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ABDOMINAL OBESITY AND LOW-GRADE INFLAMMATION: ROLE OF BIOACTIVE FOOD FACTORS IN CONTROLLING INFLAMMATORY RESPONSE

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Резюме. *Запалення низьких градацій є важливою особливістю стану хворих з ожирінням, при якому жировою тканиною вивільнюється велика кількість прозапальних медіаторів, що є причиною розвитку інсулінорезистентності та інших метаболічних порушень. У хворих з підвищеною масою тіла та діабетом 2 типу зниження концентрації маркерів запалення в крові корелює зі зниженням ваги. Здорова їжа асоціюється зі зниженням концентрації прозапальних маркерів у периферичній циркуляції. Такі продукти харчування як овочі, фрукти та риба асоціюються зі зниженням симптомів запальної відповіді. Вітамін С, Е та каротиноїди знижують рівні концентрації прозапальних маркерів у периферичному кровообігу. В аналітичному дослідженні розглядаються потенціальні механізми і сучасні дані, які обмежують наше розуміння процесів взаємодії між певними продуктами харчування та хронічним запаленням низьких градацій.*
Ключові слова: продукти харчування, запалення низьких градацій, ожиріння, цитокіни.

Резюме. *Воспаление низких градаций является важной особенностью состояния больных, страдающих ожирением, при котором жировой тканью высвобождается много провоспалительных медиаторов, что служит причиной развития инсулинорезистентности и других метаболических нарушений. У больных с повышенной массой тела и диабетом 2 типа снижение концентрации маркеров воспаления в крови коррелирует со снижением веса. Здоровая пища ассоциируется со снижением концентрации провоспалительных маркеров в периферической циркуляции. Такие продукты питания как овощи, фрукты и рыба ассоциируются со снижением симптомов воспалительного ответа. Витамин С, Е и каротиноиды снижают уровни концентрации провоспалительных маркеров в периферическом кровотоке. В аналитическом исследовании рассматриваются потенциальные механизмы и современные данные, которые ограничивают наше понимание процессов взаимодействия между определенными продуктами питания и хроническим воспалением низких градаций.*
Ключевые слова: продукты питания, воспаление низких градаций, ожирение, цитокины.

Summary. *Low-grade inflammation is a characteristic of the obese state, and adipose tissue releases many inflammatory mediators and these are believed to play a role in causing insulin resistance and other metabolic disturbances. Blood concentrations of inflammatory markers are lowered following weight loss in obese subjects and in type 2 diabetes. Healthy eating patterns are associated with lower circulating concentration of inflammatory markers. Among the components of a food products (vegetables, fruits, and fish) are all associated with lower inflammation. Vitamin C, vitamin E and carotenoids decrease the circulating concentrations of inflammatory markers. Potential mechanisms are described and research gap, which limit our understanding of the interaction between food products and chronic low-grade inflammation are indentified.*
Key words: food products, inflammation, obesity, cytokines.

Introduction

While the existence of inflammatory diseases has been long recognized, it is only more recently that the condition of chronic low-grade inflammation has received attention, particularly in relation to obesity, the metabolic syndrome and cardiovascular diseases. Chronic low-grade inflammation is characterized by raised concentrations of inflammatory markers in the systemic circulation. This article sets out to explain the nature of chronic low-grade inflammation in the context of overweight and obesity, and to describe the factors that might influence it, in particular those related to bioactive food factors.

Low-grade inflammation and obesity

The concept of systemic, chronic, but low-grade inflammation is risk factors for the metabolic syndrome and type 2 diabetes is based on the observation of elevated blood levels of inflammation-associated markers in people with incident type 2 diabetes or with the metabolic syndrome [1, 2]. The up-regulation of systemic indicators of inflammation such as leukocyte count,

and serum and plasma concentration of acute phase proteins, pro-inflammatory cytokines, chemokines, soluble adgesion molecules and protrombotic mediators is modest, usually less than 2-fold above what is observed in controls. Diagnostic criteria for low-grade inflammation have not been precisely defined, but the phenotype per se is not disputed.

Systemic concentration of pro-inflammatory mediators are higher in obese than in normal-weight persons [3, 4]. Serum or plasma concentrations of TNF-α or IL-6 in healthy adults are typically 0,01-2 pmol/l [5]. Other inflammatory mediators, such as monocyte chemoattractant protein (MCP)-1, interferon (IFN)-γ-induced protein-10 and IL-8, may reach mean concentrations of 10 pmol/l; macrophage migration inhibitory factor (MIF) and regulated and activation normal T expressed and secreted (RANTES) concentrations may get a lose to the nanomolar range; and C-reactive protein (CRP) concentrations of most mediators among non-obese or obese individuals is at least 10-fold. Hence, there is a substantial overlap between non-obese and obese persons. However, there is a positive relationship between body mass index (BMI) and other measures of obesity such as waist circumference and circulating concentration of CRP and other inflammatory markers [6].

