CNSLab

Information Sheet

Inflammation

Most chronic illness are underpinned by chronic inflammation, and this information sheet explores how to resolve inflammation through dietary interventions. This year, we launched our new high sensitivity C-Reactive Protein (hs-CRP) test as a standalone measure of inflammatory status and as a diagnostic adjunct to our FoodPrint® IgG food sensitivity tests.

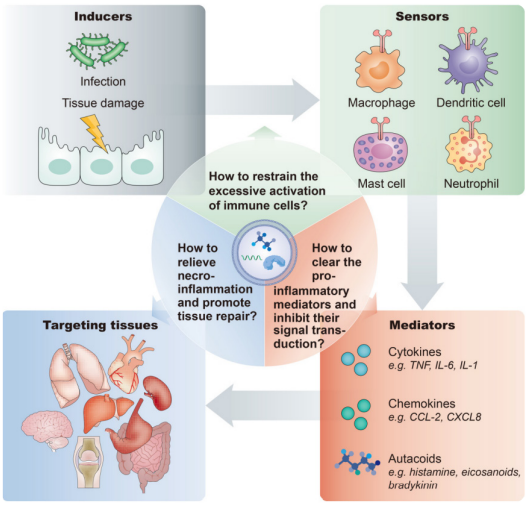
IgG-mediated reactions to foods may be a potential source of chronic, low-grade inflammation and, measuring a client's inflammatory response before and after a food elimination programme, may provide a valuable diagnostic tool for practitioners. Any interventions aimed at reducing inflammation are key to improving performance, restoring health and, with reference to sport, to supporting recovery.

What exactly is inflammation?

Inflammation is a specific white blood cell coordinated response to pathogens and trauma, stimulated by specific cytokine actions. Cytokines are signalling messengers. Inflammation is triggered to help fight an infection or illness and specific inflammatory markers, such as CRP, IL-6, TNF Alpha and ferritin, are stimulated in response [1].

The immune system's primary role is to detect the presence of pathogens and differentiate them from self. It does this with the aid of Pattern Recognition Receptors (PRRs) which are located on the surface of innate immune cells. They detect Pathogen-Associated Molecular Patterns (PAMPS) located on the surface of pathogens, and this recognition initiates an immediate microbiocidal and pro-inflammatory response. PRRs include the family of Toll-like receptors (TLRs)[2]. They also detect Damage-Associated Molecular Patterns (DAMPS)[3], molecules released from cells in response to stress or tissue damage [4] and will initiate a coordinated response. However, this process can be impaired on many levels and our diet may play a significant role. An impaired response will result in inflammation.

Resolving inflammation: Switching it on, switching it off



Source: TanTT et al

Inflammation is a necessary part of the recovery process following trauma or infection. Proinflammatory mediators such as histamine, cytokines, chemokines, and eicosanoids (including leukotrienes and prostaglandins) aid in the process by increasing blood flow and vascular permeability to the affected area, allowing the further recruitment and activation of proinflammatory immune cells, mainly neutrophils and monocytes [13].

This initiation phase needs to be counterbalanced with an equally sustained counter regulatory response with the task of clearing affected tissue, supporting tissue repair and healing, as well as preventing progression to low-grade, asymptomatic (chronic) inflammation which may provoke damage at cell level.

Low-grade inflammation will present in many forms depending on where it manifests; inflammation associated with joint pain may be different from inflammation associated with depression or cancer. Cytokine communication between different immunological cell types [5] influence both the adaptive and innate immune pathways and herein lies the complication; how to switch on the right level and type of inflammatory messaging and how to switch it off again.

Correct messaging promotes pathological cellular resilience [6] the cornerstone of health, and resilience equates to tolerance to all stressors whether mechanical or biological. The key players involved in resolution of inflammation, and thus resilience, are a group of lipid mediators called Specialised Pro-Resolving Mediators (SPMs)[7]. SPMs are having to deal with an ever-increasing amount of potentially pathogenic hostility from recent evolutionary, environmental

stressors, such as pesticide toxins, food chemicals, air, and water pollution and from new viruses, for example COVID-19 SARS[7].

Coupled with external stressors, our individual coping mechanisms are being constantly sculpted by our unique dietary choices and lifestyles. They are directly dependent on our individual biological responses, of particular importance being our oxidative stress and hypothalamic-pituitary-adrenal (HPA) axis responses[7a]. Understanding the factors responsible for oxidative stress and actively selecting foods, such as berries [7b] and supplements including vitamins C and E, zinc and selenium with high antioxidant capacity, continue to be a valuable practitioner tool[7c].

