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Impact of anti-inflammatory nutrients on obesity-associated metabolic-inflammation from childhood through to adulthood

Ruth M. Connaughton[1], Aoibheann M. McMorrow[1], Fiona C. McGillicuddy[2], Fiona E. Lithander[3] and Helen M. Roche[1]*

[1]*Nutrigenomics Research Group, UCD Conway Institute, School of Public Health and Population Science, University College Dublin, Dublin 4, Republic of Ireland*

[2]*Diabetes Complications Research Centre, UCD Conway Institute and School of Medicine, University College Dublin, Dublin 4, Republic of Ireland*

[3]*School of Medicine, Trinity College Dublin, Trinity for Health Sciences, St. James's Hospital, Dublin 8, Republic of Ireland*

Obesity-related metabolic conditions such as insulin resistance (IR), type 2 diabetes and CVD share a number of pathological features, one of which is metabolic-inflammation. Metabolic-inflammation results from the infiltration of immune cells into the adipose tissue, driving a pro-inflammatory environment, which can induce IR. Furthermore, resolution of inflammation, an active process wherein the immune system counteracts pro-inflammatory states, may be dysregulated in obesity. Anti-inflammatory nutritional interventions have focused on attenuating this pro-inflammatory environment. Furthermore, with inherent variability among individuals, establishing at-risk populations who respond favourably to nutritional intervention strategies is important. This review will focus on chronic low-grade metabolic-inflammation, resolution of inflammation and the putative role anti-inflammatory nutrients have as a potential therapy. Finally, in the context of personalised nutrition, the approaches used in defining individuals who respond favourably to nutritional interventions will be highlighted. With increasing prevalence of obesity in younger people, age-dependent biological processes, preventative strategies and therapeutic options are important to help protect against development of obesity-associated co-morbidities.

Obesity: Metabolic health: Anti-inflammatory nutrients

The underlying aetiology of obesity-related co-morbidities are multifaceted. Systemic and local inflammation, along with dysregulated fatty acid metabolism and mitochondrial dysfunction are pathological features of a number of metabolic conditions including insulin resistance (IR), type 2 diabetes (T2D) and CVD[1,2]. Childhood and adolescent obesity are associated with an adverse metabolic phenotype[3]. In the short term, some obese children experience respiratory problems and hypertension, as well as displaying markers of CVD and IR[4]. The long-term health consequences of childhood obesity include increased risk of T2D, stroke and CHD, as well as increased risk of some cancers in later life[5,6]. Biomarkers of inflammation such as circulating C-reactive protein (CRP) and IL-6, along with decreased levels of adiponectin, are potential predictors of future adverse outcomes such as CVD and T2D in overweight and obese children[7]. However, despite the present childhood obesity epidemic few studies have examined anti-inflammatory nutritional interventions in

Abbreviations: T2D, type 2 diabetes; IR, insulin resistance; AT, adipose tissue; CRP, C-reactive protein; IRS, insulin receptor substrate; IKK, IκB kinase; JNK, c-Jun N-Terminal kinase; LPS, lipopolysaccharide; TLR, toll-like receptor; NLR, nod-like receptor; LC *n*-3 PUFA, long chain *n*-3 PUFA; MetS, metabolic syndrome.

***Corresponding author**: H. M. Roche, email helen.roche@ucd.ie

a paediatric population. Ideally, reducing BMI would be the favourable strategy to attenuate T2D risk. Yet, weight management is difficult to achieve in this age group[8]. Further research into nutritional approaches to reduce risk in the absence of weight loss is needed. Furthermore, understanding the putative pathophysiology and establishing novel effective treatments have become of utmost importance.

