EXERCISE AND OXIDATIVE STRESS

AN EXERCISE PARADOX?

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Oxidative stress is the total burden placed on organisms by the constant production of free radicals in the normal course of metabolism plus whatever other pressures the environment brings to bear (natural and artificial radiation, toxins in air, food and water; and miscellaneous sources of oxidizing activity, such as tobacco smoke).

The positive health benefits stemming from physical activity are well-established. Just 30 minutes a day of moderate-intensity exercise reduces the rate of developing various non-communicable diseases including diabetes and atherosclerosis. Noteworthy is that, despite of an unclear explanation, there are epidemiological data that paradoxically imply that a very high volume of energy expenditure is related to a decrease in cardiovascular health. Although aerobic exercise has been shown to increase antioxidant defences (and therefore provide a protective effect against oxidative stress), an increase in oxidative stress stemming from a very high volume of aerobic exercise may contribute to the progression of arterial hardening (atherosclerosis) via oxidative modification of low-density lipoprotein (LDL) within the arterial wall.

In the context of these data, the aim of this article is to examine the mechanisms for exercise-induced oxidative stress, explain the potential association between oxidative stress, exercise and cardiovascular health and to consider whether elevated oxidative stress due to the high-volume of exercise may contribute to a decrease in health.

WHAT IS OXIDATIVE STRESS?

Firstly, it is important to understand what exactly oxidative stress is and from where it originates so we can appreciate the potential mechanisms for change. Oxidative stress stems from the generation of reactive oxygen species (ROS) that are produced when molecular oxygen is only partially reduced in a chemical reaction. This process results in highly reactive molecules or ions that contain at least one unpaired electron in their outer orbital or valence. They have the ability to modify lipids, proteins, carbohydrates and nucleic acids resulting in what is collectively called 'oxidative stress'.

WHAT IS THE IMPACT OF EXERCISE ON THE PRODUCTION OF OXIDATIVE STRESS?

Exercised-induced ROS production is accompanied by an increase in oxygen uptake and is believed to be due to electron 'leakage' at the site of energy production, and the increased metabolic process of exercise exacerbates this outcome. Secondly, the immune system also forms significant quantities of ROS, which are activated in response to exercise-induced muscle injury. Having arrived at the site of injury and infection, immune cells are recruited. However, a problem with this process is that certain immune cells have a poor capacity to distinguish between foreign and host antigens therefore, if target selection processes are not stringently controlled, immune cells may release their toxic agents on normal host tissues resulting in a further development of oxidative stress.

WHAT IS THE LINK BETWEEN EXERCISE-INDUCED OXIDATIVE STRESS AND LONG-TERM HEALTH IMPLICATIONS?

The relationship between oxidative stress and negative health outcomes stems from the oxidative transformation of trapped LDL and the mechanism is believed to be the same at rest as it is in exercise. However, the magnitude of LDL oxidation increases with exercise[1]. Oxidative stress and the subsequent oxidation of LDL is considered a major contributor to the impairment of endothelial function and the development of atherosclerotic lesions[2]. Research has shown