As our cellular resilience declines with age, accelerated aging (inflammaging) [8,9] is initiated along with a reduced capacity to respond to stressors such as changes in temperature, blood sugar imbalance, immune triggers, and social and psychological stress.

Early detection of inflammation with the adoption of appropriate intervention strategies may arrest cellular damage, including neurological damage [43] and this is where nutrition becomes a key player. Supporting our production of SPMS is a nutritional imperative wherever inflammation is present. As SPMs are derived from polyunsaturated acids (PUFAs) [10,11,12], both their ratio in our diet and our level of intake are of primary importance. SPMs include:

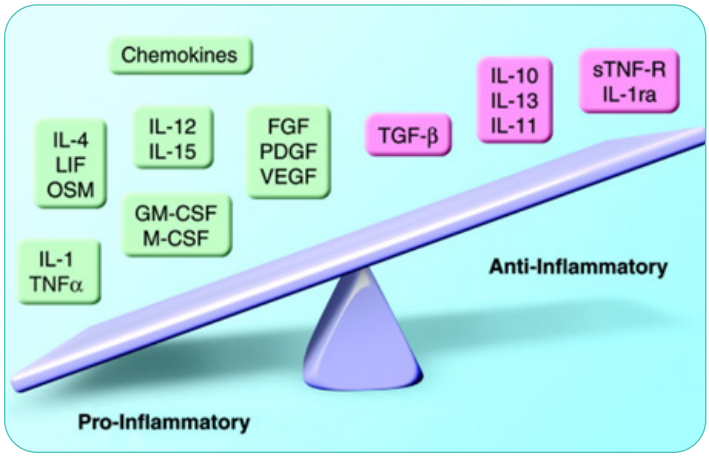
- E series resolvins derived from EPA. (Eicosapentaenoic acid), notably 18-hydroxyeicosapentaenoic acid (18-HEPE, RvE1-RvE3)
- D series resolvins derived from DHA (docosahexaenoic acid) notably 17-hydroxyeicosapentaenoic acid (18-HEPE, RvD1-RvD6
- Arachidonic acid-derived lipoxins (LXA4 and LXB4) and prostaglandins, leukotrienes and thromboxanes
- Protectins, neuroprotectins and maresins
- DPA (docosapentaenoic acid) derived resolvins (RvT1-TvT4) (65, 66, 67) _

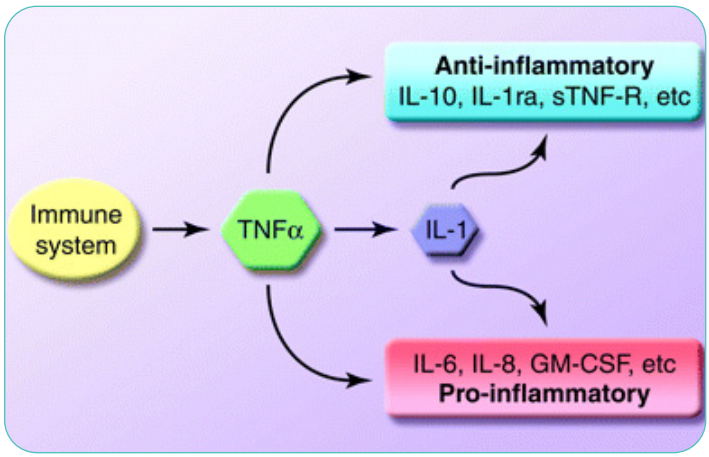
SPMs arrest the initial infiltration of neutrophils to the site of injury and signal them to undergo programmed death to limit damage to surrounding tissues with their histotoxic cell contents. They then signal phagocytosis [13], wherein macrophages are recruited to ingest these dead cells and clear them via a process called efferocytosis. SPMs then orchestrate the shift from the production of proinflammatory (M1) to anti-inflammatory (M2) mediators. This is termed lipid mediator class switching.[14]

Prostaglandins are central to the upregulation of proinflammatory processes and if switching is impaired then resolution deficit and reduced resilience result[15]. If phagocytosis and efferocytosis are not checked and the dead and dying neutrophils are not cleared, they may release harmful contents that damage surrounding tissue and either amplify the inflammatory response or lead to inappropriate autoimmune responses.[15]

Inflammaging results when the lipid mediator profile alters resulting in lower levels of SPMs including d-series resolvins, maresins and lipoxins and a greater proportion of proinflammatory lipid mediators, such as LTB4 and PGF2alphas[16]. The slower the return to baseline the higher the resolution deficit and the lower the resilience.