Obesity and dysregulated insulin signalling

Obesity-induced IR is a key risk factor for T2D[9]. The primary role of insulin in its target tissues is to facilitate glucose disposal, as well as inhibiting hepatic glucose production[10,11]. IR is defined as the inadequate response by insulin target tissues such as adipose tissue (AT), skeletal muscle and liver to the physiological effects of insulin[12]. The main characteristics associated with IR are: (1) decreased insulin-stimulated glucose-uptake into skeletal muscle and AT; (2) impaired insulin-mediated inhibition of hepatic glucose production and (3) reduced ability of insulin to inhibit lipolysis in AT[12,13]. Additionally, as a result of IR, there is a compensatory increase in insulin leading to enhanced lipogenesis in the liver. Hyperinsulinaemia is known to decrease the expression of insulin receptor substrate (IRS)-1 and IRS-2 in liver and AT by inducing the degradation of IRS-1 protein and inhibition of IRS-2 at a transcriptional level[14–16]. Insulin signalling is negatively regulated via phosphorylation of serine residues on IRS[11,12], impeding tyrosine-induced phosphorylation of IRS-1 by the insulin receptor blocking downstream propagation of signalling[17]. Several kinases such as mammalian target of rapamycin, protein kinase C-θ, inflammatory kinases IκB kinase (IKK) and c-Jun *N*-terminal kinase (JNK) have been shown to phosphorylate serine residues on IRS-1[18,19]. These inflammatory components impede insulin signalling leading to the development of IR, providing a potential link between obesity-induced inflammation and dysregulation of insulin signalling[10].

The role of metabolic-inflammation in obesity-induced insulin resistance

The association between obesity, IR and subsequently T2D and CVD may be partially attributable to the presence of low-grade chronic inflammation also known as metabolic-inflammation. Metabolic-inflammation is orchestrated by prolonged nutritional and metabolic cues and manifests at tissue level[20]. This is in contrast to classic inflammation in response to an acute trigger such as infection or tissue damage, which is typically assessed in response to lipopolysaccharide (LPS). Classic inflammation is usually rapidly resolved, whereas metabolic-inflammation can persist long-term. Furthermore, metabolic-inflammation is characterised by an influx of inflammatory cells to metabolic tissues and the release of pro-inflammatory cytokines locally and systemically, leading to a sub-acute, chronic inflammatory state that is characteristic of metabolic-inflammation.

To date a number of inflammatory features have been identified in the obese state including AT inflammation, immune cell infiltration and dysregulated resolution of inflammation[21–23]. While these features have primarily been observed in adults, as the inflammatory phenotype is more pronounced, the presence of these features in childhood and adolescent obesity remains to be fully established[24]. Interestingly, Sbarbati *et al.* noted the presence of 'inflammatory lesions' consisting of fragments of adipocytes with the presence of macrophages in perivascular positions in the AT of obese children[25]. Importantly, these lesions were absent in non-obese children[25]. Furthermore, obese children as young as age 6 years demonstrate increased circulating TNF-α and soluble CD163 with reduced adiponectin and innate immune cell frequency compared with their lean counterparts[26].

Adipose tissue inflammation

AT plays an essential role in energy homeostasis with the potential of having detrimental effects if adipose capacity is exceeded[27]. During normal homeostasis adipocytes secrete an array of proteins termed adipokines which play an important role in glucose and lipid metabolism[28,29]. However, the progressive expansion of adipocytes as a result of obesity leads to the secretion of cytokines and chemokines of a pro-inflammatory nature[30]. Increased levels of TNF-α, IL-6 and monocyte chemoattractant protein-1 are secreted from inflamed AT found in obese mice and man when compared with AT from healthy subjects[31]. Intercellular adhesion molecule-1 also aids immune cell recruitment, which further exacerbates the pro-inflammatory environment[28,32].

Immune cell infiltration

Accompanying the expansion of adipocytes is the infiltration of immune cells such as T-cells and macrophages[10,33]. T-cells play an important role in metabolic-inflammation by preceding and potentially modifying AT macrophage number and activation state[33]. Secretion of interferon-γ by T helper-1 cells aids in the recruitment of macrophages into the AT, which surround dying or dead adipocytes, forming crown-like structures. The release of pro-inflammatory cytokines from these newly recruited AT macrophage, also known as M1 macrophages, propagates further immune cell infiltration and exacerbates AT inflammation[19]. With the onset of obesity M1 AT macrophages accumulate, overwhelming the protective effects of anti-inflammatory M2 macrophages, altering the inflammatory balance to favour increased levels of pro-inflammatory cytokines[34].

Production of these pro-inflammatory cytokines activates key signalling pathways and regulators of inflammation[10]. TNF-α activates a number of serine kinases such as JNK and inhibitor of κB kinase (IKKβ), leading to serine phosphorylation of IRS-1[18,35]. Additionally, TNF-α and IL-6 increase secretion of a family of proteins termed suppressor of cytokine signalling which binds to

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insulin receptors impairing insulin signalling[36,37]. In an animal model of diet-induced obesity SFA prime pro-IL-1β[38]. Pro-IL-1β is then cleaved by activation of the NLRP3 inflammasome, a protein complex, leading to the cleavage and activation of caspase-1, which in turn cleaves pro-IL-1β into its mature form[39,40]. IL-1β in turn impedes *de novo* adipogenesis and induces adipocyte IR by inducing serine phosphorylation of IRS-1[41].

