Inflammation and type 2 diabetes

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Abstract

Low-grade inflammation is a common feature in subjects with type 2 diabetes (T2D). Heart disease, the metabolic syndrome and T2D all have in common the increased concentration of circulatory cytokines as a result of inflammation. Inflammatory cytokines are produced by different cell types and secreted into the circulation, where they regulate different tissues through their local, central and peripheral actions. This review focuses on C-reactive protein (CRP), a well-established marker of the development of inflammation, on tumour necrosis factor (TNF-α), an inflammatory marker strongly associated with diabetes, and on adiponectin, a cytokine produced by adipose tissue and associated with insulin sensitivity. While it is clear from the literature that these cytokines play a major role in the development of T2D or, in the case of adiponectin, its prevention, the best strategy for favourably altering the inflammatory response is still a matter of debate.

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1. Introduction

Heart disease, the metabolic syndrome and type 2 diabetes (T2D) all have in common the increased concentration of circulatory cytokines as a result of inflammation [1,2]. Inflammatory cytokines are produced by different cell types and secreted into the circulation, where they regulate different tissues through their local, central and peripheral actions [3].

Low-grade systemic inflammation is characterized by a two-to threefold increase in systemic plasma concentrations of cytokines such as tumour necrosis factor (TNF)-α, interleukin (IL)-6 and C-reactive protein (CRP) [4]. Cytokines are small proteins (25 kDa) that are released in response to an activating stimulus and induce responses through binding to specific receptors [5]. The cytokines produced by adipose tissue have a key role in promoting atherosclerosis and, therefore, cardiovascular disease (CVD) [6]. The term ‘adipokines’ includes a group of polypeptide hormones that are expressed predominantly, but not exclusively, by adipose tissue [6]. Adiponectin is the only cytokine discussed in the present report that is produced mainly by adipose tissue [4]. In contrast, although TNF-α is produced
by adipose tissue, it is also secreted by macrophages and other cells. This cytokine plays a major role in the inflammatory process and, at elevated concentrations, may promote the synthesis of interleukins such as IL-8, the function of which is to induce monocyte adherence, thereby contributing to the atherosclerotic process [7]. TNF-α is also an inflammatory cytokine that has been implicated in metabolic disorders, including obesity and insulin resistance (IR) [8]. CRP is a cytokine that is mainly produced by the liver. Elevated concentrations of CRP have been associated with coronary heart disease (CHD), obesity, diabetes, smoking and a sedentary lifestyle [9]. In contrast, high concentrations of adiponectin are related to greater insulin sensitivity and a lower risk of CVD [4].

2. Obesity, inflammation and diabetes

Inflammation appears to be a common link between atherosclerosis, obesity and IR [10]. The increase in adipose tissue mass observed in obesity can lead to chronic activation of the innate immune system that, in turn, can lead to IR and T2D over time. Although implicated in the pathogenesis of chronic disease, the innate immune system serves as the critical first line of defense against invading organisms. Innate immune cells recognize molecular prototypes present on pathogens through pattern-recognition receptors expressed on cell surface membranes.Binding to pattern-recognition receptors activates nuclear factor-kappa-B (NF-κB) signaling pathways, thus leading to an inflammatory response [11]. The most studied of these receptors are the toll-like receptors (TLR), a 12-member family known to be activated by lipids. For instance, TLR2 recognizes lipoproteins and glycolipids, while TLR4 recognizes lipopolysaccharide (LPS) [5]. There is evidence that both TLR2 and TLR4 can recognize fatty acids and induce proinflammatory cytokines in macrophages [12].

These findings lead to one burning question: how does obesity activate the immune system? This question can be answered by briefly explaining two of the proposed mechanisms underlying the initial stages of obesity-induced, low-grade inflammatory processes. These proposed mechanisms stem from: (1) adipocyte organelle dysfunction; and (2) adipose tissue hypoxia.

