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Inflammation, sedentary behaviour, COVID-19 and lockdown

In this white paper, Dr Paul Batman unpacks the association between inflammation, sedentary behaviour and the effects of lockdown, and COVID-19.

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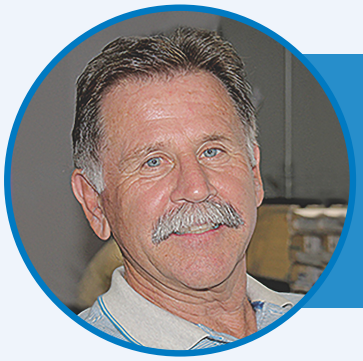

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Content

Inflammation: The root cause of chronic disease

Perhaps one of the most important discoveries in public health over the past 20 years has been the association between low-grade chronic inflammation, the immune system and the onset of chronic diseases. Over 50% of all deaths globally are related to inflammation-caused diseases, such as heart disease, metabolic disease, cancers, Alzheimer's disease, autoimmune diseases and neurological diseases caused by high blood sugar levels, increased food intake, oxidative stress and sedentary behaviour.

The role of inflammation is to eliminate the initial cause of cell injury, remove damaged tissues and begin the repair and restoration process.

Infection is at the centre of the body's basic survival instincts. Fundamentally, when we cut ourselves, our immune system is activated and mobilised by releasing white blood cells that attack the bacteria. After the battle, the white blood cells clean up the affected area, promoting and assisting with healing and, finally returning to normal levels.

This typical acute inflammatory response is activated by receptors on the innate immune system cells and, once the threat has been removed, the body goes back to maintaining its normal homeostatic environment, ready to act again when a new threat is recognised.

However, when the inflammation remains in the absence of any threat, the immune system stays activated and continues to release and create a pro-inflammatory environment, which increases the levels of circulating inflammatory cytokines (CRP, TNF and IL-6) causing long-term collateral damage to cells, tissues, organs and systems. This is particularly evident in obese, sedentary and older people, often caused by chronic infections, weak immune systems, lifestyle and cultural factors, sedentary behaviour, gut health, diet and environmental toxins.

A study of the causes of inflammation reveal that anti-inflammatory agents have been in existence for thousands of years, while the pro-inflammatory agents

are relatively new, possibly starting with industrial changes in the late 19th century and accelerated more recently by a rapidly expanding sedentary society and
COVID-19.

Given that modern bodies have only had a couple of hundred years to adapt to these new pro-inflammatory agents, the immune system has developed this holding pattern of **low-grade chronic inflammation** to combat their side effects, including reducing the effectiveness of insulin released from the pancreas to control and transport glucose, potentially leading to a dramatic increase in type 2 diabetes and heart disease.

How does inflammation work?

Simplistically, there are five different types of white blood cells responsible for immune responses. These are basophils, eosinophils, lymphocytes, monocytes/macrophages and neutrophils.

T cells, B cells and natural killer cells (NK) are part of the lymphocyte group. T cells direct the immune response for killing cells infected with viruses or other pathogens. B cells produce antibodies that fight the infection and natural killer cells destroy the host cells that contain the infection.

Initially, macrophages and neutrophils chase the irritant, engulf it and break it down. Neutrophils travel rapidly to the infected site and begin the inflammation process. The macrophages release inflammatory proteins that are responsible for sending signals between cells and systems. To maintain successful immune function, it is important to create a balance between the pro- and anti-inflammatory cytokines.

Markers of inflammation

The inflammatory response is generally measured by an increase in inflammatory circulating markers such as cytokines, growth factors and reactive oxygen species.

The key cytokines include interleukin-6 (IL-6), tumour necrosis factor (TNF) and C reactive protein (CRP) that act as messengers between the immune system, blood and vessels and the endocrine system. For example, the accumulation of abdominal fat is accompanied by an increase in pro-inflammatory immune cells that release inflammatory substances leading to the low-grade inflammation response throughout the body. These pro-inflammatory markers cause a cross-talk between the immune system, adipose tissue, muscle cells and the brain's hypothalamus.

Chronic low-grade systemic inflammation is associated with a decrease in insulin sensitivity, atherosclerosis and tumour growth, all of which have been termed 'Diseasome of Physical Inactivity' and is regarded as a strong predictor of all-cause mortality and cardiovascular disease in older populations.

CRP is the most studied inflammatory marker responsible for coronary artery disease. CRP is one of the first proteins elevated in response to obesity, smoking, blood pressure, injury, infection and oxidative stress and is regarded as an independent predictor of cardiac death. Elevated levels of CRP double the risk of having a stroke, triple the risk of a future myocardial infarction and quadruple the risk of peripheral artery disease.

Another marker used to identify an increase in inflammation is TNF or tumour necrosis factor. This marker has been identified in increased numbers in the overweight and obese population and is indirectly responsible for insulin resistance. Alternately, weight loss has been shown to reduce the release of this marker.

Additionally, TNF is a contributor to atherosclerosis through the release of adhesion molecules from the inner lining of the walls of the artery restricting blood flow through the artery. Increased levels of TNF are also responsible for decreases in lean body mass, increases in muscle damage and a reduction in the building of proteins necessary for muscle growth.

IL-6 plays a major role at the site of inflammation by producing key proteins in the early stages of the infection. It also plays an important role when moving

into the chronic inflammation stage by changing the nature of some of the white blood cells and stimulating their inflammatory actions.

The role of inflammation in heart disease

Heart researchers were among the first to identify inflammation as the root cause of atherosclerosis. Initially, it was thought that atherosclerosis was caused by plaque building up on the inside of the artery caused by eating a diet too high in fats. It is now recognised as being caused by low-grade chronic inflammation in the artery wall.

The low-density lipoprotein (LDL) or bad cholesterol is absorbed between the tissues of the artery, where it forms a blister-like formation. This process triggers an **inflammatory response** by the immune system that acts on the blister so that it swells within the arterial tissues, blocking and restricting the flow of blood to the heart. As the blister becomes inflamed, it finally forms a scab-like plaque that, if ruptured, causes the contents to block the artery even further, reducing blood flow to the heart, potentially causing a heart attack or stroke.

Those most 'at risk' of this **low-grade chronic inflammation** are the unfit and sedentary who do not regularly engage in physical activity and whose immune system is in an overactive state, resulting in a high-energy demand.

The concentration of anti-inflammatory molecules that are important in the control of inflammation are much lower in sedentary, obese and chronically ill people, further contributing to the low-grade chronic inflammatory state.

The inner lining of the artery wall that is responsible for the vasodilation and vasoconstriction of the blood vessel is called the endothelium. It regulates vagal tone, promotes vascular changes **controls inflammation** and increases the production of nitric oxide. Any imbalance in these functions renders a condition called endothelial dysfunction, caused by the unavailability of nitric oxide (NO), an increase in free radical production, **increased inflammation** and an increase in endothelial activity.

