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REVIEW

Exercise, illness and drug use: guiding principles for approaching a complex triad

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Introduction and background

Regular, low to moderate intensity exercise is considered beneficial to the human body, not only having ergogenic advantages, but also being anti-inflammatory, cardio- and neuroprotective.[1] On the other hand, although high intensity training (HIT) is able to exaggerate cardiac conditions, e.g., hypertension[2] as well as exacerbate inflammatory and oxidative stress responses,[1,3] such exercise programs are becoming more popular as they too have shown demonstrable health benefits if performed appropriately. Indeed, various studies have reported on the superior beneficial cardiac and vascular effects of high intensity exercise programs over that of moderate intensity continuous training (MICT),[4-7] contributing to the growing popularity of such time-efficient programs. As such, exercise can accurately be described as a double-edged sword – able to induce positive, beneficial physiological effects when performed chronically at lower intensities, but generating harmful effects when performed at high intensities without sufficient recovery periods. From a toxicological point of view, exercise mediates hormesis, i.e., the biphasic dose response to an environmental agent characterised by a low dose stimulation or beneficial effect and a high dose inhibitory or toxic effect.[8]

Clinical illness on the other hand, most notably those conditions that are associated with significant peripheral inflammation and interfering with cardiovascular, pulmonary, and skeletal muscle function, generally reduce the maximum exercise capacity of individuals.[9] As clinicians and pharmacists are often confronted with questions related to uncertainties of whether patients may or may not exercise while being ill – here we will refer to illness as those *acute* conditions that transpire in most individuals over time, e.g., common colds and upper respiratory infections – and considering that such individuals are generally being treated for their symptoms, the current review will address broad principles that may provide some direction in this regard. Instead of focusing on certain specific conditions and drugs per se, we will summarise key points for consideration when advising patients with respect to exercising while they present with clinical symptomology and/or are undergoing drug treatment. In terms of exercise, HIT will be applied as a reference to explain potential illness-drug-exercise interactions. For this purpose, HIT will be defined as exercising at a level which will result in a heart rate ranging between 70–100% of an individual's maximum theoretical heart rate for at least 30 minutes,[10] where the maximum theoretical heart rate is roughly calculated by subtracting age from 220. Further, although a number of organ systems are involved in and influenced by HIT, e.g., the central nervous system, the gastro-intestinal system and the endocrine system as broadly referred to, the current review will be written against the backdrop of the major organ systems that are directly functionally involved in training, i.e. the cardiovascular, pulmonary and skeletal-muscular systems.

Exercise, illness and the human body: a two-way street of physiological change

Fundamental exercise-induced responses in the human body

Cardiovascular function

Exercise induces increased sympathetic, together with decreased parasympathetic output, resulting in increased heart rate, stroke volume and cardiac output in order to meet the metabolic demands of the activated skeletal muscles recruited to perform a specific exercise.[11] Such metabolic demands are related to an increase in the oxygen and nutrient utilisation of activated skeletal muscles, which is met by two main mechanisms: first, increased cardiac output and, secondly, redistribution of blood flow from non-essential (inactive) organs to the skeletal muscles involved. The former is achieved by an increase in both heart rate and stroke volume, proportional to the intensity of the exercise. Moreover, exercise-induced dehydration (as low as 1% of body weight) further increases heart rate while at the same time modulating arterial baroreflex sensitivity.[12,13] In addition, exercise-induced dehydration also raises internal body temperature, which is known to increase the firing rate of the sinoarterial (SA) node,[12-14] thereby contributing to an increased heart rate. It is noteworthy that as opposed to trained athletes, stroke volume does not increase further when 50% of VO_{2max} in untrained individuals is reached. In fact, in the untrained individual, the stroke volume plateaus at exercise intensities beyond 50% of VO_{2max}, whereas heart rate continues to increase,[11,15] placing a significant cardiac burden on untrained individuals who suddenly commence with HIT. Conversely, both stroke volume and heart rate continue to increase in parallel with exercise intensity, in endurance athletes, largely due to improved ventricular filling, increased plasma volume and/or enhanced myocardium contractility.[11] With regards to the redistribution of

