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The effect of quantity and quality of dietary fat intake on subcutaneous white adipose tissue inflammatory responses

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The global prevalence of obesity and obesity-associated cardiometabolic diseases is a significant public health burden. Chronic low-grade inflammation in metabolic tissues such as white adipose tissue (WAT) is linked to obesity and may play a role in disease progression. The overconsumption of dietary fat has been suggested to modulate the WAT inflammatory environment. It is also recognised that fats varying in degree of fatty acid saturation may elicit differential WAT inflammatory responses. This information has originated predominantly from animal or cell models and translation into human participants *in vivo* remains limited. This review will summarise human intervention studies investigating the effect of dietary fat quantity and quality on subcutaneous WAT inflammation, with a specific focus on the toll-like receptor 4 (TLR4)/NF-κB and nucleotide-binding and oligomerisation domain-like receptor, leucine-rich repeat and pyrin domain-containing 3 (NLRP3) inflammasome molecular signalling pathways. Overall, firm conclusions are hard to draw regarding the effect of dietary fat quantity and quality on WAT inflammatory responses due to the heterogeneity of study designs, diet composition and participant cohorts recruited. Previous studies have predominantly focused on measures of WAT gene expression. It is suggested that future work includes measures of WAT total content and phosphorylation of proteins involved in TLR4/NF-κB and NLRP3 signalling as this is more representative of alterations in WAT physiological function. Understanding pathways linking the intake of total fat and specific fatty acids with WAT metabolic-inflammatory responses may have important implications for public health by informing dietary guidelines aimed at cardiometabolic risk reduction.

Dietary fat: White adipose tissue: Inflammation: Obesity

An individual will be characterised as overweight or obese if they possess a BMI of 25·0–29·9 or ≥30·0 kg/m^2, respectively. Both conditions are caused by a chronic positive energy balance (i.e. insufficient energy expenditure and/or excessive energy intake). Obesity, especially central (abdominal) obesity, is of great public concern as it increases the risk of developing cardiometabolic disorders, including CVD and type-2 diabetes (T2D)[1]. It also plays a significant role in the pathogenesis of the metabolic syndrome, which includes hyperglycaemia, hypertension, dyslipidaemia and insulin resistance (IR)[2,3].

Abbreviations: AMPK, AMP activated protein kinase; BMDM, bone marrow-derived macrophages; CCR, C-C chemokine receptor; CD, cluster of differentiation; CHO, carbohydrate; CRP, C-reactive protein; GPR120, G-protein coupled receptor 120; HFD, high-fat diet; IκB, inhibitory factor κB; IκBα, inhibitory factor κBα; IKK, inhibitor of NF-κB kinase; IR, insulin resistance; IRS, insulin receptor substrate; LPS, lipopolysaccharide; LBP, LPS-binding protein; MAPK, mitogen-activated protein kinase; mCD14, membrane bound CD14; MCP-1, monocyte chemoattractant protein-1; NLRP3, nucleotide-binding and oligomerisation domain-like receptor, leucine-rich repeat and pyrin domain-containing 3; PA, palmitic acid; PPARγC1A, PPARγ coactivator 1 α; sCD14, soluble CD14; T2D, type-2 diabetes; TLR, toll-like receptor; TNFRSF1A, TNF receptor superfamily member 1A; WAT, white adipose tissue.

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An underlying factor of obesity that is potentially important in the development of associated disorders is chronic low-grade inflammation. Metabolic-inflammation (i.e. chronic low-grade inflammation occurring as a result of obesity) occurs in multiple tissues, including white adipose tissue (WAT), skeletal muscle, the liver and the pancreas[2,4]. This review will focus on inflammatory responses in WAT. The two main types of WAT are visceral (major depots: epicardial, mesenteric, omental, retroperitoneal and gonadal) and subcutaneous (major depots: abdominal, gluteal and femoral) fat[5]. Central, rather than gluteofemoral (lower-body) adiposity, is closely linked with metabolic complications[6]. Visceral and subcutaneous WAT depots are both correlated with multiple metabolic risk markers, but risk factors associations with visceral WAT are significantly stronger than subcutaneous WAT[7]. However, accessing visceral WAT is challenging and more invasive than sampling the major subcutaneous fat stores, meaning it may not be feasible for many researchers to obtain this tissue[8]. Furthermore, subcutaneous WAT traditionally represents a larger depot than visceral WAT[9] and therefore should not be overlooked in its role in the development of obesity-related metabolic complications.

A state of chronic positive energy balance, commonly caused by the consumption of an energy-dense, high-fat diet (HFD), leads to weight gain and expansion of WAT to accommodate excess nutrients in the form of TAG. As will be discussed in further detail below, overnutrition can lead to disruption in WAT cellular signalling pathways and dysregulation of cytokine secretion which can lead to metabolic-inflammation and promote IR[4,10] (Fig. 1). Dietary fatty acids may also modulate the WAT inflammatory response[4,11–13]. Within the UK, it is recommended that total fat should contribute to ≤35 % food energy (%E)[14,15] and SFA should contribute to ≤11 %E at a population level[16]. The replacement of SFA with MUFA and PUFA is also advised[16]. Although UK National Diet and Nutrition Survey data indicate that adults aged 19–64 years are meeting recommendations for total fat intake (34·7 %E), mean SFA consumption exceeds current dietary guidelines for health promotion, at 12·5 %E[17].

Scope of the review

The primary aim of the current review is to summarise human intervention studies investigating the effect of quantity and quality of dietary fat intake on subcutaneous WAT inflammation. The summarised human intervention studies include participants not presenting with CVD, T2D and other endocrine or inflammatory disorders. This review will focus on the toll-like receptor (TLR) 4/NF-κB and nucleotide-binding and oligomerisation domain-like receptor, leucine-rich repeat and pyrin domain-containing 3 (NLRP3) inflammasome molecular signalling pathways in WAT. Key mediators of these pathways are shown in Fig. 2 (for detailed review, see[4]). Before summarising the human intervention studies, we provide a general overview of metabolic-inflammation and findings from animal and cell models which have explored the link between dietary fat/fatty acids and WAT inflammation.

Metabolic-inflammation

WAT acts as a reservoir for lipid storage, storing TAG when in positive energy balance and mobilising these stores during periods of negative energy balance[18]. An expanded adipose tissue mass releases more NEFA via lipolysis (TAG hydrolysis); this can contribute to obesity-associated increases in systemic NEFA and metabolic dysregulation[19,20]. Indeed, this lipid overspill leads to fatty acid accumulation in visceral WAT and peripheral organs such as the liver, skeletal muscle and the pancreas, which causes lipotoxicity and the activation of inflammatory signalling pathways[21,22]. WAT also serves as an endocrine organ which releases cytokines, including TNF-α, IL-1β, IL-6, leptin and adiponectin[23]. The production of pro-inflammatory cytokines (including TNF-α) can act systemically causing metabolic stress and dysregulation of whole body insulin signalling[10]. Hotamisligil *et al.*[24] first demonstrated in mice that visceral WAT TNF-α production was a key player in IR within obesity. However, a more recent series of studies conducted by Shimboayashi *et al.*[25], which included mice, cell and human data, suggested that visceral WAT inflammation is a secondary phenomenon which occurs subsequent to IR. The impairment of insulin signalling by TNF-α is attributed to changes in gene expression and protein content of the insulin receptor substrate (IRS)-1 and GLUT4[26,27]. TNF-α has also been suggested to reduce tyrosine phosphorylation and induce serine phosphorylation of IRS-1, which attenuates insulin receptor signalling[28,29]. TNF-α also acts locally in WAT to regulate lipid metabolism through factors including suppression of NEFA uptake and promotion of lipogenesis, induction of lipolysis, inhibition of the expression of lipid metabolism-related enzymes and regulation of other adipose tissue-secreted cytokines[19,30,31].