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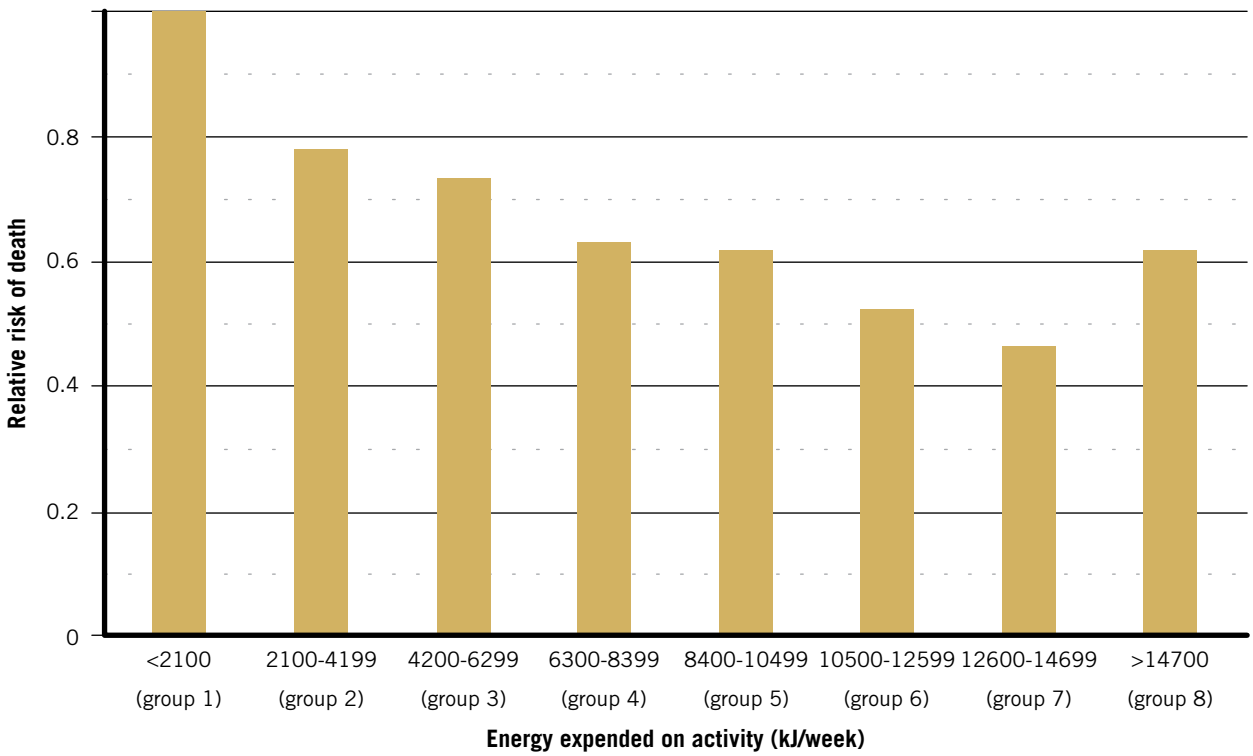

Figure 1: Relative risk of death corresponding to energy expenditure.

that acute bouts of exercise can increase markers of LDL oxidation[3]. Therefore, it is plausible that very-high volumes of energy expenditure may advance the progression in atherogenesis through an increase in free radical production, oxidative stress and LDL oxidation.

WHAT IS THE EVIDENCE OF EXERCISE-INDUCED OXIDATIVE DAMAGE?

The relationship between exercise and oxidative stress has been examined in many studies ranging from acute short exercise sessions[4] to long distance triathlons (those exceeding 4 hours in length)[5]. Early research in regards to exercise-induced oxidative stress showed an increase that was four times the resting value in healthy male subjects cycling with increases in intensity corresponding to 45%, 60% and 75% of maximal oxygen uptake (VO^2 Max)[4]. One explanation put forth for this is that antioxidant defences are sufficient to meet an increase in ROS production during low-intensity exercise, but as exercise-intensity increases, these defences are surpassed resulting in significant oxidative stress. This is supported by research showing the results stemming from a high-intensity endurance triathlon vs a long-distance/lower-intensity triathlon. The results showed a significant increase in oxidative stress and a corresponding decrease in antioxidants in the high-intensity shorter duration triathlon in comparison to the long distance/low-intensity triathlon where antioxidants decreased but no significant impact on oxidative stress[5].

In summary, research has shown that in general, acute bouts of endurance exercise at a moderate- to high-intensity increases oxidative stress. However, longer duration lower-intensity events do not exhaust all antioxidants and oxidative stress remains unchanged.

