

Mechanisms of Physical Activity – How does it work?

THE ANTI-INFLAMMATORY

Chronic low-grade inflammation is a key player in the pathogenesis of most long term conditions including cancers, heart disease, diabetes, dementia and arthritis.

Inactivity and obesity both cause damaging low grade inflammation through a complex pathway that includes the mitochondria.

Exercise generates a powerful anti-inflammatory response due to the release of Myokines that rise 200 fold after a bout of exercise. One of these Myokines called interleukin 6 (IL6) increases insulin sensitivity, oxidises fat and as well as acting as an anti-inflammatory.

The muscle is now thought to be an important endocrine organ releasing IL6 when it contracts leading to a powerful anti-inflammatory response, insulin sensitivity and fat oxidation.

ANTI-OXIDANT EFFECT IN THE MITOCHONDRIA.

Mitochondria are the key to healthy aging. When they are damaged not only do they accelerate aging but also lead to most long term conditions. They are damaged by Free Radicals or (Reactive Oxidative Species) that are created inside a mitochondrion.

When someone is inactive the energy and oxygen accumulate to dangerous levels instead of being burned off. This creates an excess of free radicals. If one is consuming too many calories this adds more energy to the mitochondrion and contributes to the free radicals. Anti-oxidants generated within the mitochondrion can neutralise the free radicals and help prevent damage. Physical activity helps to stimulate antioxidants. ¹

It is now thought that inactivity leads to a toxic levels of unused oxygen and a high energy state in a mitochondrion. This creates more free radicals which cause damage to the mitochondrion and therefore the cell. Damaged mitochondria create inflammation, faster aging and lead to most long term conditions. Exercise therefore increases the resilience of every cell and this is why physical activity has such far reaching benefits to health.

CARDIOVASCULAR EFFECTS: MECHANISMS

A large study ² of 27,000 women demonstrated that the most active women (>1500kcal/wk compared to <200kcal/wk) had a 41% reduction in CVD events after 10 years. The risk factors that are modified by physical activity account for 59% of this reduction (see Table 8), with inflammation and reduced blood pressure making the largest contribution.

Inflammatory haemostatic	33%
Blood pressure	27%
Traditional Lipids (total Cholesterol, LDL, HDL,)	19%
Novel Lipids (Lipoprotein, Apolipoprotein)	15%
BMI	10%

HbA1c and Diabetes	9%
Homocysteine	1%
All risk factors above/td>	59%

Table 8 : Risk factors modified by physical activity and the percentage contribution they each make to reducing CVD events: i.e. the mechanisms behind how physical activity benefits CVD mortality. Factors contributing to the remaining 31% was not measured in this study.

ENDOTHELIAL FUNCTION

The endothelium, the cell layer lining the blood vessels, plays a key role in a number of vascular functions. Impairment of arterial endothelial function is an important early step in the atherosclerotic process and a predictor of cardiovascular disease ³. Brachial artery flow-mediated dilation (FMD) is widely used as a marker of systemic arterial endothelial function. FMD is associated with coronary atherosclerosis ⁴ and predicts the likelihood of cardiovascular events. ⁵

In men and women with metabolic syndrome, 12 weeks of aerobic interval training, resistance exercise training or combined training, increased brachial artery FMD by up to 38% in all groups, despite no change in body weight. ⁶

In one study, a one year period of resistance exercise training in overweight women was reported to increase brachial artery FMD by 41%, without a reduction in total body fat mass. ⁷

HAEMOSTASIS

Physical activity “thins” the blood by decreasing levels of fibrinogen and other clotting factors ⁸. In a large study of 4000 elderly men, physical activity showed a significant and inverse dose-response relationship with fibrinogen, plasma and blood viscosity, platelet count, coagulation factors VIII and IX, von Willebrand factor, fibrin D-dimer, tissue plasminogen activator antigen, C-reactive protein and white cell count, even after adjustment for possible confounders. ⁹

In a 16-week, home-based aerobic exercise intervention ¹⁰ of ≥ 150 minutes per week in 25 sedentary, overweight subjects with type 2 diabetes there was a 17% decrease in fibrinogen and a 30% decrease in C-reactive protein (CRP), despite no change in BMI.