Dysregulated resolution of inflammation

The metabolic-inflammatory state develops gradually and remains unresolved over time[42]. Attenuated resolution of metabolic-inflammation has been implicated in the development of obesity-associated co-morbidities[43,44]. The classic inflammatory response mechanism protects the host from infection and other insults, while restoring homeostasis at infected or damaged sites[42]. Response to triggers such as microbial products and tissue damage activate several inflammatory pathways including toll-like receptor (TLR) and nod-like receptor (NLR) signalling pathways[32]. Acute activation of these inflammatory processes causes a catabolic state of inflammation with increased energy expenditure, along with IR and immune cell infiltration to the site of infection[20]. Furthermore, the classic characteristics of inflammation namely redness, pain, swelling and heat are displayed once a response to the invading pathogen or injury is mounted[20]. Importantly, once the trigger is eliminated or under control, mechanisms come into play to terminate inflammation, limiting further damage[45]. This self-regulating process known as resolution of inflammation is a negative feedback mechanism involving secretion of anti-inflammatory cytokines and inhibition of pro-inflammatory signalling pathways[45,46].

Resolution of inflammation is an active process which requires the activation of a number of endogenous programmes that enables the host tissue to maintain homeostasis[45]. The process of resolution is programmed at the initial phase of the inflammatory response via the cyclooxygenase and lipoxygenase signalling pathways[44,47]. Biosynthesis of pro-inflammatory eicosanoids prostaglandins and leukotrienes which are derived from the fatty acid arachidonic acid aid, inflammation by modifying vascular permeability, blood flow and vascular dilation needed for the recruitment of inflammatory cells[44]. Furthermore, prostaglandins and leukotrienes actively switch on the transcription of enzymes required for the generation of other classes of eicosanoids[48]. Lipoxins which are anti-inflammatory, pro-resolving and anti-fibrotic are produced endogenously at sites of inflammation as counter-regulating lipid mediators[43]. Lipoxins play an important role in a number of experimental models of metabolic disease such as CVD and T2D[44,49]. Lipid mediators generated from long chain *n*-3 PUFA (LC *n*-3 PUFA) termed resolvins and protectins also aid the resolution phase of inflammation[23,43]. Resolvins and protectins down-regulate or impede polymorphonuclear neutrophil infiltration, while regulating inflammation, reducing fibrosis and stimulating phagocytosis of apoptotic polymorphonuclear neutrophil cells by macrophages[45].

During metabolic-inflammation, the characteristics of inflammation (redness, pain, swelling and heat) are absent with no increase observed in basal energy expenditure[20]. Macronutrients and their derivatives such as fatty acids, ceramides, uric acid and glucose, which are often associated with metabolic surplus are the primary triggers and activate several inflammatory kinases[50]. Additionally, the formation of resolving mediators are severely dysregulated, with a deficit of endogenous resolvins RvD1 and RvD2 seen in AT isolated from obese mice when compared with AT from lean mice[51]. Therefore, dysregulation of the resolution process in an obese setting, in conjunction with a constant supply of metabolic triggers may result in pro-inflammatory signalling becoming pathological[46,48]. Thus, properly controlling the resolution of inflammation may be essential in terms of maintaining homeostasis with a view of attenuating the impact of metabolic-inflammation.

Pro-inflammatory effect of dietary factors on inflammation and metabolic health

Nutrient metabolism is a key player in shaping the nature of the immune response, as reviewed by McArdle *et al.*[32]. Nutrients influence inflammatory pathways by interacting with extracellular receptors and mediate intracellular signalling in either a beneficial or detrimental manner. The pro-inflammatory effects of SFA are well characterised[40,52,53]. Interestingly, the structure of SFA and the bacteria component LPS, a classic TLR4 agonist, share similarities[54,55]. A number of studies have investigated the potential of SFA in activating TLR4[56]. Studies *in vitro* show that addition of palmitate to macrophages and adipocytes elicits a TLR4 dependent pro-inflammatory response consisting of increased NF-κB and JNK activation, while increasing TNF-α secretion[54]. In addition, cytokines, secreted upon activation of TLR4 by SFA bind to plasma membrane receptors or intracellular lipid mediators such as diacylglycerol, initiating inflammatory signalling pathways through several stress kinases such as JNK and IKK[57–59].