A mechanistic link between obesity and low grade inflammation was first proposed by Hotamisligil et al. [7] who showed that white adipose tissue synthesizes and releases the pro-inflammatory cytokine TNF-α. The expression of TNF-α is elevated in adipocytes of obese and insulin-resistant mice, while insulin sensitivity is improved following administration of anti-TNF-α antibodies. The discovery of leptin introduced the concept of "adipocytokines" or "adipokines", substances produced by tissue and which circulate in the bloodstream, so exerting systemic effects as hormones [8, 9]. Some adipokines are produsedwithin adipose tissue exclusively by adipocytes (e.g. leptin, adiponectin, serum amyloid A (SAA)), while others are produsedby both adipocyte fraction of adipose tissue. It is now recognized that macrophages accumulate in the adipose tissue in obesity [10, 11] and that these may represent major contributors to the production of adipokines [12, 13].

Adipose tissue as a source of inflammatory mediators

Adipose tissue expresses and secretes into the system circulation a growing list of hormones, inflammatory mediators and immune system effectors. The products of adipose tissue can be categorized into several groups (Table 1).

MCP, monocyte chemoattractant protein; CCL, chemokine (C-C motif) ligand; RANTES, regulated on activation, normal T expressed and secreted; MIP, macrophage inflammatory protein; IL-1ra, IL-1 receptor antagonist; IP, interferon γ-induced protein; TGF, transforming growth factor.

It should be noted that the liver and lymphoid organs are usually the major production sites of the inflammatory mediators but in obesity, adipose tissue becomes a major producer resulting in a chronic and constant local and systemic inflammation milieu.

Abdominal obesity is a risk factor for type 2 diabetes, hypertension, dyslipidaemia and cardiovascular diseases [14] and also probably obesity-assosiated hepatic diseases (non-alcoholic fatty liver disease and non-alcoholic steatohepatitis). Glucose intolerance is significantly more common in subjects with abdominal obesity compared with those with fat mass accumulation in their lower part of the body. The profile of adipokines produced is dissimilar between the subcutaneous and abdominall adipose tissues. Thus, leptin is preferentially expressed and secreted by subcutaneous adipose tissue [15], while the expression of adiponectin, visfatin, omentin, resistin, PAI-1, IL-8, IL-7, IL-1α, MCP-1,TGF-β, growth-related oncogen-α, CCL5 and MIP-1β is higher in abdominal fat. In contrast to such distributions, there are reports that IL-6 and TNF-α seem to be equally synthesized by the different sites [16-24]. It is important to mention that in severe obesity, the part played by the abdominal or the very abundant subcutaneous adi-

Table 1

Cytokines expressed or secreted by human adipose tissue

Family	Examples
Chemokines	MCP-1 (known as CCL2), MCP-3, MCP-4, RANTES (known as CCL5), MIP-1α (known as CCL3)
IL	IL-6, IL-8 (act as chemokine), $IL\text{-}1_{ra}$, IL-10, IL-10
Interferons	IP-10
TNF	TNF-α
Growth factors	Vascular endothelial growth factor, TGF-β, Hepatocyte growth factors
Others	Leptin

pose tissue in the systemic delivery of inflammatory mediators is still not well understood. Nevertheless, the distinct profile of adipokine secretion between the abdominal and subcutaneous adipose tissues probably contributes to the increased risk of metabolic and cardiovascular complication and to the development of other complication such as hepatic steatosis and non-alcoholic steatohepatitis in obese individuals. Finally, other adipose tissue depots in so-called "ectopic sites", such as within the liver, heart or skeletal muscles, may contribute to the production of inflammatory mediators in the absence of obesity. In this regard, the local production of the inflammatory molecules by adipose tissue within the heart may be important the amount of this tissue and its proximity to the coronary vessels could contribute to the development of coronary pathologies [25, 26].

Adipose tissue is a heterogeneous tissue composed of several cell types: mature adipocytes, preadipocytes, fibroblasts, endothelial cells, mast cells, granulocytes, lymphocytes, and macrophages. Cells within adipose tissue apart from mature adipocytes are collectively termed "the stroma-vascular fraction" [27]. Adipocyte size determines the production of IL-6, IL-8, MCP-1 and granulocyte colony-stimulating factor [28]. Although adipocyte hypertrophy precedes the development of type 2 diabetes [29], a growing number of studies indicate that the principal site of production of inflammatory mediators appears to be the stroma-vascular fraction [17, 27, 30, 31].