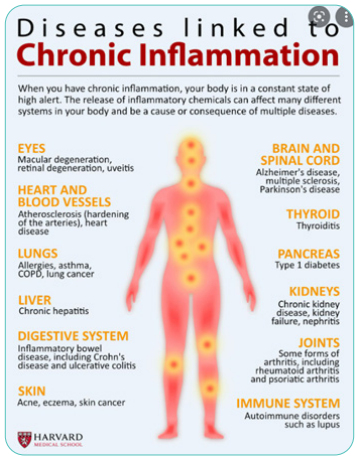
PRO INFLAMMATORY CYTOKINES AND ANTI-INFLAMMATORY CYTOKINES





Source: Marc Feldmann, and Charles D. Pusey JASN 2006;17:1243-1252

Conditions associated with unresolved inflammation



There are a multitude of prevalent chronic illnesses which are underpinned by systemic inflammation.

Obesity is associated with unresolved inflammation. The visceral adipose tissue of individuals with obesity reveals an imbalance between the levels of SPMs and pro inflammatory mediators, increasing inflammatory markers and promoting the inflammatory state[17]. The white blood cells from obese individuals show an impaired ability to produce resolvins supporting the theory that obesity may be a condition of resolution failure [18].

One paper looking at the correlation between obesity-induced inflammation and diet found that high sensitivity C-Reactive protein (hs-CRP) concentrations increased with increasing BMI and that a higher intake of vegetables/ legumes was inversely associated with hs-CRP among obese adolescents, demonstrating that diet can exert a modulatory anti-inflammatory potential as early as in adolescence[34].

Insulin resistance may also be driven by a lack of resolution. Insulin-resistant tissues are less metabolically flexible and less resilient in the face of dietary change and fuel availability patterns[19].

With regards immunity and antibody production, the reduced status of SPMs may be linked with impaired B-cell numbers and overall antibody production[20].

As low-grade inflammation is often "silent" and therefore undetected, it may underlie a variety of unrelated conditions, with particular relevance to coronary artery disease. With chronic heart failure (CHF) it is noted that circulating pro-inflammatory biomarker levels are elevated in patients with both ischaemic and non-ischaemic cardiomyopathies[68]. The practitioner's role to support their clients with a heart healthy diet to address inflammation is strongly evidenced[69].

Highlighting two markers of inflammation: ferritin and hs-CRP

Ferritin is commonly used as an inflammatory marker; it represents an important host defence mechanism by depriving bacterial growth of iron and protecting immune cell function. It may also have a protective function by limiting the production of free radicals and mediating immunomodulation [30].

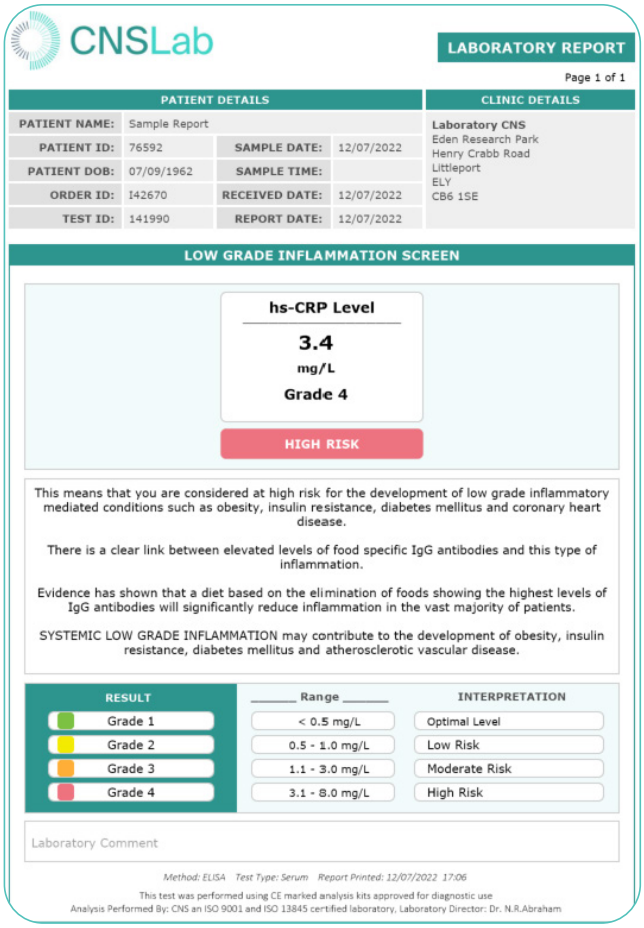
C-reactive protein (CRP) is a valuable non-specific marker of inflammation. It is an ancient highly conserved molecule [31] which is secreted by the liver in response to a variety of inflammatory cytokines. CRP levels rise rapidly in response to trauma, inflammation and infection and will decrease equally as rapidly with resolution of the condition and can be used as a tool in monitoring various inflammatory states.