In man, it is well acknowledged that habitual SFA intake is inversely associated with insulin sensitivity, assessed by insulin sensitivity index and directly with homeostatic model of assessment-IR, particularly in T2D subjects[38]. In a cohort of individuals with metabolic syndrome (MetS), a multi-component condition characterised by abdominal obesity, IR, dyslipidemia and hypertension, high SFA intake is associated with elevated AT caspase-1 and pycard-1 mRNA expression. This impacts upon NLRP3-mediated IL-1β processing[38]. This association between high dietary SFA intake and inflammation has been observed as early as adolescence. Overweight adolescents had higher plasma SFA concentrations when compared with normal-weight counterparts, with obese adolescents also having elevated IL-6 and CRP concentrations[60].

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From a personalised nutrition perspective, the impact of dietary insults may be more evident according to inflammatory genotype/phenotype. Studies have demonstrated the influence of a variety of pro-inflammatory cytokine polymorphisms including TNF-α and IL-6 in the risk of central obesity, diabetes and MetS phenotype, as reviewed by Phillips[61]. A significant interaction between total PUFA and IL-1β was found on MetS risk in a cohort of 1120 men and women with and without MetS[62]. Individuals homozygous for GG and GA heterozygotes in the lowest 50th percentile of EPA and DHA had a higher risk of MetS than AA homozygotes[62]. These results suggested that a diet high in LC *n*-3 PUFA may obliterate an increased genetic pre-disposition towards developing MetS, further promoting the potential benefits of personalised nutrition[62]. However, while providing insight into the importance of genetic pre-disposition and dietary response, elucidating the functional consequences of such polymorphisms in metabolic-inflammation is essential.

Modulation of inflammation and metabolism by anti-inflammatory dietary factors

Cellular processes

The anti-inflammatory properties of nutrients and non-nutrients such as polyphenols have been an important discovery with respect to novel therapeutics for metabolic-inflammation and related metabolic diseases. From the cellular perspective, Fig. 1 illustrates that LC *n*-3 PUFA EPA and DHA decrease the production of classic pro-inflammatory cytokines by modulating components of the NF-κB signalling pathway[63–67]. In conjunction with decreasing NF-κB activity, DHA increases phosphorylation of 5′-AMP-activated protein kinase catalytic subunit α1, leading to increased sirtuin-1 activity. This increase in sirtuin-1 activity results in deacetylation of NF-κB subunit p65, leading to suppression of cytokine secretion[65]. Interestingly, DHA-treated macrophages when co-cultured with adipocytes resulted in partial protection against IR, demonstrating enhanced insulin signalling through modulation of inflammatory pathways by DHA[67].

A number of antioxidant nutrients have demonstrated additional anti-inflammatory properties. Evidence from *in vitro* studies demonstrate that components of the NF-κB and mitogen-activated protein kinase signalling pathways are prime targets of antioxidants, as illustrated in Fig. 1[68–70]. Epigallocatechin gallate, lycopene and vitamin C impede NF-κB signalling, by targeting IKK and attenuate phosphorylation of extracellular signal related kinase, p-38 and JNK[67–69,71]. α-Tocopherol, in conjunction with vitamin D_3 ameliorates IL-6 production as well as increasing mRNA and protein expression of adiponectin in 3T3-L1 adipocytes[71,72]. Moreover, Yang *et al.* proposed that epigallocatechin gallate may improve insulin sensitivity in AT through reactive oxygen species scavenging functions, thus improving insulin-stimulated glucose-uptake[70]. In the context of NLRP3 and IL-1β signalling, the MUFA oleic acid neither primes IL-1β nor does it enhance LPS-induced IL-1β compared with palmitic acid[73,74]. Furthermore, oleic acid impedes LPS and ATP-mediated IL-1β activation and secretion from bone marrow-derived macrophages both *in vitro* and *ex vivo*[74]. While it is important to acknowledge the putative anti-inflammatory effects of dietary factors *in vitro* and in animal studies, the validity of this concept in man is controversial.