Most recently, it has been shown that pro-inflammatory T-lymphocytes are present in visceral adipose tissue and may contribute to local inflammatory cell activation before the appearance of macrophages, suggesting that these cells could play an important role in the initiation and perpetuation of adipose tissue inflammation as well as the development of insulin resistance [32].

It has been proposed that macrophages and mature adipocytes are derived from the same precursor cells and show close gene expression profiles including the Toll-like receptors (TLR). Preadipocytes exert macrophage-like effects when exposed to strong pro inflammatory environments [33, 34]. It should be noted, however, that the vast majority of the macrophage infiltration in adipose tissue in obesity originates most probably from the circulation. In obese subject, these macrophages typically aggregate in crowns around apoptotic adipocytes [35, 36]. Although these macrophages express activation markers, they could be pro- or anti-inflammatory depending on the degree of obesity and its evolution as suggested by studies in mice showing that weight gain is accompanied by transformation from a macrophagic M2 (anti-inflammatory) phenotype towards an M1 (pro-inflammatory) profile [36]. Consequently, secretion profile of the adipose tissue can change depending on the phenotype of the cell population infiltrating in during the different stages of obesity (initiation, aggravation, maintenance and weight loss) [37].

Adipose tissue macrophages may contribute to the maintenance of low-grade inflammatory state linked to obesity [17]. Factors that induce the infiltration and activation of macrophages in the adipose tissue are probably multifactorial. Paracrine, autocrine and endocrine signals, as well as mechanical modification (hypertrophy and adipocyte hyperplasia), could play a role in this phenomenon. Many adipokines synthesized by the adipose tissue are candidates to attract inflammatory cells. In vitro studies have suggested that leptin itself (at supra-physiological levels) induces adhesion proteins, hence facilitating the migration of monocytes [38]. Conversely, adiponectin may inhibit this process [39]. Very little is known about the role of selectins, integrins and element of adhesion to the extracellular matrix, in the process of macrophage attraction to the adipose tissue.

Local hypoxia could play important role in the attraction and retention of macrophages within the adipose tissue [40]. Hypoxia-inducible factor-1α, a transcriptional factor normally induced by hypoxia, is overexpressed in the subcutaneous adipose tissue of obese subjects and its expression is decreased during weight reduction [41]. Tissue hypoxia induces macrophage attraction into solid tumors as well as into atherosclerotic plagues. Adipose tissue of obese subjects could be hypoxic in some areas and a local expression of chemokines could be induced. It should be noted that leptin, which possesses indirect chemoattractant properties, is induced by hypoxia [42].

Inflammatory molecules — adipokines are likely candidates exerting a molecular link between the adipose tissue and the metabolic, cardiovascular, hepatic and thrombotic complications, and certain cancer types occurring in conjunction with or as a consequence of human obesity. A myriad of candidate adipokines are proposed to play this role [43-45]. In the cardiovascular field, they can be considered as risk factors, and even directly play a pathophysiological role favouring the initiation and progression of atherosclerosis. Relationships between abnormalities of cardiac function in obese subjects, the accumulation of abdominal fat and low-grade inflammation have been suggested [46-47].

Several inflammatory mediators produced by adipose tissue, such as CCL5, IL-1β, IL-8, as well as markers of oxidative stress, are increased in diabetic or glucose-intolerant patients, and the amelioration of hyperglycaemia by insulin therapy reduces circulating concentrations of these molecules [48, 49]. The increase in the concentrations of TNF-α, IL-6, IL-1β, IL-8, resistin and many other factors produced by macrophage activation could contribute to the deterioration of insulin sensitivity [50].

Many studies have shown that weight loss induced by a decrease in energy intake, and sometimes an

increase in exercise, reduces systemic inflammation [51]. Reduction in concentrations of numerous inflammatory molecules and endothelial risk factors, and in increase in adiponectin concentration have been observed during weight-loss programmes, and these are sometimes associated with improvement of insulin sensitivity [52]. Such changes have been described for CRP [53], IL-6 [54], IL-18 [55], IL-1ra [56], PAI-1 [57], SAA [58, 59], cathepsin S [60], matrix metalloproteinase-g [61], soluble adhesion molecules (soluble intercellular adhesion molecule — 1 (sICAM-1)), soluble vascular cell adhesion molecule — 1 (sVCAM-1) [51], tissue factors [62], MIF [63], MCP-1 [64], soluble receptors of TNF (sTNFR) and for eotaxin, an inflammatory factor implicated in asthma, another complications of obesity [65].

