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Dietary fatty acids and CD36-mediated cholesterol homeostasis: potential mechanisms

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Abstract

Currently, the prevention and treatment of CVD have been a global focus since CVD is the number one cause of mortality and morbidity. In the pathogenesis of CVD, it was generally thought that impaired cholesterol homeostasis might be a risk factor. Cholesterol homeostasis is affected by exogenous factors (i.e. diet) and endogenous factors (i.e. certain receptors, enzymes and transcription factors). In this context, the number of studies investigating the potential mechanisms of dietary fatty acids on cholesterol homeostasis have increased in recent years. As well, the cluster of differentiation 36 (CD36) receptor is a multifunctional membrane receptor involved in fatty acid uptake, lipid metabolism, atherothrombosis and inflammation. CD36 is proposed to be a crucial molecule for cholesterol homeostasis in various mechanisms including absorption/reabsorption, synthesis, and transport of cholesterol and bile acids. Moreover, it has been reported that the amount of fatty acids and fatty acid pattern of the diet influence the CD36 level and CD36-mediated cholesterol metabolism principally in the liver, intestine and macrophages. In these processes, CD36-mediated cholesterol and lipoprotein homeostasis might be impaired by dietary SFA and *trans*-fatty acids, whereas ameliorated by MUFA in the diet. The effects of PUFA on CD36-mediated cholesterol homeostasis are controversial depending on the amount of *n*-3 PUFA and *n*-6 PUFA, and the *n*-3:*n*-6 PUFA ratio. Thus, since the CD36 receptor is suggested to be a novel nutrient-sensitive biomarker, the role of CD36 and dietary fatty acids in cholesterol metabolism might be considered in medical nutrition therapy in the near future. Therefore, the novel nutritional target of CD36 and interventions that focus on dietary fatty acids and potential mechanisms underlying cholesterol homeostasis are discussed in this review.

Key words: **Fatty acids: CD36: Cholesterol metabolism: CVD**

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Introduction

In the last decade, CVD has become the leading cause of mortality and morbidity, with increasing prevalence worldwide[1,2]. One of the main causes in the pathogenesis of CVD is impairment of cholesterol homeostasis[3]. Cholesterol and lipoprotein homeostasis is influenced by the endogenous synthesis of cholesterol, absorption of dietary cholesterol in the gastrointestinal tract, transport of cholesterol via lipoproteins in the circulation, and the reabsorption of cholesterol excreted in the form of bile acids. Likewise, recent studies have noted that the levels and/or expressions of enzymes, transporters, receptors and transcription factors involving in cholesterol metabolism are influenced by dietary fat and fatty acids[3-6].

The amount of dietary total fat, fatty acids and fatty acid pattern are important for cholesterol homeostasis and CVD. Dietary fatty acids affect cholesterol homeostasis in different ways depending on the existence of double bonds and their *cis* or *trans* forms[7]. Under these circumstances, high dietary SFA and *trans*-fatty acids (TFA) might cause dyslipidaemia and hypercholesterolaemia by impairing cholesterol metabolism[8,9]. On the contrary, it has been reported that a diet high in MUFA might be protective against CVD by improving cholesterol and lipoprotein homeostasis[10]. Though the effects of total PUFA, *n*-3 PUFA and *n*-6 PUFA content in the diet on cholesterol homeostasis are still controversial, the amount of total PUFA, *n*-6 PUFA and *n*-3 PUFA, and the *n*-3:*n*-6 PUFA ratio are important for cholesterol homeostasis[5,6].

Although some of the mechanisms by which dietary fatty acids affect cholesterol metabolism are clearly known, novel mechanisms that may influence cholesterol metabolism are also argued in the literature[6,11]. One of the proposed novel mechanisms is the function of CD36 (fatty acid translocase/cluster of differentiation 36) as a fatty acid transporter, but there are a limited number of studies clarifying this role in cholesterol homeostasis[12,13]. Dietary fatty acids might influence CD36-mediated cholesterol metabolism by altering CD36 levels

Abbreviations: ABC, ATP binding cassette transporter; ACAT, acetyl-CoA acetyltransferase; AHA, American Heart Association; CD36, cluster of differentiation 36; CYP7A1, cholesterol 7α hydroxylase; CYP27A1, sterol 27 hydroxylase; EFSA, European Food Safety Authority; FABP, fatty acid binding protein; HDL-C, HDL-cholesterol; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; LCFA, long-chain fatty acid; LDL-C, LDL-cholesterol; LDLR, LDL receptor; LKB1, liver kinase B1; LXR, liver X receptor; MTTP, microsomal TAG transfer protein; NPC1L1, Niemann–Pick C1-like 1; oxHDL, oxidised HDL; oxLDL, oxidised LDL; SR-BI, scavenger receptor class B tip I; SREBP2, sterol regulatory element-binding protein 2; TFA, trans-fatty acid; TSP, thrombospondin; VLDL-C, VLDL-cholesterol.

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and/or expression in macrophages, liver, small intestine, and some other cells and tissues involved in cholesterol homeostasis[12,14,15]. All this information highlights that the CD36 receptor is thought to be a novel nutrient-sensitive biomarker for cholesterol homeostasis.

Nowadays, there is an increasing number of studies related to the effect of dietary fatty acids on cholesterol metabolism induced by CD36 in the literature[16,17]. However, there is a lack of knowledge in combining the potential mechanisms of dietary fatty acids on CD36-mediated cholesterol metabolism. Thus, the novel nutritional target of CD36 and interventions that focus on dietary fatty acids on potential mechanisms underlying cholesterol homeostasis need to be discussed. Therefore, the present review is written to reveal the novel effects of dietary fatty acids on CD36-mediated cholesterol homeostasis in terms of absorption, endogenous synthesis, circulation and excretion of cholesterol.

Method of literature search

The literature search was performed by using the databases of PubMed, Science Direct, Google Scholar and Scopus with the keywords 'dietary fatty acid types and CD36 and/or the CD36 related mechanisms of cholesterol metabolism'. Reviews, systematic reviews, meta-analyses, epidemiological studies, randomised controlled trials and experimental studies conducted on human subjects, animals and cell cultures were included from the relevant literature. Articles in the English language and published between 2000 and 2019 were involved in the present review.