Mitochondria and the endoplasmic reticulum (ER) are two adipocyte organelles that can be affected by the changes in cellular nutrient homeostasis found in obesity. Mitochondrial functions include biosynthetic and energy pathways, cellular redox homeostasis, calcium buffering and regulation of programmed cell death [13]. The ER is the main site of protein synthesis and folding, but it is also involved in triglyceride (TG) and cholesterol synthesis as well as calcium homeostasis [14]. In dysfunctional hypertrophic adipose tissue, there is an increase in lipolysis, resulting in hyperlipidaemia and an excess of cellular free fatty acids (FFAs). The latter, in combination with glucose overload, result in increased activity of oxidative pathways. Over time, this energy overload leads to mitochondrial dysfunction and a consequent increase in reactive oxygen species (ROS) [13]. Such oxidative stress can activate the immune system by inducing redox-sensitive transcription factors such as NF-κB [15]. In addition, nutrient excess overloads the functional capacity of the ER, resulting in greater instances of protein misfolding through activation of the unfolded protein response (UPR) [16]. The UPR induces activation of three transmembrane proteins: PKR-like eukaryotic initiation factor 2-alpha kinase (PERK); inositol-requiring enzyme-1 (IRE-1); and activating transcription factor-6 (AFT-6) [13]. PERK, IRE-1 and AFT-6 subsequently promote proinflammatory responses through activation of NF-κB, which then contributes to the initial stages of obesity-induced, low-grade inflammation.

The secondary proposed mechanism underlying this phenomenon is based on the relatively new ‘hypoxia theory’ reported by Trayhurn and Wood [17], who proposed that localized hypoxia serves as the initiator of adipokine dysregulation in obesity. Adipose tissue comprises a variety of cell populations, including adipocytes (which represent the majority), preadipocytes, resident macrophages, fibroblasts and endothelial cells. As adipose tissue continues to expand, it requires increased angiogenesis to mitigate its poor vascularization [18]. In response to hypoxic signals, the cells activate transcription factors such as hypoxia-inducible factor, which is involved in the activation of the genes associated with angiogenesis, glucose metabolism, cellular stress and inflammation [19,20]. Data in vitro have shown that human preadipocytes subjected to hypoxic conditions increase leptin expression while decreasing expression of peroxisome proliferator-activated receptor gamma (PPARγ) [21]. PPARγ agonists can improve insulin sensitivity and also reduce low-grade systemic inflammation. In addition, hypoxia also induces inflammatory responses in macrophages and inhibits preadipocyte differentiation [22].

A continuous postprandial state as the result of excess overnutrition may also lead to an inflammatory response. Hyperglycaemia in T2D results in an increase in advanced glycation end-products (AGEs), a heterogeneous group of molecules formed by the non-enzymatic reaction of bonding reducing sugars with free amino groups of proteins, lipids and nucleic acids [23]. However, there may be exogenous sources of AGEs through diet as a result of heat-generated reactions between sugars and proteins or lipids. AGE receptors are also found among the pattern-recognition receptors on cell surfaces. Plasma proteins modified by AGE precursors bind to AGE receptors on macrophages, vascular endothelial cells and vascular smooth muscle cells [24]. Binding of AGEs to their cognate receptors elicits pro-oxidant and proinflammatory responses [25]. Indeed, a crossover study demonstrated that these dietary AGEs can increase plasma CRP and TNF-α in the mononuclear cells of diabetic patients compared with a diet low in AGEs [26].

3. Metabolic consequences of proinflammatory cytokines

3.1. C-reactive protein

There are several metabolic consequences specific to T2D due to chronic elevation of proinflammatory cytokines. Elevated concentrations of CRP have been associated with CVD, obesity,
diabetes, inflammation, smoking and a sedentary lifestyle. CRP is produced in the liver upon stimulation by IL-6 and TNF-α [27], but it can also be released by mature adipocytes under inflammatory stimulation by LPS, TNF-α and resistin [28]. CRP increases the production of intracellular adhesion molecule-1 (ICAM-1) [29] and monocyte chemotactic protein-1 (MCP-1) by endothelial cells [30]. The current belief is that these two molecules are involved in the development of atherosclerosis. Soluble intracellular adhesion molecule 1 (sICAM-1), for example, mediates the adhesion of mononuclear cells to endothelium to enter the subendothelial space. In general, individuals diagnosed with T2D with high CRP levels are at greater CVD risk [31].

