Low-grade inflammation – what is it and why does it matter?

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Chronic low-grade inflammation (CLGI) is described with pathophysiology, blood tests, and clinical features defined. Risk factors for the development of CLGI are considered and the use of dietary changes and lifestyle features highlighted. Inflammatory changes in osteoarthritis (OA), chronic pain and psychiatric conditions are covered. Therapeutic interventions in the presence of CLGI including exercise, diet and lifestyle changes, and pharmacological interventions are considered.

LEARNING OUTCOMES
TO SUPPORT PHYSIO FIRST QAP

1 Chronic low-grade inflammation (CLGI) can occur through unresolved acute inflammation or as an independent state on its own.
2 Obesity can increase systemic inflammation through fat cell (adipocyte) action.
3 Regular exercise, lifestyle change and dietary manipulation can all reduce systemic inflammation.

Introduction to inflammation

Inflammation is part of the body's normal defence mechanism created by the immune system. It is a physiological response to threat posed by tissue damage (injury) or invasion by a pathogen (bacteria, virus). In a soft tissue injury, these changes can be termed damage associated molecular patterns (DAMPs), and when linked to an infection, they can be termed pathogen associated molecular patterns (PAMPs). In each case, the aim of the tissue changes is to restore metabolic balance (homeostasis) and promote healing and repair. Acute inflammation builds quickly and normally resolves within a short period. For example, when related to a sprained ankle injury, the affected tissues are initially hot and red, reflecting acute inflammation which calms down in a matter of days.

In the case of invasion by bacteria or virus, for example in acute pneumonia, the air sacs of the lungs are affected, and this can lead to a dry or productive cough, breathlessness and a high temperature. Rest will usually allow the inflammation to resolve, although more severe cases will respond to antibiotics. Generally, acute inflammation lasts from a matter of days to a few weeks and represents the initial finite stage of the healing process. However, if inflammation is maintained and does not progress to a natural healing resolution, it is referred to as chronic, or long-term, inflammation.

CHRONIC INFLAMMATION

Chronic low-grade inflammation (CLGI), also known as long-term inflammation or systemic chronic inflammation (SCI), can occur through unresolved acute inflammation or as an independent state on its own. Table 1 illustrates some causes of CLGI. It can occur where a substance causing the acute inflammation remains in the body, or as a result of a chemical toxin permanently being within a person's close environment. Some auto-immune conditions such as rheumatoid arthritis or lupus have low-grade inflammation as one of their features. In addition, lifestyle factors which increase the production of free radicals or other inflammatory mediators can be an aspect in the development or maintenance of CLGI.

Although chronic inflammation is a term relatively unknown to the general public, it is a feature of diseases such as heart conditions, obesity, cancer, diabetes, chronic respiratory conditions, and stroke that are responsible for the annual deaths of three out of every five people worldwide. In addition to death,

TYPE	FEATURES
Unresolved acute state	Failure to eliminate agent causing acute inflammation, such as infectious organism, fungi, protozoa, parasite
Exposure to irritant which cannot be eliminated	Foreign material such as industrial chemical which cannot be broken down
Auto-immune disorder	Immune system recognises part of the body as a foreign substance (rheumatoid arthritis, systemic lupus erythematosus)
Defect in inflammatory mediating cells	Auto-inflammatory disorder
Recurrent episodes of acute inflammation	Acute inflammation unresolved prior to onset of second episode
Oxidative stress and mitochondrial dysfunction	Production of free radicals, advanced glycation end products, uric acid crystals, homocysteine, oxidised lipoproteins

TABLE 1: Causes of chronic low-grade inflammation (data from Pahwa *et al* 2022)

chronic inflammation reduces the quality of life of more than 350 million people worldwide through joint disease such as arthritis (Pahwa *et al* 2022). Respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD), often seen in children and older adults respectively, can be exacerbated where CLGI is present.