Immune cell contribution

WAT consists of two compartments, the adipocytes that store TAG and the stromal vascular fraction which contains immune cells. During obesity, immune cells (mainly macrophages preceded by t-lymphocytes[32]) infiltrate the adipose tissue or undergo expansion[33]. Classical (cluster of differentiation (CD)$14^{++}CD16^{-}$) monocytes account for about 80 % of the circulating population and have high C-C chemokine receptor (CCR) 2 receptor expression[34]. CCR2, and its ligand monocyte chemoattractant protein-1 (MCP-1), play an important role in the recruitment of inflammatory macrophages into adipose tissue[35–39], although this is not the only factor initiating obesity-associated macrophage recruitment (as discussed extensively elsewhere[40–44]). Monocyte migration into adipose tissue is induced by chemokines such as MCP-1 (also known as C–C motif ligand 2) and regulated on activation normal, T cell expressed and secreted (RANTES; also known as C–C motif ligand 5), which are upregulated in obese adipose tissue[33,45–47], and then differentiate into macrophages[48]. Fractalkine (also called C–X3–C motif ligand 1) and its receptor (C–X3–C chemokine

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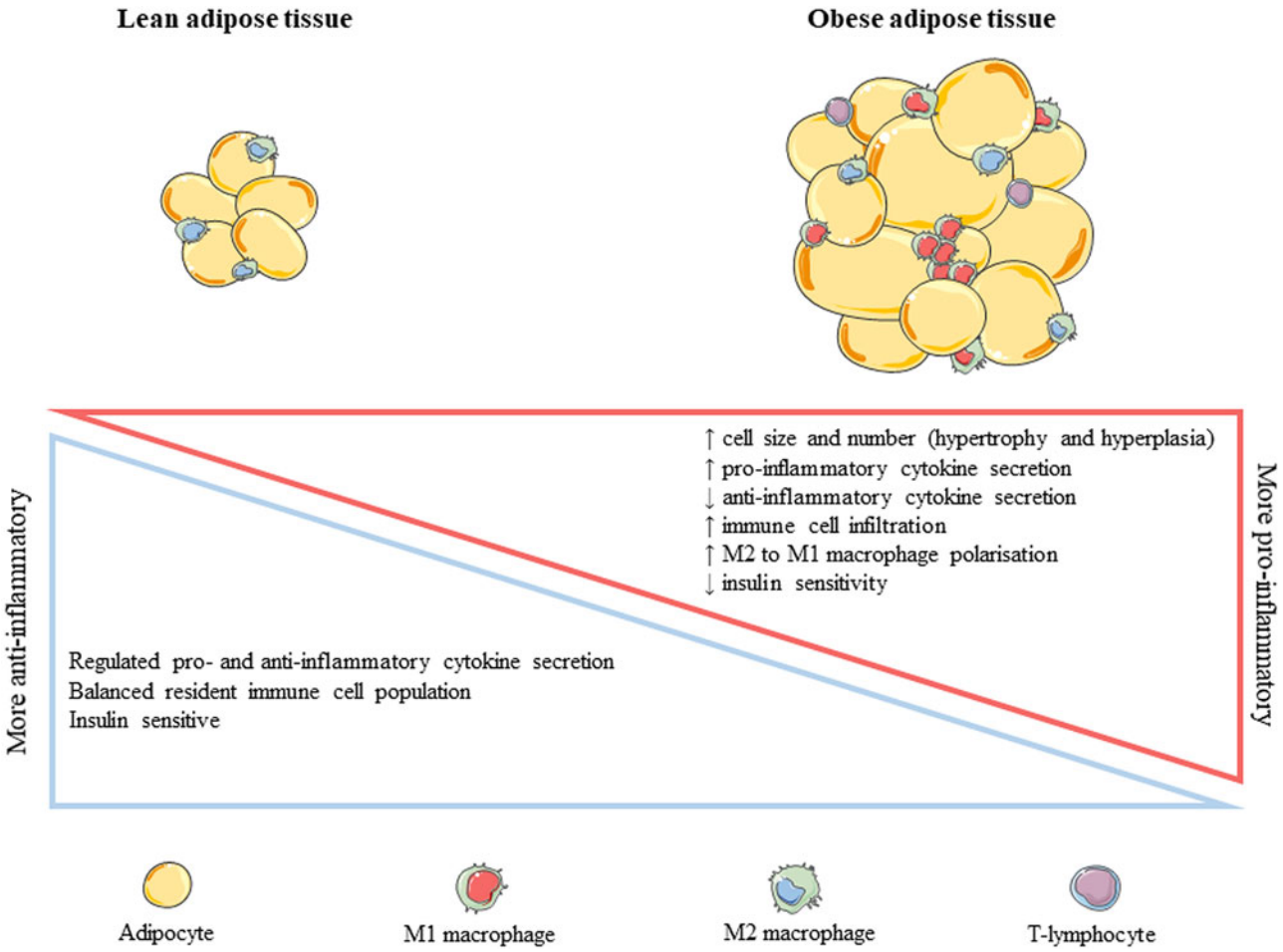

Fig. 1. (Colour online) Adipose tissue expansion in response to overnutrition results in metabolic dysregulation and inflammation. This occurs through increased cell size and number, a dysregulation of cytokine secretion, increased immune cell infiltration, increased M1 macrophage polarisation and reduced insulin sensitivity, compared to a leaner phenotype. Figure produced using Servier Medical Art (https://smart.servier.com). Figure adapted from Ralston *et al*. 2017[4]. Modified with permission from the Annual Review of Nutrition, Volume 37© 2017 by Annual Reviews, http://www.annualreviews.org.

receptor 1) have also been implicated in the recruitment of both monocytes and t-lymphocytes. Fractalkine is expressed on macrophages[49] and is upregulated in obese adipose tissue[50]. Adipose tissue macrophages in lean tissue have a more alternatively activated (M2) anti-inflammatory phenotype, whereas macrophages in diet-induced obese tissue have a more classically activated (M1) pro-inflammatory phenotype[46] and are commonly found in crown-like structures around dying adipocytes[46]. Adipose tissue macrophages are however likely part of the spectrum from M1 to M2 polarisation, rather than two distinct populations[51]. The change in number/function of these cells with obesity alters the WAT inflammatory cell populations and impact upon WAT inflammation and systemic insulin sensitivity (Fig. 1)[52].