Risk factors associated with endothelial dysfunction include smoking, obesity, diabetes, hypertension, oxidative stress, inflammation, high cholesterol levels and sedentary behaviour.

Nitric oxide is important as it has anti-inflammatory, anti-hypertensive, anti-thrombotic and anti-atherosclerotic properties. Arteries require nitric oxide to increase blood flow through vasodilation (opening).

Sedentary behaviour decreases the availability of nitric oxide to the vessels, increasing inflammation and contributing to atherosclerosis and endothelial dysfunction. Physical activity causes changes in nitric oxide (NO) production, up regulation of the NO gene, increases in vascular endothelial growth factor and an increase in the antioxidant and anti-inflammatory defence system.

Major changes in endothelial function are subject to the availability of nitric oxide. If nitric oxide formation is interrupted, vasoconstriction (narrowing) of the blood vessel occurs. If the amount of nitric oxide remains low in a number of different vessels, there is a strong possibility of a reduction in blood flow to the inner lining of the artery and the formation of a coagulation or eventually a clot or thrombus damaging the arterial wall and predisposing the body to the onset of cardiovascular disease. Over time, any damage to the endothelial wall is seen as the starting point for atherosclerosis and/or cardiovascular disease.

Endothelial dysfunction is regarded as the beginning of cardiovascular disease, with damage to the endothelium changing the vessel's vasodilation (opening) responses, increasing anti-clotting mechanisms, promoting pro-inflammatory responses and producing ongoing adverse structural changes.

The role of inflammation in metabolic disease

Increases in **low-grade inflammation** can occur after a meal, especially one that is high in fat, refined carbohydrates, sugar and other foods that have a high caloric equivalent. It acts to control any potential problems associated with the food eaten and is a normal response across all cohorts of the population. The readily available access to food, the increased volume eaten of both good and

bad food, and the frequency of meals in these vulnerable populations all contribute significantly to a constant cellular inflammatory state.

Air pollution, low humidity and increased carbon dioxide levels in the bloodstream can also cause an increase in ‘metaflammation’.

As more food is eaten and energy not expended, the adipocyte increases in size (hypertrophy) and number (hyperplasia) to store more triglycerides. Hypertrophy of the adipocyte creates oxidative stress in the mitochondria. When excessive amounts of fat cannot be burned by oxygen in the mitochondria, it releases immune cells that produce a **pro-inflammatory response**, causing an over-production of free radicals and oxidative stress in the cell.

As the energy imbalance increases, it is accompanied by abnormal changes in the adipocyte, particularly in two of its key factories: the endoplasmic reticulum (ER) and mitochondria. The ER is responsible for storing the fat, building proteins and sensing and regulating cholesterol. The proteins that are built in the ER must be folded correctly to do their job and then packaged in the Golgi apparatus (GA) where they are stored for future use.

Normally, as the amount of food eaten is increased, the ER builds more proteins for the cell and surrounding structures and everything remains in balance. However, an oversupply of food forces the adipocyte to increase in size, causing the ER to become overwhelmed and produce damaged proteins, making them unable to fulfil their cell-building and repairing role. At the same time, the ER’s ability to store fat and its cholesterol-sensing ability are also adversely affected. The damaged proteins and excess nutrients build up in the cytosol (inside of the cell) interfering with other functions of the cell.

To overcome this situation, the adipocyte slows down the building of proteins and increases the clearance of the damaged proteins. If the ER and the cell cannot restore order, the damaged proteins die, causing the ER additional stress. At this point, the ER releases free fatty acids and **inflammatory**

molecules into the system to cope with the problem. Once this occurs, there is an increase in fat and glucose concentrations throughout other cells in the body, as well as serious cellular insulin resistance, potentially leading to hyperglycaemia (high blood sugar) and long-term diabetes. The insulin resistance extends to both the liver and muscle cells.

Obesity can cause a depletion in antioxidant resources needed to neutralise the over-production of free radicals and the subsequent increase in low-grade inflammation. The production and release of key antioxidant enzymes are severely depleted in sedentary obese people. The increased oxidative stress and increase in inflammation causes damage to the adipocyte cell membrane, covers the membrane with a plastic coating and hinders the action of the mitochondria.

Uncontrolled oxidative stress causes an increase in chronic inflammation in the lining of blood vessels and is the major contributor to cardiovascular disease and metabolic syndrome, as well as damage to other tissues throughout the body.

What the research tells us

Research review 1

Title: *Effect of aerobic exercise on inflammatory markers in healthy middle-aged older adults: A systemic review and meta-analysis of randomised controlled trials*

Authors: Gouhua Zheng, Pingting Qui, Rui Xia, Huiying Lin, Bingzhau ye, Jung Tao and Lidian Chen

Source: *Frontiers in Neuroscience, 2019, 11: 98*

Introduction

Chronic inflammation has been identified as a major contributor of ageing and the development of chronic diseases. Low-grade inflammation affects all systems in the body through the release of pro-inflammatory cytokines and has been reported in the majority of middle-aged and older adults, accelerating the ageing process and contributing to cardiovascular disease, cancer, diabetes and dementia.

Chronic low-grade inflammation can cause the following changes to organs and systems:

- Brain: Pro-inflammatory cytokines cause auto-immune reactions in the brain, potentially leading to depression, autism, poor memory, Alzheimer's disease and multiple sclerosis.
- Skin: Chronic inflammation damages the liver and kidneys, and causes skin rashes, dermatitis, eczema and acne.
- Cardiovascular: Inflammation of the heart, and arteries and walls of the veins, contributes to heart disease, atherosclerosis, high blood sugar and strokes.
- Kidneys: Inflammatory cytokines restrict blood flow to the kidneys resulting in hypertension, nephritis, oedema and kidney failure.

- Bones: Inflammation interferes with the body's natural ability to repair bone mass, increasing the number of potential fractures leading to osteopenia and osteoporosis.
- Liver: A build-up of inflammatory cytokines can lead to an enlarged liver or fatty liver disease, as well as an increased concentration of toxic substances.
- Thyroid: Inflammation can lead to a reduced total thyroid receptor count and a disruption of thyroid hormone functioning.
- Gastrointestinal tract: Inflammation damages the internal lining of the intestines and can result in GERD, Chrohn's disease and celiac disease.
- Muscles: Inflammatory cytokines can cause muscle pain and a reduction in the force of muscle contractions.

Physical activity has been recommended as an intervention to reduce pro-inflammatory cytokines, contributing to a reduction in low-grade inflammation.

The purpose of this study is to evaluate the effects of aerobic exercise on inflammatory markers in middle-aged and older adults.

Method

From an initial review of 19,568 records from four major databases, 11 studies met the study criteria, consisting of 1,250 subjects (40-95 years). The criteria for selection included: randomised control study; and subjects must be middle-aged and older-aged adults over 40 years without any disease or medical condition. Subjects could participate in any aerobic-style exercise for at least four weeks for three or more sessions per week at a heart rate of 45-80% maximum heart rate.