Chronic low-grade inflammation and insulin resistance

In obesity and the metabolic syndrome, key organs displaying increased insulin resistance are the liver, skeletal muscles, adipose tissue and the endothelium. Experimental model system in vitro have shown that hepatocytes as well as muscle cells, adipocytes and endothelial cells respond to exposure to the pro inflammatory cytokines TNF-α, IL-6 and/or IL-1β with impaired insulin signalling [66]. The impairment of insulin signalling by TNF-α has been observed in vivo after infusion of cytokine into rodents [67, 68]. A critical mediator downstream of TNF-α appears to by MIF ("macrophage migration inhibitory factor"), since mice with a disrupted MIF gene preserve normal insulin signalling [69]. In this context, it is of interest that adipocytes are able to secrete MIF [70].

The impact of insulin on cellular metabolic activity, proliferation and differentiation can also be impared by inflammatory mediators via an indirect pathway, i.e. enhancing or suppressing the production of hormones that modulate cellular response to insulin. These effects include the up or down-regulation of the resistin [71], leptin, adiponectin [72], lipocalin 2 [73], ostepontin [74], and insulin itself.

Hepatocytes, adipocytes, muscle cells and endothelium are sites of inflammatory mediator synthesis, but local activated macrophages appear to be the dominant site of synthesis and secretion, which lead to spillover into the general circulation [31, 75]. Paracrine concentrations of inflammatory mediators are sufficient to induce insulin resistance [66]. Indeed, co-culture of adipocytes with macrophages caused impairment of insulin signalling. In addition to paracrine effect, it is conceivable that the functions of liver cells are affected by inflammatory mediators released from the abdominal adipose tissue because of their blood link.

In human subjects, the most direct approach to assess the contribution of low-grade inflammation to the development of insulin resistance and the metabolic syndrome is to analyse the consequence of anti-inflammatory pharmacotherapy. The longest experience is with use of salycilates which are weak inhibitors of IkB kinase β and of serine phosphorilation of IRS proteins [76, 77]. Early clinical trials with high doses of salicylates, notably aspirin, yielded both positive and negative effects on glycaemia and insulin resistance. Later studies have revealed that only very high doses are effective in improving glucose metabolism [78]. Randomised placebo-controlled pilot trials of salicylate treatment for 1 month in twenty non-diabetic obese individuals found decreased blood glucose and insulin responses to oral glucose consistent with improved insulin sensitivity [79].

A first controlled double-blind trial was performed with daily injection of recombinant human IL-1ra for 13 weeks. This resulted in decreased Hb levels and enhanced endogenous insulin production [80]. Another target-specific approach is the neutralization of TNF-α by injections of recombinant antibodies or sTNFR. In animal models of insulin resistance, infusion of TNF-α antibodies has been reported to ameliorate insulin signalling [7, 81]. In obese non-diabetic or diabetic individuals, several studies have observed improvement of insulin sensitivity after prolonged treatment with neutralizing TNFα antibodies [82, 83], whereas other trials did not report such effects of TNF-α antibody injections, despite dampening of specific inflammation [84].

The overall conclusion is that results of studies of anti-inflammatory therapy generally support the concept of inflammatory mediators as contributors to the pathogenesis of insulin resistance, but have as yet not provided clear evidence of a critical pathogenic role of TNF-α or IL-1.

Bioactive components of food and markers of chronic low-grade inflammation

Whole grains/refined grains. Published studies have so far investigated a narrow and low range of whole grain intakes, which limits the interpretation of associations between whole grain intake and markers of low-grade chronic inflammation. Observational studies [85-89] including data from NHANES III have suggested that a high intake of whole grain is inversely associated with plasma CRP concentration (quintile (Q) 1 < 3,5 servings/d, Q 5 > 9,7 servings/d) [85]. In contrast, Jensen at al [86] reported no association between a moderate whole grain intake (Q1 — 8,2 g/d, Q5 — 43,8 g/d) and markers of inflammation (CRP, IL-6 and fibrinogen) in the health professionals' follow-up study. However bran intake collected inversely with CRP concentration and germ intake with IL-6 concentration [86]. Data from the multi-ethnic study of atherosclerosis (MESA) showed a higher whole grain intake to be associated with lower CRP concentration in elderly subjects [87]. Evidence from intervention studies [90-93] includes a study whereby

overweight and obese subjects consumed a hypoenergetic diet with or without whole grain foods. CRP concentration decreased by 38% (CRP at baseline 5,9-9,0 mg/l) in the whole-grain group independent of the observed weight loss [93]. Replacing a refined-wheat flour pizza by a similar pizza prepared from whole-wheat flour resulted in a decreased postprandial concentration of the pro-inflammatory cytokine IL-18 in both non-diabetic and diabetic subjects [92]. In summary, whole grain intake appears to inversely associate with markers of low-grade inflammation. Processing status of whole grain products should be more precisely defined in future studies. Potential mechanisms still have to be elucidated, as well as the active constituents which may include dietary fibre, minerals, vitamins and phytochemicals such as lignans and phenolic acids.