How the body reacts to chronic inflammation

The chemical reactions which are a result of CLGI progress from the changes that occur in acute inflammation. Increased blood flow due to an expansion of vessels (vasodilation), and increased vessel permeability, is paralleled by changes to white blood cells. In acute inflammation, neutrophils migrate into an affected body area, but if the acute phase moves into a chronic stage, macrophages and lymphocytes begin to replace the neutrophils.

These different cells produce cytokines (proteins which affect the immune system), including Interleukin one and six (IL-1, IL-6), and tumour necrosis factor alpha (TNF-α). Importantly, the cytokines mediate inflammation, keeping the process active. Further, cytokines have an effect on the brain and can initiate changes such as sickness, behaviour and depression (Dantzer *et al* 2008).

In addition, there is an overproduction of C-reactive protein (CRP) that normally circulates at low levels and is produced by the liver in response to macrophage activity and circulating fat cells (adipocytes). The measurement for CRP is through a blood sample and expressed in milligrams per litre (mg/L), with optimal values being between 0.8mg/L and 3.0mg/L, although higher values are seen in later life. In acute inflammation, CRP values can increase to 5mg/L very quickly, i.e. within hours, and double every eight hours, peaking between 36 and 50 hours after the condition onset. Bacterial infection can see CRP levels as high as 100mg/L to 500mg/L.

With chronic low-grade inflammation, CRP levels may remain between 2mg/L and 10mg/L. High sensitivity C-reactive protein (hs-CRP) may also be used as a test, and its range is generally between 05mg/L to 10mg/L compared to a standard CRP test which typically measures in a range of 10mg/L to 1,000mg/L. Although more sensitive, and able to measure trace amount of CRP in the blood, hs-CRP is more often used clinically to analyse cardiovascular risk.

Another blood test which may be raised with inflammatory conditions is erythrocyte sedimentation rate (ESR). This classically measures the rate, expressed in millimetres per hour (mm/h), at which red blood cells drop in a standard (Westergren) tube. This, however, is a non-specific measure of inflammation, and a centrifuge test is commonly used to give a more rapid result. Where inflammation is present, red blood cells stick to each other more easily, and ESR will be higher 24-48 hours after condition onset. The level of ESR rises with age. From between the ages of 20 years to 90 years the optimal values for men are between 12mm to 19mm/h respectively, and for women between 18mm to 23mm/h (Pepys & Hirschfield 2003; Bray *et al* 2016).

Essentially, CLGI inflammatory factors in the blood are measurable at slightly higher levels than average, but still within a normal range. Local inflammatory factors seen in acute inflammation resulting from tissue damage or pathogenic invasion normally lead to resolved healing. These same factors, if unresolved, are associated with systemic chronic inflammation and can result in collateral body system damage (Furman *et al* 2019).

Several symptoms are associated with CLGI, but they can also be seen in other pathologies so are not specific to this condition. Pain in multiple body sites, chronic fatigue and insomnia, mood disturbances, low energy, gastrointestinal symptoms, skin changes, swollen lymph glands and frequent infections may all be seen in combination.

The risk demographic for chronic inflammation conditions

An increased bodyweight or body mass index (BMI) is often seen as a risk factor in the exacerbation of conditions such as arthritis of the weight-bearing lower limb joints. Typically, this is viewed through a biomechanical lens, with the suggestion that greater bodyweight increases joint loading and may drive symptoms.

However, the metabolic effect of obesity on inflammation must also be considered. Increased abdominal adipose tissue often observed in obesity leads to tissue hypoxia as the speed of enlargement of the abdominal region can exceed the tissue perfusion capacity of local blood vessels. In addition, adipocytes increase in size, filling with triglycerides, a change which shifts the cell fundamental characteristics (phenotype) to pro-inflammatory. The combination of low-oxygen availability of truncal fat and increased fat cell size leads to cell death (apoptosis), accelerating a local inflammatory reaction (Margioris *et al* 2013), which may be a significant factor in arthropathy.