Gut microbiota contribution

Overnutrition[53] and HFD consumption[54] cause metabolic endotoxemia as a result of lipopolysaccharide (LPS) from gram-negative gut bacteria translocating into the circulation[54,55]. The increased absorption of LPS is thought to occur due to impairments in gut barrier function[56] as well as it being incorporated into chylomicrons during dietary fat absorption[57,58]. Impairments in gut barrier function have also been associated with the development of low-grade inflammation[59] as a result of gut-derived LPS and SCFA activating TLR4 and nucleotide-binding oligomerisation domain-containing protein 1 receptors[48]. LPS binds to LPS-binding protein (LBP) and then transfers to CD14, which exists in membrane bound (mCD14) or circulating soluble (sCD14) states[60]. Subsequently, the LPS–LBP complex binds to mCD14 receptors on the surfaces of innate immune cells, including monocytes and macrophages, to initiate TLR4 signalling[60,61]. LPS in plasma attaches to sCD14 or LBP which are located on HDL[62,63]. In adipocytes, increased LPS concentrations have been shown to increase TLR4 activation and increase TNF-α and IL-6 secretion[64]. Further human intervention studies are required in this area to understand how dietary patterns and alterations in the gut microbiome contribute to metabolic-inflammation[65,66].

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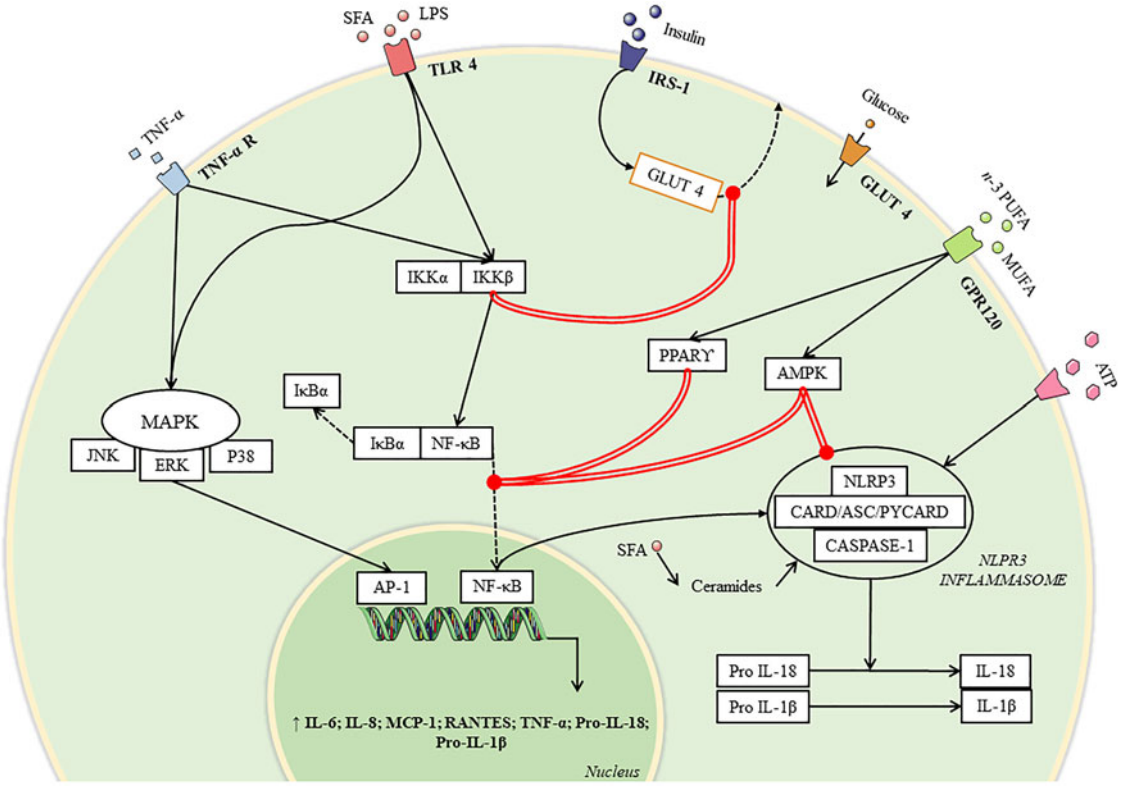

Fig. 2. (Colour online) The NF-κB and NLRP3 inflammatory signalling pathways and its impact on insulin signalling. The inflammatory signalling pathways are activated by SFA or pro-inflammatory cytokines and suppressed by MUFA and *n*-3 PUFA. The solid black arrows show increased signalling, the red double lines with circle show suppression of signalling and dashed black arrow show translocation. Figure produced using Servier Medical Art (https://smart.servier.com). AP-1, activator protein-1; GPR120, G-protein coupled receptor 120; IRS-1, insulin receptor substrate-1; IκBα, inhibitory factor κBα; IKKα, inhibitor of NF-κB kinase subunit α; IKKβ, inhibitor of NF-κB kinase subunit β; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; NLRP3, nucleotide-binding and oligomerisation domain-like receptor, leucine-rich repeat and pyrin domain-containing 3; RANTES, regulated on activation, normal T cell expressed and secreted; TLR4, toll-like receptor 4; TNF-α R, TNF-α receptor.

Effect of fatty acid quality on white adipose tissue inflammation: animal and cell studies

SFA

SFA, especially long-chain SFA, are thought to promote a pro-inflammatory environment in WAT (Fig. 2). In adipocytes treated with palmitic acid (PA; a common long-chain SFA), NF-κB binding and TNF-α secretion were increased, whereas IL-10 production was decreased[67]. PA has also been shown to prime the NLRP3 inflammasome via TLR4/NF-κB signalling in bone marrow-derived macrophages (BMDM)[68] leading to increased IL-1β production. Palmitate, but not lauric acid, has also been shown to activate the NF-κB pathway and increase IL-6 and TNF-α expression in adipocytes[69]. The translocation of NF-κB to the nucleus necessary to up-regulate the production of pro-inflammatory cytokines is dependent on inhibitory factor κB (IκB) phosphorylation by the upstream regulator inhibitor of NF-κB kinase (IKK); this is initiated by either TNF-α or TLR4 activation (e.g. with LPS stimulation)[70]. BMDM were sensitive to priming by both PA and LPS, and secreted higher levels of cleaved IL-1β in response to ATP stimulus[68]. In BMDM and dendritic cells, the SFA component of the diet, and not the obese phenotype alone, was responsible for increased IL-1β secretion[68]. However, the stimulation of TLR4 by SFA remains ambiguous with the suggestion that TLR4 may not be a receptor for palmitate[71]. Erridge *et al.*[72] investigated the effects of common SFA (including lauric acid, myristic acid, PA and stearic acid) on TLR4 signalling in a broad range of cell types including macrophages and adipocytes and found that LPS stimulation of TLR4 may account for the activation commonly attributed to SFA treatment. However, TLR4 does mediate palmitate-induced inflammation indirectly through the priming of macrophages and modification of macrophage lipid metabolism[71].

Increases in plasma LPS concentrations have been attributed to altered gut microbiota and increased gut permeability in response to increased dietary SFA[73]. Both LPS and PA promote M1 polarisation of

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macrophages[74,75], which leads to a more pro-inflammatory macrophage phenotype. In addition, stearic acid and PA have been shown to stimulate MCP-1 expression via the TLR4/NF-κB pathway[76]; this enables increased recruitment of monocytes to the adipose tissue and macrophage polarisation from an M2 to an M1 inflammatory phenotype.