Structure and functions of CD36

CD36, of which many functions have been discovered in recent years, was first found in platelets and was named platelet glycoprotein IV (GPIV). After that, CD36 was defined as fatty acid transporter (FAT) and receptor in macrophages for oxidised LDL (oxLDL)[18,19]. In spite of its simple molecular structure, the transmembrane domain provides receptor properties in addition to its carrier protein property. Additionally, CD36 is a part of the class B scavenger receptor family along with scavenger receptor class B tip I (SR-BI) and lysosomal integral membrane protein II (LIMP II)[18,19]. The molecular weight of CD36 ranges from 80 to 90 kDa and has two transmembrane domains (Fig. 1). First, it was determined that the amino acid sequence 93–120 is the binding site for thrombospondin (TSP) 1 and TSP2. Subsequently, it was revealed that the binding site located in amino acid sequence 155–183 is for oxLDL, advanced glycation endproducts and apoptotic cells, sequence 146–164 is for *Plasmodium falciparum*-infected erythrocytes, and sequence 127–279 is for long-chain fatty acids (LCFA)[18-20]. Additionally, hexarelin and EP80317 are ligands for the CD36 receptor[18,19].

In humans, CD36 is expressed on many cells and tissues including platelets, microvascular endothelial cells, monocytes, macrophages, adipocytes, heart and skeletal muscle cells, retinal pigment epithelial cells and enterocytes, whereas it is partially expressed on hepatocytes and smooth muscle cells[18]. Initially, CD36 was described as a scavenger receptor that plays

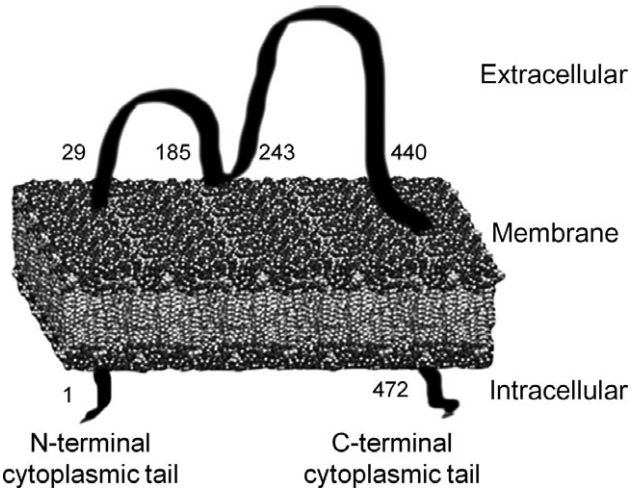

Fig. 1. Transmembrane structure of the cluster of differentiation 36 (CD36) receptor[19,20].

a role in endocytosis by binding to its ligands such as TSP1 and oxLDL. Nowadays, CD36 has a variety of metabolic effects since it is expressed in many cells and tissues and has many ligands. Therefore, it is currently being discussed whether CD36 might influence the pathogenesis of hyperlipidaemia, dyslipidaemia, inflammation, atherothrombosis and angiogenesis[17,18].

Fatty acid uptake into cardiomyocytes, adipocytes, enterocytes and skeletal myocytes requires protein-mediated transport by fatty acid transport protein (FATP), fatty acid binding protein (FABP) and CD36[21,22]. LCFA uptake into cardiomyocytes is regulated by the vesicular recycling of CD36 from endoplasmic reticulum to the plasma membrane[22]. In this context, short-term regulation of LCFA uptake at the plasma membrane is provided both by heart muscle contraction and insulin signalling[21]. For long-term regulation, expression of CD36 in the nucleus is regulated by PPAR and other transcriptional factors[23,24]. Furthermore, CD36 accelerates the entry of fatty acids from the cytoplasm to mitochondria for β-oxidation[23]. Since fatty acid uptake into the cytoplasm initiates the signalling pathways related to PPAR, the expressions of genes especially involved in lipid metabolism are circuitously altered by CD36[23,24]. In this context, CD36 may cause the degradation of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) and inactivation of sterol regulatory element-binding protein 2 (SREBP2) by inducing PPARγ and thus decrease endogenous cholesterol synthesis[16,25]. Furthermore, CD36-mediated liver X receptor (LXR) activation might accelerate reverse cholesterol transport by up-regulating the activities of ATP-binding cassette transporter (ABC) A1 (ABCA1) and G1 (ABCG1) in the liver and macrophages[17,26,27]. Considering its roles in cholesterol synthesis, transport and reverse cholesterol transport, CD36 might be effective in cholesterol homeostasis and play an important role for dyslipidaemia and hyperlipidaemia-induced CVD[17,23].

In addition to its role for LCFA uptake and lipid metabolism, the binding of CD36 to oxysterols, TSP1, oxLDL and oxidised phospholipids in endothelial cells, macrophages and platelets is important in the onset and development of atherosclerosis by inducing platelet aggregation, thrombosis, production of

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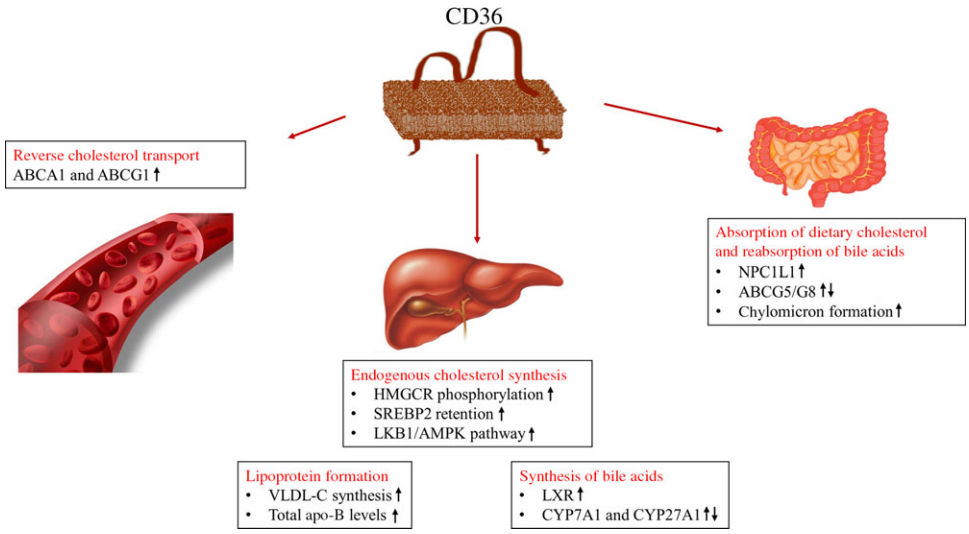