blood flow to active skeletal muscles, as much as 85% of total cardiac output is directed away from inactive organs, such as the liver, kidneys and GI-tract. This transpires as a function of skeletal muscle arterial dilation[15,16] coupled with peripheral vasoconstriction in the inactive organs, reducing the overall blood flow to these organs to only 20–30% of its maximum.[15] To the contrary, cerebral blood flow (CBF) increases proportionally to the exercise intensity,[17] so that total coronary blood flow is actually slightly increased during heavy exercise, in relation to resting values.[15] Nevertheless, mean overall blood pressure increases during acute high intensity exercise programs[11,15] and could therefore be expected to pose an increased risk for cardiac complications. That said, caution is warranted as, due to central and peripheral vasodilating mechanisms,[18] exercise is often followed by an immediate and rapid reduction in mean blood pressure. Early evidence implied nitric oxide (NO) and peripheral prostaglandin release to mediate post-exercise hypotension, yet recent work suggests that these mediators play a negligible role.[19,20] In fact, peripheral histamine release is theorised to play a key role in post-exercise vasodilation (that can be maintained for up to 2 hours following HIT). In this regard, it has been shown that H_1- and H_2-receptor antagonism following exercise may reduce post-exercise vasodilation and hypotension by up to 80% and 65%, respectively,[21-23] thereby demonstrating the potential of antihistamines to prevent post-exercise syncope.[24] Taken together, constant cross-talk between vasodilatory and vasoconstricting mechanisms regulates blood pressure to such an extent that optimal blood flow to the required muscles (and vital organs, such as the brain) is maintained, yet simultaneously preventing this pressure from reaching the critical levels at which adverse cardiovascular events can be precipitated. Still, patients with underlying cardiovascular pathology, such as, but not limited to, arterial stiffness and hypercholesterolemia, might be unable to auto-regulate these changes in blood pressure efficiently and consequently be at risk for cardiovascular adverse events.

As mentioned earlier, exercise-induced dehydration may impact on arterial baroreflex sensitivity.[12] Further, a decrease in essential minerals, such as sodium (Na^+) and potassium (K^+) brought about by an increased perspiration rate, can significantly increase the risk for adverse exercise-induced cardiovascular events.[13,25] Considering the central role of Na^+ in muscle contraction, exercise-induced hyponatraemia (EIH) is often observed following exhaustive exercise, due to increased perspiration. However, EIH is of great concern during exercise, especially because of its potential fatal consequences.[26] In fact, Na^+ supplementation (and overall hydration) during and immediately following exercise is suggested as a key preventative mechanism for exercise-induced hyponatraemia.[26-28] On the other hand, and especially of relevance to endurance athletes, the effect of Na^+ and K^+ loss is mitigated via adaptive responses to aldosterone secretion. Indeed, aldosterone secretion is increased by up to 28% during HIT. However, aldosterone secretion can be increased by up to 62% when strenuous exercise is performed while being dehydrated under conditions of increased environmental temperature[13] which in turn will contribute to hypertensive symptoms and an increased risk for cardiovascular incidents.

Pulmonary function

Strenuous exercise elicits a number of pathophysiological responses in the respiratory system. For example, because of its role in muscle contraction, EIH also affects respiratory function, during and immediately after HIT. During high intensity exercise, an increase in pulmonary workload is observed, which could lead to respiratory muscle fatigue, especially in women,[29] resulting in impaired respiratory function. Although HIT-induced respiratory muscle fatigue may not have a significant impact on healthy individuals, patients with underlying oxidative-inflammatory dysfunction and even asymptomatic respiratory conditions, might be adversely affected. Conversely, exercise-induced bronchoconstriction (EIB) is observed in patients with no personal or familial asthmatic history.[30] The mechanism of EIB is thought to involve the immediate release of bronchoconstrictory mediators, e.g., leukotrienes, prostaglandins and histamine (alluded to earlier) which are released in response to the exercise-induced hyperosmolar environment[30,31] in turn resulting from an increased ventilation rate and the inhalation of dry air together with compensatory water loss.[31,32] Importantly, the described mechanism may only act as a trigger for EIB, whereas epithelial damage to pulmonary tissue, may be a predominant contributing factor,[32] with or without autonomic dysregulation.[33] As before, dehydration and environmental temperature are strong contributing factors to EIB, with the latter reported to have a greater impact.[31] In addition, HIT is thought to exaggerate the parasympathomimetic cooling mechanisms of the respiratory system, e.g., increased mucus production, contributing to the observed EIB.[34]