Vegetables and fruits. A number of cross-sectional studies have investigated the association between vegetable and fruit intake and biomarkers of inflammation [94-98]. A high number of varieties of vegetables and fruits were inversely correlated with blood CRP levels [94]. This suggests that plant specific constituents of vegetables and fruits such as phytochemicals may contribute to the anti-inflammatory activities. Most studies have used fruits or fruit extracts high in polyphenols. Results from such studies suggest anti-inflammatory effects; however, mostly, only a single biomarker was affected, and never the complete set of inflammatory biomarkers investigated [99-104]. In conclusion, current evidence for specific effects of single vegetable and fruit varieties is not convincing, while a high overall intake of vegetables and fruits seems to be associated with a lower state of inflammation.

Nuts. To date, only few studies have investigated the effect of nuts on inflammatory markers. The MESA reported that a high intake of nuts and seeds ($\geq$ 5 times/week) compared with a low intake (rarely or no consumption) was associated with lower plasma concentration of CRP, IL-6 and fibrinogen [105]. In contrast, data from the Nurses' Health Study suggest that nut intake is not associated with inflammatory markers including sTNFR, CRP, fibrinogen, sICAM-1, and SE-selectin [106]. A systematic review on walnut consumption and inflammatory markers also reported inconsistent results for plasma CRP, while walnuts added to a Mediterranean diet resulted in significantly lower sVCAM-1 concentration [107]. This suggested that rather than a general anti-inflammatory effect, walnuts may exert anti-inflammatory effect primarily in the endothelium. Major contributors to any anti-inflammatory activity of nuts are likely to include PUFA, Mg and phytochemicals including ellagic acid [108, 109].

Fish. Increased frequency of fish consumption was associated with lower CRP and IL-6 concentrations in a cohort of 727 adults [110]. sICAM-1 and SE-selectin concentrations also decreased but the effect of fish consumption was weaker than what was observed for CRP and IL-6. sTNFR2 concentration was not associated with fish consumption [111]. A study in 3102 adults reported that fish consumption was "dose-dependently" associated with lower CRP, IL-6, TNF-α and SAA concentrations and white blood cell count; individual consuming > 300 g fish/week (n-259; 9%) had significantly lower concentrations of CRP (33%), IL-6 (32%), TNF-α (21%), SAA (28%) and leucocytes (4%) than seen in individuals not consuming fish (n-319; 11%) [112].

Tea. A cross-sectional study from Japan reported no relationship between green tea consumption and the concentrations of several inflammatory markers [113]. Most studies indicate that tea consumption has no significant effect on the markers of inflammation reported [114-119]. However, a longer supplementation period of 6 weeks with black tea in healthy non-smoking men reduced plasma CRP concentrations significantly [120, 117]. Overall, there are no consistent data that tea consumption (black or green) has beneficial effects on inflammatory status, but studies of longer duration than those currently reported need to be performed. The modest or even absent effects of tea on inflammatory and oxidative stress markers in vivo are surprising in view of the potent inhibitory effects of tea components such as catechins on the expression of pro-inflammatory mediators in vitro [121-123]. This may be due to the fact that the majority of teas catechins undergo methylation, glucuronilation and sulfation during uptake which may limit bioavailability [124].

Coffee. Habitual coffee consumption was analysed for association with markers of low-grade inflammation in cross-sectional epidemiological studies which yield conflicting results [125-127]. The contradictory findings from observational studies may reflect the fact that coffee contains a mixture of bioactives with divergent effects on physiology [128, 129]. Plasma caffeine concentrations were positively associated with plasma adiponectin concentration [130]. Taken together, the available data do not allow a firm conclusion as to whether coffee consumption modulates low-grade inflammation.