Fig. 2. Roles of cluster of differentiation 36 (CD36) in cholesterol metabolism[17,18]. ABC, ATP binding cassette transporters; AMPK, 5′AMP-activated protein kinase; CYP, cytochrome P450 family; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; LKB1, liver kinase B1; LXR, liver X receptor; NPC1L1, Niemann–Pick C1-like 1; SREBP2, sterol regulatory element-binding protein 2; VLDL-C, VLDL-cholesterol.

inflammatory cytokines and foam cell formation[18,19,28,29]. Studies have shown that there was a positive correlation between soluble CD36[28] or macrophage CD36[30] levels and formation of atherosclerotic plaques. Furthermore, CD36 cooperates with toll-like receptors (TLR) and their heterodimers (TLR4-TLR6) to bind oxLDL and stimulate inflammation-induced atherosclerosis[31]. Moreover, it has been reported that CD36 has an important role for the accumulation of cholesterol within the macrophages resulting in lysosomal disruption and activation of NLR family pyrin domain containing 3 (NLRP3) inflammasomes[31,32]. Human studies have reported that CD36 increases the release of inflammatory cytokines such as TNFα, IL-1β and interferon-γ by inducing activation of NF-κB in monocyte-derived macrophages[33]. On the other hand, CD36 is a receptor for several proteins containing peptide domains known as TSP1 repeats. Thus, in endothelial cells, CD36 functions as an endogenous negative regulator of angiogenesis[34]. CD36 accomplishes this function by suppressing growth factor-induced pro-angiogenic signals and generating anti-angiogenic signals that cause apoptosis[34,35]. All these functions of CD36 reveal the vital role of this receptor in cardiovascular metabolism.

Role of CD36 in cholesterol metabolism

Cholesterol homeostasis is a metabolic process that involves the absorption of dietary cholesterol, endogenous synthesis, transport of cholesterol, cholesterol excretion in the form of bile acids and reabsorption of bile acids. Any change in cholesterol homeostasis might cause pathophysiological conditions and induce increased risk of cardiometabolic disorders[36]. The effects of CD36 on lipid metabolism might be different due to its expression level in many cells and the presence of many ligands. As shown in Fig. 2, the possible effects of CD36 on cholesterol homeostasis include absorption of dietary cholesterol, cholesterol synthesis, lipoprotein formation, reverse cholesterol transport, and synthesis and reabsorption of bile acids (Fig. 2)[17,18].

One of the components of cholesterol homeostasis is the absorption of dietary cholesterol in the gastrointestinal tract. CD36 is expressed in the small intestine, especially on the apical membranes of the duodenum and jejunum, and, therefore, is proposed to facilitate the absorption of fatty acids and cholesterol[37]. Drugs (i.e. ezetimibe), used in the treatment of hypercholesterolaemia, are known to suppress the absorption of cholesterol in the small intestine by inhibiting important carriers for cholesterol absorption (such as CD36, Niemann–Pick C1-like 1 (NPC1L1), SR-BI)[36,38]. In animal studies, it has been shown that dietary cholesterol absorption in the small intestine[37,39] and the rate of passage to the lymph circulation of cholesterol[37] are lower in CD36 gene knock-out mice. It has also been reported that CD36 increased the absorption of cholesterol by affecting the level of NPC1L1 carrier protein[39]. On the other hand, it was found that, in CD36 and SR-BI knock-out mice, cholesterol absorption was delayed with a high-fat diet compared with standard chow feed[40]. Additionally, it has been shown that secretion of apo-B to the lymphatic circulation is decreased in CD36 knock-out mice and therefore, the absence of CD36 suppresses chylomicron formation in enterocytes[37].

In addition to the effect on the absorption of dietary cholesterol, CD36 might affect cholesterol homeostasis by altering the activities and/or levels of regulatory enzymes for endogenous cholesterol synthesis in many tissues, especially in the liver. CD36 binding to ligands such as hexarelin, oxLDL or oxysterols induces PPARγ expression by activating PPARγ coactivator 1α (PGC1α)[17,41]. PPARγ is a member of a nuclear receptor family that regulates the expression of many glycogenic and lipogenic genes in many tissues, mainly in the liver, cardiomyocytes and adipose tissue[16,17,42]. Increased expression of PPARγ might decrease endogenous cholesterol synthesis by activating insulin-stimulated gene 1 (Insig1) and insulin-stimulated gene 2

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(Insig2) and inducing the degradation of HMGCR and retention of SREBP2 in the endoplasmic reticulum[17]. In a study, it was found that expression of PPARγ in adipose tissue was reduced and therefore Insig1 level was decreased in CD36 gene knock-out mice[43]. However, in a recent study, it was reported that CD36 expression increased in macrophages incubated with advanced glycation endproducts, and the expression levels of HMGCR and acetyl-CoA acetyltransferase (ACAT) 1 were elevated[44]. Furthermore, a study conducted on mice showed that the expressions of CD36 and HMGCR were increased in epididymal white adipose tissue, while PPARγ expression was not affected[45]. Also, CD36 activates liver kinase B1 (LKB1), which is serine/threonine kinase 11 (STK11), known as a tumour suppressor[46]. 5′AMP-activated protein kinase α (AMPKα) stimulated via LKB1 activation might inhibit cholesterol synthesis by providing phosphorylation of HMGCR[17,47]. In a recent study, it was reported that liver CD36 expression was decreased, hepatic fatty acid and cholesterol accumulation was increased, and blood lipoprotein profile was impaired due to decreased activity of the LKB1/AMPK pathway in mice fed with a high-fructose diet[48].

In reverse cholesterol transport, another pathway induced by ligands binding to CD36 is the LXR-mediated pathway, and increased hepatic LXR expression was found to positively correlate with CD36 expression in the liver[49]. Increased LXR expression in the liver may have an impact on the levels of ABCA1 and ABCG1 transporters that are important for reverse cholesterol transport, and hence may influence the formation of foam cells in the vessels by altering cholesterol transport from peripheral tissues, primarily from macrophages, to the liver[17,50]. Elevating the level of ABCA1 in macrophages transfers phospholipids and cholesterol to apo-A1, while ABCG1 transfers cholesterol to immature HDL-cholesterol (HDL-C)[50]. In CD36 gene knock-out mice, liver expressions of apo-A1 and apo-A4, which are mainly found in the HDL-C structure, were higher than in wild-type mice[51]. In addition to reverse cholesterol transport and HDL-C, elevation of CD36 in the liver may induce the synthesis and release of VLDL-cholesterol (VLDL-C) due to the fact that CD36 increases the uptake of LCFA into the liver[52,53]. Also, it was found that serum total cholesterol and LDL-cholesterol (LDL-C) levels were significantly elevated in type II CD36-deficient humans (CD36 is expressed on monocytes but not on platelets)[53].