The synthesis of the lipid-derivative, ceramide, is dependent on the quantity of long-chain SFA in the diet[77]. Pro-inflammatory cytokines and SFA can upregulate genes involved in ceramide biosynthesis[78]. Ceramides can initiate assembly of the NLRP3 inflammasome[4,79], which enables the cleavage of pro-IL-1β and pro-IL-18 into active IL-1β and IL-18. The NLRP3 inflammasome is also activated by SFA through the production of reactive oxygen species[11,80].

MUFA

In comparison with long-chain SFA, MUFA are thought to promote a more anti-inflammatory WAT environment. In adipocytes treated with oleic acid, TNF-α secretion and NF-κB binding were unaltered, which is in contrast to the pro-inflammatory effect of PA described above[67]. In obese mice, a MUFA- compared to a SFA-rich diet, improved insulin sensitivity through increased phosphorylation of protein kinase B, increased GLUT4 gene expression, reduced priming of IL-1β and increased AMP activated protein kinase (AMPK) activation[81]. The MUFA palmitoleate has also been shown to maintain AMPK phosphorylation compared to the SFA palmitate in BMDM derived from mice[82]. AMPK activation reduces NLRP3 activation[11] and inhibits NF-κB signalling[83]. Therefore, maintenance of AMPK activity may help to mediate the anti-inflammatory effect of MUFA (Fig. 2)[81,82].

In BMDM of chow fed mice, palmitoleate was also reported to increase anti-inflammatory related genes and oxidative metabolism, which are indicative of M2 macrophage polarisation[82]. In BMDM derived from HFD fed mice, palmitoleate incubation reduced the pro-inflammatory gene expression profile suggesting macrophage polarisation from a more M1 to M2 phenotype[82]. Moreover, in mice fed an SFA-rich diet that were then transferred to a MUFA-rich diet, the negative effects of the prior SFA-rich diet were not completely reversed[81]. Furthermore, the co-incubation of BMDM with PA and palmitoleic acid, reduced the SFA-induced increase in M1 macrophage polarisation and NF-κB signalling by preventing inhibitory factor κBα (IκBα) degradation and NF-κB translocation to the nucleus[82]. Collectively, these findings indicate that MUFA can at least impede some of the negative effects of SFA.

n-*3 PUFA*

The *n*-3 PUFA EPA and DHA appear to have anti-inflammatory and insulin-sensitising effects *in vitro* (Fig. 2). In human monocyte-derived macrophages, EPA and DHA reduced TNF-α, IL-1β and IL-6 expression through downregulation of LPS-induced NF-κB binding[84]. In addition, in macrophages pre-treated with DHA and then stimulated with LPS, NF-κB activation and TNF-α secretion were reduced[85]. DHA but not EPA increased IL-10 secretion and reduced M1 macrophage polarisation[85]. In adipocytes, incubation with both EPA and DHA (complexed to albumin) increased adiponectin secretion compared to a control (albumin alone)[86]. DHA increased adiponectin secretion to a greater extent than EPA and only DHA enhanced PPARγ and adiponectin gene expression compared to the control[86]. Adiponectin is known to be upregulated, in part, through PPARγ activation[87]. Long-chain *n*-3 PUFA can act through PPARγ[86,88], which inhibits NF-κB signalling through NF-κB and inhibitory factor κBα[89,90]. These PUFA act through the receptor G-protein coupled receptor (GPR120), inhibiting NF-κB signalling and reducing its pro-inflammatory and insulin desensitising effects[91]. They can also promote the M2 polarisation of macrophages[48,92]. In addition, in transwell co-cultured macrophages from mice fed a HFD, and contact co-cultures with macrophages from mice fed a low-fat diet, fish oil enrichment showed reduced NLRP3 activation, reduced IL-6 and TNF-α secretion and reduced expression of M1 macrophage polarisation genes[93].

Effect of fatty acid quantity and quality on white adipose tissue inflammation: human intervention studies

Hyperenergetic interventions

WAT inflammatory responses to overnutrition (i.e. hyperenergetic feeding) can provide early insight into the development of obesity and cardiometabolic disorder progression. Four out of six studies (3–56-d) reported no effect of a hyperenergetic, HFD on markers of WAT inflammation (Table 1)[94–97]. Specifically, following a 3-d period of overfeeding (+5230 kJ requirements/d; 45 %E total fat), no change in WAT gene expression of macrophage markers or MCP-1 but increased HOMA-IR (a marker of systemic IR) was reported, relative to baseline[97]. In this study, no further details of the diet were provided[97]. In the study of Tam *et al.*[94], healthy individuals completed a 28-d overfeed (+5230 kJ/d; 45 %E total fat); this was achieved by asking participants to supplement their habitual diet with high-fat snacks (crisps, chocolate, cheesecake and a dairy dessert containing a liquid oil-based supplement[98]). No change in WAT gene expression of macrophage markers, MCP-1 or IL-10 was reported, relative to baseline[94]. These authors also reported no change in the number of circulating monocytes or the absolute number of WAT macrophages. However, a change in macrophage polarisation may have occurred, as indicated by the increased CD40/CD206 ratio following the intervention[94]. In agreement with Tam *et al.*[94], following 56-d overfeeding (140 %E requirements/d; 44 %E total fat) no change in gene expression of macrophage markers, MCP-1, NF-κB or adiponectin was reported, relative to baseline[95]. A strength of this study was the controlled nature of the intervention; all meals were prepared by the research team and consumed under supervision, ensuring dietary adherence. However, the foods used in this

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Table 1. Summary of hyperenergetic human studies examining the effect of a dietary intervention differing in fat quantity or quality on fasted subcutaneous white adipose tissue (WAT) inflammatory responses