An important reason why CRP, measured by highly sensitive assays, emerged as a biomarker in clinical practice was that the cytokine has a relatively long half-life without diurnal variation, and remains stable over long periods of time in people without acute infections or inflammatory diseases [32]. CRP is an independent predictor of future cardiovascular events that can also predict the risk of hypertension and diabetes incidence [33]. The relative impact of CRP as a CVD risk factor is at least as great as that of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein (HDL-C) and blood pressure [34]. Results from the randomized Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) illustrate this point [33]. The trial was conducted to test the hypothesis that individuals with LDL-C < 130 mg/dL, but high CRP levels (≥ 2 mg/L), would benefit from statin treatment. After only 2 years, the JUPITER was stopped early because of the 44% reduction noted in all CHD events, including myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina and death from CHD, in the group receiving the statin [33].

It appears that the main function of CRP is to stimulate the synthesis of tissue factor production and to activate complement when aggregated. Studies in vitro have shown that aggregated CRP binds to LDL and very low-density lipoprotein (VLDL), leading to the activation of complement and the initiation of coagulation, thus explaining in part the connection between CVD and CRP [35]. Reductions in CRP are generally found after weight loss and are related to high adiponectin values [36]. In the ATTICA population study (involving a region in Greece including the main metropolitan area of Athens), 1514 men and 1528 women were recruited to determine the key factors for predicting CVD [37]. Results showed that those who closely followed the Mediterranean diet had lower levels of CRP, IL-6, fibrinogen and homocysteine, even after adjusting for confounding factors. It was concluded that CRP in combination with age, hypertension and diabetes were the most outstanding risk factors associated with CVD in this population [37].

Central obesity is one of the features associated with CRP, whereas physical activity (PA), independent of weight loss, has been associated with CRP reduction in patients with T2D. Furthermore, being more physically active might prevent further body-fat accumulation, which is associated with a higher inflammatory status. Obese people also tend to have high plasma leptin levels, which is associated with leptin resistance. Experiments both in vitro and in vivo support the hypothesis that CRP can induce leptin resistance by binding to leptin and impairing its signaling processes [38].

A recent study involving 10,276 individuals from a population cohort reported that polymorphisms in the CRP gene were closely associated with observed increases in CRP levels [39]. However, these polymorphisms were not associated with an increased risk of CHD, suggesting that the increased CRP levels observed in patients with CHD may simply be a marker of atherosclerosis and ischaemic disease [39].

4. Tumor necrosis factor (TNF)-α

TNF-α belongs to the TNF family, which is produced by macrophages, natural killer cells and T cells. In adipose tissue, infiltrated macrophages are the main source of TNF-α [40]. The cytokine is produced 7.5 times more by adipose tissue in obese subjects than in their lean counterparts [8]. TNF-α promotes inflammation and endothelial activation, increasing vascular permeability [5]. The acute local release of TNF-α induces a local inflammatory response to contain infections and, thus, can be beneficial. However, the acute systemic release of TNF-α leads to sepsis and shock [5]. Similarly, chronically elevated TNF-α, as seen in obesity, is also detrimental specifically to glucose metabolism [41]. TNF-α can alter insulin sensitivity in different ways: by attenuating insulin receptor signaling pathways [65]; by decreasing glucose transporter-4 in adipocytes [41]; and by suppressing adiponectin [42]. In addition, TNF-α increases the expression of the genes encoding IL-6 and MCP-1, and contributes to the progression of atherosclerosis [43].

NF-κB is a transcription factor that has a key function in integrating the intracellular regulation of the immune response, inflammation and cell cycle regulation; it also modulates the expression of many inflammatory cytokines, including TNF-α [44]. Plasma concentrations of TNF-α have been positively correlated with elevated plasma TG and with heart failure [44]. TNF-α mRNA and protein are expressed in the failing, but not in the normal, human heart [45]. TNF-α also has multiple detrimental effects on the heart, including cardiomyocyte hypertrophy and apoptosis, and impairment of contractile function, thereby explaining its relationship to heart failure [45]. In addition, there is evidence indicating that TNF-α induces the overproduction of VLDL particles, which might explain its direct relationship with plasma TG [46]. However, some studies indicate that TNF-α may be reduced by weight-loss interventions [47,48].