Skeletomuscular function

Continued HIT without sufficient recovery between exercise sets is known to cause muscle fatigue. Although the exact mechanism of exercise-induced muscle fatigue is not yet fully understood, it is believed to result from the accumulation of lactate, hydrogen atoms, ADP and free radicals, i.e., reactive oxygen/nitrogen species (ROS/RNS), within the active muscle fibres.[35] Importantly, an increase in the latter may either be beneficial or detrimental, dependant on the magnitude, location and duration of the ROS/RNS-production, as well as the efficacy and functionality of the antioxidant defence systems and age of the individual,[36,37] again highlighting the hormesis characteristic of exercise. Indeed, when the production rate of ROS/RNS overpowers the endogenous antioxidant defence system's neutralising ability, increased oxidative stress is observed resulting in cellular dysfunction and muscle damage. Further, intensive exercise routines increase metabolic demand. Consequently, ATP-turnover is accelerated, leading to elevated levels of AMP, uric acid and xanthine,[38] all of which facilitate the generation of ROS and exacerbates oxidative stress.[39,40] Another adverse effect of exercise-induced oxidative stress is the suppression of Na^+/K^+-pump function in active skeletal muscles. As the Na^+/K^+-pump is responsible for the adequate concentration of Ca^{2+} in the sarcoplasmic reticulum of muscle cells, inhibition of the pump results in inhibited muscle fibre contractility, which accelerates and exacerbates muscle fatigue.[41] Exhaustive exercise may also induce temporary immunosuppression due to the increased synthesis and release of cortisol.[42] However, although an

immediate anti-inflammatory response is often observed as a result of HIT, this may over time also contribute to increased tissue ROS-production[3,43] in itself eliciting an inflammatory response and thereby undermining the potential beneficial effect of acute anti-inflammatory responses. That said, although a definitive link exists between exercise-induced muscle damage and oxidative stress, evidence supporting dietary anti-oxidants as a preventative measure is lacking.[44] In fact, findings related to *antioxidant-induced stress during exercise*[45] suggest the cause of tissue, muscle and/or tendon damage to be more complicated than simply being related to physical damage or a dysfunctional inflammatory response, at least also involving mitochondrial dysfunction.[46] Furthermore, exercise-induced inflammation may, amongst others, cause swelling of the recruited muscle groups utilised during training. As such, compression garments have been used during and after training as a preventative measure to lower the risk of muscle damage. Indeed, recent meta-analyses indicate that muscle recovery and the risk of muscle damage is in fact decreased by the appropriate use of compression garments.[47-49]

Taken together, although HIT may induce all of the above mentioned effects, healthy individuals should not be significantly affected, or at least should not present with symptomology following HIT-routines characterised by sufficient recovery periods. However, patients presenting with underlying illness may be at an increased risk for developing unfavourable exercise-induced effects. Therefore, the following section will briefly describe the physiological effects of systemic inflammation that may contribute to the individual's increased risk for developing such adverse effects.

Inflammation and the human body

Considering the abovementioned pathophysiological changes brought about by HIT, the question arises whether patients presenting with clinical illness - within this context referring to those acute conditions that are associated with systemic inflammation and that occur in most individuals over time - can safely engage in exercise. For this to be answered, we need to place the organ systems reviewed in the previous section, against the background of an inflammatory response.

Cardiovascular function

Although an in-depth review of cardiovascular involvement during acute illness falls outside the scope of the present review, several key aspects for consideration will be highlighted here. Systemic inflammation, as brought about by infection, e.g., viral influenza and bacterial bronchitis, is associated with a number of pathological changes that may influence the cardiovascular response. In fact, viral influenza causes up to 300 000 deaths annually, with cardiac pathology being the most common cause of death in the majority of cases.[50] In this case, the cardiovascular system is either directly affected resulting in myocarditis, changes in contractility and deterioration of cardiac muscle,[51] or indirectly compromised via the exacerbation of existing cardiac pathology.[50] While the mechanisms underlying direct cardiac involvement is largely unknown, myocardial viremia, i.e., extra-pulmonary viral spread into the myocardium,[51] as well as abnormal coagulopathy has been implicated.[52] However, systemic inflammation in itself is also a contributing factor to cardiovascular pathology.[53,54] In this regard, increased levels of pro-inflammatory cytokines, e.g., interleukin-1 (IL-1), IL-6 and tumour necrosis factor-α (TNF-α), as well as high levels of ROS/RNS are observed during both viral and bacterial infection.[55] Further, high levels of C-reactive protein (CRP), a marker of systemic inflammation, are associated with an increased risk of cardio-vascular incidents.[56] Although the mechanisms underlying a potential causal relationship between systemic inflammation and cardiovascular pathology during illness still need to be confirmed, vascular epithelial involvement and damage is believed to play a major role in the pathological sequelae of acute inflammation.[57] That said, in healthy patients, infection-induced inflammatory responses are mitigated via various negative feedback mechanisms, including the synthesis and release of anti-inflammatory cytokines, e.g., IL-10, and the generation of increased ROS/RNS.[55] Yet, as eluded to earlier, patients who already present with underlying immunological or cardiovascular pathology, may be more susceptible to the cellular and tissue damaging effects of systemic inflammation, and ultimately be at an increased risk for pathophysiological manifestations.