EXERCISE/PHYSICAL ACTIVITY, ENERGY EXPENDITURE AND MORBIDITY

Numerous prospective epidemiological studies have investigated the effects of exercise or estimates of physical activity (derived from energy expenditure data) on mortality[6,7]. The consistent conclusion from these investigations is that low levels of exercise/physical activity are strongly associated with increased mortality independent of other factors[6–8]. However, a closer look at data presented from some of these studies reveals a number of interesting features. In one of the first studies to describe the relationship between energy expenditure and mortality[8,9,16], 936 participants were divided into eight groups based on activity-derived energy expenditure. The study reported a decline in the relative risk of death with increasing physical activity up to an energy expenditure of >14,700 kJ/week, whereby the trend began to reverse, creating an upward trend. Unfortunately there was no mention made as to whether this trend reversal was significantly different from the previous expenditure groups (Figure 1).

The same cohort of participants had their energy expenditure and mortality data analysed 10 years later with a similar outcome. In addition, if the activity was vigorous it was associated with the same trend. However, it occurred at a lesser energy expenditure[10]. The authors note that this finding is similar to that reported in the British Regional Heart Study conducted on 7,735 men aged 40 to 59 years, where vigorously active men had higher rates of heart attacks than men performing moderate or moderately vigorous activity[11]. One explanation for this outcome may be an

elevation in oxidative stress stemming from increased in particular vigorous activity[1].

Quinn et al[12] looked at the relationship between the caloric expenditure and mortality in 348 subjects from the Michigan State University Longevity Study. Six caloric groups were established based on the amount of energy expended per week on aerobic activities such as cycling, rowing, jogging and swimming. Not surprising was the data showing mortality rates were high in the two lowest caloric expenditure groups. However, the investigators also found that data from subjects who reported cardiovascular disease (CVD) was the highest in groups 1 and 6 (Figure 2).

HOW DOES THIS RELATE TO THE HEALTH OF HIGH-LEVEL TRAINING ATHLETES?

Although epidemiology is an excellent form of research, it provides information relevant to various groups of the general population. We therefore now need to explore this relationship in athletes to determine the mechanisms and the potential relationship between long-term, high-energy expenditure and cardiovascular health.

One way we can do this in a pre-existing population of athletes is by investigating ultra-endurance athletes. These are athletes who compete in events lasting between 4 and 15 hours. Many of these athletes can train more than 20 to 30 hours per week, which far exceeds the energy expenditure associated with an increase in the risk of CVD.

WHAT DOES THE RESEARCH SAY ABOUT ULTRA-ENDURANCE EXERCISE AND OXIDATIVE DAMAGE?

Despite the relatively small population of athletes participating in this type of exercise, research into acute ultra-endurance events has consistently shown an increase in oxidative stress. Kanter et al[13] showed that oxidative stress increased in response to an 80 km ultra-marathon. Of interest in this study was that there was also an increase in creatinine kinase, suggesting the muscle damage may be related to exercise-induced oxidative stress. This is worthy of note given the continuous high volume of training in this sample (121 km/week) and the potential sustained levels of oxidative stress. Others have found similar results with similar training distances. However, not all studies have found high volumes of exercise to result in oxidative stress. For example, Margaritis et al[14] reported no evidence of oxidative stress following an ultra-endurance triathlon.

Inconsistencies between the studies reviewed may be explained by differences in the exercise demands (e.g. intensity, type, duration, training protocols and dietary status), training status of the participants (endogenous antioxidant status) and methods of detecting oxidative stress. Indeed, it has been suggested that in response to a single bout of exercise, there is an intensity below which oxidative stress does not occur[1]. Furthermore, there is evidence to suggest that excessive production of free radicals occurs only when the exercise is exhaustive[15]. However, exercise duration is not a variable that resolves the inconsistencies. This is highlighted by research that has found a significant increase[13], a decrease[16] and no change[14] in the production of oxidative stress in response to ultra-endurance exercise.