References	Study design, duration and intervention	Diet composition (%E, unless specified)*					Participant characteristics (*n*, mean age and BMI)	WAT outcomes (relative to baseline)†,‡	Systemic and body mass outcomes (relative to baseline)†
		Total fat	SFA	MUFA	PUFA	Other			
Chen *et al*.[97]	OL, SA 3-d, +5230 kJ requirements/d	45·0	NR	NR	NR	CHO: 40·0 protein: 15·0	Healthy; *n* 31, 21 y, 22·9 kg/m^2	↔ CD40, CD68, CD163, MCP-1	↑ glucose, insulin, HOMA-IR, ↔ MCP-1, CRP, ↑ body mass (+0·7 kg; men and women combined)
Luukkonen *et al*.[100]	OL, R, P 21-d, +4184 kJ/d						OW; *n* 38; 48 y; 31·0 kg/m^2	↑ NOD-like receptor signalling for SFA diet, ↑ antigen processing and chemokine signalling for SFA and CHO diet	↑ HOMA-IR, ceramides, LBP: soluble CD14 ratio, HDL-C, LDL-C for SFA diet, ↔ TAG, adiponectin, ↑ body mass (+1·4 kg)
	SFA§	86·0	76·0	21·0	3·0	CHO: 1·0, protein: 13·0			
	MUFA§	91·0	21·0	57·0	22·0	CHO: 2·0, protein: 7·0			
	CHO§	0·0	0·0	0·0	0·0	CHO: 100·0			
Tam *et al*.[94]	OL, SA 28-d, +5230 kJ/d	45·0	NR	NR	NR	CHO: 40·0 protein: 15·0	Healthy; *n* 36; 37 y; 26·0 kg/m^2	↔ CD68, CD206, CD11c, MCP-1, IL-10	↑ CRP, MCP-1, glucose, insulin, TC, HDL-C ↔ IL-6, LDL-C, TAG, ↑ body mass (+2·7 kg)
Perfilyev *et al*.[99]‖,¶,**	DB, R, P 49-d, +3138 kJ/d§						Healthy; *n* 31; 27 y; 20·9 kg/m^2	↑ adiponectin (SFA diet) ↑ MCP-1, IL-6, insulin receptor (*n*-6 PUFA diet) ↑ adiponectin, PPARγC1A, TNF-α (data for both interventions combined)	↑ HDL-C, ↔ glucose, insulin, TC, LDL-C, TAG, ↓ LDL-C:HDL-C ratio for SFA diet, ↑ insulin, ↔ glucose, TC, HDL-C, LDL-C, LDL-C:HDL-C ratio, TAG for *n*-6 PUFA diet, ↑ body mass (SFA diet:+1·7 kg; *n*-6 PUFA diet:+1·6 kg)
	SFA (high in refined palm oil)	36·8	16·4	12·9	4·5	CHO: 47·7, protein: 11·5			
	n-6 PUFA (high in refined linoleic acid)	40·3	11·5	12·4	12·9	CHO: 43·3, protein: 11·8			
Tam *et al*.[95]	OL, SA 56-d, 140%E requirements/d	44·0	NR	NR	NR	CHO: 41·0 protein: 15·0	Healthy men; *n* 29; 27 y; 25·5 kg/m^2	↔ CD68, IL-6, MCP-1, NF-κB, adiponectin	↑ TC, HDL-C:LDL-C ratio, leptin, insulin ↔ CRP, adiponectin, TNF-α, IL-6, IL-8, IL-10, TAG, NEFA, glucose, ↑ body mass (+7·6 kg)
Alligier *et al*.[96]**	OL, SA 56-d (interim visit at d 14),+3180 kJ/d	47·9	64·4††	57·1††	16·6††	CHO: 34·1 protein: 16·8	Healthy men; *n* 44; 33 y; 18–30 kg/m^2	↑ LBP at d 14, ↑ LBP, TNFAIP8L1 at d 56	↑ insulin, HOMA-IR, leptin, ↔ glucose, TAG, ↓ NEFA at d 14, ↑ HOMA-IR, leptin ↔ glucose, insulin, TAG, TC, ↓ NEFA at d 56, ↑ body mass (d 14:+0·8 kg; d 56:+2·5 kg)

OL, open-label; SA, single-arm; NR, not reported; CHO carbohydrate; CD, cluster of differentiation; MCP-1, monocyte chemoattractant protein-1; HOMA-IR, homeostatic model of insulin resistance; CRP, C-reactive protein; R, randomised; P, parallel; OW, overweight; NOD, nucleotide-binding oligomerisation domain, LBP, lipopolysaccharide-binding protein; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; TC, total cholesterol; DB, double-blind; PPARγC1A, PPAR γ coactivator 1 α; y, years; %E, percentage total energy; ↓, significant decease; ↑, significant increase; ↔, no change.

* Diet composition data are presented as dietary intervention targets, unless otherwise stated.

† Results are significant to $P < 0{\cdot}05$.

‡ All WAT outcomes for gene expression, unless otherwise stated.

§ Percentage of overfeed energy.

‖ DNA methylation WAT outcomes.

¶ Diet composition data taken from Rosqvist *et al*.[122].

** Diet composition data are taken from dietary intake records.

†† Data reported as g/d.

intervention were not described[95]. Following 14 and 56 d overfeeding (+3180 kJ/d; 48 %E total fat), which involved adding high-fat snacks (cheese, butter, almonds) to the habitual diet, Alligier and colleagues[96] also reported no change in expression of WAT genes related to inflammation. However, increases in LBP gene expression were reported at 14 and 56 d[96]. This provides some support for the potential of an inflammatory response as LBP is known to transfer LPS to mCD14 on monocytes and initiate TLR4 signalling[60]. At 14 and 56 d, HOMA-IR was increased suggesting increased systemic IR following the intervention. No evidence of macrophage infiltration was observed following the 56-d overfeeding period.

The remaining two studies reported increased WAT inflammatory responses to a hyperenergetic intervention (Table 1). Perfilyev *et al.*[99] employed a 49-d overfeeding intervention (+3138 kJ/d), which was achieved by supplementing the habitual diet with high-caloric muffins containing refined palm or sunflower oil for an SFA- and *n*-6 PUFA-rich intervention, respectively. Mean DNA methylation of adiponectin increased in WAT following the SFA-rich diet, whereas the methylation of MCP-1, IL-6 and insulin receptor was increased following the *n*-6 PUFA-rich diet[99]. These authors also pooled data from both intervention arms. In response to the overall effect of overfeeding, increased DNA methylation of anti-inflammatory cytokine adiponectin and PPARγ coactivator 1 α (PPARγC1A), and the pro-inflammatory cytokine TNF-α were observed. A shorter hyperenergetic intervention (21-d; +4184 kJ/d) was employed by Luukkonen and colleagues[100], where the habitual diet of overweight participants was supplemented with SFA- (coconut oil, butter and blue cheese), MUFA- (olive oil, pesto, pecan nuts and butter) or carbohydrate (CHO)-rich foods (orange juice, sugar-sweetened beverage and candy)[100]. The authors reported increased HOMA-IR, ceramides and LBP:sCD14 ratio following the SFA-rich diet. Ceramides are known to increase WAT NLRP3 inflammasome assembly[4,79] and LBP is known to play a role in TRL4 signalling. In WAT, the SFA- but not the MUFA-rich diet increased expression of genes related to nucleotide-binding oligomerisation domain-containing receptor signalling and leucocyte transendothelial migration. It is possible that the more 'at risk' population (overweight/obese participants) recruited by Luukkonen *et al.*[100] demonstrated an enhanced inflammatory response to the overfeeding protocol. This is in contrast to the findings from the above-mentioned studies, where leaner cohorts were studied[94,95,97]. In more 'at risk' populations (obese and diabetic participants) levels of metabolic inflexibility have been reported[101]. It has also been suggested that lean and obese individuals have differential WAT gene expression responses to energy surplus[102]. Whilst Luukkonen *et al.*[100] reported increased expression of WAT genes related to inflammation following overfeeding, changes in WAT gene expression of inflammatory markers were not typically observed following interventions of 3–56-d[94–97]. However, increased HOMA-IR was reported in a number of these studies[96,97,100], suggesting that WAT inflammation may occur subsequent to weight gain and IR[94–97].

To date, only a limited number of human intervention studies have been conducted in this area. Dietary adherence was assessed subjectively in some of these hyperenergetic studies through weekly contact with a research dietitian[94,100], supervised meal consumption[94] and by asking participants to complete daily food checklists[97] or 5-d dietary records[96]. In two of the studies, adherence to the diets was assessed objectively by measurement of the fatty acid composition of WAT TAG[99] (a biomarker which reflects long-term dietary fatty acid intake[103]) and plasma cholesterol esters[99] or plasma very LDL TAG[100] (circulating biomarkers which can be influenced by recent dietary fatty acid intake[103]). Firm conclusions are hard to draw due to methodological differences, including study designs, duration, total fat and fatty acid composition of the diets, foods included in the intervention and participant characteristics. Further work is warranted to investigate the early WAT inflammatory response to overfeeding. More severe HFD interventions (approximately 150 % estimated energy requirements, approximately 65 %E total fat), which are known to alter glycaemic control following a 7-d intervention[104–106], provide a good starting point for future work.