Pulmonary function

Inflammation and pulmonary function is intrinsically linked. Not only are patients with underlying pulmonary disease, e.g., chronic obstructive airway disease (COPD) and asthma, at risk of symptom exacerbation,[58] but also individuals without a prior history of pulmonary pathology. Although the majority of inflammatory symptoms observed in the respiratory system are directly related to primarily pulmonary conditions, e.g., viral pneumonia, conditions of systemic inflammation, e.g., allergic rhinitis, anaphylactic shock, lupus erythematosus, rheumatoid arthritis and inflammatory bowel disease, may also contribute to acute airway inflammation.[57-59] Revisiting the pulmonary complications of HIT reviewed above, inflammation contributes to increased secretion of local autacoids, e.g., leukotrienes, histamine, prostaglandins and bradykinin, which in turn cause smooth muscle contraction, vascular leakage, increased mucus production and bronchoconstriction.[60,61] Further, the pulmonary pathology resulting from high concentrations of circulating leukocytes is well-established.[62] Although inflammation also coincides with increased circulating levels of glucocorticoids,[63,64] the acute and immediate effects of inflammatory factors on airway physiology are likely to dominate until glucocorticoid inhibition of such responses is adequate. Another, potentially life-threatening, complication of pulmonary inflammation within the current context is its bidirectional relationship with cardiovascular disease. In fact, emerging evidence points to a direct association between lung inflammation and the exacerbation of cardiovascular conditions.[65] Whether this association may have clinically important consequences during circumstances of acute inflammation and simultaneous HIT remains to be established. Suffice to say, caution is warranted when patients presenting with both pulmonary pathology and cardiovascular disease are advised if wanting to exercise while demonstrating clinical symptomology.

Skeletomuscular function

Perhaps one of the most striking and unexpected pathophysiological consequences of inflammation is its significant interference with skeletal muscle integrity and function. Early evidence pointing to associations between inflammation and a deterioration in skeletal muscle integrity resulted from investigations into muscle wasting in patients suffering from COPD.[66,67] Later, it has been suggested that the link between COPD and skeletal muscle deterioration is founded in systemic inflammatory responses, rather than being related to COPD-specific mechanisms per se.[68] In fact, not only has the degree of systemic inflammation been shown to correlate with COPD-symptom severity, but also with cardiovascular disease, skeletal muscle deterioration and increased mortality rates.[68] More specifically, systemic inflammation as evinced by increased plasma IL-6- and CRP-concentrations, inversely correlates with maximum muscle workload, muscle strength and exercise tolerance.[68] Proposed mechanisms underlying inflammation-related loss of skeletal muscle function include IL-6-induced inhibition of insulin-like growth factor secretion, TNF-α related atrophy of muscle fibres,[69] and excessive ROS/RNS-generation resulting in a loss of muscle strength and mass.[70] Further, under circumstances of inflammation-related impaired skeletal muscle function, injury occurs readily,[71] while the regenerative processes involved in muscle recovery are suboptimal. Importantly, we frame said inflammation-related muscle deterioration against the backdrop of *pre-existing inflammation,* as post-injury inflammation in itself is a crucial mediator of muscle recovery.[71,72]

Taking together the role of inflammation on cardiovascular, pulmonary and skeletomuscular function, the risk for cellular damage and eventual dysfunction caused by inflammatory processes is significant. To this extent, patients with underlying symptoms of systemic inflammation – irrespective of cause – who take part in HIT, are at risk of exaggerating the abovementioned pathophysiological processes, thereby increasing their risk for adverse cardiovascular events, pulmonary insufficiency and/or skeletal muscle injuries. In addition, in the case of individuals undergoing treatment for conditions associated with inflammation, be it curative, i.e., antibiotic treatment, or for symptomatic purposes, i.e., nasal decongestants or analgesics, an additional risk of injury, poor recovery and secondary pathology is introduced. Therefore, the following section will provide a brief overview of drug classes that may potentially exacerbate the pathophysiological processes reviewed above as elicited by both HIT and inflammation.