Collectively considered, however, the limited research has generally shown that high-volume exercise increases ROS production and various markers of oxidative stress. Given the association between oxidative stress and atherosclerosis, it certainly seems plausible that participating in long-term ultra-endurance exercise significantly increases oxidative stress. Negative health implications may result

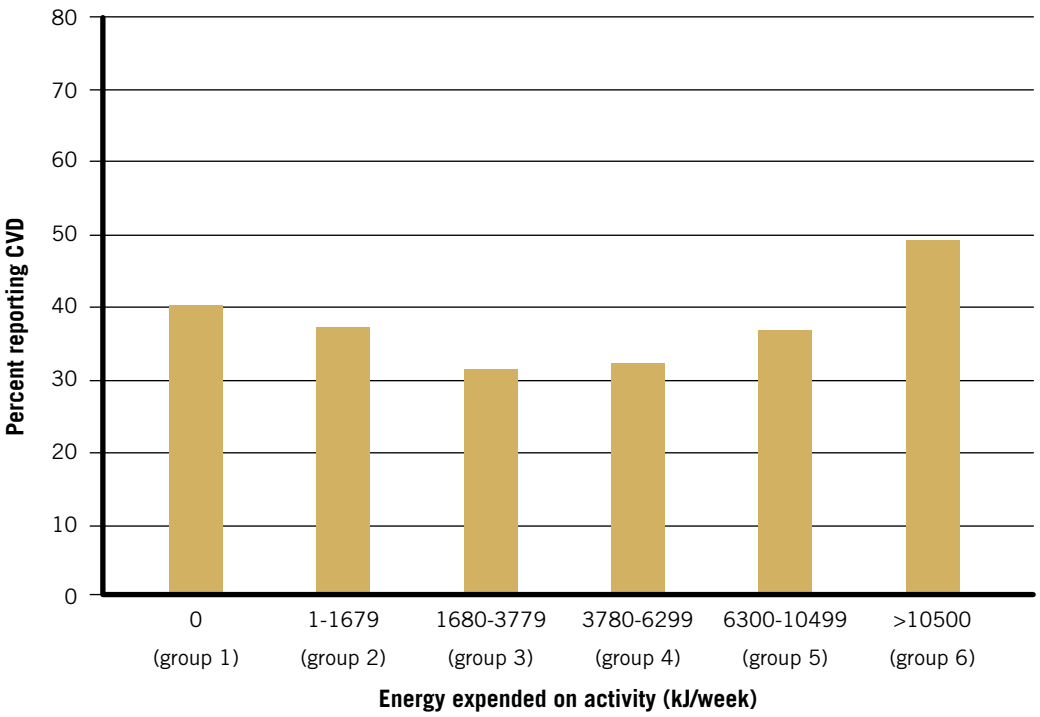

Figure 2: Percentage of participants reporting CVD corresponding to energy expenditure. CVD=cardiovascular disease.

Image: 2011 World Champion Australian Triathlete Craig Alexander.

unless exercise-induced pro-oxidant activity is neutralised or balanced by adaptations in ultra-endurance athletes.

CAN WE MINIMISE THE DAMAGING IMPACT OF OXIDATIVE STRESS?

THE ANTIOXIDANT DEFENCE SYSTEM

To counteract the damaging impact of oxidative stress we require an active defence system known as the antioxidant defence system. This system includes both endogenous (body's existing defence) and exogenous (dietary) antioxidants, which reduce the extent of oxidative damage by creating a less active radical. The processes by which these antioxidants can reduce the damage inflicted by ROS vary greatly including modifying the free radical to metabolic water and oxygen.

> ***trained individuals are less likely to experience localised inflammation in exercised muscles***

HOW DOES EXERCISE TRAINING INFLUENCE ANTIOXIDANT ADAPTATIONS?

The ability of exercise to improve the activities of key antioxidant enzymes is one of the most important adaptions in the modification of ROS of oxidative stress. In addition, an increase in mitochondrial volume in response to endurance training results in a relatively lower oxidative load, which may attenuate the generation of ROS[17]. Exercise may similarly assist in a combative role against ROS damage that can occur during exhaustive exercise by decreasing the loosely bound iron in muscles[18].