Cholesterol is used in the synthesis and reabsorption of bile acids from the intestine, which are metabolic pathways for cholesterol excretion. Increasing levels of CD36 in the liver might cause elevation of the key enzymes of bile acid synthesis, i.e. cholesterol 7α hydroxylase (CYP7A1) and sterol 27 hydroxylase (CYP27A1)[54]. Furthermore, studies have reported that CD36-mediated LXR stimulation influences the reabsorption of bile acids by increasing ABCG5/G6 expression and decreasing NPC1L1 transporter expression[26,49]. It was also been reported that an increase in CD36 expression in the hepatocytes of mice fed with a high-fat and high-cholesterol diet leads to an increase in LXR and therefore ABCG5/G8 levels[55].

Accordingly, ligand-receptor downstream signalling of CD36 might affect cholesterol metabolism via different proposed mechanisms. CD36 may elevate dietary cholesterol absorption, increase or decrease endogenous cholesterol synthesis and reverse cholesterol transport, and may increase synthesis and reabsorption of bile acids[17,18,26]. The results of human studies have shown that CD36 deficiency induces dyslipidaemia (elevated blood TAG, total cholesterol and LDL-C, and decreased HDL-C) and increases the concentration of lipoprotein remnants[52,53]. However, more preclinical and clinical studies are needed to clarify the mechanisms of how CD36 affects cholesterol metabolism.

Dietary fatty acids, CD36 and cholesterol metabolism

The dietary fatty acid pattern is essential for cardiovascular health which may increase or decrease blood total cholesterol, and circulating lipoprotein and apolipoprotein levels[5,7,56]. Moreover, the saturation (saturated, monounsaturated, polyunsaturated) and the form (*cis/trans*) of fatty acids may change the expression of CD36 in many tissues and cells involved in cholesterol homeostasis, especially in the liver, small intestine, adipose tissue and macrophages[12,30,57]. Therefore, the studies on the combining effects of novel biomarkers (i.e. CD36) and dietary fatty acid intake on cholesterol metabolism have been currently accumulating in the literature.

SFA and CD36-mediated cholesterol metabolism

Dietary SFA might have an impact on cholesterol homeostasis due to various mechanisms including absorption of dietary cholesterol in the small intestine, endogenous cholesterol synthesis, circulating lipoproteins and cholesterol excretion in the form of bile acids[6,58]. Depending on the source of food, high dietary SFA intake resulted in higher serum total cholesterol, LDL-C[59,60] and non-HDL-C levels[61] in meta-analyses. It was also shown that consumption of red and processed meat was positively associated with serum non-HDL-C level[61]. Though, since dairy products, butter, red meat, fish, eggs and poultry have different SFA contents[56], they might influence cholesterol homeostasis depending on the dietary fatty acid pattern[61,62].

Cholesterol absorption. NPC1L1 has been identified as a cholesterol transporter localised at the apical membrane of the small intestine; while ABCA1, ABCG5 and ABCG8 are presumed to facilitate cholesterol efflux from the enterocyte[63]. As summarised in Table 1, it has been generally hypothesised that high dietary SFA might result in elevated cholesterol absorption (NPC1L1 and CD36), chylomicron formation (microsomal TAG transfer protein (MTTP) and ACAT), and cholesterol efflux from enterocytes to lymphatic circulation (ABCA1/G1/G5/G8)[64-68]. These results showed that the absorption/transport of cholesterol from the apical and basolateral membranes of enterocytes was a complex process with many carriers, proteins and enzymes. In this context, the hypothesis of acceleration of cholesterol absorption and chylomicron formation in the small intestine via CD36 has been presented in the literature in the last decade[37,39]. Expression of CD36 at the proximal end of the small intestine was higher than at the distal end of the body and cholesterol absorption decreased by 50 % in $CD36^{(-/-)}$ mice compared with $CD36^{(+/+)}$ mice[37]. Hence, down-regulation,

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Table 1. Potential effects of SFA on CD36-related cholesterol homeostasis

	Species	Cells/tissues	Fat component*		Main outcomes	References
			Total fat/SFA (% energy)	SFA (mM)		
Cholesterol absorption	C57BL/6 mouse	Intestine	42/26		SR-BI and NPC1L1 ↓ ABCG5/G8 =	(65)
			45/11·3		ABCA1/G5/G8 ↓ NPC1L1 ↓ MTTP ↑	(64)
			45/22·5		DGAT1 ↑ apo-B ↑	(14)
	Cell line	Caco-2 line		0·5 or 1	NPC1L1 ↑ ACAT2 ↑	(66)
Cholesterol synthesis	C57BL/6 mouse	Liver	60/22·6		HMGCR and SREBP2 ↑ Insig1 ↑	(13)
			41·5/29·8		PPARγ2 ↑ CD36 ↑	(70)
			45/11·3		HMGCR ↑	(64)
	F1B hamster	Liver	26·7/20·7		HMGCR, SREBP2 ↑ PPARα ↓	(67)
	Cell line	HepG2 line		0·3	HMGCR and SREBP2 ↑ Total cellular cholesterol ↑	(13)
Cholesterol transport	C57BL/6 mouse	Serum and liver	60/22·6		Liver TC, serum TC ↑ Liver PCSK9 and LDLR ↑	(13)
			42/27·3		Serum TC, HDL-C, oxLDL, oxHDL ↑ Liver ABCG1/G5/G8 ↑	(15)
		Plasma and liver	45/22·3		Liver TC, plasma TC, non-HDL-C ↑ Liver SR-BI and ABCB1 ↑	(73)
	ddY mouse	Serum and liver	58/41		Liver TC ↑ CD36 ↑	(69)
	F1B hamster	Serum and liver	26·7/20·7		Serum TC, non-HDL-C ↑ Liver SR-BI and apo-A1 ↑	(67)
	Human	Serum	40·45/18·2		TC, LDL-C and LDL-C:HDL-C ↑	(71)
Cholesterol excretion	C57BL/6 mouse	Liver and intestine	42/27·3		Liver CYP7A1 ↑ Intestine ABCG1/G5/G8 ↑	(15)
			42/26		Intestine ABCG1/G5/G8 ↑ CYP7A1 and SR-BI =	(65)
		Liver	45/11·3		CYP7A1 ↓	(64)
			31·3/29·5		Bile acid pool ↓ CYP7A1 ↓	(103)
	F1B hamster	Liver	26·7/20·7		NPC1L1, ABCG1/G5/G8 =	(67)
	Golden Syrian hamster	Liver	27·3/20·6		CYP7A1 and CYP27A1 =	(81)