Cocoa. Cocoa has a high content of monomeric (epicatechin and catechins) and oligomeric (procyanidin) flavanols [131, 132]. These later polymeric fractions are present in higher concentrations/amount in cocoa compared with other flavanol-rich foods such as red wine or green tea [133, 134]. Thus, certain cocoa-based products are rich in flavanols [135, 136], some of which have been found in model systems to possess potential anti-inflammatory activities. However, the effect of cocoa flavanols and their related procyanidins appears to be related to the degree of polymerization, and opposing effects on inflammatory cytokine production in vitro of low- and

higher-degree of polymerization flavanols have been reported [137, 138]. In a small uncontrolled intervention study healthy subjects (n-25) consumed dark chocolate (36-39 g/d) and cocoa powder drink (30-95 g powder/d) for 6 weeks: there were no changes in concentrations of CRP, TNF-α, IL-1β, IL-6 or soluble P-selectin (sP-selectin) [139]. Another small (n-28), uncontrolled intervention study with dark chocolate for 1 week found a reduction in CRP concentration in women but not in men [140]. Most recently Monagas et al. [141] reported the effect of 4-week randomised cross-over trial of 40g cocoa powder in skimmed milk dairy vs. skimmed in forty-two older subjects: serum concentrations of sICAM-1 and sP-selectin were lower after the cocoa powder intervention. Thus, there is some evidence that cocoa and cocoa-rich foods reduce low-grade inflammation.

Fatty acids. Dietary fatty acids (macronutrients) may affect inflammatory processes through modulation of eicosanoids metabolism, and by eicosanoids-independent mechanisms such as regulation of membrane and cytosolic signalling processes that influence the activity of transcription factors involved in inflammation [142, 143]. These latter transcription factors include NF-kB and PPAR-γ, both of which are sensitive to fatty acids. There is an intriguing interaction between these latter two transcription factors because PPAR-γ inhibits NF-KB activation [144]. A number of different fatty acids including saturated, monounsaturated, trans-, conjugated linoleic and polyunsaturated of both n-6 and n-3 families have been investigated in the context of inflammation.

Saturated fatty acid may promote inflammatory processes, possible via activation of NF-KB [145, 146]. Using a subgroup of the Nurses' Health Study, Lopez-Garsia at al. [147] identified significant positive associations between the intake of trans-fatty acids in the diet and the concentrations of all six inflammatory markers assessed, including CRP, IL-6 and three soluble adhesion molecules. In a 5-week intervention in healthy men a trans-fatty acid enriched diet resulted in higher CRP and IL-6 concentrations than diets rich in oleic acis, stearic acid or the combination of lauric, myristic and palmitic acid [148].

In vitro and animal feeding studies have suggested marked effects of conjugated linoleic acid (CLA) on inflammation [149-150]. However, results from human intervention studies using CLA-rich capsules are equivocal [151-154]. For example, two studies demonstrate that CLA, especially the trans-10, cis-12 isomer, increases CRP concentrations, but not the concentrations of cytokines or soluble adhesion molecules [153].

Linoleic (18:2n-6) and α-linoleic (18:3n-3) acid — two fatty acids are the parent n-6 and n-3 PUFA, respectively. Because of the role of linoleic acid as the precursor of arachidonic acid (20:4n-6), which is, in turn, the substrate for the synthesis of pro-inflammatory eicosanoids such as PGE2, and 4-series leukotriens, it is widely considered that elevated n-6 and low n-3 acids (i.e. a high n6:n3 PUFA ratio) in the food products will promote inflammation. However, available evidence does not support this contention. The concentration of linoleic acid in blood lipids [155, 156] or granulocytes [111] was not associated with CRP or IL-6 concentrations, although a large Swedish study reported an inverse association between linoleic acid in cholesteryl esters and CRP concentration [157]. In a study on subgroup of the Nurses' Health Study, α-linolenic acid intakes were not associated with CRP, sICAM-1, sE-selectin or sTNFR2 concentrations but were associated with lower IL-6 and sVCAM-1 concentrations [110]. The changes in inflammatory markers seen with the α-linolenic acid food products were greater than with the linoleic acid food (75, 80, 37,5 and 12% decrease in CRP, sVCAM-1, sICAM and sE-selectin concentration respectively) [158]. Since this food product is effective replacing some linoleic acid with α-linolenic acid, relative to the amounts in the linoleic acid food product, these results suggested that α-linolenic acid is more potent than linoleic acid with regard to reducing inflammation.

Marine-derived long-chain n3 PUFA (EPA, eicosapentaenoic acid, (20:5n-3) and DHA, docosapentaenoic acid, (22:6n-3)) are found in seafood, especially oily fish. They are also present in fish oils and certain algal oils; in some preparations, the fatty acids are in a more concentrated form than in natural fish oils. The incorporation of EPA and DHA into human inflammatory cells is partly at the expense of arachidonic acid, resulting in less substrate available for the synthesis of the classic inflammatory eicosanoids such as PGE2. The effects of long-chain n-3 PUFA have been examined in many model systems and findings from cell-culture systems and from animal models are generally consistent in identifying anti-inflammatory action [142]. Furthermore, clinical trials have demonstrated anti-inflammatory effects and clinical benefit from fish oil administration in diseases with a frank inflammatory basis including rheumatoid arthritis [159], inflammatory bowel diseases [160] and childhood asthma [161]. Recently identified genetic differences among individuals, which may have an impact on the ability of n-3 PUFA to exert an anti-inflammatory effect. This was first identified by Grimble et al. [162] who showed that the ability of fish oil to lower the LPS-stimulated production of TNF-α by blood mononuclear cells was determined in part by polymorphism within the TNF-α and TNF-β genes. Another example of such an interaction was identified by Shen et al [163]. They first identified that the IL-1β 6054G>A SNP was significantly associated with the prevalence of the metabolic syndrome among a group of 1120 men and women with a mean age of 59 years. The results suggest that IL-1β genetic variants are associated with measures of chronic low-grade