LIPIDS

Physical activity has favorable effects on lipids and lipoproteins, even with unchanged body weight. ¹¹ A meta-analysis of 27 studies concluded that aerobic exercise was associated with a small but statistically significant effect on increasing high-density lipoprotein cholesterol (HDL-C) levels and exhibited a trend toward decreasing serum triglyceride levels. ¹²

Aerobic exercise may be of particular value in treating individuals with the most atherogenic lipid profiles. In one study, 20 weeks of aerobic exercise training was effective at improving lipid and lipoprotein profiles in overweight men. High-density lipoprotein cholesterol was increased by 4.9% and triglycerides were reduced by 15%, despite small changes in weight (−0.7 kg) and fat mass (−1.1 kg). ¹³

INSULIN RESISTANCE

Insulin resistance increases the risk of both diabetes and cancer of the breast, colon, pancreas and endometrium. Insulin can enhance tumour development by stimulating cell proliferation or inhibiting apoptosis. ¹⁴

Both physical activity and obesity independently cause insulin resistance. There is little evidence that the aging process alone increases insulin resistance ¹⁵. Instead it is more likely that older age is related to increasing inactivity and weight gain. Physical activity on its own can significantly:

- Increase glucose tolerance
- Reduce fasting glucose
- Enhance insulin sensitivity
- Reduce HbA1C

Acute bouts of physical activity improve insulin sensitivity and increase glucose uptake by skeletal muscle, even in those with type 2 diabetes mellitus, for up to 12 hours ¹⁶.

Chronic exercise training results in prolonged improvements in insulin sensitivity ^{17 18 19}. Resistance exercise may be more effective since the mechanism of insulin sensitivity is based in the muscles. ²⁰

PHYSICAL ACTIVITY AND MUSCULOSKELETAL STRUCTURES: MECHANISMS

OSTEOARTHRITIS

Contrary to the popular myth that exercise causes more 'wear and tear' of joints in fact regular moderate physical activity protects and strengthens joints and as a result reduces pain and increases function.

There appear to be three mechanisms by which physical activity helps to prevent osteoarthritis.

- Increased muscle strength and proprioception
- Improved quality of cartilage
- Weight loss
- Muscle strength
- Muscles are important in maintaining a healthy joint. They produce movement, absorb loading, and provide dynamic joint stability. ^{21 22}
- Muscle weakness is thought to be one of the main risk factors of osteoarthritis along with poor limb alignment and obesity ^{23 24}. Weaker muscles occur as a result of inactivity, aging, after injury or with joint pain such as OA. Weak muscles not only tire more rapidly, but they also display a slower voluntary and reflex motor control.
- Once the protective muscular control is lost, excessive joint movement and instability with pathological shear and peak joint forces occur. This leads to:
 1. Stress-induced micro-trauma to the articular cartilage.
 2. Consequent cartilage degeneration.
 3. Pathological sub-chondral pressure increase.
 4. Consequent sub-chondral bone sclerosis.
 5. Joint collapse with axis deviation.

QUALITY OF CARTILAGE

- Studies using MRI scans have shown that after just 10 weeks of moderate physical activity the glycosaminoglycan levels are increased in knee cartilage ^{25 26}. This suggests chondro-protective effects which will be valuable in OA prevention.

- In a systematic review ²⁷ of the knee, physical activity was associated with reduced cartilage defects, greater cartilage volume but increased osteophytes. However it was discussed that osteophytes increase stability and distribute the load and so when associated with healthier cartilage may actually create a healthier joint.

MUSCLE

Aerobic exercise training results in an increase in mitochondrial function and an increase in capillarization both of which are highly related to improving insulin sensitivity and fat disposal. It may only take 12 weeks of combined resistance and aerobic exercise in obese patients to restore mitochondrial function to the level of a healthy control subject despite no change in weight. ²⁸

PHYSICAL ACTIVITY AND BACK PAIN: MECHANISMS

Despite considerable academic attention low back pain remains difficult to fully explain particularly as emotional and psychosocial factors play a major role. This creates large differences both within and between individuals.

Peripheral nerve endings (nociceptors) are in each part of the spine except the central disc ²⁹. However recent research has found that these nociceptors migrate into the centre of degenerative discs through scar tissue ³⁰. When stimulated they cause pain that may directly contract back muscles ³¹. These muscles may then continue to contract long after the initial stimulus has healed (usually 2-3 days) ³².

Even after a few days of pain and rest, muscles around the lumbar spine start to atrophy. This may be exacerbated by negative reflexes from nociceptors that inhibit movement in some muscles ³³.

There is associated lower bone mineral content in patients with chronic low back pain resulting in not only weaker vertebrae but also weaker tendons, ligaments and other soft tissue ³⁴.

The direct effects of aerobic training on back pain have not been completely established but the following are current theories. General physical activity:

- Increases endorphin production.
- Generates movement of the spine when walking or jogging which transports pain inducing metabolites in and out of the relatively avascular disc. ³⁵
- Has an 'activating' effect on painful and contracted back muscles.
- Breaks down the fear of movement, increases self-confidence and reduces social isolation and exclusion that can all contribute to better pain control. ^{36 37}

PHYSICAL ACTIVITY AND THE IMMUNE SYSTEM: MECHANISMS

Physical activity can improve the number or function of natural killer cells, which have a role in tumour suppression and reduction of infections ³⁸. Bouts of exercise have been shown to result in acute increases in of components of immune function (for example, neutrophils, monocytes, eosinophils and lymphocytes), followed by a dip below pre-exercise levels lasting up to 1–3 hours ³⁹. There is an inverted J-shaped dose-response relationship between chronic physical activity and enhanced immune function whereas exhaustive exercise, overtraining or high-intensity exercise may lead to immunosuppression, which can give rise to e.g. increased susceptibility to upper respiratory tract infections.