Isoenergetic interventions

Four studies have been identified that investigated the effect of a chronic, isoenergetic dietary intervention differing in fatty acid quality on fasted WAT inflammation (Table 2). van Dijk and colleagues[107] compared the WAT gene expression profile of overweight participants following a 56 d SFA- or MUFA-rich intervention. The assessment of plasma NEFA and WAT fatty acid composition provided objective evidence of dietary adherence[107]. In response to the SFA-rich intervention, these authors reported an increased expression of WAT pro-inflammatory genes involved in inflammation and immune function (including TLR, NF-κB, IL-6, T-cell receptor and P38 mitogen-activated protein kinase (MAPK) signalling) and decreased expression of WAT anti-inflammatory genes (including adiponectin and PPARγ). Following the MUFA-rich intervention, a decreased WAT gene expression of macrophage markers was reported. Moreover, WAT genes that were upregulated following the SFA-rich intervention were either unchanged or down-regulated (TLR, T-cell receptor) or upregulated to a much lesser extent (NF-κB, IL-6, P38 MAPK) following the MUFA-rich intervention. Pre-intervention WAT samples were collected when participants were consuming their habitual diet, before beginning a 14 d SFA-rich run-in diet prior to the intervention. Thus, it is possible that the SFA-rich nature of the run-in diet may have dampened an anti-inflammatory effect of the MUFA-rich intervention, as shown previously in a dietary intervention with mice[81]. It is also important to note that in a comment on this work[108], the results reported by van Dijk *et al.*[107] were suggested to exaggerate the effect of fatty acid composition on WAT gene expression responses as the authors did not make any adjustments for multiple analysis for their

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Table 2. Summary of isoenergetic human studies examining the effect of a dietary/supplemental intervention differing in fat quantity or quality on fasted subcutaneous white adipose tissue (WAT) inflammatory responses

References	Study design, duration and intervention	Diet composition (%E, unless specified)*					Participant characteristics (*n*, mean age and BMI)	WAT outcomes (relative to baseline, unless specified)†,‡	Systemic and body mass outcomes (relative to baseline)†
		Total fat	SFA	MUFA	PUFA	Other			
Itariu *et al.*[110]§	OL, R, P 56-d						Severely OB, non-diabetic; *n* 55; 39 y; 46·7 kg/m^2	*n*-3 PUFA relative to SFA supplement: ↔ adiponectin, IL-6, CD68 CD163, CD206, ↓ MCP-1, CCL3, CD40	↓ IL-6, TAG for *n*-3 PUFA supplement, ↔ CRP, adiponectin, leptin, TC, LDL-C, HDL-C, glucose, insulin for both interventions, ↔ TAG, IL-6 for SFA supplement, ↔ body mass across groups
	SFA supplement: 5 g butter/d	30·0	NR	NR	NR	CHO: 55, protein: 15 (all diets)			
	n-3 PUFA supplement: 3·36 g/d long-chain *n*-3 PUFA	30·0	NR	NR	NR				
van Dijk *et al.*[107]||	SB, R, P 56-d						OW; *n* 20; 55 y; 27·2 kg/m^2	↑ genes involved in inflammation and immune function for SFA diet, ↓ adiponectin, PPARγ for SFA diet, ↑ anti-inflammatory profile for MUFA diet	↓ adiponectin for SFA diet, TC, LDL-C for MUFA diet, ↓ RANTES for both interventions, ↔ adiponectin for MUFA diet, ↓ body mass (SFA diet: −1·3 kg; MUFA diet: −0·9 kg)
	SFA	36·8	19·0	11·0	5·4	CHO: 47·3, protein: 13·5			
	MUFA	39·9	11·0	20·0	7·0	CHO: 46·4, protein: 11·4			
de Mello *et al.*[109]¶	OL, R, P, PC 84-d						Pre-diabetic; *n* 79; 58 y; 29·4 kg/m^2	↔ MCP-1, IL-1β, IL-6, IL-10, TNF-α, TNFRSF1A, TNFRSF1B, RELA/p65, TLR2, TLR4, adiponectin (all interventions), ↓ IL1RN (fatty fish intervention), ↔ all other interventions	↔ body mass across groups
	Camelina sativa oil	41·8	12·0	14·9	11·5 *n*-3 13·4** *n*-6 14·5**	CHO: NR, protein: NR (all diets)			
	Lean fish	34·3	11·0	13·4	6·1 *n*-3 3·1** *n*-6 10·5**				
	Fatty fish	38·7	12·5	14·7	6·9 *n*-3 5·1** *n*-6 12·0**				
	Control	35·2	11·6	13·3	5·6 *n*-3 2·4** *n*-6 8·6**				
Kratz *et al.*[111]¶	SB, R, P, PC 98-d						OW/OB; *n* 24, 39 y, 30·3 kg/m^2	↔ TNF-α, IL-6, CD14, MCP-1, adiponectin, CD206, CD284 (both interventions)	↑ CRP (both interventions), ↔ IL-6, MCP-1, sTNFR1, sTNFR2, ↓ body mass (amount NR across groups)
	Control	34·0	8·5	18·3	*n*-6 4·8 *n*-3 0·5	CHO:49·5, protein: 15·8			
	n-3 PUFA	34·2	8·3	15·2	*n*-6 4·8 *n*-3 3·5	CHO: 49·1, protein: 16·1			

OL, open-label; R, randomised; P, parallel; NR, not reported; CHO, carbohydrate; OB, obese; CD, cluster of differentiation; MCP-1, monocyte chemoattractant protein-1; CCL3, C–C motif chemokine ligand 3; CRP, C-reactive protein; TC, total cholesterol; LDL-C, LDL-cholesterol; HDL-C, HDL-cholesterol; SB, single-blind; OW, overweight; RANTES, regulated on activation normal, T cell expressed and secreted; PC, placebo-controlled; TNFRSF1A, TNF receptor superfamily member 1A; RELA/p65, NF-κB p65 subunit; TLR, toll-like receptor; IL1RN, IL 1 receptor antagonist; sTNFR, soluble TNF receptor; y, years; %E, percentage total energy; ↓, significant decease; ↑, significant increase; ↔, no change.
* Diet composition data are presented as dietary intervention targets, unless otherwise stated.
† Results are significant to $P < 0{\cdot}05$.
‡ WAT outcomes for gene expression.
§ WAT biopsies collected post-intervention only.
|| Additional diet composition data taken from Bos *et al.*[123].
¶ Diet composition data are taken from dietary intake records.
** Data reported as g/d.

microarray data. However, findings indicate that the substitution of dietary SFA with MUFA could help to mitigate WAT inflammation[107]. This is in agreement with cross-sectional data, where metabolic syndrome patients that were high-SFA consumers, but not high-MUFA consumers, presented with increased gene expression of caspase-1 and pycard-1 (part of the NLRP3 inflammasome)[81].