↑, Increase; ↓, decrease; =, no change; ABC, ATP binding cassette transporter; ACAT, acetyl-CoA acetyltransferase; CD36, cluster of differentiation 36; CYP7A1, cholesterol 7α hydroxylase; CYP27A1, sterol 27 hydroxylase; DGAT1, diacylglycerol acyltransferase 1; HDL-C, HDL-cholesterol; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; Insig1, insulin-stimulated gene 1; LDL-C, LDL-cholesterol; LDLR, LDL receptor; MTTP, microsomal TAG transfer protein; NPC1L1, Niemann–Pick C1-like 1; oxHDL, oxidised HDL; oxLDL, oxidised LDL; PCSK9, proprotein convertase subtilisin/kexin type 9; SR-BI, scavenger receptor class B type I; SREBP2, sterol regulatory element-binding protein 2; TC, total cholesterol.

* The molarity or percentage of the energy for total fat/SFA is recorded or calculated from the diets in the reference studies.

dysfunction or deficiency of CD36 in the intestine might lead to a delay of efficient chylomicron formation (MTTP, FABP) and clearance (apo-C2) in the jejunum induced by impaired gene expression[37,39]. A study conducted on mice fed with a high-SFA diet showed that although CD36 and NPC1L1 expressions in the small intestine did not change, the expressions of diacylglycerol acyltransferase 1 (DGAT1), MTTP, FABP and apo-B increased in enterocytes, inducing chylomicron formation[14].

Cholesterol synthesis. SFA might induce the endogenous synthesis of cholesterol in many tissues. As shown in Table 1, in this process, SREBP2 might be up-regulated by dietary SFA which regulates the synthesis and uptake of cholesterol by altering the expression of HMGCR and LDL receptor (LDLR)[12,67]. Additionally, PPARγ coactivator 1α (PGC1α) may be stimulated by dietary SFA and contribute to higher SREBP2 mRNA levels. In the endoplasmic reticulum, a sterol sensor was proposed for the modulation of SREBP2 transcriptional activity in response to changes in intracellular free cholesterol levels[67]. Although ACAT2 is responsible for the esterification of cholesterol, the effects of high SFA intake on ACAT2 have not been clarified yet[68]. Mice fed with a high-SFA diet showed increased endogenous cholesterol synthesis by decreasing expression of CD36 and thus expression of PPARγ in the liver[69,70]. SFA are generally thought to increase endogenous cholesterol synthesis, but the effect of CD36 on this mechanism is still unclear.

Cholesterol transport. Intervention studies showed that SFA elevated atherogenic lipoproteins/apolipoproteins and decreased non-atherogenic lipoproteins/apolipoproteins[11,59,71-75] as

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summarised in Table 1. It was also reported that high dietary SFA intake increased the oxidation of lipoproteins (such as oxLDL and oxHDL) in serum compared with dietary unsaturated fatty acids[15]. In the literature, it has been generally reported that high dietary SFA intake might decrease plasma HDL-C levels. However, a meta-analysis found that high dietary SFA intake from hydrogenated vegetable oils consisting of TFA might elevate plasma HDL-C[59]. Likewise, high dietary SFA due to dietary total fat intake might cause higher plasma HDL-C level relative to increase in plasma total cholesterol level in the case of hyperlipidaemia[76]. In addition, cholesteryl ester transfer protein (CETP) might be up-regulated by high SFA intake, induce cholesterol transport from HDL-C to VLDL-C, and thus decrease reverse cholesterol transport[77]. Moreover, high dietary SFA has been shown to up-regulate[15,78], down-regulate[13] or not change[79] the expression of transporters such as CD36, SR-BI, ABCA1 and ABCG1 in reverse cholesterol transport in the liver and macrophages.

Cholesterol excretion. As shown in Table 1, high dietary SFA might inhibit the synthesis of bile acids in the liver via CYP7A1 and CYP27A1 enzymes, and might accelerate the reabsorption of bile acids via ABCG5/G8 in the intestine[15,64,80,81]. Moreover, activation of LXR increases bile acid synthesis from cholesterol and cholesterol excretion into bile. CD36 might be involved in this mechanism due to the fact that it stimulates LXR expression[17,49]. However, studies on how SFA affect CD36-mediated bile acid synthesis in the liver and reabsorption in the intestine are not completely clarified yet.

To sum up, high dietary SFA intake might impair cholesterol homeostasis by a variety of mechanisms including absorption, synthesis, transport and excretion of cholesterol (Table 1). In these mechanisms, many enzymes, transcription factors and transporters such as CD36 may be influenced by dietary SFA content. Thus, according to the results of recent studies it was indicated that SFA of 12–43 % from daily energy intake disrupts cholesterol homeostasis and elevates atherogenic lipoprotein levels in the blood[59,71,74]. International authorities recommend limiting dietary SFA due to the adverse effects of SFA intake on cholesterol metabolism and homeostasis[5,7,82]. In this context, the European Food Safety Authority (EFSA) recommends reducing SFA intake as low as possible in order to prevent the elevation of LDL-C[83], while the American Heart Association (AHA) recommends limiting SFA to 5–6 % of the daily energy intake for healthy adults[7]. The European Society of Cardiology, the 2015–2020 US Department of Agriculture Dietary Guidelines for Americans, and Turkey Dietary Guidelines[84] recommend that dietary SFA should be <10 % (as little as possible) of daily energy intake[1,84]. Therefore, since dietary SFA might influence CD36-induced cholesterol homeostasis, the importance of CD36 in human nutrition and diet therapy should be considered in the future.