Measurements of inflammatory markers included CRP (C reactive protein), TNF (tumour necrosis factor) and IL-6 (interleukin-6).

Results

In the majority of studies selected for analysis, CRP, TNF and IL-6 were

reduced in middle-aged and older adults as a consequence of participating in an aerobic exercise intervention compared to controls.

Discussion

This review supports the theory that aerobic exercise between 45-80% of maximum heart rate can reduce the pro-inflammatory cytokines CRP, TNF and IL-6 in middle-aged and older adults. As there is a strong correlation between inflammation and ageing, moderate-to-vigorous exercise appears to regulate some of the chronic conditions associated with ageing by regulating the production and release of these pro-inflammatory cytokines.

Physical activity has been found to be the single most important lifestyle factor in reducing sick days and inflammation, particularly at moderate workloads, through the increased activity of the lymphocytes and neutrophils returning to normal levels, signifying their short lifespan.

During physical activity and for approximately three hours after, important immune cells circulate throughout the body at a faster rate than normal. The most effective are neutrophils (situated in bone marrow and lung), natural killer cells (located in spleen) and macrophages, which are part of the innate immune system (front line of defence, preventing many pathogens). Physical activity brings these cells out from the lymphoid tissue and into the blood compartments to roam throughout the body. After three hours of recovery, everything returns to nearby tissue.

It is not necessary to undertake high-intensity exercise for the anti-inflammatory response to occur. In the aged, unhealthy, unfit and obese populations, high-intensity exercise can add to their already inflamed state due to an increase in oxidative stress through the release of rebel oxygen molecules that can damage the internal structure of the cell by increasing pro-inflammatory molecules.

Research review 2

Title: *Does replacing sedentary behaviour with light or moderate-to-vigorous physical activity modulate inflammatory status in adults?*

Authors: Catherine Philips, Christina B Dillon and Ivan J Perry

Source: *International Journal of Behavioural Nutrition and Physical Activity, 2017, 14: 138*

Introduction

A sedentary lifestyle and inactivity are associated with high levels of circulating pro-inflammatory cytokines promoting low-grade chronic inflammation. Sedentary behaviour increases the risk of diabetes, cardiovascular disease, cancer and high mortality rates.

It has been reported that a 20-60% reduction in the levels of pro-inflammatory mediators is possible by participation in physical activity. This is reportedly achieved by increasing the anti-inflammatory capability of skeletal muscle and fat tissue, as well as causing a reduction in reactive oxygen species and preserving nitrogen oxide, all causing an anti-inflammatory effect. Active people tend to have lower levels of the inflammatory cytokines CRP, TNF and IL-6.

While it has been shown that a favourable inflammatory status is important to regulate the onset of chronic diseases, the exact dose of exercise required is still open to debate. Some of the problems of identifying the optimum workloads has been the measurements used to track activity and intensity. Many of the earlier studies used short-answer questionnaires, while the recent availability of reliable trackers has provided a more reliable measuring tool.

The purpose of this study is to investigate the relationship between objectively measured physical activity and the presence of inflammation. It also aims to investigate if substituting sedentary behaviour with low-intensity and moderate-to-vigorous exercise can reduce low-grade inflammation.

Method

A population sample of 396 subjects (50-69 years) was randomly selected from a cross-sectional sample cohort of 2,047 adults from a large primary care centre in Ireland. Subjects wore an accelerometer to measure their activity levels for seven consecutive days, replacing 30 minutes a day of sedentary time with equal amounts of light, moderate-to-vigorous activity.

Clinical data collected included blood samples, health questionnaire, food frequency questionnaire, age, gender, lifestyle factors, alcohol consumption, bodyweight and anthropometric measurements. CRP, TNF alpha, IL-6, adiponectin, leptin and resistin were determined.

Results

The results indicated that the obese subjects presented with a larger waist circumference, insulin resistance, unfavourable inflammatory profiles with increases in CRP, TNF, IL-6 alpha and leptin, and increased levels of white blood cells. This group tended to report high levels of sedentary behaviour and lower physical activity levels compared to non-obese and non-insulin-resistant subjects.

Among all subjects, irrespective of obesity levels or BMI, increased time spent in sedentary behaviour was associated with a more pro-inflammatory profile shown by increased levels of CRP, TNF, IL-6, leptin and white blood cell concentrations.

When sedentary time was reduced and substituted with moderate-to-vigorous physical activity, there was a lowering of pro-inflammatory markers and an improved inflammatory profile.

Discussion

This study demonstrates that increased levels of sedentary behaviour are associated with the release of pro-inflammatory cytokines and a poor

inflammatory profile. The increased concentration of pro-inflammatory markers can contribute to an increased chance of chronic diseases.

Substituting sedentary behaviour with light physical activity produced positive changes to the subjects' inflammatory profile. More significant changes were observed in moderate-to-vigorous activity for middle-aged adults with lower levels of CRP, TNF, IL-6 and white blood cells. Other studies have reported significant improvements in inflammatory profiles across light-to-moderate to vigorous-intensity activities when the volume is kept constant.

Reports suggest that moderate-to-vigorous exercise could be a potent public health tool, with as much as a 50% reduction in mortality rates based on cardiovascular disease risk factors as a consequence of replacing 30 minutes of sedentary time with moderate-to-vigorous physical activity.

This could be particularly relevant today, with the world gripped by the COVID-19 pandemic, a severe and aggressive respiratory condition that causes significant damage to the lungs. The infection causes a local immune response resulting in the release of macrophages and monocytes releasing cytokines initiating a response from T cells and B cells. In most cases, this immune response would neutralise the virus and resolve the infection. However, the COVID-19 virus causes an over-production of pro-inflammatory cytokines, resulting in a cytokine storm, leading to multi-organ damage to respiratory tissue, cardiac, liver, vascular and kidneys.

To increase the virus severity, sedentary lifestyles are also associated with immune dysfunction. Prolonged inactivity and lockdowns can cause an increase in tissue inflammation, impaired natural killer cell activity, reduced T cell proliferation and cytokine production. These responses lead to greater susceptibility to viral and bacterial infections.

Inactive older adults present with lower concentrations of anti-inflammatory biomarkers and higher levels of low-grade chronic inflammation. Improvements in immune function in older adults require continual muscle contractions that can trigger anti-inflammatory responses through the release of myokines.

Research review 3

Title: *Inflammatory effects of high- and moderate-intensity exercise: A systemic review*

Authors: Erica Cerqueira, Daniel A Marinho, Henrique P Neiva and Olga Lourenco

Source: *Frontiers in Physiology, 2020, 10: 1,550*

Introduction

In the aged, overweight, obese, unhealthy and unfit, low-grade chronic inflammation is always present and can become progressively more difficult to control and neutralise ,with cells always thinking they are under attack. This causes the immune system to become overworked and unable to fight legitimate infections, potentially leading to chronic diseases.