Also relevant to rehabilitation is the fact that the ratio of white (metabolically inactive) to brown (metabolically active) adipocytes changes with obesity and exercise. Lean active individuals tend to have more brown fat cells. Additionally, obesity can increase transient postprandial inflammation due to the larger size of adipocytes (Blackburn *et al* 2006). White adipose tissue is typically found subcutaneously or within the trunk

> "INCREASED BODY MASS INDEX IS OFTEN SEEN AS A RISK FACTOR IN THE EXACERBATION OF CONDITIONS SUCH AS ARTHRITIS OF WEIGHT-BEARING LOWER LIMB JOINTS"

surrounding the viscera, while brown adipose tissue is found, in adults, within the paravertebral, axillary, and supraclavicular regions (Viranen *et al* 2009). Cells undergo programmed apoptosis when they reach a certain size, to maintain tissue homeostasis. This cut-off size is smaller in white adipocytes, and so triggers an earlier inflammatory response.

Interestingly, there is even a difference between white adipocytes found subcutaneously and those placed within the trunk, with the subcutaneous type being more resistant to apoptosis (Tchkonia *et al* 2005). General characteristics of white adipocytes include a single large fat lobule, few mitochondria, and storage of energy as triglycerides. They are typically found in high concentrations and are pro-inflammatory. Brown adipocytes have multiple small fat droplets, large numbers of mitochondria, a tendency to expend energy as heat and have an anti-inflammatory effect on cytokines (Margioris *et al* 2013).

With increasing age there is a general increase in inflammatory markers. Several factors may be of relevance to this change including free radical accumulation over a lifetime, increased visceral fat, reduced physical activity and co-morbidities such as diabetes. Whilst lifestyle factors such as diet and exercise have an anti-inflammatory effect, cigarette smoking lowers the production of anti-inflammatory chemicals. Cell senescence (cessation of cell division), combined with environmental factors and stress, build up over time. Immune cell phenotype alteration and increasing pro-inflammatory molecules, including cytokines, are commonly found in healthy seniors. Those free of chronic pathologies have a balanced increase in both pro- and anti-inflammatory chemicals, and it is the ratio between these two factors, rather than the amount of pro-inflammatory chemicals per se, that is important (Morrisette-Thomas *et al* 2014).

Additionally, sex hormones including testosterone and oestrogen suppress the production of pro-inflammatory chemicals, and lower sex hormone concentrations in later life may reduce this capacity. Emotional stress and sleep reduction is related to cytokine release, and poor sleep patterns are associated with CLGI (Pahwa *et al* 2022). In a systematic review of 72 studies, sleep disturbance and shorter duration sleep, i.e. < 7 hours per night, were both associated with higher CRP levels, whilst extreme long sleep duration, > 8 hours per night, was associated with higher levels of CRP and IL-6 (Irwin *et al* 2016). Sleep disturbance is not associated with age, but women may suffer a greater effect than men (Prather *et al* 2013).

Environmental and industrial toxins, and tobacco smoking, have also been cited as possible causes or co-factors of CLGI. Chemicals such as phthalates, polyfluorenes, bisphenols, flame retardants and aromatic hydrocarbons can promote inflammatory activity via oxidative stress or endocrine alterations beginning in utero (Furman *et al* 2019). Even prior to conception, paternal factors can have an epigenetic effect, transmitting risk for CLGI between generations, and programming the immune system prior to birth (Macpherson *et al* 2017). Additionally, exposure to a wide variety of microbes in early life lessens the likelihood of chronic inflammation in adult life, independent of socioeconomic status, current body fat level and other health behaviours (McDade *et al* 2010).

Dietary factors and CLGI

Several dietary factors are associated with reducing chronic inflammation and these are summarized in table 2. Use of a low-glycaemic index (GI) diet over 10 weeks has been shown to be associated with lower levels of CRP and IL-6 in obese adolescents (Rouhani *et al* 2016). Saturated fatty acids (SFA) are associated with higher levels of inflammatory markers (Bujtor *et al* 2021), as are trans fatty acids (TFA) also known as partially hydrogenated fats (Mozaffarian 2006). Monounsaturated fatty acids (MUFA) from nuts and seeds are associated with lower IL-6 levels, while omega-3 polyunsaturated fatty acids (PUFA) from oily fish have been shown to inhibit the activation of pro-inflammatory pathways (Calder 2015).