5. Adiponectin

Adiponectin is an adipose-specific plasma protein with anti-inflammatory [49] and insulin-sensitizing effects [50] induced by activity of the nuclear receptor PPARγ [51]. A decrease in adipose tissue has been associated with increases in adiponectin [52]. Adiponectin is unique in that, unlike other adipokines, its circulating concentrations are reduced in obesity [53]. Data from epidemiological studies indicate that circulating adiponectin is reduced in patients with CVD and diabetes [54]. More important,
low adiponectin concentrations are strongly correlated with IR [55]. Therefore, high concentrations of adiponectin are related to greater insulin sensitivity and a lower risk of CVD. Also, low concentrations of adiponectin in plasma can affect plasma HDL-C, as adiponectin has been inversely correlated with HDL–apoA1 catabolism. This suggests that the low adiponectin levels present in T2D prevent the otherwise CVD protection afforded by this adipokine.

Using several mouse models of differing insulin sensitivity, Yamauchi et al. [56] were the first investigators to clearly demonstrate a relationship between adiponectin expression and insulin responsiveness. Consistent with earlier studies that noted altered adiponectin expression with obesity [56], db/db mice—a genetic model of obesity and T2D due to a mutation in the gene encoding the leptin receptor—displayed reductions in both adipose adiponectin mRNA and plasma levels in response to hyperglycaemia and hyperinsulinaemia. Administration of the PPARγ agonist rosiglitazone reversed this situation and, in addition, a modest attenuation of the elevated plasma glucose and insulin in these mice was observed. Replenishing these mice with an intraperitoneal injection of low-dose (50 μg) recombinant adiponectin significantly decreased circulating insulin and glucose levels. Thus, the insulin-resistant state that occurred in these obese and non-obese diabetic mouse models was accompanied by a reduced expression of adiponectin, which was reversed when adiponectin was provided, thus suggesting that adiponectin treatment might be a novel strategy against IR and T2D [56].

Many of the positive effects of adiponectin occur via the upregulation of adenosine monophosphate protein-activated protein kinase (AMPK) in both the liver and skeletal muscle [57]. Adiponectin phosphorylates AMPK which, in turn, inhibits acetyl-CoA carboxylase (ACC), the rate-limiting enzyme in fatty acid synthesis [57]. The inhibition of ACC lowers the concentration of malonyl-CoA, the product of the reaction. Malonyl-CoA is an inhibitor of carnitine palmitoyl transferase 1, the rate-limiting enzyme in fatty acid oxidation. Therefore, reduction of the concentration of malonyl-CoA by AMPK increases fatty acid oxidation. Greater skeletal muscle fatty acid oxidation decreases the delivery of FFAs to the liver, leading to a reduction in liver TG synthesis and VLDL secretion [58]. AMPK also stimulates PPARα, which increases the expression of enzymes involved in fatty acid β-oxidation, resulting in an improvement in insulin sensitivity [59]. There is also a reduction in the concentration of FFAs in the peripheral tissues, preventing lipotoxicity and the interference of fatty acids with insulin receptor signaling [51]. In addition, adiponectin reduces glucose production in the liver by directly inhibiting the gluconeogenic enzymes phosphoenolpyruvate carboxykinase and glucose-6-phosphate [57], thereby improving glycaemic control and insulin sensitivity.

The reduction of adiponectin in obesity and diabetes most likely arises from an increase in adipose tissue macrophage infiltration, resulting in inflammation. The proinflammatory cytokines TNF-α and IL-6 also reduce adiponectin expression [4]. Conversely, adiponectin has an anti-inflammatory effect by inhibiting the activation of NF-κB by TNF-α [52]. Interventions known to reduce inflammation associated with obesity may elevate adiponectin concentrations. Also, adiponectin may increase in response to diet-induced weight loss, although it appears that the weight loss must be > 10% of body weight [60,61]. Although the effects of exercise on plasma adiponectin are not completely known at this time, exercise programmes do not consistently affect adiponectin [62]. However, as with dietary weight-loss interventions, it appears that positive effects are more consistently seen with aerobic and resistance-training programmes that are of adequate intensity and duration to promote significant fat loss [2].