Human perspectives

In adults, cross-sectional studies demonstrated that anti-inflammatory nutrients are consistently associated with lower levels of inflammatory markers[75–77]. LC *n*-3 PUFA is independently associated with lower levels of pro-inflammatory markers IL-6, TNF-α and CRP[75,76]. Furthermore, vitamin C and α-tocopherol were inversely associated with several biomarkers of inflammatory status including CRP and reactive oxygen species, markers related to increased risk of CVD[77]. Similarly, in an overweight adolescent cohort LC *n*-3 PUFA, and in particular EPA, was inversely related to CRP concentrations[60].

However, the paradigm that anti-inflammatory nutrients may resolve the pro-inflammatory phenotype and metabolic dysregulation in man may or may not be the case. Several intervention studies have shown variable results[78–80]. A well-powered study with 324 participants investigating the effect of LC *n*-3 PUFA supplementation showed favourable effects on circulating CRP and IL-6 concentrations, when compared with sunflower oil[78]. Purified LC *n*-3 PUFA supplementation significantly reduced circulating CRP and IL-6 concentrations in thirty-four hypertriglyceridaemic men after supplementation with DHA (3 g/d)[81]. Supplementation with EPA (1·8 g/d) also significantly lowered CRP concentrations after 3 months in a cohort of ninety-two obese Japanese subjects with MetS[82]. A cross-over study showed a significant reduction in CRP and IL-6 in thirty overweight, but otherwise healthy women following 12 week supplementation with fish oil (4·2 g/d)[79]. In an 8 week randomised control trial conducted in a healthy cohort with moderate hypertriglyceridaemia, participants were enrolled to take either a low (3·4 g EPA and DHA) or high dose LC *n*-3 PUFA intervention (8·5 g EPA and DHA)[80]. In contrast to the other studies mentioned, plasma concentration levels of IL-1β, IL-6, TNF-α and CRP did not significantly change following this intervention[80]. LIPGENE, a European wide human dietary intervention, also demonstrated that LC *n*-3 PUFA supplementation in conjunction with a low-fat high complex carbohydrate diet did not significantly alter plasma IL-6, TNF-α, resistin or CRP concentrations[83].

In keeping with these results, intervention studies in children and adolescents have shown varied results. Supplementation with LC *n*-3 PUFA was shown to reduce fasting insulin concentrations and homeostatic model of assessment-IR, along with inflammatory marker TNF-α and liver fat content[84,85], while other studies demonstrated that fish-oil supplementation did not result in beneficial effects on lipid profile or metabolic rate and