Three isoenergetic studies investigated the impact of an *n*-3 PUFA-rich intervention on WAT inflammation[109–111]. De Mello *et al.*[109] compared WAT gene expression following an 84-d intervention of differing *n*-3 PUFA quantities (camelina sativa oil, lean fish, fatty fish or control condition). No change in WAT gene expression of MCP-1, IL-1β, IL-6, IL-10, TNF-α, TNF receptor superfamily member 1A (TNFRSF1A), TLR2 or TLR4 was reported for all conditions, relative to baseline. A strength of this study was the comparison between different food sources of *n*-3 PUFA including fish and vegetable oil. The interventions were achieved by informing participants how to make dietary choices to achieve the desired intake of macronutrients. For the control group, participants were asked to minimise intake of fish to one meal per week and maintain habitual fat intake by replacing some fish meals with lean meat or skin-free chicken. This reduced participant burden compared to a fully supervised dietary intervention. Kratz *et al.*[111] also employed a long-term intervention (98 d) but all foods were provided by the research team. These authors investigated the effect of an *n*-3 PUFA-rich diet compared to a control diet on WAT inflammation in overweight/obese participants, although this was a secondary aim of the investigation. Rapeseed and flaxseed oil were used for the *n*-3 PUFA intervention and high-oleic safflower and sunflower oils were used for the control intervention; total fat %E remained similar between interventions. Following both the control and *n*-3 PUFA-rich diet, systemic C-reactive protein (CRP) was increased but IL-6 and MCP-1 remained unchanged. WAT gene expression of TNF-α, IL-6, CD14, MCP-1, adiponectin, CD206 and CD284 were unchanged following both interventions. Itariu *et al.*[110] employed a shorter intervention of 56 d and assigned morbidly obese participants to either an *n*-3 PUFA (3·36 g EPA/DHA; achieved in 4 capsules/d) or control SFA (5 g butter fat/d) supplement condition (matched for caloric intake) prior to undergoing elective bariatric surgery. Systemic CRP and adiponectin remained unchanged pre- to post-intervention for both conditions, however IL-6 was reduced following the *n*-3 PUFA intervention. In WAT, these authors reported no difference in gene expression of adiponectin, IL-6, CD68 or CD163 in the *n*-3 PUFA group compared to the control group post-intervention. A decreased gene expression of MCP-1, C-C motif ligand 3 and CD40 was also reported in the *n*-3 PUFA group compared to the control group. As acknowledged by the authors, it was not feasible to examine change-from-baseline gene expression inflammatory responses in WAT as only post-intervention WAT biopsies were collected[110]. Baseline characteristics (including age, sex, BMI, blood pressure, HOMA-IR) were however comparable between participants randomly assigned to the *n*-3 PUFA or control group.

The ambivalent nature of the results from studies investigating PUFA-rich interventions may, in part, be due to differences in study design, participant cohorts recruited and the duration and composition of the dietary or supplemental intervention. All studies were conducted in 'at risk' populations (i.e. overweight/obese or pre-diabetic) and therefore responses in lean, healthy individuals also require investigation. An objective measure of compliance was employed in two of these studies, as assessed by fatty profile of plasma phospholipids[109,110] and cholesterol esters[109], compared to twice-weekly reviews of dietary records and weighing of returned foods or supplements[111]. Although there is strong *in vitro* evidence for the anti-inflammatory effects of *n*-3 PUFA, differences in doses achievable in cell or animal models compared to the physiologically achievable dose *in vivo* in human participants may account for the difficulty in translating these findings to man. Overall, the effect of *n*-3 PUFA on WAT inflammation remains unclear[107,109–111]. Further well-controlled intervention studies are therefore required to confirm the effect of *n*-3 PUFA on WAT inflammation.

Acute studies

It is also important to consider the WAT inflammatory response to feeding since we spend most of the waking day in a postprandial (fed), rather than a fasted state[112]. WAT may be a key mediator in the promotion of systemic low-grade inflammation, an early component of the postprandial pro-atherogenic phenotype[113,114]. Few studies to date have investigated the effect of a single high-fat meal on WAT inflammatory responses (Table 3); this includes studies comparing the macronutrient content or fatty acid quality of a meal.

Travers *et al.*[115] compared the WAT inflammatory response to a single mixed meal (54 % total fat) in lean, overweight and obese participants. The meal provided energy equivalent to about 65 % of each participant's RMR and consisted of brioche, strawberry jam, margarine, a milkshake and decaffeinated tea. Increased WAT gene expression of IL-6 and MCP-1 and a decrease in IRS-2 were reported 6 h post-meal consumption. These results were independent of adiposity. This may suggest that a postprandial inflammatory response is a normal response to feeding or an apparently normalised response. As suggested by the authors, normalisation of the response may be due to reduced responsiveness of WAT to the mixed meal components, insulin or similar net exposure per g WAT (as adjustments for adipose tissue mass were made in the analysis of this study). In addition, Dordevic *et al.*[116] compared WAT inflammatory responses to three different beverages: high-CHO, high-fat and placebo (water) beverage meal. WAT gene expression of MCP-1, IL-6, TNF-α and CD68 were increased at 2 and 4 h following all beverages. Dordevic and colleagues[116] collected three WAT samples from a single incision; they altered the needle inclination for the second and third biopsy sample. As an

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Table 3. Summary of acute human studies examining the effect of meal differing in fat quantity or quality on postprandial subcutaneous white adipose tissue (WAT) inflammatory responses

References	Study design, duration (postprandial period) and intervention	Meal composition (%E, unless specified)*					Participant characteristics (*n*, mean age and BMI)	WAT outcomes (relative to baseline)†,‡	Systemic outcomes (relative to baseline)†
		Total fat	SFA	MUFA	PUFA	Other			
Dordevic *et al.*[116]	R, P, PC 4-h Biopsies: 0, 2, 4 h						Healthy; *n* 33; 25 y; 24·1 kg/m^2	↑ MCP-1, IL-6, TNF-α, ↓ CD68 (2 h) ↔ between meals	↑ insulin for high-CHO meal (2 h), ↑ NEFA for high-fat meal (2 and 4 h), ↓ adiponectin (all meals; 2 h), ↔ TNF-α (all meals)
	Placebo: 0 kJ	NR	NR	NR	NR	NR			
	High-CHO: 1856 kJ	0·0	0·0	0·0	0·0	CHO: 100·0			
	High-fat: 1988 kJ	93·0	NR	NR	NR	CHO: 3·5, protein: 3·5			
Travers *et al.*[115]	P, SA 6-h Biopsies: 0, 6 h						Lean, OW and OB men; *n* 30; 46 y; lean: 23·6 kg/m^2, OW: 26·7 kg/m^2, OB: 30·7 kg/m^2	↑ IL-6, MCP-1, ↓ IRS2, ↔ GLUT4, IL-1β, IL1RA, IL-10, IL-8, TNF-α	
	Energy content: 65% RMR	54·0	NR	NR	NR	CHO: 39·0, protein: 7·0			
Meneses *et al.*[117]§	R, P 4-h Biopsies: 0, 4 h Energy content: 40·2 kJ/kg body weight						Metabolic syndrome; *n* 39; 57 y; 35·3 kg/m^2	↑ p65 for high-CHO and high-CHO + PUFA meals, ↑ IκBα, MCP-1, IL-1β (all meals), ↔ IκBβ2 (all meals)	↑ IL-6 for high-CHO and high-CHO + PUFA meal, ↔ MCP-1 (all meals)
	High-SFA	65·0	38·0	21·0	6·0	CHO: 25·0, protein: 10·0 (all meals)			
	High-MUFA	65·0	12·0	43·0	10·0				
	Low-fat, high-complex CHO (high-CHO)	65·0	21·0	28·0	16·0				
	Low-fat, high-CHO +1·24 g/d *n*-3 PUFA (high-CHO + PUFA)	65·0	21·0	28·0	16·0				
Pietraszek *et al.*[118]	R, CO 4-h Biopsies: 0, 3·5 h						Relatives of patients with T2D and healthy controls; *n* 34, 51 y, 24·8 kg/m^2	↑ CD16 IL-1β, IL-6, IL-6R, TNF-α in controls for high-SFA meal, ↑ adiponectin, TNFRSF1A in controls and ↑ MCP-1, IL-1β, IL-6, IL-6R, TNF-α, TNFRSF1A in relatives for high-MUFA meal	↔ CRP, adiponectin (both meals), ↑ IL-6 (both meals)
	High-SFA: 3547 kJ	87·0	79·0	NR	NR	CHO: 11·0, protein: 2·0 (both meals)			
	High-MUFA: 3547 kJ	87·0	NR	72·0	NR				