MUFA and CD36-mediated cholesterol metabolism

Cholesterol absorption. Intestinal cholesterol absorption and chylomicron formation involve several cholesterol transporters including NPC1L1, ABCG5/8, SR-BI and CD36[85], enzymes and proteins such as apo-B48, MTTP and and ACAT2[86]. Since absorption of dietary cholesterol mainly occurs in the proximal side of the small intestine, NPC1L1, CD36 and ABCG5/G8 are highly expressed on the proximal side[87]. According to results of the studies, a high MUFA intake might decrease cholesterol absorption by suppressing the expression of these transporters[6,7,88,89] or might not affect the absorption (Table 2)[66,67,88]. It was also reported that CD36 expression in enterocytes increased after high olive oil intake in mice[87]. Although this suggests that a high MUFA intake might increase cholesterol absorption, the increase in cholesterol absorption might be due to high fat intake rather than high MUFA intake.

Cholesterol synthesis. As summarised in Table 2, the MUFA content of the diet might decrease endogenous cholesterol synthesis by reducing HMGCR and SREBP2 expression[67,90,91]. Although these effects are not clear, studies have shown that a high oleic acid intake reduces HMGCR activity[90] or does not have an impact on HMGCR enzyme level[91]. A high consumption of MUFA may induce LDLR expression by stimulating ACAT1 and by increasing intracellular cholesteryl ester content[92]. In addition, CD36 stimulates PPARγ expression in the liver, and therefore might suppress cholesterol synthesis. In rodent studies, it has been reported that a high consumption of MUFA elevates CD36 and PPARγ expression, and accordingly decreases plasma and liver total cholesterol levels[93,94]. These results of studies propose that a relatively higher dietary MUFA content might reduce cholesterol biosynthesis and the levels of plasma and liver total cholesterol to prevent dyslipidaemia or hyperlipidaemia.

Cholesterol transport. MUFA are generally thought to have positive effects on cholesterol homeostasis[95,96]. The results of studies reported that high dietary MUFA intake might reduce atherogenic lipoproteins/apolipoproteins[72,97,98], and might increase non-atherogenic lipoproteins/apolipoproteins[71,99], as shown in Table 2. In contrast, as high dietary MUFA intake might result in high dietary fat intake, the levels of total cholesterol, LDL-C and non-HDL-C might increase after high MUFA intake[73]. Moreover, high dietary MUFA might activate the synthesis of TAG-rich lipoproteins containing apo-E and apo-CIII and therefore might accelerate the catabolic pathways for these TAG-rich lipoproteins[98]. In macrophages, since CD36-mediated PPARγ and LXR activation may suppress ABCA1 and ABCG1 expression, decreasing ABCA1/G1 levels might cause impairment of reverse cholesterol transport[100]. In human studies, it has been found that the CD36 in monocytes is decreased[101] or is not affected[102] in the individuals consuming a high intake of olive oil. Studies on how MUFA influence the CD36-mediated circulating lipoproteins levels and reverse cholesterol metabolism are controversial depending on the fatty acid source of the food, other dietary components, research model and dietary manipulation.

Cholesterol excretion. Removal of excess cholesterol from the body in the form of bile acids in the liver is one of the important steps for maintaining cholesterol homeostasis[103]. It has been reported that a high MUFA intake might up-regulate the

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Table 2. Potential effects of MUFA on CD36-related cholesterol homeostasis

	Species	Cells/tissues	Fat component*		Main outcomes	References
			Total fat/MUFA (% energy)	MUFA (mM)		
Cholesterol absorption	F1B hamster	Intestine	26·7/20·7		NPC1L1 and ABCG5/G8 =	(67)
	Cell line	Caco-2 line		0·5 or 1	NPC1L1 and ACAT2 ↑	(66)
				0·5 or 1	NPC1L1 ↓ ABCG8 =	(88)
				0·5	NPC1L1 and ABCA1 ↓	(89)
Cholesterol synthesis	C57BL/6 mouse	Liver	49/34·4		CD36 ↑ PPARα =	(94)
			45/22·3		LXRα ↑	(73)
	KK-A^{y} mouse	Liver	15·6/10		PPARγ, CD36 and LPL ↑	(93)
	F1B hamster	Liver	26·7/20·7		HMGCR and SREBP2 ↓ PPARα ↑	(67)
	Cell line	C6 glioma		0·1	HMGCR ↓	(91)
Cholesterol transport	C57BL/6 mouse	Liver and plasma	45/22·3		Liver ABCA1, ABCG5 and SR-BI ↓ Plasma TC, non-HDL-C ↓ Plasma HDL-C =	(73)
		Liver and serum	31·3/23·2		Serum TC, LDL-C, HDL-C and LDL:HDL ↓ Liver TC ↓	(103)
		Macrophages	40·3/35·9		CD36 ↓	(79)
	Human	Plasma	35/15·3		TC and LDL-C ↓ HDL-C =	(75)
		Plasma and liver	37/24		Liver VLDL-C catabolism ↑ Synthesis and catabolism TRLs containing apo-E and apo-CIII ↑	(98)
		Serum	40/28		TC, LDL-C and LDL-C:HDL-C ↓	(71)
			45/26		apo-A1 production rate and pool size ↑ apo-A1 catabolism ↓	(99)
		Serum and monocytes	40/22		LRP1, LDLR and CD36 =	(102)
Cholesterol excretion	C57BL/6 mouse	Liver	31·3/23·2		Liver bile acid pool ↑ CYP7A1 ↑	(103)
			42/31·5		CYP7A1 ↑	(104)
		Faeces	45/22·3		Faeces cholesterol content ↑	(73)
	F1B hamster	Liver and intestine	26·7/20·7		Liver CYP7A1 = Intestine ABCG5/G8 =	(67)

↑, Increase; ↓, decrease; =, no change; ABC, ATP binding cassette transporter; ACAT, acetyl-CoA acetyltransferase; CD36, cluster of differentiation 36; CYP7A1, cholesterol 7α hydroxylase; HDL-C, HDL-cholesterol; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; LDL-C, LDL-cholesterol; LDLR, LDL receptor; LPL, lipoprotein lipase; LRP1, LDL receptor-related protein-1; LXR, liver X receptor; NPC1L1, Niemann–Pick C1-like 1; SR-BI, scavenger receptor class B type I; SREBP2, sterol regulatory element-binding protein 2; TC, total cholesterol; TRLs, TAG rich lipoproteins; VLDL-C, VLDL-cholesterol.
* The molarity or percentage of the energy for total fat/MUFA is recorded or calculated from the diets in the reference studies.

synthesis of bile acids in the liver[103,104], but might have no significant effect on the expression of transporters involving the reabsorption of bile acids (Table 2)[67,89]. The mechanisms of synthesis and release of bile acids in the liver and the reabsorption of bile acids in the intestine might be affected by the CD36 receptor in the liver and intestines[54,55]. Studies have reported that a diet high in MUFA up-regulates the expression of CD36 in the liver[94] and small intestine[39]. However, because the effects of dietary MUFA on cholesterol excretion are not yet clear, there is need for further randomised, controlled human studies related to the effect of high MUFA intake on CD36, and other related factors in bile metabolism.