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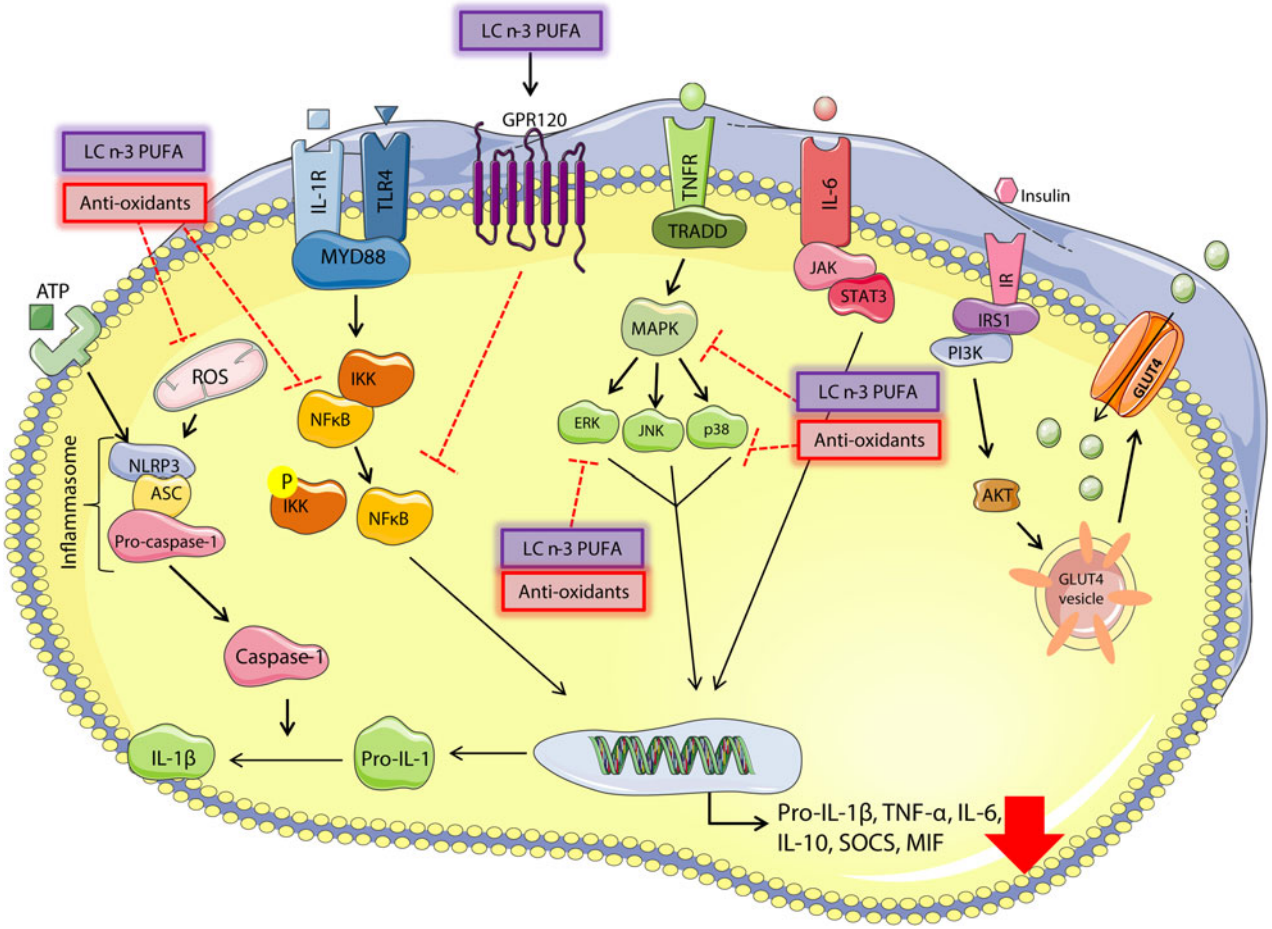

Fig. 1. (colour online) Anti-inflammatory nutrients modulate components of inflammatory signalling pathways. Anti-inflammatory nutrients such as long chain (LC) *n*-3 PUFA, vitamins C and E, epigallocatechin gallate and lycopene have been shown to modulate components of NF-κB, mitogen-activated protein kinase (MAPK) and IL-1β signalling. This leads to decreased pro-inflammatory secretion and potentially improved insulin signalling. TLR, toll-like receptor; GPR, G-protein coupled receptor; JAK, Janus kinase; STAT, signal transducer and activator of transcription; MYD, myeloid differentiation primary response gene 88; MIF, macrophage migration inhibitory factor; AKT, protein kinase B;TNFR, tumour necrosis factor receptor; TRADD, tumour necrosis factor receptor type 1-associated DEATH domain protein; NLRP, nod-like receptor pyrin domain-containing protein; IR, insulin resistance; IRS, insulin receptor substrate; ERK, extracellular signal related kinase;IKK, IκB kinase; JNK, c-Jun N-Terminal kinase; ROS, reactive oxygen species; SOCS, suppressor of cytokine signalling. (This figure was prepared using the Servier medical art website http://www.servier.fr/servier-medical-art.)

fat oxidation, respectively[86,87]. However, it should be noted that the doses of LC *n*-3 PUFA used, length of intervention and cohort characteristics differed between studies and could explain the varied results. Together these studies highlight the inconsistencies in relation to the putative beneficial effect of LC *n*-3 PUFA on inflammatory biomarkers associated with metabolic disease.