As the inflammation progresses, it is possible that the immune system will react against itself as seen in autoimmune diseases such as Lupus, Grave's disease and Crohn's disease. This low level of constant inflammation within the tissues of their body predisposes them to cardiovascular disease, colorectal cancer, type 2 diabetes, chronic obstructive disease and different types of dementia. The cause of these diseases can be traced back to this consistent low-grade inflammation that can persist for decades.

While the national guidelines for physical activity recommend at least 150 minutes of moderate or 75 minutes of vigorous physical activity per week, there are some older adults, obese or overweight, unhealthy and unfit, who are unable to complete this prescription.

Exercise causes an acute response at the beginning and conclusion of the exercise. As the acute effects of the exercise last only a few days, it appears that the frequency of the bout might be more important for longer-lasting immune benefits.

The purpose of this study is to examine the effects of different levels of exercise intensity on inflammatory markers.

Method

The meta-analysis for this study examined 18 studies consisting of 255 healthy subjects. Subjects performed different kinds of exercise interventions, including running, cycling, resistance training and kayaking. Their ages ranged from 18-53 years and all were reported in good health. The exercise was classified into moderate and high intensity based on: moderate = 64-76% maximal heart rate reserve, 12-13 on Borg RPE scale, 40-60% of VO2max, 3-6 METs; high intensity = >76% VO2max, >6 METs, >13 on Borg RPE scale.

Inflammatory markers, including creatine kinase (CK), IL-6, CRP and leukocytes, were evaluated from blood samples.

Results

Both levels of intensity induced increases in pro-inflammatory biomarkers during and immediately after the exercise bout; however, the changes were not consistent across all markers.

White blood cells increased after intense exercise but not after moderate-intensity exercise. IL-6 increased after intense exercise, while CRP increased after both intense and moderate intensity, peaking at 28 hours' post exercise. CK, a marker of muscle damage, was increased only after intense exercise and longer duration.

Even though there were increases in pro-inflammatory markers at both levels of intensity, overall increases occurred to more significant levels in more intense exercise.

Discussion

This meta-analysis suggests that all intensities of exercise have a powerful effect on inflammation markers.

Significantly, the immune system receives no long-term effect from a single bout of physical activity. The results are purely from the accumulation of the acute effects of one bout of physical activity building upon another bout, indicating that the immune responses are frequency dependent. Physical activity is the only stimulus that permits the transient surge of important immune cells as it releases the front line of defence and improves pathogen surveillance.

Following high-intensity activity, the lymphocyte levels drop dramatically below normal levels, with the duration of immunity suppression depending on the intensity and duration of the activity. This suggests that high-intensity exercise can reduce the effectiveness of the immune system response due to the low concentration of circulating lymphocytes and suppressed natural immunity. It is important to recognise the importance of recovery periods to ensure adequate time for the inflammatory markers to return to normal levels before stressing them again with another exercise bout.

The International Society of Exercise and Immunology recommends intensities of between 55-75% of VO2max and durations of up to 1.5 hours for optimising immune system responses.

The national physical activity guidelines recommend intensities of between 40-59% VO2max, which is classified as moderate intensity, while between 60-84% VO2max is classified as high intensity. This would indicate that a physical activity prescription should include both moderate and vigorous intensity to maximise immune system benefits, bearing in mind that progression to high-intensity physical activity is achieved through progressive overload from low to moderate to high intensity.

Research review 4

Title: *Lifestyle risk factors, inflammatory mechanisms, and COVID-19 hospitalization: A community-based cohort study of 387,109 adults in the UK*

Authors: Mark Hamer, Mika Kivimaki, Catherine R Gale and G David Batty

Source: *Brain, Behaviour and Immunity, 2020, 87: 184-187*

Introduction

Patients suffering from COVID-19 display severe respiratory symptoms caused by an overly aggressive immune system. This process releases increased amounts of cytokines, resulting in a cytokine storm.

Under normal conditions,cytokines are important in combating viruses by bringing immune cells to the place of infection, enhancing the function of the immune system. If the cytokine actions become uncontrollable, they cause a massive release of pro-inflammatory mediators, resulting in an overactive immune system releasing excessive specialised monocytes and macrophages that generate the cytokine storm, causing damage to tissues and organs especially in the overweight and those with metabolic syndrome. Both these groups have high levels of blood glucose that stimulates the action of the monocytes and macrophages. The COVID-19 virus attaches to a protein on the cell called ACE2. High levels of glucose increase the concentration of ACE2 on the macrophages and monocytes, causing the virus to infect the cells that are designed to kill it.

Upon entering the cell, the virus now overstimulates the release of inflammatory cytokines, initiating the cytokine storm. The greater the glucose levels, the greater success that virus has of reproducing itself inside of the cell. In addition, the virus produces an increase in reaction oxygen species or free radicals (oxidative stress) in the lungs, creating more pro-inflammatory cytokines.

Lifestyle factors have long been associated with an increase in non-communicable diseases, resulting in high mortality and morbidity rates. Physical inactivity and smoking have been reportedly associated with increased risk of pneumonia and other respiratory conditions.

This study examined the association between lifestyle factors and COVID-19 infections and hospitalizations.

Method

Data was treated from a cohort sample from the UK Biobank that was collected between 2006 and 2010 across 22 research centres in the UK, accessing 502,655 people between the ages of 40-69 years.

Physical activity levels, smoking and alcohol consumption were assessed for all subjects. Personal information was also collected. All data was treated in collaboration with COVID-19 testing and subsequent hospital visits to evaluate the relationship between lifestyle factors and COVID-19.

Results

The final analytical sample numbered 387,109 subjects who were alive at 5 March 2020. Subjects are mainly white British (94.5%). From this sample, 35.5% exceeded the recommended alcohol intake guidelines, 23.5% were obese, 9.7% were smokers, 17.8% were physically inactive (<30 minutes per day), 4.9% had diabetes, 56.1% had hypertension and 5.2% had cardiovascular disease. Approximately 760 subjects from the sample (0.02%) were eventually hospitalised during the intervening period.

The typical profile of a subject requiring hospitalisation due to COVID-19 was male, older age, smoker, physically inactive, less education and possessing a high risk of cardiometabolic factors.

Interestingly, high levels of CRP (pro-inflammatory cytokine) were correlated with poor lifestyle scores and an increased risk of COVID-19 hospitalisation.

Discussion

The results of this study demonstrated important associations between poor lifestyle choices and a high risk of COVID-19 and consequent hospitalisations. It was estimated that unhealthy behaviours accounted for 51% of the population contracting COVID-19.

Results suggest that physical activity provided some protection against contracting COVID-19, even at the lowest levels below the current guidelines, possibly due to its anti-inflammatory effects and heightened immune system responses.

Overweight and obesity were also identified as increased risk factors for contracting the virus, possibly due to immune system hyperactivity, persistent low-grade chronic inflammation, poor metabolic responses and poor lung function.