Basically, it is accepted that sufficient dietary MUFA improves cholesterol homeostasis and prevents the impairment of cholesterol metabolism. Studies have shown that 15–25 % of total energy from MUFA decreases the endogenous synthesis of cholesterol[67,90] and levels of atherogenic lipoproteins/apoproteins, but increases non-atherogenic lipoproteins/apoproteins[73,99] and cholesterol excretion via increased synthesis of bile acids[103]. Therefore, the guidelines published in European countries recommend that daily MUFA intake to be 10–15 % of the total energy intake for healthy adults[105]. Also, the AHA[106] and Turkey Dietary Guidelines[84] recommend increasing dietary MUFA intake, while decreasing dietary SFA[84,106]. Nonetheless, there is need for more preclinical and clinical studies to combine the effects of dietary MUFA and CD36-mediated cholesterol homeostasis.

Trans-fatty acids and CD36-mediated cholesterol metabolism

Dietary TFA are generally assumed to have adverse effects on cholesterol metabolism[6,107]. TFA might be formed industrially in the production process of foods as well as naturally in animal-based foods[9,108]. Although the effects of TFA both obtained from animal-based foods[9] and processed foods[9,109] on CD36-mediated cholesterol metabolism have not been explained yet, the general belief is that they may disrupt cholesterol homeostasis.

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High dietary TFA intake impairs the blood lipoprotein profile by elevating the levels of blood total cholesterol[9,110], VLDL-C[111], LDL-C, apo-B[112] and Lp(a)[9] and by decreasing HDL-C and apo-A1 levels[72,111]. However, the consumed amount of TFA is important and ≤0·6 % of the daily energy requirement has no significant effect on cholesterol metabolism[113]. In parallel, a few epidemiological[107] and randomised controlled studies[114] have reported that TFA (2–4 % of daily energy) taken from animal-based foods had no significant effect on blood lipoprotein profile and would not pose a risk for CVD. On the other hand, a study concluded that replacement of 1 % of the daily energy intake of TFA with SFA, MUFA or PUFA decreased the ratios of total cholesterol:HDL-C and apo-B:apo-A1 and Lp(a) levels[96].

There are few studies in the literature on the effects of TFA on CD36-mediated cholesterol metabolism. In a study conducted on mice, it was reported that high dietary TFA intake resulted in an increased level of CD36 in hepatocytes and thus induced the synthesis and release of apo-B and VLDL-C[115]. On the contrary, it was been reported that a diet high in TFA did not alter CD36 expression in hepatocytes and cardiomyocytes in mice[116]. Nevertheless, it is not clear how TFA affect CD36-mediated cholesterol metabolism in the liver and other tissues involved in cholesterol homeostasis.

The literature has indicated that taking more than 0·6 % of total energy from TFA has a negative impact on cholesterol homeostasis[96,113], while the potential factors affecting these mechanisms such as CD36 need to be further explained. Due to the undesirable effects of TFA on cholesterol metabolism, EFSA recommends the reduction of TFA intake as much as possible[5]. The Turkey Dietary Guidelines and AHA reported that daily TFA intake should be less than 1 % of total energy[7,84]. In this context, more studies are needed to combine the effects of TFA on cholesterol homeostasis mediated by CD36 and other related factors.

PUFA and CD36-mediated cholesterol metabolism

Dietary *n*-3 PUFA and *n*-6 PUFA amounts and *n*-3:*n*-6 PUFA ratio are important for cholesterol homeostasis, since the amount and pattern of PUFA in the diet may distinctly affect cholesterol metabolism[6,7]. Thus, the dietary PUFA pattern might influence several mechanisms related to cholesterol homeostasis including the absorption, endogenous synthesis and transport of cholesterol, and bile acid metabolism[54]. Although PUFA generally have positive effects on the metabolism, the effects of excess intake of *n*-6 PUFA on cholesterol homeostasis are debatable. Hence, international guidelines for nutrition recommend paying attention to the consumed amounts of PUFA[5,7,117]. Therefore, for healthy adults, EFSA recommends taking 5–10 % of daily energy intake from PUFA and increasing the *n*-3 PUFA:*n*-6 PUFA ratio[5]; the Turkey Dietary Guidelines and AHA recommend that PUFA intake should be 7–10 % of daily total energy intake[7,84].

n-3 PUFA and CD36-mediated cholesterol metabolism

Cholesterol absorption. Dietary cholesterol is absorbed from micelles with fatty acids and phospholipids in the proximal parts of the small intestine, re-esterified into cholesteryl esters for the assembly into lipoproteins, and transported to the lymph and then to the circulation[66]. As shown in Table 3, studies have shown that *n*-3 PUFA inhibit cholesterol uptake and transport by down-regulating the expression levels of NPC1L1 and ABCA1/G5[66,89,118]. Moreover, caveolin 1, as a chaperone complex, regulates cholesterol influx or efflux via plasma membrane caveolae. A cell culture study reported that cholesterol absorption might be inhibited by down-regulating caveolin 1 expression in Caco-2 cells incubated with *n*-3 PUFA[66]. The combined effects of NPC1L1, ABC transporters, SR-BI and CD36 may play a critical role in modulating the amount of cholesterol that eventually reaches the lymph from the intestinal lumen[66,89].