An interesting development in recent years is the role of endogenous lipid mediators derived from LC *n*-3 PUFA as a novel strategy to enhance the resolution process of inflammation[51,88]. In a western diet, fat composition is skewed towards increased consumption of *n*-6 PUFA, with the ratio of *n*-6 PUFA/*n*-3 PUFA now thought to be 10–20 : 1[89]. Potentially, sub-optimal LC *n*-3 PUFA content could lead to a deficit in pro-resolving mediators, particularly in an obesity setting. Therefore, achieving a 4 : 1 *n*-6 PUFA/*n*-3 PUFA ratio may result in increased availability of substrates for resolution mediators. Evidence suggests that increased tissue LC *n*-3 PUFA status in a transgenic mouse model that endogenously biosynthesised LC *n*-3 PUFA from *n*-6 PUFA resulted in a significant increase in the formation of anti-inflammatory Rv, reducing tissue injury and obesity-linked inflammation and IR[90,91]. Importantly, following 3 weeks supplementation with LC *n*-3 PUFA, resolvins RvD1 and RvD2 were elevated in plasma of twenty healthy volunteers[92]. Therefore in theory, improving LC *n*-3 PUFA status in relation to *n*-6 PUFA would effectively mean targeting key components of inflammatory pathways, while aiding resolution of inflammation. However, while these LC *n*-3 PUFA lipid mediators may be promising therapeutically, they are prone to oxidation and dehydrogenation *in vivo*, rendering them inactive. The development of analogues has been a promising avenue[49,93,94]. Recently, it has been reported that LXA_4 and its stable analogue

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BenzoLXA$_4$ attenuate obesity-associated inflammation, with a shift from M1 to M2 macrophages in the AT[49]. However, further work is needed to further elucidate their role in metabolic-inflammation in children and adolescents, as well as in adults.

With respect to antioxidants, animal studies and human interventions have also shown mixed results[95–98]. α-Tocopherol supplementation, in conjunction with vitamin D$_3$, was demonstrated to decrease IL-6 concentrations *in vitro* and in a mouse model of obesity[72]. In a cohort of T2D patients, while α-tocopherol supplementation ameliorated systemic oxidative stress, no positive effect was seen on plasma markers of inflammation[97]. Additionally, long-term supplementation with vitamin C and vitamin E had no effect on the risk of development of T2D in women at high risk of developing CVD[95]. Supplementation of young overweight and obese adults with one glass of tomato juice reduced TNF-α and IL-6 after 20 d[99]. Similarly, McEneny *et al.* demonstrated decreased serum amyloid A, an independent marker of CVD risk, following 12 weeks supplementation with lycopene[100]. In contrast, lycopene supplementation for 12 weeks showed no improvement in inflammatory markers such as CRP and IL-6, while homeostatic model of assessment-IR remained the same[96]. Studies of mice supplemented with green tea polyphenol extracts showed decreased levels of TNF-α after LPS injection[98]. However, this did not translate into an adult cohort, where supplementation with epigallocatechin gallate did not alter features of the MetS or biomarkers of inflammation such as IL-6, IL-1β and CRP, but did significantly reduce serum amyloid A[101]. In two separate cohorts of overweight and obese adolescents, treatment with an antioxidant supplement influenced anti-oxidant defence and oxidative stress positively, with no improvement in inflammatory markers observed[102,103].

Inflammatory pathways have been targeted by pharmaceutical agents as potential therapeutic avenues for T2D. Pharmaceutical agents such as Anakinra (IL-1 receptor blocker), salsalate (IKKβ–NF-κB inhibitor) and IL-1β and TNF-α specific antibodies (IL-1β and TNF-α antagonism) have all been shown to increase insulin sensitivity[104]. However, while these treatments have been shown to be promising, the long-term immunesuppression and safety remains unclear[105]. In contrast to pharmaceutical agents, nutrients are considerably less potent and may be an alternative treatment option. However, this difference in potency may be a contributing factor to the varied results seen between randomised control trials involving anti-inflammatory and anti-oxidant nutrients. Interestingly, Minihane *et al.* highlighted with respect to anti-inflammatory nutrients that to date, the majority of nutritional randomised control trials have taken a 'reductionist' approach. Primary focus has been on the effect of individual dietary components on inflammation and metabolic health. Diet-derived anti-inflammatory and anti-oxidative compounds in combination could potentially target multiple components of inflammation and metabolic stress in an additive or synergistic manner[106,107]. A study by Bakker *et al.* showed that a combination of anti-inflammatory nutrients in overweight men increased adiponectin by 7 %, independent of weight loss, as well as influencing AT inflammation, oxidative stress and metabolism. The choice of nutrients was based on their anti-inflammatory capabilities, aiming to cover a wide range of inflammation mediators[107]. Together these findings suggest that a combination of a number of anti-inflammatory and anti-oxidative nutrients may be more beneficial at modulating metabolic-inflammation than the effect of single nutrients and polyphenols, by targeting multiple pathways.