6. Diabetes and proinflammatory cytokines

As shown in Fig. 1, a genetic predisposition combined with an ‘obesogenic’ environment can lead to obesity and central adiposity. An obesogenic environment is characterized by excess caloric intake and a lack of PA [63]. This may ultimately lead to increases in body weight, resulting in adipose tissue dysfunction, macrophage infiltration [64], and the greater release of cytokines such as IL-6 and TNF-α. Chronically elevated levels of these molecules promote IR in skeletal muscle [64] and endothelial dysfunction in the vasculature [65], as well as the release of acute-phase proteins such as CRP from the liver [11].

Chronically elevated levels of specific inflammatory markers such as IL-6 and TNF-α appear to be involved in metabolic disorders [66]. TNF-α and IL-6 can alter insulin sensitivity by triggering different key steps in the insulin-signaling pathway [47]. These cytokines stimulate phosphorylation of serine residues instead of tyrosine in insulin receptor substrate-1 (IRS-1), thereby preventing the activation of insulin signaling and perpetuating IR [66]. In addition, elevated FFAs also contribute to IR by activating TLR and the consequent cytokine response or by directly activating Jun N-terminal kinase (JNK), which stimulates phosphorylation of the serine residues present in IRS-1 [67]. These pathways appear to create a vicious circle, as
hyperglycaemia also induces IL-6 production from endothelium and macrophages. In addition, hyperglycaemia enhances suppressor of cytokine signaling (SOCS) action, thereby impairing insulin release and signaling cascades. The family of SOCS proteins are capable of inhibiting Janus kinase (JAK)/signal transducers and activators of transcription (STAT) signaling in various tissues [68]. This suggests that improving glycaemic control might reduce the inflammatory response supporting the link between inflammation and glucose metabolic disorders.

In adipose tissue, the protective adiponectin secretion is diminished and leptin release is increased. Furthermore, studies of adipocytes in vitro have demonstrated that IL-6 [69] and CRP [70] both downregulate adiponectin and its mRNA expression. Leptin, a protein involved in glucose metabolism and appetite regulation, is influenced by the status of energy stores in fat. Also, experiments in vitro and in vivo support the hypothesis that CRP can induce leptin resistance by binding to leptin and impairing its signaling capacities [38]. Overall, these data support the relationship between inflammatory markers and metabolic disorders such as occurs in IR.

This complex metabolic milieu is also associated with dyslipidaemia—specifically, high plasma TG and low plasma HDL-C—resulting in an increased risk of atherosclerosis [65]. As insulin inhibits lipolysis, in a state of IR, the lack of insulin function leads to greater mobilization of FFAs. This occurs after consuming a meal that, in combination with lower lipoprotein lipase activity, creates a chylomicron remnant rich in TG [71], resulting in increased availability of hepatic FFAs and secretion of TG-rich VLDL particles. The latter also affects HDL metabolism through the interchange with TG-rich lipoproteins via cholesteryl ester transfer protein, thus producing HDL particles containing higher concentrations of TG. After hepatic lipase has hydrolyzed TG, the HDL particles become smaller and less antiatherogenic, and more easily removed by the kidneys.

Furthermore, IR in T2D is associated with a higher risk of endothelial dysfunction, which can also lead to CVD [72]. Insulin increases the availability of endothelium-derived nitric oxide (NO), a potent vasodilator. Therefore, endothelial cells in IR conditions may lack this positive vasodilatory stimulus. Endothelial dysfunction also contributes to the development of atherosclerosis, as it favours coagulation, cell adhesion and inflammation by promoting inappropriate vasodilatation and allowing the transendothelial transport of atherogenic lipoproteins [73].

