observed between psychological stress and increased MSD prevalence and incidence. In fact, our sense from the literature is that the impact psychological stress has on healing might have a greater impact on the MSD development than the increases in loading that may accrue from such stress. However, it may well be that psychological stress has an influence on both damage accrual and impaired healing.

As discussed earlier, however, it is not just psychological stress that can negatively affect the healing process. Personal characteristics such as age, sex, and obesity are known to influence the healing process. Figure 4 provides an overall model of this relationship, incorporating both cumulative damage development (left side) and factors impairing the healing process (right side) on MSD development. In this model, we will talk in terms of the kinetics of damage development and healing. If the damage kinetics are lower than the healing kinetics, this would be expected to lead to a restorative repair of the musculoskeletal tissue. However, if damage kinetics exceed the healing kinetics, damage will accumulate in the tissue and this accumulation will continue if repeated stress is experienced, leading to development of an MSD (acute injuries are not included in this model). Damage kinetics are primarily the result of repeated stress (which may include a combination of cyclic and creep loading)

experienced by the tissues and the resultant process of fatigue. The higher the rate of cumulative damage, the greater the risk that damage may exceed the healing capacity. Healing kinetics can be positively influenced by factors such as good quality sleep and exercise (not shown in the model). However, the focus of this article is that psychological stress, ageing, obesity, and certain disease states (such as diabetes) can negatively impact healing rates. Obviously, lower rates of fatigue damage and a higher rates of healing kinetics are the most desirable condition and would lead to restorative repair of the damage incurred. However, all too often, the damage kinetics exceed the healing capacity, potentially leading to accumulating damage in the tissues and development of MSDs. When examining the model in Figure 4, it should be kept in mind that physiological pathways to impaired healing due to psychological stress, age, and obesity have been previously provided in Figures 1–3, respectively.

Because the processes of damage development and healing are generally hidden from view (much occurs at the microscopic level), the damage/repair relationship in biological tissues is not easily measured, and much remains to be understood. Many important questions need to be answered. For example, a common finding when performing fatigue failure tests of musculoskeletal tissues in vitro is that the number of cycles to failure (even at lower levels of stress) is much smaller than the materials are known to last during a lifetime (Schechtman and Bader 1997; Brinckmann, Biggemann, and Hilweg 1988; Thornton and Bailey 2013). Certainly, the presence of a healing process would be expected to confer some benefit in this regard, but how much? Another question is: to what degree is rest helpful to the healing process? These and many other factors are poorly understood and require additional research.

VIII. Discussion

Our "Impaired Healing Hypothesis" suggests that in addition to physical loading factors, MSDs may also be due (in part) to an impaired healing response resulting from factors such as psychosocial stress, age, sex, and/or obesity. This model has some attendant limitations which should be noted. For example, it is currently difficult to measure healing rates of musculoskeletal tissues in the living state. It is much easier to observe and measure the healing rate of skin or mucosal wounds, and this is undoubtedly the reason why most the research on the effects of psychosocial stress on wound healing has focussed on these tissues (Guo and DiPietro 2010). However, there are certainly research methods that may be employed to assess this hypothesis. For example, animal models that could control fatigue (and/or creep) loading on musculoskeletal tissues and control factors such as psychological stress, obesity, sex, and/or age could observe the effects on the fatigue life of tissues. There may be epidemiological methods that could be employed to examine these relationships as well.

While engineered self-healing materials discussed above were inspired by the biological healing process, there are clearly differences in the healing processes between the biological healing process versus the engineered variety. Notably, the engineered healing procedure is more rapid than the biological one. However, the biological process of remodelling tissues, though slow, is continuously at work helping to adapt the musculoskeletal system to the mechanical loads being experienced. There are reasons to believe that slow and steady remodelling could have a very substantial benefit on the fatigue life of tissues (through repair of damaged tissues prior to or early in the fatigue process). Nonetheless, the general trends observed regarding the benefits of a healing process (versus none) in extending fatigue life and the effects of different healing rates would seem to be perfectly in line with what would be anticipated in biological tissues. That is, one would expect a material that self-repairs would have increased fatigue life and that the faster the healing kinetics, the greater the anticipated benefit to material fatigue life (or vice versa).

In this paper, we have focussed on fatigue failure theory as it is well-supported in the literature and is considered "the predominant hypothesis for the development of overuse injuries" (Zitnay et al. 2020). A primary benefit of this approach is that the effects of damage development and healing can both be easily incorporated using this model. Like all models, however, there may be certain individual factors that might influence the development of MSDs that have not been incorporated. Nonetheless, we believe that the model we present here provides a useful perspective regarding factors important in influencing musculoskeletal health.

The rate of damage accumulation and the rate of healing are clearly both important determinants of MSD health. In the ergonomics literature, much greater emphasis has been put on the former compared to the latter. However, when we look at factors apart from those on the physical loading side (i.e. repeated stress), we find that those most associated with MSDs (psychological factors, older age, female

sex, and obesity) are all factors that exhibit a reduced rate of healing. Fatigue failure techniques can help us quantify the cumulative damage associated with application of repeated stress; however, the healing side of the equation may be equally as important but less well understood. A clearer understanding of the interplay between the rate of damage accumulation and the rate of healing would appear to be one of the more important research goals in the field of musculoskeletal disorders. Without a clearer picture of the interaction of these two factors, our understanding of the development of MSDs will remain unacceptably deficient.

IX. Conclusion

The fatigue life of musculoskeletal tissues is a function of tissue strength, the stress magnitude and repetition of the loading experienced, and the ability of the healing process to renew or restore damaged tissue. Much research has focussed on the physical loading aspects of this equation; however, the remodelling/healing processes are also an important aspect of musculoskeletal health and deserve increased attention. Several well-established MSD risk factors such as psychological stress, increasing age, being female, and obesity are known to negatively impact the healing process, which would be expected to reduce fatigue life and increase MSD risk. High levels of fatigue loading in conjunction with factors that impair the healing response would be anticipated to substantially elevate MSD risk. The fatigue failure model is well-positioned to incorporate healing due to its focus on cumulative damage development, as healing would simply account for a decrease (or impaired healing an increase) in cumulative damage development. Unfortunately, our current understanding of the interaction between damage accumulation and healing in musculoskeletal tissues is lacking and would greatly benefit from targeted research.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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