Future perspectives: a personalised nutrition approach

With inherent variability observed between individuals, response to nutritional interventions can vary considerably, with potentially only a small percentage of subjects responding favourably[108]. Factors such as genotype and environment can impact an individual's response to an intervention[109]. In the context of personalised nutrition, determination of an individual's metabolic-inflammatory phenotype prior to a nutritional intervention may be important. Stratification of obese adults based on their metabolic phenotype classified using fasting blood samples, may highlight those who are metabolically overburdened and unresponsive to dietary intervention, compared with those who are metabolically healthy, yet obese[110]. In contrast, adolescents who responded to a lifestyle intervention appear to display a distinct adverse metabolic profile compared with non-responders, as reviewed in McMorrow *et al*[3]. Establishing metabolic phenotype may highlight individuals who are in the at-risk population and may respond favourably to an intervention, with potentially adolescence a unique opportunity for intervention.

Alternatively, establishing inflammatory phenotype might be of use in classifying those at risk individuals. Individuals with elevated complement C3 concentrations have a 3-fold higher risk of MetS compared with individuals with lower complement C3 concentrations, which was further accentuated in high-fat consumers[111]. These individuals may benefit by adhering to the public health recommendations of reduced dietary fat intake[111]. A randomised control trial in an overweight female cohort demonstrated that individuals who were considered to have a high inflammatory phenotype based on sialic acid concentrations responded favourably to an LC *n*-3 PUFA intervention. Following a glucose load, individuals with high inflammatory phenotype demonstrated improved insulin area under the curve, with no change seen in fasting markers[79]. This may raise the question as to whether fasting markers are suitable for assessing metabolic-inflammation and its impact on metabolic health. Conventional methods of profiling metabolic parameters using fasting blood samples may not reveal changes in response to a nutritional intervention[112]. Metabolic challenges such as oral glucose tolerance tests and oral lipid tolerance tests trigger substantially different molecular responses, which may be linked to other key processes such as inflammation

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and oxidative stress, which may not be reflected in fasting samples[113]. Thus, relying on plasma cytokine or adipokine profiles, although easily measured, may not directly reflect organ specific metabolic dysregulation which is the core of metabolic-inflammation. A recent report assessing suitable biomarkers for evaluation of inflammation suggested that potentially patterns or clusters, as opposed to single inflammatory variables, may be more robust as biomarkers of inflammation[46]. In line with this report, a number of research groups have utilised inflammatory scores encompassing a range of inflammatory and anti-inflammatory markers to assess sub-clinical inflammation and relating this to insulin sensitivity, which could be used to stratify cohorts based on inflammatory phenotype[114–116]. An increase in the inflammatory score was associated with an increase in IR, with a high inflammatory score associated with increased BMI, waist circumference and higher blood pressure[115]. In a separate study, those who were above the median for four out of the six markers assessed in that study had a 2–4-fold higher risk of developing diabetes compared with individuals with no markers above median values[116]. Furthermore, high inflammatory score in T2D individuals strongly correlated with whole-body insulin sensitivity as evaluated by euglycaemic clamp, β-cell function, glucose levels in oral glucose tolerance tests and HbA1c[114,116]. Indeed further studies would be needed to determine sensitivity of an inflammatory score in assessing changes in IR and to fully elucidate the role metabolic-inflammatory phenotype may play in response to dietary intervention.

Conclusion

Evidence supports the role of sub-acute, metabolic-inflammation in obesity-induced IR not only in adults, but also in children and adolescents. Dysregulation of key inflammatory pathways, ineffective resolution of inflammatory response, as well as dysregulated metabolism appear to be key factors in inflammation observed in obesity. It is clear that nutrition plays an important role, both in a negative and positive manner. The use of nutrients with anti-inflammatory and anti-oxidant properties as well as manipulating dietary fats may be helpful in modulating several mechanisms associated with obesity-induced inflammation. Furthermore, establishment of effective tools to assess efficacy of novel anti-inflammatory neutriceuticals as a strategy for treating obesity-induced chronic inflammation is vital, particularly in children and adolescent cohorts. Finally, establishing those at-risk individuals who will respond favourably to nutritional interventions will be beneficial with regard to prevention and treatment of obesity-induced inflammation and metabolic disease.

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Conflict of Interest

None.

Authorship

R. M. C. completed the review. A. M. M., F. C. M., F. E. L. and H. M. R. advised in relation to review content. A. M. M. and H. M. R. critically evaluated the manuscript.

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