A diet higher in wholegrains and fibre (coarse grains) has been shown to favourably affect inflammatory biomarkers in obese children using a wholegrain diet over a six-week period (Hajihashemi *et al* 2014). Some studies have found an association between high intake of meat and dairy and inflammatory markers, but others have not. Diets high in refined grains, red meat, ultra-processed foods, trans fatty acids, and high-fat dairy typically found in a western diet have a positive association with pro-inflammatory markers (Khayyatzadeh *et al* 2018). Of the separate components found in these diets, the ratio of pro-inflammatory SFA intake to that of fats inhibiting the inflammatory response such as PUFA and MUFA may be significant (Bujtor *et al* 2021).

Sugar and sugar-sweetened beverages (SSB) are associated with obesity and Type-1 diabetes, but their direct link to inflammatory biomarkers is less clear. High SSB intake has been shown to be associated with increased CRP in young children, age three to 11 years, using a sample of 4,880 individuals. However, this was also associated with increased lipid profiles and waist circumference (Kosova *et al* 2013). A reduction of just 10% in body weight through use of a low-energy Mediterranean diet in obese females is associated with reduced plasma levels of cytokines (Esposito *et al* 2003), so weight loss may be a consideration in reducing CLGI.

Micronutrients including vitamins C, A, D, and E, beta-carotene, high levels of sodium, magnesium, zinc, selenium, polyphenols found in green and black tea, and curcumin found in turmeric have been linked to inflammatory conditions (Bujtor *et al* 2021; Pahwa *et al* 2022). Plant-derived flavonoids (naturally occurring polyphenols) have been used to modulate CLGI. Using a fruit / berry / vegetable juice powder TNF-α, CCL2 (monocyte chemoattractant protein), IL-1β, and reactive oxygen concentrations have been shown to significantly reduce CLGI over an eight-week period (Shiva Ayyadurai *et al* 2022), suggesting a possible alternative or adjunct to pharmacological management.

DIETARY FACTOR	EFFECT ON CLGI
Glycaemic index	Use of low glycaemic diet associated with lower levels of CRP. High sugar content of food associated with CRP levels in some studies
Fats	Saturated fatty acids and trans fatty acids associated with higher levels of inflammatory markers Omega 3 polyunsaturated fatty acids associated with lower levels of inflammatory markers
Mediterranean diet	Results in lower levels of C-reactive protein, interleukin 6 (IL-6) and tumour necrosis product alpha (TNF- α)
Fruit and vegetables	Colourful fruit and vegetables are often high in polyphenols and other anti-inflammatory compounds
Fibre	Both soluble and insoluble fibre lower IL-6 and TNF-α levels
Meat	Some studies show an association between high meat intake with raised IL levels
Nuts and seeds	Associated with lower risk of cardiovascular disease and diabetes
Whole / refined grains	Wholegrain intake associated with lower CRP and IL levels
Micronutrients	Vitamins D and E, zinc, selenium, and magnesium shown to either act as antioxidants, have anti-inflammatory effects or suppress inflammatory mediators
Other foods	Polyphenols in tea reduced CRP levels, curcumin from turmeric shown to reduce inflammatory disease in animal models

TABLE 2: Dietary factors in chronic low-grade inflammation (data from Bujtor *et al* 2021; Pahwa *et al* 2022)

CLGI in osteoarthritis

The pathogenesis of osteoarthritis (OA) is accelerated by several factors in CLGI, including an increased catabolic response of chondrocytes, and inflammation of the joint synovium associated with pain sensitisation (Scanzello 2017). Although not considered an inflammatory arthropathy like rheumatoid arthritis (RA), OA does have inflammation as part of its clinical picture. Synovial inflammation, instigating both joint swelling and pain, is found with mononuclear cell (MNC) infiltration, and production of pro-inflammatory cytokines including TNF-α is seen (Brooks 2003).