CRP binds to damaged tissue and, similar to immunoglobulin IgG, it activates complement, binds to Fc receptors on the surface of specific cells and acts as an opsonin for various pathogens [31]. Opsonins facilitate the recognition, binding, ingestion, and killing of microorganisms by phagocytes. This interaction of CRP with Fc receptors leads to the generation of proinflammatory cytokines that amplify the inflammatory response [31].

Unlike IgG, which recognises specific antigenic epitopes, CRP recognises altered self and foreign molecules (PAMPs) based on pattern recognition and thus acts as a surveillance molecule for both altered self and for certain pathogens. This recognition provides early defence and leads to a proinflammatory signal and activation of the humoral, adaptive immune system. [32]

An hs-CRP test is a highly sensitive marker, detecting lower levels of inflammation than a standard CRP test. hs-CRP is not specific to chronic inflammation, but it has a greater reliability and accuracy than other biomarkers including erythrocyte sedimentation rate, IL-6, or TNF-Alpha. Of importance is that hs-CRP is modified by diet and is predictive of disease so can be used as a nutrition-related biomarker of disease. [32]

It may therefore be helpful to test your clients hs-CRP levels immediately preceding a three-month elimination diet following an IgG food sensitivity test and again after three months to measure the impact on inflammation of excluding and reducing those foods that are shown as reactive on a FoodPrint report. An hs-CRP score will indicate the level of hs-CRP between 0.1-8.0 mg/L of blood with its associated risk level. It cannot explain the cause or location of the inflammation and an elevated result does not necessarily mean a medical condition is present. If, however, it remains elevated a healthcare provider may recommend further tests or give a referral to a general practitioner.



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LABORATORY REPORT

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PATIENT DETAILS			
PATIENT NAME:	Sample Report		
PATIENT ID:	76592	SAMPLE DATE:	12/07/2022
PATIENT DOB:	07/09/1962	SAMPLE TIME:	
ORDER ID:	I42670	RECEIVED DATE:	12/07/2022
TEST ID:	141990	REPORT DATE:	12/07/2022

CLINIC DETAILS

Laboratory CNS
Eden Research Park
Henry Crabb Road
Littleport
ELY
CB6 1SE

LOW GRADE INFLAMMATION SCREEN

hs-CRP Level
3.4
mg/L
Grade 4

HIGH RISK

This means that you are considered at high risk for the development of low grade inflammatory mediated conditions such as obesity, insulin resistance, diabetes mellitus and coronary heart disease.

There is a clear link between elevated levels of food specific IgG antibodies and this type of inflammation.

Evidence has shown that a diet based on the elimination of foods showing the highest levels of IgG antibodies will significantly reduce inflammation in the vast majority of patients.

SYSTEMIC LOW GRADE INFLAMMATION may contribute to the development of obesity, insulin resistance, diabetes mellitus and atherosclerotic vascular disease.