Potential levels for clinically relevant exercise-illness-drug interactions

Considering the pathophysiological changes elicited by both HIT and systemic inflammation reviewed above, the overall principle when providing patients with advice should be that drug treatment cannot not be introduced in a way that may increase the risk of adverse health outcomes in exercising patients. Here we will provide some examples of potentially relevant drug-inflammation-exercise interactions as they apply to the three organ systems discussed and while we will refrain from providing highly detailed and exhaustive discussions of drugs that may all be theoretically contraindicated in exercise, these examples should suffice to kindle deductive reasoning during future decision making in clinical practice.

Drugs acting on cardiac and smooth muscle function

Cardiovascular function is significantly impacted by various drug classes, while both drugs that improve and inhibit cardiac function may be equally detrimental during exercise. For example, β-receptor antagonists, i.e., propranolol and atenolol, have several important effects that may negatively impact exercise on the one hand, and exacerbate inflammation-induced damage on the other. First, due to the heart rate lowering effects of these drugs, estimations of actual heart rate level may be problematic, leaving individuals susceptible to overtraining. More specifically, non-selective β-blockers may elicit acute increases in systolic blood pressure during exercise as they block noradrenergic arterial dilation via the β_2-adrenoceptor and therefore increase vascular resistance.[73,74] Under conditions of increased workload during exercise, such an effect will also result in a lower degree of oxygen perfusion in skeletal muscle, exacerbating an anoxic state and potentially bolstering the build-up of lactic acid.[75] Further, they might predispose the individual to hyperthermia and hypoglycaemia during exercise.[76] Therefore, when β-blockade is required in a physical active individual, a combined α-β_1-receptor blocker is preferred, due to the average reduction in vascular resistance caused by α adrenoceptor blockade.[74,76] Although chronic use of β-blockers together with a controlled training program will in most otherwise healthy individuals have no negative impact on overall performance,[76] this may change abruptly once an extra burden of systemic inflammation is introduced. Further, other drugs that target the cardiovascular system that could potentially exaggerate HIT-induced physiological effects, include angiotensin converting enzyme inhibitors (ACEIs) and diuretics. As with the β-blockers, all of these drug classes reduce cardiac output, which could potentially increase the risk for adverse exercised-induced cardiovascular symptoms. In fact, the ACEIs may exaggerate the post-exercise hypotensive symptoms, increasing the risk for syncope;[76] yet they remain the preferred choice in physically active, hypertensive patients.[74,77] Diuretics contribute to additional decreased electrolyte levels and could therefore impair exercise performance and capacity,[78] as well as increase the risk for hypovolemia, hypokalaemia and hyponatraemia.[74,79] As such, the combination of an ACEI and a diuretic may significantly increase the risk for hospitalization[80] should exercise-naive patients suddenly engage in HIT. Conversely, drugs that boost cardiac function, e.g., the xanthine-derivative, theophylline, β_2-receptor agonists, albeit at high doses, and other sympathomimetics, could potentiate the adverse cardiovascular effects induced by HIT and inflammation. For example, in the case of theophylline, its effects on the sympathetic system will become exacerbated during acute exercise as it functions as an indirect potentiator of the actions of noradrenalin. Thus, during circumstances of increased sympathetic outflow observed during both HIT and inflammation – known as the inflammatory reflex[81] – a marked increase in the toxicity of theophylline will be observed. As such, patients will be at risk for developing cardiac arrhythmias, hypertension and convulsions.[82] Another example is that of the nasal decongestant pseudoephedrine,[83]

which apart from being a direct acting α_1-receptor agonist, also causes noradrenalin release from sympathetic neuron terminals. Therefore, as opposed to direct acting α_1-agonists, the effects of pseudoephedrine will be broad in terms of cardiovascular function, resulting in both cardiac stimulation and vasoconstriction. As such, the drug is listed along with other cardiac stimulants and central nervous system stimulants as a banned substance in athletes.[84]

Patients treated with drugs that may influence the cardiac QT interval, i.e., the contracted state, may be at risk of developing *Torsades de Pointes*. Such a response is strongly associated with the use of antibiotics, e.g., the fluoroquinolones (ciprofloxacin and others), the macrolides (erythromycin and others), and new-generation antihistamines (mizolastine), among others.[85-87] Moreover, the former has recently been associated with increased risk for aortic ruptures,[88] which is of great concern in physically active patients with underlying cardiovascular dysfunction.