WAT, white adipose tissue; R, randomised; P, parallel; PC, placebo-controlled; NR, not reported; CHO, carbohydrate; MCP-1, monocyte chemoattractant protein-1; CD, cluster of differentiation; SA, single-arm; OW, overweight; OB, obese; IRS2, insulin receptor substrate 2; IL1RA, IL 1 receptor antagonist; IκBα, inhibitory factor κBα; IκBβ, inhibitory factor κBβ; CO, crossover; T2D, type-2 diabetes; TNFRSF1A, TNF receptor superfamily member 1A; CRP, C-reactive protein; y, years; %E, percentage total energy; ↓, significant decease; ↑, significant increase; ↔, no change.
* Diet composition data are presented as dietary intervention targets.
† Results are significant to $P < 0·05$.
‡ WAT outcomes for gene expression.
§ This study reported results on an acute response to a chronic (12-week) dietary intervention.

increased WAT inflammatory response was reported following all meals, it is likely that the sampling technique confounded the results.

Meneses *et al.*[117] compared postprandial responses to differing qualities of fatty acids in metabolic syndrome patients from the LIPGENE study. Firstly, participants completed a 12-week intervention (low-fat, high-complex CHO (high-CHO); low-fat, high-complex CHO + 1·24 g/d *n*-3 PUFA (high-CHO + PUFA); high-SFA; high-MUFA) before the postprandial response to a high-fat meal was investigated. The fatty acid composition of the meal was reflective of the prior dietary intervention although total fat intake remained equal for all meals (65 %E). These authors reported increased systemic IL-6 and WAT gene expression of p65 (part of the NF-κB complex) 4 h following the high-CHO and high-CHO + PUFA meal, but not following the high-MUFA or high-SFA meal. Gene expression of inhibitory factor κBα, MCP-1 and IL-1β was increased 4 h following all meals. However, no change in systemic MCP-1 was reported following all meals[117]. It is also important to note that this work may have been confounded by the fact that the test meal was administered following a 12-week dietary intervention. Pietraszek *et al.*[118] compared an SFA-rich meal (49 %E medium-chain SFA, primarily lauric acid; 30 %E long-chain SFA, primarily myristic acid) to a MUFA-rich meal (72 %E MUFA, primarily oleic and palmitoleic acid) in healthy first-degree relatives of patients with T2D (relatives) and healthy controls. The meals consisted of white bread and soup made with macadamia nut oil or coconut oil for the MUFA- and SFA-rich meals, respectively. Systemic CRP was unchanged and IL-6 was increased following the SFA- and MUFA-rich meal. For IL-6 there was no difference in response between relatives and healthy controls. In WAT, gene expression of IL-1β, IL-6 and TNF-α were upregulated at 3·5 h following the SFA-rich meal in controls but not relatives. In response to the MUFA-rich meal, increased WAT gene expression of MCP-1, IL-1β, IL-6 and TNF-α was observed in relatives at 3·5 h postprandially, while adiponectin and TNFRSF1A were upregulated in the WAT of the controls. The findings of Pietraszek *et al.*[118] suggest that healthy participants and relatives who are at increased risk of developing T2D and CVD, have differential WAT but not systemic responses.

Overall, research investigating the postprandial WAT inflammatory response is limited[115–118] and only two studies examined the effect of a high-fat meal varying in fatty acid quality[117,118]. Furthermore, one of these studies examined the postprandial response following a chronic dietary intervention varying in fat quantity and quality[117]. Therefore, it is not currently possible to draw firm conclusions regarding the impact of fatty acid quality on postprandial WAT inflammatory responses. Further randomised controlled trials are warranted to determine whether fatty acid quality (SFA *v.* unsaturated fatty acids) can differentially affect WAT inflammatory responses as this could have important implications for cardiometabolic disease risk reduction. Additionally, different participant cohorts could be examined since healthy controls and more 'at risk' populations (i.e. relatives of patients with T2D) may have differential WAT responses. In addition, sampling timepoints employed in previous postprandial studies have been inconsistent (ranging from 2–6 h) and limited to one biopsy postprandially[115,117,118], except in the study conducted by Dordevic *et al.*[116]. However, the sampling technique employed in the latter study[116] likely confounded the results. The time-course of the WAT postprandial inflammatory response to fatty acid ingestion remains unknown. Future work is required to investigate postprandial WAT inflammatory responses (through repeated biopsy collection). However, it is imperative the sampling technique employed does not elicit a local inflammatory response[119].

Conclusions

Excess energy and fatty acid composition have been suggested to modulate the WAT inflammatory environment in cell and animal models, although work *in vivo* in human participants remains limited. Overall, it is hard to draw firm conclusions regarding the effect of dietary fat quantity and quality on WAT inflammatory responses in human participants due to the limited number of studies conducted to date and due to the heterogeneity within study designs, intervention lengths, participant cohorts and studies not always reporting fatty acid composition of the diets. Understanding the effect of dietary fat quantity and quality on WAT metabolic-inflammatory responses may have important implications for public health by informing dietary guidelines aimed at reducing WAT inflammatory responses for cardiometabolic risk reduction. It is suggested that future studies are highly controlled and present total fat content and fatty acid composition of dietary interventions. Previous human intervention studies have primarily focused on gene expression of targets involved in WAT inflammatory pathways. However, this method does not provide information on protein abundance or protein activity as these are heavily influenced by post-transcriptional and post-translational events[120,121]. The amount and phosphorylation of proteins involved in WAT inflammation, rather than gene expression, may more accurately represent changes in the physiological function of WAT. Thus, it is essential that total content and phosphorylation of proteins involved in WAT inflammatory signalling are investigated in future work.

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Conflict of Interest

None.

Authorship

The concept for this manuscript was developed by all authors. R. D-T. drafted the manuscript. C. J. H. and O. M. provided advice on content inclusion. C. J. H. and O. M. revised and edited the manuscript critically for important intellectual content. All authors have read and approved the final manuscript.

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