7. Gut microbiota and diabetes

Over the past few years, intestinal microbiota have been reported to have a causal relationship in the development of metabolic diseases, including diabetes [74]. Recent advances in DNA sequencing have permitted the collection of microbial communities associated with the human gut [75]. Although there are changes in the microbiota between newborns and the elderly, the adult intestinal microflora have been shown to be stable over time [76]. However, metabolic abnormalities have been associated with changes in the microbiota. For example, obesity is associated with reduced bacterial diversity [77]. It has also been demonstrated that deviations in the core microbiome at the gene level are associated with different physiological states, for example, obese vs lean [78]. Characterization of the intestinal microbiota in T2D patients has recently been published [79]. The ratio of their microflora correlated with plasma glucose concentrations, but not with body mass index (BMI), suggesting that bacterial sequences specific to T2D can be considered signatures of hyperglycaemia [79].

Amar et al. [80] investigated the capacity of the broadly specific marker 16S rDNA to predict the onset of diabetes and obesity in the general population. They concluded that 16S rDNA was an independent marker of the risk of diabetes, thus reinforcing the concept that tissue bacteria are involved in the onset of diabetes in humans [80]. Furthermore, it has been demonstrated that, in fat-induced hyperglycaemia and IR, there is translocation of intestinal bacteria to both the adipose tissue and bloodstream, where they can then induce inflammation [81]. Interestingly, this translocation can be reversed by treatment with probiotic bacterial strains, thereby improving overall inflammatory status [81]. From these studies, it is clear that the gut microbiota are an emerging and interesting area of research with multiple possibilities. Indeed, the gut microbiota could be used as the basis for treating or preventing metabolic diseases, and to identify patients at risk of specific metabolic abnormalities such as diabetes.

8. Diet and proinflammatory cytokines in people at risk of or with type 2 diabetes

There is a fair amount of evidence from epidemiological studies confirming the relationship between diet and variations in inflammatory markers. It is also known that a diet poor in fruits and vegetables is often characterized by low fibre content, and there are also epidemiological data from single-nutrient approaches on how a low intake of fibre is associated with more inflammatory markers and higher T2D risk. The British Regional Heart Study was a case-control study in which 3428 men (aged 60–79 years) free of T2D were followed for 7 years, after which 162 cases of diabetes were found [82]. Participants were divided into quartiles according to fibre intake. CRP and the marker of hepatic function, gamma-glutamyltransferase (GGT), were also assessed. Total fibre intake was inversely associated with CRP and GGT levels. In addition, low dietary fibre (< 20 g) was associated with a higher risk of developing diabetes [82]. Masters et al. [83] studied 941 participants free of T2D in the Insulin Resistance Study (IRAS), and found that CRP and whole grains were inversely correlated, after adjusting for lifestyle; however, when waist circumference was added to the model, this relationship was no longer significant. These results support the role of visceral adiposity in increasing CRP.

One of the disadvantages of the single dietary approach is that it may not capture nutrient interactions, as the daily diet includes consuming several nutrients concomitantly. However, dietary patterns can be described by a dietary evaluation in which multiple foods and/or nutrients are examined collectively [84]. Data from the Multi-Ethnic Study of Atherosclerosis showed that the ‘whole grains and fruit’ dietary pattern was inversely
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FFQ: Food Frequency Questionnaire; PCA: principal component analysis; RRR: reduced rank regression; CRP: C-reactive protein; IL-6: interleukin-6; SAA: serum amyloid A; TNF-$\alpha$: tumour necrosis factor-$\alpha$; sICAM-1: soluble intracellular adhesion molecule 1; sVCAM-1: soluble vascular cell adhesion molecule-1; WC: waist circumference; BMI: body mass index; T2D: type 2 diabetes; PA: physical activity; CVD: cardiovascular disease
associated with plasma sICAM-1, CRP and IL-6. Meanwhile, the ‘fats and processed meat’ dietary pattern was directly associated with plasma CRP and IL-6 [85]. Previous findings are also consistent with data from the Nurses’ Health Study [86], in which researchers reported that the ‘Western’ dietary pattern was positively associated with plasma CRP and sICAM-1 after adjusting for confounding factors, including BMI [86]. The so-called Western dietary pattern included red and processed meats, desserts, French fries and refined grains. Conversely, the ‘prudent’ dietary pattern, rich in fruits and vegetables, was inversely associated with plasma CRP after adjusting for confounding factors [86]. Likewise, in the European Prospective Investigation into Cancer and Nutrition, Heidemann et al. [87] found that the dietary pattern characterized by high intakes of fresh fruits, and low intakes of soft drinks, red and processed meats, poultry, beer and refined bread, was associated with higher plasma HDL-C and adiponectin, and lower CRP and glycosylated haemoglobin (HbA1c) levels. A higher score in the identified dietary pattern also resulted in a reduced incidence of T2D independently of BMI, energy intake, age, exercise, PA and smoking status [87].