The use of non-steroidal anti-inflammatory (NSAID) drugs may present significant risks for a training individual who is suffering from conditions related to systemic inflammation. While the risk of cardiac complications with NSAID-use – a much publicised and highly controversial debate during the past few decades[89-92] – are at most relevant after chronic use, this may be different in patients who are relatively exercise-naive and suffering from systemic inflammation; therefore, caution needs to be applied. That said, it is the effects of especially the non-selective cyclooxygenase (COX) type 1 and 2-inhibitors that may pose a significant risk for pulmonary pathology. Revisiting the effects of HIT and systemic inflammation on pulmonary pathology, it is worth noting that non-selective COX-inhibitors can predispose patients to develop a paradoxical inflammatory airway response by increasing the risk for leukotriene-associated bronchoconstriction.[93] Although such a response may not be clinically relevant in healthy individuals, those affected by systemic or local pulmonary inflammation demonstrate an increased turnover of arachidonic acid, the chemical precursor of both prostaglandins and leukotrienes. As the non-selective COX-inhibitors prevent the conversion of arachidonic acid to prostaglandins, an increased turnover or arachidonic acid to leukotrienes is observed.

Drugs acting on the skeletomuscular system

As optimal muscular function is of particular importance for physical activity, interactions between HIT, inflammation and drug treatment could be significant. First, as alluded to earlier, overall muscular function is impaired by various drug classes and via numerous mechanisms. For instance, as stated earlier, β-blockers decrease blood flow to skeletal muscles,[73] whereas the ACEIs reduce physical function via exaggerated vasodilation, which ultimately leads to reduced cardiac output and subsequently diminishes physical performance.[94] Conversely, chronic use of β_2-receptor agonists, as often abused by body-builders, reduces HIT-performance by preventing exercise-induced upregulation of oxidative and glycogenolytic proteins.[95] Statins, e.g., simvastatin and rosuvastatin, may induce enhanced muscle weakness via antagonistic effects on voltage gated calcium channels,[96] whereas the antibacterial aminoglycosides are known to cause neuromuscular blockade.[97]

Alternatively, decreased physical performance and injury can also be borne from muscle dysfunction and/or damage. In this regard, NSAID-use, including paracetamol, is not only associated with cardiovascular and pulmonary pathophysiology as alluded to above, but also with an increased risk for muscle damage.[98,99] Indeed, NSAID-induced inhibition of COX- and prostaglandin (PG)-activity, decreases inflammation, and could thereby desensitise how patients respond to pain. Moreover, COX and PGs are also involved in collagen synthesis, and interference in these pathways may reduce overall muscle strength and integrity, further increasing the risk for muscle damage and delaying and undermining the healing process when injury does occur.[98] A further complication of NSAID-use during HIT is that the natural adaptive potential to the mechanical loading effect of exercise is blunted. In this regard, the mechanical stimulus ensued by exercise activates COX-2, thereby modulating muscle formation in order to adapt to similar future stimuli. Yet, in the presence of NSAIDs, this adaptation process remains suboptimal.[98,100,101]

Mitochondrial damage and dysfunction is another key contributing factor to impaired muscular function. In this regard, statins induce mitochondrial dysfunction in skeletal muscle cells, interfering with aerobic capacity and training adaptations,[102] resulting in an increased muscle damage/injury risk.[103] Finally, the drug class that is consistently associated with muscular damage is the fluoroquinolones, which increase the risk for tendonitis and tendon rupture, due to collagen and mitochondrial damage.[86,104,105]

Ultimately, while all of the described effects may be sub-clinical in otherwise healthy individuals, it is against the backdrop of interactions between HIT and inflammation, where they might become more relevant.

Conclusion

Taken together, no clear guidelines exist that prescribe how and to what extent patients presenting with systemic inflammation should engage in exercise. Indeed, the beneficial and curative effects of moderate, and in some cases even HIT, in mild inflammatory conditions, are well described.[106,107] That said, HIT, inflammation and various pharmacological drug classes have all also been independently linked to an increased risk for various, and possibly fatal, conditions. As such, this paper attempted to highlight some major issues for consideration with respect to these three constructs. We first elaborated on the major pathophysiological responses that may transpire with respect to the cardiovascular, pulmonary and skeletomuscular systems during HIT. We subsequently built on this by interweaving the effects of systemic inflammation on these three organ systems and closed by providing some examples of drug interactions that may be of importance within this framework. In the end, while exercise during states of clinical illness is not contraindicated, objective evaluation of the specific circumstances is paramount to provide safe and accurate patient advice.

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