Daily physical activity is a key to immune protection as it has the potential to exceed the levels of protection more than any other method, including medications and supplements. If the pathogen gets through the slower-acting immune cells, the T cells and B cells are then brought into action.

While physical activity can assist in the prevention of infection or disease, it cannot be therapeutic, as it does not help once the virus has been contracted. Where this does occur, it is important to rest for a full recovery. Active people generally are also not as ‘at risk’ of cancers and heart disease due to the acute immune surge of the natural killer cells that are effective in neutralising these cells.

Muscles are the forgotten members of the immune system, with muscle contractions causing a release of major anti-inflammatory molecules. Physical activity is so powerful that the levels of anti-inflammatory molecules can increase their concentration 100-fold!

Spontaneous physical activity, NEAT and programmed exercise overrides the chronically active immune system and reduces inflammation across all populations through the increased release of these anti-inflammatory myokines that inform the immune system to slow down and relax. This relaxation response allows the immune system to react to normal danger signals rather than be in a constant state of alert, which not only requires additional energy but also down regulates the pro- inflammation response. In studies that cross-referenced different age groups with activity levels and inflammation it was found that, regardless of age, the critical variable was still physical activity. Those at the higher physical activity levels had the lower markers of inflammation, irrespective of BMI.

Other factors that exacerbate the inflammatory process include smoking, age, increase in the number of fat cells, sedentary lifestyle, obesity, poor diet and high blood pressure. Ironically, in the early stages of a fitness programme, a pro-inflammatory response has been noted but as fitness levels improve the response becomes anti-inflammatory, indicating that the best results occur with a strong adherence to a physical activity programme over time.

Research review 5

Title: *Sedentary time and markers of chronic inflammation in high grade populations*

Authors: Joseph Henson et al

Source: *PloS ONE, 8(10): e78350.doi:10.1371*

Introduction

Constant low-grade inflammation is associated with the development of many chronic diseases, including type 2 diabetes. Obesity is also regarded as a chronic inflammatory disease, with the adipocyte responsible for releasing a large number of inflammatory cytokines. Insulin sensitivity, glucose tolerance and triglyceride concentration can be controlled by physical activity, sometimes independent of any change in bodyweight, fat mass or aerobic fitness. Metaflammation has been used to describe the low-grade inflammation caused by the over-production of cytokines in the adipocyte.

The production and release of key antioxidant enzymes and anti-inflammatory myokines are severely depleted in sedentary obese people. The increased oxidative stress causes damage to the adipocyte cell membrane, covers the membrane with a plastic coating and hinders the action of its mitochondria.

The mechanism for the control of high blood sugar begins with an increase in blood sugar in the bloodstream. To combat this increased blood sugar, the pancreas releases insulin, which provides passage for the blood sugar into the muscles and organs, thereby reducing and controlling blood sugar. The greatest peak in blood sugar does not occur immediately after the meal but within 60 minutes of finishing the meal. At this time, there is a significant increase in the release of insulin, causing the blood sugar to be initially shuttled to the large muscles of the thigh, buttocks and trunk. The sugar delivery system is designed to provide the muscles and organs with fuel for energy and allows the body to move continuously after eating.

During sedentary behaviour, the elevated blood sugar remains unused, moving around the blood vessels. The sedentary muscles have no need for the increased blood sugar and, by remaining dormant, they do not assist insulin with the movement of the blood sugar into the muscle.

The increased blood sugar plays havoc with the insulin receptors on the muscles and organs. If, eventually, high blood sugar becomes chronic, the insulin receptors become resistant to insulin, causing a significant amount of surplus sugar to remain in the blood, eventually leading to pre-diabetes or diabetes.

The purpose of this study was to examine the effects of sedentary behaviour and breaks in sedentary behaviour on the release of pro-inflammatory markers in diabetic subjects.

Method

A cohort of 558 diabetic subjects was assessed from 10 primary care practices in the UK in 2010. Subjects were required to wear an accelerometer for seven consecutive days during waking hours. Sedentary time was defined at <25 counts per 15 seconds, while MVPA was assessed at >488 counts per 15 seconds. Breaks in sedentary time were defined as a transition from sedentary time of <24 counts per 15 seconds to an active count of >25 counts per 15 seconds.

Biochemical assessments were completed on IL-6, CRP, leptin and adiponectin.

Results

Sedentary behaviour caused an increase in IL-6, CRP and leptin. When subjects performed MVPA exercise, CRP and leptin decreased while IL-6 remained high.

Breaks in sedentary time reduced IL-6 and leptin. In inactive subjects, sedentary time caused a greater increase in IL-6 than in an active group.

Discussion

In high-risk diabetic subjects, sedentary time caused an increase in pro-inflammatory cytokines of CRP, IL-6 and leptin, resulting in a low-grade inflammation. When subjects became more active, the levels of CRP and leptin were reduced, while IL-6 remained high.

Breaks in sedentary time can produce favourable reduction in inflammatory cytokines, although statistically not significant in this study.

The CRP, leptin and adiponectin were controlled by MVPA exercise, with the exception of IL-6, particularly in those classified as chronically sedentary. IL-6 is a particularly potent cytokine seen in elevated concentrations in chronic diseases.

Apparently, MVPA did not reduce the effect of all pro-inflammatory cytokines caused by sedentary behaviour. These results suggest an exercise resistance to reducing low-grade inflammation in very sedentary groups. Continual transitional breaks in sedentary time have been shown to reduce IL-6 and other inflammatory markers, indicating that frequency of the muscle contractions might be a more powerful stimulus to control low-grade inflammation in high-risk diabetic groups, rather than a single bout of MVPA exercise. IL-6 acts as a key myokine when released during muscle contractions. In the correct concentration, IL-6 is important in anti-inflammatory responses but, when uncontrolled, becomes a cytokine, causing an excessive inflammatory response.

Prolonged sitting has been known to reduce the positive effects of inflammation and contribute to a pro-inflammatory response caused by a lack of muscle activity. This is made worse by a blunted triglyceride uptake and low HDL cholesterol, which contribute further to more inflammation.

Sedentary diabetic groups often have difficulty in maintaining MVPA exercise. A more realistic alternative is to start with low-to-moderate physical activity performed throughout the day in an intermittent fashion. Activities of daily living can be very effective in motivating diabetic patients to move more throughout the day and control low-grade chronic inflammation.

Research review 6

Title: *Physical activity, sedentary behaviour and inflammatory and homeostatic markers in men*

Authors: Tessa Parsons et al

Source: *Med Sci Sports Exerc, 2017, 49(3): 459-465*

Introduction

Ageing is associated with increases in sedentary behaviour and an increase in low-grade chronic inflammation, contributing to chronic disease such as cardiovascular disease and type 2 diabetes. One common inflammatory marker is IL-6, which is strongly linked with coronary artery disease in older adults. Other coagulation markers also increase the risk of cardiovascular events. When inflammation and coagulation markers interact, inflammation increases, which in turn increases coagulation markers.