These cytokines, in turn, lead to the development of proteases and prostaglandins, together with matrix degrading enzymes. In parallel with inflammation and degradation, there is a reduction in the expression of joint lubricants, including lubricin and hyaluronic acid (Rahmati *et al* 2016). Chondrocytes are associated with the production of cytokines, nitric oxide (NO), prostaglandins, proteinases, and matrix metalloproteinases (MMPs), a group of matrix degenerating enzymes. These substances have a damaging effect by splitting type II collagen and accelerating cartilage degeneration (Goldring & Otero 2011). Activated synovial macrophages also drive inflammation, and NO that presents in the cartilage of OA patients is linked to cartilage chondrocyte apoptosis (Rahmati *et al* 2016).

As has been discussed, obesity can be related to CLGI through metabolic processes associated with adipocytes, and the mechanical factors related to obesity are also important in OA, especially when related to the knee. Chronic mechanical stress can also cause chondrocytes to produce degenerative enzymes. Intercellular signals through gap junctions may spread throughout several joint tissues, encouraging the release of MMPs and cytokines even in the presence of a low-level inflammation (Rahmati *et al* 2016).

CLGI in chronic pain

Chronic pain has been defined as a pain that lasts longer than it takes for damaged / pathological tissues to heal, i.e. for more than three to six months, and may be continuous or episodic in nature. Chronic primary pain cannot be directly explained by a pathology and is typically associated with psychosocial characteristics and functional impairment. Included within this pain category are conditions such as non-specific low back pain (NSLBP), fibromyalgia, and irritable bowel syndrome (IBS), where biological changes contributing to the creation of pain may not be present (Treede *et al* 2015). Zhou *et al* (2021) hypothesize that CLGI "may act as a functional link between chronic pain and psychosocial stress". Pathologies which can create chronic pain secondary to a defined pathology are shown in table 3.

Pro-inflammatory chemicals have been detected in both primary and secondary chronic pain patients, and anti-inflammatory cytokines are lower in patients without pain, and controls (Zhou *et al* 2021). In addition, injection of an immunogenic antigen, lipopolysaccharide, in healthy subjects has been shown to induce systemic inflammation and increase pain sensitivity, measured as pressure pain threshold, mechanical pain sensitivity, and cold pain sensitivity (Wegner *et al* 2014). As mentioned previously, ageing increases

PAIN AETIOLOGY	EXPLANATION
Cancer	Created by a tumour or metastases, or cancer treatment such as chemotherapy or radiotherapy
Post-surgical	Occurring after a surgical procedure
Post-trauma	Resulting from tissue disruption (e.g. burns)
Neuropathic	Lesion affecting the nervous system
Headache or orofacial	Primary and secondary headache, cranial neuralgia
Visceral	Pain perceived in the superficial body tissues which receive the same innervation as an internal organ
Musculoskeletal	Pain arising directly from bone, joint, muscle or a related soft tissue

TABLE 3: Sources of chronic secondary pain (data from Treede *et al* 2015)

> "PRO-INFLAMMATORY CHEMICALS HAVE BEEN DETECTED IN BOTH PRIMARY AND SECONDARY CHRONIC PAIN PATIENTS"

pro-inflammatory markers, and this parallels the incidence of chronic pain which is between 25%-50% in the general senior population, increasing to up to 83% in nursing home residents with cognitive decline (Cravello *et al* 2019). This figure is compared to between 7% and 22% in young adults.

Most parts of the nervous system are protected against circulating pro-inflammatory molecules, with only the nerve terminals and dorsal root ganglia resting outside barriers that protect the central nervous system, e.g. the blood brain barrier, blood nerve barrier, blood spinal cord barrier, the blood lymph barrier that protects the lymphatic system, and the blood retinol barrier protecting the eye.