RESULT	Range	INTERPRETATION
Grade 1	< 0.5 mg/L	Optimal Level
Grade 2	0.5 - 1.0 mg/L	Low Risk
Grade 3	1.1 - 3.0 mg/L	Moderate Risk
Grade 4	3.1 - 8.0 mg/L	High Risk

Laboratory Comment

Method: ELISA Test Type: Serum Report Printed: 12/07/2022 17:06

This test was performed using CE marked analysis kits approved for diagnostic use
Analysis Performed By: CNS an ISO 9001 and ISO 13845 certified laboratory, Laboratory Director: Dr. N.R.Abraham

Stimulating resolution with nutrition, general strategies

Dietary factors that predispose us to Systemic Chronic Inflammation (SCI) include low intake of fruits, vegetables, wholegrains, legumes, fish and nuts and a high intake of refined grains, sugar, fried foods, processed meats, and other processed foods [21,22]. Food represents one potentially modifiable factor that may be used if not specifically to regulate the inflammatory response, then to reduce the impact of systemic low-grade inflammation. [23]

Improving our essential fatty acid balance is an excellent starting point as a low intake of omega 3 essential fatty acids and a high omega 6 to 3 ratio reduce the important dietary fatty acid intake that provides substrate for the lipid mediators, discussed above, which are vital for resolution. [24, 35].

Focusing on low glycaemic index (GI) carbohydrate sources such as beans, pulses, lentil, peas, whole grains, and unpeeled root vegetables directly ameliorates post prandial inflammation. Carbohydrates with a high GI index activate a post prandial inflammatory response. [25]

Consumption of wild and organic meat sources is recommended as modern grain-fed beef has been shown to provoke a post prandial inflammatory response compared to wild game meat. [26]

Aiming to reduce the consumption of packaged and processed foods that contain food additives may be particularly beneficial. Food additives may contribute to intestinal barrier dysfunction by disrupting the gastrointestinal microbiome, disturbing the intestinal tight junctions of the gut wall, predisposing to leaky gut and the leakage of partially digested foods and pathogens into the bloodstream [27] initiating the inflammatory response.

Processed foods, devoid of necessary antioxidants, vitamins, and phytonutrients, contribute to oxidative stress which sustains inflammatory mediators. [28]. Aim to eat fresh, unprocessed whole foods.

Advance glycation end products (AGEs) found in fried and barbecued and burnt foods such as meats and crisps contribute to higher circulating inflammatory mediators[29]; these foods should be avoided wherever possible.

Supplements used should always be directed by a qualified practitioner but there is a large body of studied evidence that both vitamin D [36] and magnesium [37,38] supplementation may be used therapeutically to directly address inflammation.

Diets such as the Mediterranean diet, Nordic diet, DASH diet and the DII (Dietary Inflammatory Index) diet can be utilised in clinic as therapeutic, nutritional protocols. These diets have been studied to directly reduce inflammation and significantly reduce CRP. [39,40,41]

Stimulating resolution with nutrition, specific food strategies

Omega 3

Eat plenty of sources of omega 3 including oily fish and flax, chia and pumpkin seeds, walnuts and/or supplements containing EPA and DHA. Omega 3 essential fatty acid EPA (eicosapentaenoic acid) is a precursor to the 3 series prostaglandins which exert membrane stabilising and anti-inflammatory properties. [42]

Both EPA and DHA (docosahexaenoic acid) are converted at the site of inflammation into the specialised pro-resolving mediators resolvins, protectins and maresins, as discussed above. In this 2016 trial, using a control of 164 patients, DHA was shown to be more effective than EPA in modulating specific markers of inflammation as well as blood lipids. Together these mediators orchestrate inflammation resolution and deficiency may result in suboptimal resolution of inflammation. [43,44,45]

Foods to reduce that are high in pro inflammatory fatty acids include farmed meats, dairy products, and vegetable oils (such as sunflower and corn oils).

Carotenoids should always be a first line choice with an anti-inflammatory dietary protocol. The following vegetables and fruits, rich in carotenoids, have all been found to reduce CRP; dark, green leafy vegetables, carrots, green beans, broccoli, courgettes, tomatoes, Brussels sprouts, red cabbage and spinach, and apples, pears, kiwis, peaches, nectarines, cherries, strawberries and red currants. [46].

In this 2021, longitudinal retrospective chart review [47] patients were required to eat a specific diet high in dark green, beta-carotene rich, leafy vegetables, and were shown to have significant reductions in plasma high-sensitivity CRP (hs-CRP) levels. The dietary protocol was termed the Low Inflammatory Foods Everyday (LIFE) diet.

Cruciferous vegetables and anthocyanin rich foods have important anti-inflammatory effects and may be successfully used as part of a dietary protocol. The Isothiocyanates in cruciferous vegetables have been demonstrated to modulate signalling pathways critical to carcinogenesis, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-KB), a central regulator of inflammation. In this controlled trial [48] the consumption of cruciferous vegetables reduced serum concentrations of interleukin (IL)-6 by 20% after two weeks compared with a base diet containing no fruits and vegetables. This was achieved by consuming 7g/per kilo body weight per day of minimally cooked cruciferous veg such as broccoli and cauliflower, cabbage and radish.