Glucose tolerance decreases with age and inactivity. Diabetes is reported in 27% of the over-65 years group. During the ageing process, clients as older adults become less active, lose lean body mass, increase fat mass and are often on medication, all of which can affect glucose metabolism.

The available literature suggests that physical activity can have a favourable effect on inflammatory markers, while sedentary behaviour can cause chronic inflammation.

As a muscle begins to atrophy, physical activity performed at a specific intensity will be completed at a higher percentage of maximal capacity, placing greater stress on the moving body. This indicates that a level of intensity undertaken when young, when performed as an older adult, will represent a greater level of effort, which may cause a greater reliance on carbohydrate utilisation.

The increased stress is compounded by an impairment of glucose transport and enzymatic changes. There is an age-related insulin resistance found in older adults 60 years or greater, mainly due to skeletal muscle atrophy. The increased resistance to insulin on the skeletal muscle is caused by a lower level of tyrosine kinase on the insulin receptor, which is responsible for the movement of intracellular transporters (glut-4 protein) from the intracellular compartment to the sarcolemma.

The purpose of this study was to quantify the association between device-measured physical activity and sedentary behaviour and the level of inflammatory markers in older males.

Method

A final population cohort of 1,274 older males from 24 British towns and part of the British Regional Heart Study were invited to be part of this study. The subjects were required to wear an accelerometer over the right hip for seven days during waking hours. Intensities were measured corresponding to sedentary time (<1.5 METs), light intensity (1.5-3 METs) and moderate-to vigorous intensity (>3 METs). Subjects completed a health-risk questionnaire, as well as BMI.

Results

The men in the final sample recorded a mean of 4,938 steps per day and 164,749 accelerometer counts per day. They spent on average 616 minutes in sedentary behaviour, 199 minutes in low-intensity physical activity and 40 minutes in MVPA. Those subjects who spent more time in MVPA and were younger had a lower BMI. Subjects who were older and more sedentary had a higher BMI and suffer from a chronic condition.

Overall, those subjects with higher total physical activity levels at low intensity, higher daily steps and higher MVPA presented with lower levels of IL-6, CRP and other coagulation factors. Every additional 10 minutes of physical activity was associated with 3.2% lower IL-6 and CRP.

Discussion

Older males who had higher levels of physical activity showed lower levels of IL-6 and CRP and a more favourable inflammatory profile. Conversely, those who had higher levels of sedentary time had higher levels of inflammatory markers and a more pronounced low-grade inflammation. Those subjects who were classified with a higher BMI and active still had lower levels of inflammatory markers than those classified as higher BMI and sedentary. Those at the higher physical activity levels had the lower markers of inflammation, irrespective of BMI.

Physical activity can override the chronically active immune system and reduces inflammation across all populations through the increased release of these anti-inflammatory myokines that inform the immune system to slow down and relax. This relaxation response allows the immune system to react to normal danger signals, rather than be in a constant state of alert, which not only requires additional energy but also down regulates the pro-inflammation response.

In studies that cross-referenced different age groups with activity levels and inflammation, regardless of age the critical variable is physical activity irrespective of the intensity. The total amount of physical activity was the most important variable. It is better to do something than nothing.

Older age groups tend to have higher levels of inflammation when compared to younger groups, irrespective of physical activity levels, while active individuals produced anti-inflammatory responses that can counter lower chronic inflammation seen in vulnerable populations.

A sedentary lifestyle and inactivity are also associated with high circulating levels of TNF, leading to an increased inflammatory state with a possible reduction in the levels of anti-inflammatory mediators by 20-60% by participation in physical activity. This is achieved by increasing the anti-inflammatory capability of skeletal muscle and fat tissue, as well as causing a reduction in reactive oxygen species and preserving nitrogen oxide, all causing an anti-inflammatory effect.

An area of increasing interest is the effect that sedentary behaviour has on mood changes and disorders and inflammation. Strongly associated with mood disorders is the presence of inflammatory cytokines that indicate a probable link with systemic inflammation.

Increases in sedentary behaviour due to COVID-19 lockdowns can have a negative impact on mood and depressive symptoms caused by an increase in pro-inflammatory responses, resulting in an increased systemic low-grade inflammation.

People who are suffering from mental illness could be at a higher risk of inflammation from high-intensity physical activity in a similar way to the obese, overweight, aged, unfit and unhealthy. It further supports the need to include more multiple intermittent activities throughout the day to further reduce sedentary time rather than just rely on 30-60 minutes per day of MVPA for five days per week.

Research review 7

Title: *Physical activity, sitting time and mortality from inflammatory diseases in older adults*

Authors: Veronica Cabanas-Sanchez et al

Source: *Frontiers in Physiology, 2018, 9: 898*

Introduction

Inflammation has been documented as a major cause of chronic diseases. During ageing, low-grade chronic inflammation increases the long-term stimulation of the immune system, causing an increase in oxidative stress within the cells.

If uncontrolled during the ageing process, the long-term result is a chronic stimulation of the innate immune system called inflammaging, which can become damaging.

There is substantial evidence that increases in physical activity and a reduction in time spent sedentary can produce anti-inflammatory actions that can prevent cardiovascular disease, cancer, mitochondrial dysfunction, diabetes and sarcopenia.

There are three possible explanations supporting physical activity as a key player in reducing and controlling systemic low-level inflammation. These include a reduction in visceral fat, an increased production and release of anti-inflammatory cytokines from the contracting skeletal muscle, and a reduction in the activity of the immune system's white blood cells. As the skeletal muscles contract during physical activity, their muscle fibres produce and distribute anti-inflammatory myokines that act on all regions of the body and protect the arteries against atherosclerosis and stenosis (narrowing).

This study examines the combined associations between physical activity

sitting time with long-term mortality caused by increased pro-inflammatory responses.

Method

A cohort of 3,677 subjects aged >60 years were selected for this study. Each subject was asked to complete a structured questionnaire, personal information and physical examination. Information on physical activity and sedentary behaviour was self-reported.

Results

Higher levels of physical activity were associated with lower risk of death from total inflammatory diseases. Those who sat for >7 hours per day were at a higher risk of all-cause mortality. Subjects with low physical activity levels and high sedentary time were consistently at a higher risk of mortality due to increased inflammation.

Those subjects in the higher risk groups were older, had higher a BMI, were less educated and were more likely to suffer from diabetes or coronary artery disease.

Discussion

Subjects who were moderately active or very active had lower mortality rates than inactive and sedentary subjects. Active subjects also presented with reductions in inflammatory markers IL-6 and TNF and CRP, as well as higher anti-inflammatory markers such as IL-10. Those with high sedentary time had a higher mortality rate, with increases in pro-inflammatory markers IL-6, TNF and CRP.

Global death rates from inflammatory-related diseases are significant, particularly diabetes, kidney diseases, cardiovascular disease and respiratory diseases.