Similarly, data from a cross-sectional study of Iranian women demonstrated that levels of plasma CRP and soluble vascular cell adhesion molecule-1 (sVCAM-1) were inversely associated with the ‘healthy’ dietary pattern. Also, plasma IL-6 was directly associated with the ‘Western’ dietary pattern after adjusting for waist circumference and BMI. In addition, the ‘traditional’ dietary pattern, characterized by refined grains, legumes, hydrogenated fats and potatoes, was directly associated with IL-6 in this group of Iranian women [88].

Thus, in general, the epidemiological evidence supports an inverse relationship between inflammatory markers and a dietary pattern rich in fruits and vegetables (Table 1).

Data from randomized controlled trials also support the relationship between diet and inflammatory markers, although these data are scarce in comparison to the epidemiological evidence. This could be related to the inherent difficulty and complexity of carrying out trials controlling for diet under free-living conditions over time. However, a randomized single-blind trial was conducted in 180 adults with the metabolic syndrome to evaluate the effects of a Mediterranean-style diet on endothelial dysfunction and vascular inflammatory markers [89]. For 2 years, the intervention group (n = 90) followed a Mediterranean-style diet, while the control group (n = 90) followed what researchers called the ‘prudent diet’ (50–60% carbohydrate, 15% protein and < 30% fat). The intervention group showed reductions in CRP, IL-6 and IR compared with the control group, after adjusting for body-weight changes. Also, endothelial dysfunction scores improved in the intervention group, but remained stable in the controls after 2 years [89]. Giugliano et al. [90] later concluded that the dietary-pattern approach is particularly promising for reducing the inflammation associated with the metabolic syndrome.

The Finnish Diabetes Prevention Study was a multicentre randomized controlled trial designed to investigate whether a lifestyle intervention aimed at increasing PA and improving diet could reduce the risk of developing T2D [91]. Using the baseline and 1-year follow-up data, the effects of diet and PA on plasma CRP and IL-6 in individuals at risk of developing T2D were evaluated. The authors concluded that increases in fibre intake were predictive of reductions in CRP and IL-6 levels even after adjusting for BMI changes in the first year of the study. Other examples of the single-nutrient approach are the studies of the polyphenols present in grapes [92] and in raisins [93], both of which have shown an effect by reducing plasma TNF-α concentrations.

Thus, the proinflammatory markers CRP, IL-6, sVCAM and sICAM-1 were inversely associated with a dietary pattern rich in fruits and vegetables, independent of however the dietary pattern was identified. On the other hand, the above-mentioned biomarkers were positively associated with a dietary pattern high in refined grains and saturated fats, such as those found in meat, processed meats and hydrogenated fats. The clinical data also provide evidence of the positive effects of diets high in fibre and polyphenols, which are both consistent with following the Mediterranean-style diet, by improving inflammation.

9. Conclusion

There is now a growing body of knowledge on the modes of action of CRP, TNF-α and adiponectin, and their specific roles in the regulation of inflammation and its implications for the development of diabetes. Population studies have reported important correlations between plasma levels of CRP and TNF-α, and an increased risk of heart disease and diabetes. However, increased concentrations of plasma adiponectin are related to insulin sensitivity and a lower risk of heart disease. While there is a consensus that weight loss is associated with decreases in TNF-α and CRP, and with increases in adiponectin, more studies aimed at addressing both the effects of the macronutrient composition of diet and antioxidant intakes, and the effects of different types of exercise, including resistance training, on these cytokines are needed.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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