Immunological changes are also likely as a result of exercise training; trained individuals are less likely to experience localised inflammation in exercised muscles. Additionally, training strengthens muscle fibres and protects against muscle damage[19]. Furthermore, the neutrophils of trained individuals have a reduced capacity to produce microbiocidal ROS[20]. Therefore, in a single bout of exercise, the magnitude of oxidative stress may be strongly influenced by an individual's training history.

A small number of studies have examined adaptations of the antioxidant system to ultra-endurance exercise. Recently, we examined changes in various antioxidants in athletes training for half (swim 1.9 km, ride 90 km, run 21.1 km) and full distance (swim 3.8 km, ride 180 km and run 42.2 km) Ironman triathlons. In half-distance Ironman athletes we found that 13 athletes exercising for 14.5 hours/week had a significantly higher antioxidant enzyme compared with age-, gender- and weight-matched controls[5]. In addition and with a different cohort of 26 athletes who were training 17 (±3.4) hours a week for a full Ironman triathlon, we also found significantly higher antioxidant activities compared with age-, gender- and mass-matched controls[5]. Our data collectively confirm that a high-volume of exercise is associated with elevated antioxidant defences against oxidative damage and that training status may influence the magnitude of adaptation of these defences. However, it is unclear whether this result translates into an improved cardiovascular health status.

WHAT IMPACT DOES EXOGENOUS ANTIOXIDANT DEFENCE SYSTEM HAVE ON EXERCISE-INDUCED OXIDATIVE STRESS?

Oxidative stress that results from exercise can potentially be minimised by dietary antioxidants such as vitamins C and E. Most of the studies investigating the effect of supplementation on the production of oxidative stress in endurance exercise have shown that either there is no change in oxidative stress (with supplementation), or that there is attenuation in its production from pre- to post-measurement [21].

Unfortunately, few studies have examined the relationship between vitamin supplementation and oxidative stress with ultra-endurance exercise. However, one study investigated the impact of exogenous antioxidant supplementation on the antioxidant defence system and oxidative stress at a resting level and in

response to exercise. The results showed that the resting concentration of oxidative stress and erythrocyte antioxidant activities were not significantly different between the supplementation and non-supplementation groups of half and full Ironman athletes. Interestingly, only the athletes taking antioxidant supplements showed a significant increase in oxidative stress from before to after both races. Despite the obvious limitations of interpreting these observational data, it is worth reporting as it has been proposed that a high dose of vitamin E in the presence of oxidative stress creates free radicals capable of initiating lipid peroxidation[22]. Certainly, what is clear is that ultra-endurance exercise and its relationship to antioxidant supplementation requires further investigation.

CONCLUSION

Investigating ultra-endurance exercise is a good model to derive an understanding of the impact of acute long distance racing and goes some way to understanding the impact of long-term energy expenditure. It is clear that acute ultra-endurance exercise can elevate oxidative stress. Oxidative stress is also associated with the development of atherosclerosis and the impairment of endothelial function. Some epidemiological evidence suggests that individuals who expend large amounts of energy through exercise maybe at increased risk of CVD and mortality, which may be associated with an increase in oxidative damage stemming from prolonged aerobic exercise. However, this response may be mitigated in endurance athletes as a result of exercise-induced adaptations (increased antioxidant defence, less ROS production). Therefore, despite the high-volume energy expenditure, this population of athletes may not be at a substantially greater risk of developing CVD. Further investigation is recommended to clarify the relationship between the accumulative effect of ultra-endurance exercise on oxidative stress, CVD and long term cardiovascular health.

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Knez WL, Coombes JS, Jenkins DG. Ultra-endurance exercise and oxidative damage: implications for cardiovascular health. Sports Medicine. 2006; 36:429-441.

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