During the ageing process, there is concomitant increase in low-grade chronic inflammation called inflammaging, contributing to age-related chronic diseases. It is generally caused by a chronic stimulation of the innate immune system that damages sensory receptors that become hypersensitive to damaging signals. t can play a significant role in the development of atherosclerosis, diabetes, cancer and heart disease.

Under normal conditions, there is a dynamic balance between the pro-inflammatory and anti- inflammatory cytokines that regulate the immune system to function normally. When the inflammatory balance is upset, there is an over-balance of cytokines such as TNF and IL-6.

There is an increase in fat mass and a reduction in lean body mass, with sedentary ageing leading to an increase in inflammatory status. An increase in visceral fat increases the production and release of inflammatory cytokines. Maintaining muscle mass is central to maintaining a strong anti-inflammatory profile, while sarcopenia contributes to muscle wasting and a proliferation of fat causing an increase in low-grade inflammation. A decrease in muscle mass contributes to changes and dysfunction in the nervous system, gut, heart, lungs, blood vessels, pancreas and many other organs.

Maintaining muscle mass and reducing fat mass through physical activity has become a critical player in controlling inflammaging. The suggested mechanisms for the anti-inflammatory responses from physical activity include a reduction in visceral fat mass that can reduce the release of inflammatory cytokines, activation of the sympathetic nervous system that can cause the inhibition of TNF, an increase in muscle contractions that induce the release of anti-inflammatory markers including IL-10, a strong anti-inflammatory marker, and an improvement in antioxidant mechanisms reducing the impact of free radical production.

It is also possible to receive an anti-inflammatory response from lifestyle changes without any significant decrease in obesity or fat levels. Regular low-to-moderate muscle contractions promote anti-inflammatory signals to other distant regions of the body in addition to skeletal muscle.

Research review 8

Title: *Responses of inflammatory cytokines following moderate-intensity walking exercise in overweight or obese individuals*

Authors: Yunsuk Koh, Kyung-Shin Park

Source: *Journal of Exercise Rehabilitation, 2017, 13(4): 472-476*

Introduction

The adipocyte or fat cell is the main type of cell in adipose tissue and is recognised as a critical player in obesity-related cardiovascular disease. An adipocyte is more than just storage for fat or adipose tissue, it is an intelligent cell that constantly monitors and changes the other molecules that are part of its structure.

The adipocyte is a tiny cell that is packed with triglycerides (stored fat) occupying most of the cell with the cytoplasm, nucleus, mitochondria, endoplasmic reticulum and Golgi apparatus pushed towards the edges of the cell.

All the adipocyte cell components are bound by a cell membrane (covering) that permits the movement of molecules into and out of the cell, monitors the environment, protects itself and has specific molecules that maintain its order.

There are over 30 billion adipocytes in the body, weighing approximately 15kg. It was originally designed as a small package of stored energy. An adipocyte weighs about 0.5 of a micron, compared to a teaspoon that can hold six million microns! Amazingly, one gram of fat releases 9kcal of energy, which translates into a combined 135,000kcal of stored energy in all the adipocytes, making it possible to go without food for between 45-60 days.

Visceral fat is associated with the release of inflammatory cytokines CRP and TNF which elevates the level of oxidative stress, leading to insulin resistance. Increases in visceral fat cause a decrease in production of adiponectin, anti-diabetic, anti-atherosclerotic and anti-inflammatory molecules, all contributing to chronic disease.

Physical activity has been regarded as a legitimate intervention to improve the inflammatory profile, independent of any weight loss, through the increased production of anti-inflammatory cytokines.

The purpose of this study was to assess the effect of short-term training on inflammatory markers without weight loss and or fat loss in overweight people.

Method

For this study, 27 inactive overweight or obese males and females aged between 18-65 years were selected. They maintained a normal diet and did not take part in any physical activity other than the requirements of the study.

Subjects were randomly assigned to either an exercise group or a control inactive group. Based on a treadmill test, a workload equal to 70% of HR max was determined for the exercise group. The exercise intervention consisted of walking on a treadmill at 70% of HR max for 60 minutes three times per week. Body composition measures including %BF, muscle mass and fat mass were taken at the start of the programme.

Blood samples were taken, measuring CRP, TNF and adiponectin.

Results

After four weeks or 12 training sessions there was no discernible change in bodyweight, BMI and %BF in either treatment group. There was a noticeable decrease in CRP after four weeks of training but not at significant levels. There was no difference in adiponectin levels and a decrease in TNF in the exercise group.

Discussion

This study confirmed the possibility of a decrease in levels of inflammatory cytokines in the absence of any weight loss. CRP decreased, but not significantly, while TNF was significantly reduced.

Inactivity and sedentary behaviour are associated with an increase in pro-inflammatory molecules, while improvements in aerobic fitness have been shown to cause significant reductions. Other studies have stated that weight loss is required for overweight and obese people to decrease inflammatory markers, albeit >5% loss of fat mass. Many of these studies were of a longer duration, which assisted with weight loss. This study was too short to show weight loss but still reduced the levels of inflammatory cytokines.

It is likely that a longer training duration would have contributed to a significant change in CRP and adiponectin.

The key message is that controlling inflammation through physical activity can assist in reducing low-grade chronic inflammation, avoiding insidious metabolic diseases. This partly explains why some obese or overweight people can reduce chronic inflammation and remain metabolically healthy yet still be overweight. Overweight people known as having metabolically healthy obesity are reported to comprise 35% of the obese population. Many studies report that lean and obese metabolically healthy people can have low levels of inflammation as measured by inflammatory markers.

Research review 9

Title: *Associations between cardiorespiratory fitness and C reactive protein in men*

Authors: TS Church, CE Barlow, CP Earnst, JB Kampert, EL Priest, SN Blair

Source: *Arterioscler Thromb Vasc Biol, 2002, 22: 1,869-76*

Introduction

C reactive protein has been reported as a key marker of chronic inflammation, responsible for contributing to cardiovascular disease. There have been studies suggesting that a reduction in bodyweight can also cause a decrease in the release of CRP. A few available studies have also found that regular physical activity can reduce CRP levels, with reductions found in those males who exercised more than once per week and more significant changes of 31% in marathoners in older males.

The purpose of this study was to examine the association with cardiorespiratory fitness and CRP levels with an adjustment for bodyweight.

Methods

A cohort of 722 males was selected from the Aerobic Longitudinal study. Data for CRP was analysed across five levels of fitness groups, with values adjusted for age, body mass index, vitamin use, statin medication, aspirin use and the presence of inflammatory disease, cardiovascular disease, diabetes and smoking habit.

Discussion

The key outcome from this study was that the highly fit males had lower levels of pro-inflammatory cytokine CRP, independent of body composition as assessed by BMI, % body fat and waist circumference. Within the overweight and obese group, the highest levels of pro-inflammatory cytokine CRP was found in the lowest fitness group. Given that CRP is a strong indicator of cardiovascular events, general levels of fitness can be a key factor in reducing CRP levels.