PHYSICAL ACTIVITY AND CANCER: MECHANISMS

Physical activity can prevent cancer in several ways,

HORMONAL

Physical activity reduces both circulating oestrogen and progesterone levels affecting endometrial, ovarian, prostate and breast cancer.

Physical activity increases insulin sensitivity that is linked to many cancers. Insulin stimulates cell proliferation. Diabetes mellitus is associated with a significant (16%) increase in postmenopausal breast cancer risk

REDUCING INFLAMMATION

Physical activity reduces chronic inflammation which is associated with a higher risk of cancer. Inactivity is associated with less intracellular antioxidant production leading to increased vulnerability of cells to reactive oxidants.

IMMUNITY

Physical activity stimulates the production of Natural Killer Cells that scavenge for cancer cells.(See PA and Immune System: Mechanisms)

PHYSICAL ACTIVITY AND DIABETES: MECHANISMS

Type II diabetics have 3-4 times higher risk of developing myocardial infarction and stroke, physical activity lowers risk factors for CHD. ^{40 41} These include decreased systemic inflammation, improved early diastolic filling (reduced diastolic dysfunction), improved endothelial vasodilator function, and decreased abdominal visceral fat accumulation. There is a modest effect on lipid profile ⁴² and blood pressure ⁴³.

Physical activity increases insulin sensitivity through several mechanisms. These include increasing aspects of insulin signaling cascade which up-regulates insulin-stimulated glucose uptake and transport and increase in GLUT 4 protein concentration. ^{44 45}

Physical activity increases numbers and size of mitochondria and switches on enzymes that manufacture anti-oxidants. Paradoxically inactivity and obesity create more reactive oxidative species (ROS or free radicals) due to unused spare electrons reacting with oxygen and damaging mitochondria. Insulin resistance is strongly linked to ROS and damaged mitochondria. ⁴⁶

PHYSICAL ACTIVITY AND DEPRESSION: MECHANISMS

There is still no clear understanding as to how physical activity benefits patients with depression however Kjellman et al in the 'Swedish Manual of Physical Activity' ⁴⁷ goes through the current thinking.

Behaviour Change

Physical activity involves a change in behaviour, a behaviour modification. In depression, a person's behaviour is often characterised by passiveness, withdrawal and isolation. Changing behaviour can affect thoughts and emotions, and in doing so contribute to reversing depression ⁴⁸. Physical exercise has been shown to encourage positive thoughts and emotions, increased confidence in coping, and increased self-confidence and capacity for self-control.

Resilience

Another possible psychological mechanism is that one becomes more resistant to stress through physical exercise. This could be linked to reduced activity in the hypothalamus-pituitary-adrenocortical axis, whose function is often pathologically increased in depression ⁴⁹. Increasingly important research shows that psychological distress is

significantly improved through just 20 minutes of physical activity a week ⁵⁰.

Neurotransmitters

Physical activity improves synthesis and metabolism of the neurotransmitters noradrenaline, serotonin and dopamine in test animals ⁵¹. Definite proof that this is the case in humans is not available yet, however, though it is a plausible hypothesis of an important underlying mechanism.

Endorphins

A popular hypothesis is that the effect of exercise is due to an increased concentration of endorphins, that is, the body's own morphine. Both rat and human trials support this hypothesis ^{52 53} but more research is needed on the effect of endorphins in the brain of patients being treated with physical exercise.

Cell regeneration

Exercise may help in cell regeneration in some parts of the brain, especially the hippocampus, which is used for learning and memory. Researchers have found a lower hippocampal volume in depressed individuals ⁵⁴ and that treatment with antidepressant drugs yields regeneration of cells there ⁵⁵. A research group at Karolinska Institute in Sweden have recently found in animal studies that physical activity regenerates parts of the brain that are depleted in depression.

PHYSICAL ACTIVITY AND OSTEOPOROSIS: MECHANISMS

Bone tissue that is subject to dynamic load responds with a cellular reaction characterized by an acute release of prostaglandins which leads to production of growth factors and subsequent bone renewal in response to the original load ⁵⁶.

Rapid bone resorption takes place in the absence of weight-bearing load as seen during space missions and immobilizations ^{57 58}.

Reduced muscle strength, balance and coordination are risk factors for falls. Physical activity can help reduce these risk factors and consequently, reduce and prevent the risk of fracture.