In the main, they consist of endothelial cells and offer vascular permeability to balance the transport of materials into, and out of, the protected body regions. Several tissues, including the blood-organ barriers described, have signalling systems that do not require production of a membrane action potential, seen in nerve and muscle. Cells within barrier tissues form interconnected networks using gap junctions to transport small molecules between the cells.

Cellular examples important to the neuromusculoskeletal system include astrocytes, chondrocytes, osteoblasts, and synovial fibroblasts. Inflammatory chemicals can change cell signalling through the linked gap junctions by increasing permeability across the tissue barriers, leading to tissue dysregulation (Hansson & Skiöldebran 2015). Barrier breakdown has been identified as part of the pathological process in auto-immune diseases, multiple sclerosis (MS), age-related macular degeneration (AMD), neurodegenerative diseases, diabetic neuropathy, and inflammatory bowel disease (Ronnback & Hansson 2019).

CLGI in psychiatric conditions

Several psychiatric conditions are associated with increased pro-inflammatory markers including schizophrenia, post-traumatic stress disorder (PTSD), and bipolar disorder. In addition, both depression and anxiety are associated with CLGI, and antidepressant medication such as selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) have been shown to produce some of their clinical effect by decreasing the release of pro-inflammatory mediators and increasing anti-inflammatory cytokines (Dionisie *et al* 2021).

The use of NSAIDS and cytokine inhibitors has been shown to be adjunctive to antidepressants and improve depressive symptoms when compared to placebo (Kohler *et al* 2014). However, not all subjects with psychiatric disorders show higher levels of pro-inflammatory serum chemicals, so subsets of patients may be identified who could respond to this type of intervention (Osimo *et al* 2018). The prevalence of low-grade inflammation (CRP > 3mg/L) in adult psychiatric inpatients was shown to be 32% for psychotic disorders, 21% in mood disorders, 22% in neurotic disorders and 42% in personality disorders (Osimo *et al* 2018). Additionally, elevated levels of maternal inflammatory markers in pregnancy are associated with a higher risk of developing schizophrenia as an adult (Canetta *et al* 2014).

Therapeutic interventions

Aiming therapy at a single painful joint may limit treatment effectiveness, given that systemic inflammation can be a part of the pathology of many musculoskeletal (MSK) pain related conditions. Lifestyle changes have an important part to play in preventing and / or managing low grade inflammation and so should be a consideration in the long-term planning of an overall care package, including the consideration of the dietary factors discussed in this article.

Exercise is an important component of many MSK treatment programmes and can have both direct (related to the injured body part) and indirect (systemic changes) effects on a condition. Muscle communicates with other tissues in the body not just through the nervous system, but through the release of myokines (a group of peptides including IL-6), establishing muscle as a secretory organ with endocrine functions (Pedersen & Febbraio 2008). Myokines influence several systems including cognition, fat, bone, muscle, skin, and endothelial cells. Additionally, myokines have important direct and indirect anti-inflammatory effects. Exercise induced IL-6 enhances lipolysis and fat oxidation, and the myokine Irisin may change white adipose tissue into brown (Severinsen & Pedersen 2020).

The production of anti-inflammatory cytokines is increased by IL 6. Starkie *et al* (2003) were able to show inhibition of subsequent TNF-α production in healthy subjects who, following a three-hour cycle ride, then ingested the endotoxin, E-coli bolus. Interestingly, the action of IL-6 on inflammation has been shown to be anti-inflammatory when it is produced by muscle, and pro-inflammatory when produced by adipocytes (Han *et al* 2020). Encouraging activity / exercise will, therefore, have effects not just on the individual body region treated. The anti-inflammatory effects detailed above, together with longer term changes in bodyfat and stress levels, will likely parallel reported changes in self-efficacy in chronic MSK and persistent pain conditions such as NSLBP (Norris 2020).