Overweight and obese subjects with low fitness levels presented with the highest CRP levels, indicating that visceral fat is a strong producer of CRP and tissue inflammation. TNF, IL-6 and CRP are released in significant amounts from adipose tissue, causing an increase in sympathetic stimulation that can be potentially controlled by regular physical activity. The most effective intervention appears to be physical activity undertaken on a frequent basis, irrespective of intensity. With regular physical activity, the impending increase in pro-inflammatory cytokines appears to become less with every movement bout, as shown in the highly fit groups.

Research review 10

Title: *Association between healthy lifestyle scores and inflammatory markers among Puerto Rican adults*

Authors: M Sotos-Prieto, SN Bhupoathiraju, X Gao, KL Tucker and J Mattel

Source: *Nutr Metab Cardiovasc Dis, 2016, 26(3): 178-184*

Introduction

While specific physical activity workloads have been identified as key interventions in controlling the release of pro-inflammatory cytokines, lifestyle behaviours might also contribute to controlling inflammation. Lifestyle factors such as dietary patterns, smoking, sleep and physical activity, as well as social support and network, might play a role in relieving stressors that trigger inflammatory responses.

The purpose of this study was to assess the associations between lifestyle factors and inflammatory markers in adults.

Method

A cohort of 842 Puerto Rican adults aged 45-75 years who lived in Boston served as subjects for this study. Each subject completed a Healthy Lifestyle Assessment, which was cross-analysed with three inflammatory markers: IL-6, TNF and CRP.

Results

Those subjects with the most favourable Healthy Lifestyle Scores were older females, with a higher total household income and high education attainment.

Discussion

Those who had high Healthy Lifestyle Scores had lower levels of pro-inflammatory markers, with larger association occurring when healthy lifestyle factors were cluttered. It appears the factors such as low income and educational levels caused poor adherence to a healthy lifestyle and impacted on inflammatory marker levels.

Simple changes in lifestyle, such as smoking cessation and a better diet, independent of physical activity, can have a favourable effect on inflammatory markers. People who have below average immunity, such as frail old people or cigarette smokers, have an immune barrier that is more fragile than a non-smoker, active or younger people.

This study reported that changes in physical activity were more pronounced if combined with other lifestyle changes, rather than just as an independent intervention. The greater the overall change in multiple lifestyle factors, the greater the reduction in inflammatory markers.

Given that low-grade inflammation is reported to precede chronic diseases, making better multiple lifestyle choices through a holistic health approach to reduce inflammatory markers can reduce the risk of disease and improve overall health.

The bottom line

1. Given the recognition that low-grade chronic inflammation can cause many chronic diseases that can be regulated by physical activity, more emphasis should be placed on the role of reducing sedentary behaviour and increasing physical activity levels globally by reducing the level of circulating pro-inflammatory cytokines. Changes in physical activity are more pronounced if combined with other lifestyle changes, rather than just as an independent intervention. The greater the overall change in multiple lifestyle factors, the greater the reduction in inflammatory markers.

The bottom line

1. Given the recognition that low-grade chronic inflammation can cause many chronic diseases that can be regulated by physical activity, more emphasis should be placed on the role of reducing sedentary behaviour and increasing physical activity levels globally by reducing the level of circulating pro-inflammatory cytokines. Changes in physical activity are more pronounced if combined with other lifestyle changes, rather than just as an independent intervention. The greater the overall change in multiple lifestyle factors, the greater the reduction in inflammatory markers.

2. During physical activity, and for approximately three hours after, important immune cells circulate throughout the body at a faster rate than normal. The most effective are neutrophils (situated in bone marrow and lung), natural killer cells (located in spleen) and macrophages, which are part of the innate immune system (front line of defence preventing many pathogens). Physical activity brings these cells out from the lymphoid tissue and into the blood compartments to roam throughout the body. After three hours of recovery, everything returns to nearby tissue.

3. The world is gripped with the COVID-19 pandemic, which is a severe and aggressive respiratory condition that causes significant damage to the lungs. The infection causes a local immune response with the release of macrophages and monocytes, releasing cytokines initiating a response from T cells and B cells. In most cases, this immune response would neutralise the virus and resolve the infection. However, the COVID-19 virus causes an over-production of pro-inflammatory cytokines, resulting in a cytokine storm leading to multi-organ damage to respiratory tissue, cardiac, liver, vascular and kidneys.

4. Substituting sedentary behaviour with light physical activity produces positive changes to the inflammatory profile. More significant changes can occur in moderate-to-vigorous activity for middle-aged adults with lower levels of CRP, TNF, IL-6 and White Blood Cells. Studies report significant improvements in inflammatory profiles across light to moderate to vigorous intensity activities when the volume is kept constant.

5. The immune system receives no long-term effect from a single bout of physical activity. The results are purely from the accumulation of the acute effects of one bout of physical activity building upon another bout, indicating the immune responses are frequency dependent. Physical activity is the only stimulus that permits the transient surge of important immune cells, as it releases the front line of defence and improves pathogen surveillance.

6. In high-risk diabetics, sedentary time can cause an increase in pro-inflammatory cytokines of CRP, IL-6 and leptin, resulting in a low-grade inflammation. When diabetics became more active, the levels of CRP and leptin, resulting in a low-grade inflammation. When diabetics became more active, the levels of CRP and leptin are reduced, while IL-6 can remain high. Regular breaks in sedentary time can produce favourable reduction in all inflammatory cytokines.

7. Daily physical activity is a key to immune protection, as it has the potential to exceed the levels of protection above any other method, including medications and supplements. If the pathogen gets through the slower-acting immune cells, the T cells and B cells are then brought into action. Muscles are the forgotten members of the immune system, with muscle contractions causing a release of major anti-inflammatory molecules. Physical activity is so powerful that the levels of anti-inflammatory molecules can increase their concentration 100-fold!

8. Sedentary behaviour plays a significant role in mood changes and disorders and inflammation. Strongly associated with mood disorders is the presence of inflammatory cytokines, suggesting a probable link with systemic inflammation. Increases in sedentary behaviour due to COVID-19 lockdowns can have a negative impact on mood and depressive symptoms caused by an increase in pro-inflammatory responses from systemic low-grade inflammation.

9. Visceral fat is associated with the release of inflammatory cytokines CRP and TNF, which elevates the level of oxidative stress leading to insulin resistance. Increases in visceral fat are related to a decreased production of adiponectin, anti-diabetic, anti-atherosclerotic and anti-inflammatory molecules that contribute to chronic disease.

10. Overweight and obese subjects with low fitness levels have the highest CRP levels, indicating that visceral fat is a strong producer of CRP and tissue inflammation. TNF, IL-6 and CRP are released in significant amounts from adipose tissue, causing an increase in sympathetic stimulation that can be potentially controlled by regular physical activity. The most effective intervention appears to be physical activity undertaken on a frequent basis, irrespective of intensity. With regular physical activity, the impending increase in pro-inflammatory cytokines appears to become less with every movement bout, as shown in highly fit groups.