inflammation and the risk of the metabolic syndrome.

Dietary fibre. Dietary fibre intake was inversely associated with serum CRP concentrations in diabetic women (n-3920) [164], as well as in subject with diabetes, hypertension and obesity (n-7891) [165]. King et al [166] conducted an intervention study with thirty-five lean normotensive and seventeen obese hypertensive adults that involved a randomised cross-over design. The two intervention diets constituted either the dietary approach to stop hypertension (DASH) diet (naturally high in fibre i.e. 30 g fibre/d) or a fibre-supplemented usual diet (30g psyllium fibre/d) each for a 3-week period. Both diets caused a reduction in CRP concentration (14 and 18%, respectively), although this was significant only in lean normotensive subjects in either intervention arm. The data generally support that dietary fibre intake is associated with reduced low-grade inflammation.

Milk peptides. Increased consumption of dairy products has been shown to have beneficial effects on plasma CRP and adiponectin concentrations in obese subjects [167]. This effect has been suggested to be partly explained by the intake of dairy protein-derived peptides. Indeed, the casein-derived peptides Ile-Pro-Pro and Val-Pro-Pro slightly, though not significantly, lowered CRP concentration in hypertensive subjects after 10 weeks [168]. Whey protein-derived peptides lowered CRP concentration (after 6 weeks) in one hypertensive subjects [169], but not in another [170]. Minor dairy proteins and peptides, especially lactoferrin, also show anti-inflammatory effects in different models [171-173], and hence there is potential for variety of milk peptides to have anti-inflammatory effect, but these are no or insufficient human studies to allow evaluation of their efficacy.

Micronutrients (iron, vitamins D, C, E) and phytochemicals (carotenoids, flavonoids, phyto-oestrogens). There is some epidemiological evidence that higher Fe intake, particularly that of haem Fe, and higher Fe status [174] are associated with increased risk of type 2 diabetes, atherosclerosis and coronary heart disease [175-177]. Past and emerging evidence indicates that chronic low-grade inflammation is associated with poor Fe status in obese persons [178-180]. In total, emerging evidence indicates that the low-grade inflammation of obesity may be associated with low Fe status; however, further investigation of this relationship is warranted.

Vitamin B plays a paracrine modulatory role in the immune/inflammatory system [181]. Although, a pro-inflammatory effect of vitamin B has also been suggested [182], epidemiological data shows an association between vitamin B deficiency and increased risk of several inflammatory diseases including type 1 diabetes and atherosclerosis [183]. Vitamin B inhibits the proliferation of lymphocytes and induces their apoptosis [184]. In addition, vitamin B affects the expression of ICAM-1 on mononuclear cells and on endothelial cells, suggesting that it suppresses the recruitment of leucocytes to sites of inflammation [184]. Most intervention studies with vitamin B have failed to identify a reduction in markers of low-grade inflammation [185-187]. Thus, these intervention studies suggest little anti-inflammatory action of vitamin B in the sorts of subjects studied. However, compared with placebo, vitamin B (82,5 mg/d for 12 months) resulted in a decrease (by 10%) in TNF-α concentration in overweight subjects on weight-reduction programme [188].

Vitamin C is a potent water soluble antioxidant. Ascorbate is the active form of vitamin C and exerts antioxidant function. Ascorbate is present at high concentration in leucocytes, suggesting a significant role in inflammation and in protection from oxidative damage. Obese subjects have lower plasma vitamin C concentrations than non-obese, and obesity was associated with moderately elevated CRP concentration [189].

Vitamin E is an umbrella term for a number of tocopherols and tocotrienols, although dietary vitamin У mainly consists of α- and γ-tocopherols. Vitamin У is a potent chain-breaking antioxidant. There are differences in the antioxidant activity between α- and γ-tocopherols. There is growing evidence that γ-tocopherols, in contrast to α-tocopherols, exert anti-inflammatory properties and supplementation with α-tocopherols decreases γ-tocopherols concentration [190, 191].