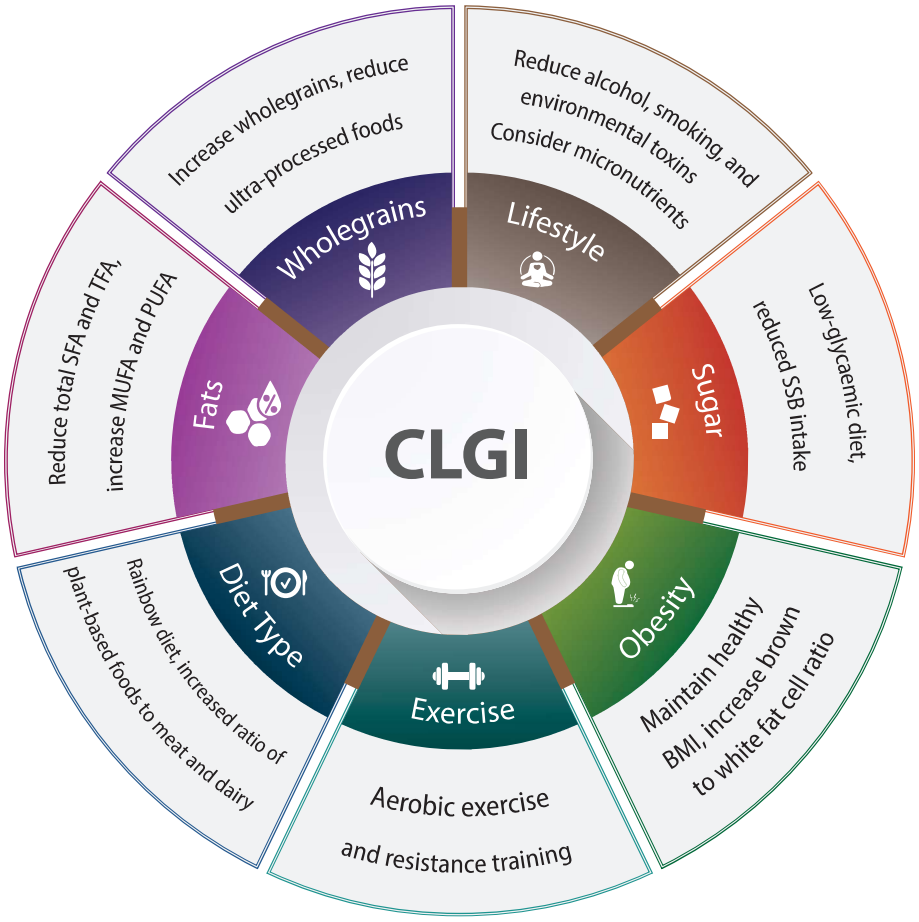

FIGURE 1: Non-pharmacological factors in the management of chronic low-grade inflammation

Common pharmacological management of CLGI can include the use of both corticosteroids such as prednisolone and dexamethasone, and NSAIDs such as aspirin and ibuprofen. These may be either localised via creams, drops, inhalers or systemic, e.g. taken as oral medication, injections, or intravenously. As with all drugs they can have side effects, so are often more useful for short- rather than long-term usage.

Additionally, disease-modifying anti-rheumatic drugs (DMARDs), such as the immunosuppressant methotrexate, or the aminosalicylate sulfasalazine may be used where chronic inflammation is part of a defined pathology, for example in RA, or in other auto-immune conditions such as spondyloarthritis (SpA), systemic lupus erythematosis (SLE), polymyalgia rheumatica (PMR) and gout. These will often allow the gradual reduction of steroids and NSAIDs. Statins such as simvastatin and atorvastatin, which are commonly used long-term for hypercholesterolemia, have also been shown to have an anti-inflammatory effect; directly by reducing CRP, and indirectly by lowering low-density lipoprotein (LDL) which is itself pro-inflammatory (Kim *et al* 2019).

Non-pharmacological interventions, mainly through diet and lifestyle factors, are summarised in figure 1, and should be considered as part of any MSK care package.

About the author

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