Blueberries and anthocyanins

There is a growing body of research to support the contribution of anthocyanins contained in berries such as blueberries to health. A meta-analysis of 32 randomised controlled trials indicated that dietary anthocyanins significantly decreased levels of CRP, IL-6 and TNF-alpha. Over 300mg/day (contained in 150g fresh weight berries) were associated with a higher effectiveness of reducing CRP.[49]

One 2021 meta-analysis evidenced the use of anthocyanin supplementation as a therapeutic anti-inflammatory treatment strategy against low grade inflammation demonstrating effects amongst both the healthy and the chronically diseased[50].

Tea

After water, tea is the second most popular beverage worldwide and its high antioxidant activity classifies it as a superfood with anti-inflammatory benefits. Its high polyphenol content (36% of fresh and between 18-36% dry weight) is mostly responsible for its biological activity. These polyphenols are predominantly in the form of flavonoids and phenolic acids. Of the flavonoids, catechins make up 12-24% of its dry weight, flavonols 3-4% and anthocyanins 2-3%. Being an antioxidant, it exerts a powerful free radical scavenging effect[51]. Green tea and black tea thioflavins bind peroxide radicals and arrest lipid peroxidation and catechins attach to red blood cells exerting an antioxidant effect [52].

In a ten year study of 8,500 subjects who drank 10 cups of tea per day as opposed to three cups revealed a three year delay on onset of cancer [53]. Reducing LDL oxidation, preventing haemostasis and inflammation and thus inhibiting the atherosclerotic process, positions tea as a potentially useful nutritional strategy, particularly related to cardioprotective health [54].

Tea polyphenols exert neuro protective activity studies demonstrated in Alzheimer's and Parkinson's due to their calcium channel blocking effect, their antioxidant capacity and their ability to reduce Advanced Glycation End products (AGE) [55,56]. One study showed a marked inhibition of histamine release induced by IgE-antigen complex stimulation, with epigallocatechin gallate (EGCG) from green tea exerting the strongest effect [57]. Catechins have been shown to reduce the incidence of arthritis by effecting endopeptidases activity[57].

Cocoa

There is increasing evidence that moderate consumption of cocoa and cocoa-containing foods may have beneficial effects on the health including vasodilatory, antioxidant, and anti-inflammatory effects. Cocoa is rich in polyphenols, including monomeric flavanols, methylxanthines, and monounsaturated fatty acids, all believed to play a role in these observed beneficial effects[58].

In a 2012 randomised, controlled, double-blind, parallel trial [59] 113 volunteers who were pre-hypertensive, stage-1 hypertensive and hypercholesterolemic were given one of 4 cocoa cream products. All results showed anti-inflammatory and antioxidant effects in addition to lowering LDL-C (low density lipoprotein cholesterol). One of the creams containing a combination of cocoa, hazelnuts, phytosterols and soluble fibre revealed a reduction in hs-CRP by 33.4%.

Cocoa flavonols may be used to support muscle recovery and exercise performance due to their potential ability to lower the secretion of pro inflammatory cytokines by decreasing M1 macrophage response. (60,61). Cocoa polyphenols in this 2020 study were shown to have a direct influence on macrophage metabolism by promoting oxidative pathways that both cleared mitochondrial complexes and increased ATP through oxidative phosphorylation. [62]

In this 2022 large-scale trial, studying the effect of a cocoa flavonol supplement with relation to cardiovascular disease prevention, their potential cardiovascular protective effects were demonstrated [63]. Of significance is that those receiving the cocoa flavonol supplement as opposed to a multivitamin supplement had a significant 39% reduction in death from cardiovascular disease. In addition, the incidence of heart attacks, strokes and cardiovascular deaths was significantly reduced although these endpoints were not being trialled.

The supplement capsules contained 500mg cocoa flavonols so could not realistically be reflected by eating in the form of chocolate without adding excessive calories, fat and sugar to the diet.

Turmeric/Curcumin

Curcumin has also been shown to inhibit Cox-2 enzymes which produce inflammatory prostaglandins so add turmeric (freshly grated root where possible) to soups, stews and vegetable cakes. [64]

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Omega Diagnostics