Carotenoids include among others, α-carotene, β-carotene, lycopene, β-cryptoxantin, lutein and zeaxanthin. They are highly prevalent in red, yellow and green vegetables and fruits. Recent data from the Women's Health Study reported that higher plasma concentrations of α- and β-carotene were associated with lower plasma CRP concentrations [192]. In 379 adults' serum lutein and lycopene concentrations were inversely associated with sICAM-1 concentrations, serum β-carotene with total blood leucocytes number and CRP concentrations, serum vitamin C with CRP concentrations, while plasma α-tocopherol concentrations were positively associated with CRP concentrations [193]. Among 704 70-year old men, dietary intake of vitamin C and α-tocopherol, but not of β-carotene, were inversely associated with CRP and IL-6 concentrations measured 7 years after the dietary information was collected [194]. Thus, overall cross-sectional and prospective studies fairly consistently demonstrate that a higher intake and status of vitamin C, vitamin E and carotenoids is associated with lower levels of low-grade inflammation.

Flavonoids are the most abundant polyphenols present in the human food products, and they can be divided into several classes according to different constituents such as flavanones, flavons, flavanols, flavonols. They can be found in almost all plant foods and among the flavonols, myricetin, kaempferol and

quercetin are the most representative, while catechins are the most abundant flavanols contained in tea leaves. Flavanones are mainly represented in the food products by taxifolin, naringinin and hesperitin. The main sources of flavonons are citrus fruits. Other classes of flavonoids are present in the products of such as proanthocyanidins and other oligomers. In a randomised human intervention trial with healthy normal-weight adults, supplementation with bilberry extract providing 300 mg anthocyanins/d (equal to 100 g of fresh bilberries) reduced plasma concentrations of several NF-KB-induces pro-inflammatory cytokines (IL-8, RANTES and IFN-α) [102]. In subjects who had survived myocardial infarction and had received statin therapy for at least 6 months, supplementation with a choke-berry flavonoid extract for 6 weeks significantly decreased CRP and MCP-1 concentrations, while adiponectin was significantly increased [195]. Quercetin (50, 100 or 150 mg/d, for 2 weeks) did not affect serum concentrations of TNF-α in adults [196].

Phyto-oestrogen — genistein is an isoflavone which primarily occurs in soybeans. Native phyto-oestrogens exist as glycosides, while in experimental studies, mostly the aglycones have been used. In two intervention studies with healthy postmenopausal women, the intake of genistein (54 or 40 mg/d) for 6 months did not significantly affect plasma CRP concentrations [197, 198]. The intake of soya either high or low in isoflavones for 1, 2 or 4 months had also no effects on CRP, SAA or TNF-α concentrations in hypercholesterolaemic men or postmenopausal women [198, 199]. In obese postmenopausal women, the combination of exercise with soya isoflavone supplement (duration 6 months) did not decrease plasma CRP concentration compared with exercise+placebo [199].

Summary

It is now recognised that a lower level of inflammation here termed chronic low-grade inflammation, can persist and may be a cause of, or result from, the abdominal obesity state. Adipose tissue releases many of the characteristic mediators of inflammation including some of the classic pro-inflammatory cytokines and chemokines, as well as adiponectin which is considered to be anti-inflammatory. People with abdominal obesity have higher circulating concentration of many inflammatory markers and these are believed to play a role in causing insulin resistance and in other metabolic disturbances of the metabolic syndrome and type 2 diabetes. Effects of bioactive food ingredients on low-grade inflammation have been identified through cross-sectional, prospective and interventional studies. Among the components of healthy food products, whole grains, vegetables and fruits, and fish are all seen to be associated with lower inflammation. Strong evidence in favour of anti-inflammatory effect of tea (black or geen), coffee (caffeinated or decaffeinated) and cocoa is lacking, despite positive effects on oxidative stress and the anti-inflammatory effects, mainly demonstrated in model system. Dietary fatty acids also influence low-grade inflammation; best studies are PUFA. Marine n-3 PUFA have the greatest anti-inflammatory potential. Hyperglycaemia induced both postprandial and chronic low-grade inflammation, acting in part through oxidative stress. Dietary fibre decreases low-grade inflammation. There may also be a role for milk peptides, but these have not been significantly evaluated. Vitamin D has the potential to reduce low-grade inflammation. There is good evidence from both model systems and from human observational and intervention studies that vitamin C, vitamin У and carotenoids decrease the concentrations of inflammatory markers. α- and β - tocopherols and the different carotenoids may have different anti-inflammatory properties and potencies. The majority of available evidence indicates that soya phyto-oestrogens and soya protein do not affect low-grade inflammation.

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