Cholesterol synthesis. It was generally thought that consumption of fish oil (source of *n*-3 PUFA) might suppress cholesterol synthesis by inhibiting HMGCR, SREBP2, proprotein convertase subtilisin/kexin type 9 (PCSK9) and LXR expression and by up-regulating CD36 expression in the liver[66,67,78,118,119], as summarised in Table 3. As a result of decreasing cholesterol synthesis, it is supposed that liver cholesterol level, especially cholesteryl ester rather than free cholesterol, decreases[78,120]. In this context, it has been reported that ACAT1 expression is elevated in parallel with decreased CD36 expression in the aorta of apo-E knock-out mice fed with a diet high in EPA and DHA[121]. Evaluating the potential mechanisms related to the effects of *n*-3 PUFA on CD36-induced cholesterol absorption and biosynthesis, *n*-3 PUFA might suppress dietary cholesterol absorption and cholesterol synthesis- and metabolism-associated mechanisms.

Cholesterol transport. As shown in Table 3, high dietary *n*-3 PUFA intake might decrease atherogenic lipoproteins/apolipoproteins[72,122,123] and oxidised lipoproteins (i.e. oxLDL, oxHDL)[124,125], but might increase anti-atherogenic lipoproteins/apolipoproteins in the blood[72,123,126]. In reverse cholesterol transport, hepatic HDL-C uptake is one of the important steps involving enzymes and transporters such as ABCA1/G1, SR-BI and lecithin cholesterol acyltransferase (LCAT), and an increased amount of *n*-3 PUFA intake might accelerate HDL-C uptake by increasing the expression of these proteins[126,127]. Additionally, CD36 in macrophages might involve reverse cholesterol transport. In this context, it has been reported that *n*-3 PUFA intake up-regulates CD36 expression in addition to ABCA1/G1 in macrophages and hepatocytes and therefore accelerates reverse cholesterol transport[128,129]. On contrary, it has been shown that *n*-3 PUFA do not alter[30,130] or decrease[121] CD36 expression in macrophages[30,130]. Moreover, up-regulation of CD36 expression might cause the degradation of PCSK9[54], which has a role in the degradation of the LDLR, and therefore down-regulation of PCSK9 might result in a decrease in LDLR degradation and increase circulating LDL-C levels[131]. As pointed out in the indicated studies, roles of CD36 in oxidised lipid uptake as a scavenger receptor and in fatty acid uptake as a fatty acid transporter in reverse cholesterol transport have been intensively studied. However, the literature is still gathering on the effects of dietary *n*-3 PUFA and CD36-mediated cholesterol transport and lipoprotein homeostasis.

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Table 3. Potential effects of *n*-3 PUFA on CD36-related cholesterol homeostasis

	Species	Cells/tissues	Fat component*		Main outcomes	References
			Total fat/*n*-3 PUFA (% energy)	*n*-3 PUFA (mM)		
Cholesterol absorption	C57BL/6 mouse	Intestine	47/12		NPC1L1 ↓ ABCG5/G8 =	(132)
	Golden hamster	Intestine	12·2/1		ABCG8 ↓ ABCG5 =	(118)
	Cell line	Caco-2		0·5	NPC1L1 and ABCA1 ↓ SR-BI =	(89)
				0·5 or 1	NPC1L1, ABCA1 and caveolin 1 ↓ Cholesterol uptake ↓	(66)
Cholesterol synthesis	Golden hamster	Liver	12·2/1		HMGCR, SREBP2 and LXRα ↓	(118)
	F1B hamster		24·3/7·4		HMGCR and LDLR ↓	(119)
	Sprague–Dawley rat		45/4·5		TC level ↓ HMGCR and PCSK9 ↓ CD36 ↑	(54)
Cholesterol transport	Sprague–Dawley rat	Plasma and liver	45/4·5		Liver TC, plasma TC and LDL-C ↓ HDL-C = MTTP, apo-B and LDLR ↑	(54)
		Serum and liver	45/8·4		Serum TC and HDL-C = Serum apo-A1 ↑ Liver ABCA1 and apo-A1 ↑	(126)
	Golden hamster	Plasma and liver	12·2/1		Plasma TC, HDL-C and non-HDL-C ↓ Liver LDLR ↑	(118)
	F1B hamster		24·3/7·4		Plasma TC, non-HDL-C and HDL-C ↓ Liver apo-A1 ↓	(119)
	Human	Plasma	26·4/2·6		TC, LDL-C, HDL-C, total apo-B, apo-A1 ↓ apo-B in LDL-C ↓ Production rate of apo-B100 and apo-B48 in TRLs ↓	(122)
Cholesterol excretion	C57BL/6	Liver	47/12		ABCG5/G8 ↑ CYP7A1 =	(132)
	Sprague–Dawley rat	Liver	45/4·5		ABCG1/G5/G8 ↑ CYP7A1 and CYP27A1 ↑	(54)
	Golden hamster	Liver	12·2/1		CYP7A1 ↓	(118)
			45/10		ABCG5/G8 and CYP7A1 ↑	(127)
	Cell line	Caco-2 line		0·5 or 1	ABCG5/G8 ↑	(66)

↑, Increase; ↓, decrease; =, no change; ABC, ATP binding cassette transporter; CD36, cluster of differentiation 36; CYP7A1, cholesterol 7α hydroxylase; CYP27A1, sterol 27 hydroxylase; HDL-C, HDL-cholesterol; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; LDL-C, LDL-cholesterol; LDLR, LDL receptor; LXR, liver X receptor; MTTP, microsomal TAG transfer protein; NPC1L1, Niemann–Pick C1-like 1; PCSK9, proprotein convertase subtilisin/kexin type 9; SR-BI, scavenger receptor class B type I; SREBP2, sterol regulatory element-binding protein 2; TC, total cholesterol; TRLs, TAG-rich lipoproteins.
* The molarity or percentage of the energy for total fat/*n*-3 PUFA is recorded or calculated from the diets in the reference studies.

Cholesterol excretion. Cholesterol excretion via bile acids might be induced by high dietary *n*-3 PUFA by elevating the expression of CD36, CYP7A1 and CYP27A1 in the liver and ABCG1/G5/G8 transporters in the liver and intestine (Table 3)[54,66,120,127,132]. In contrast, a study has reported that the liver expression of CYP7A1 in hamsters fed with high DHA is reduced. The study suggested that it might depend on low liver total cholesterol levels due to low HMGCR expression[118]. Yet, there is limited knowledge about the dietary *n*-3 PUFA associated with CD36-induced bile acid metabolism.

Considering the proposed mechanisms in the literature, high dietary *n*-3 PUFA (in the form of fish oil, EPA or DHA) and/or *n*-3:*n*-6 PUFA ratio (1:3–1:10) might suppress cholesterol absorption and endogenous synthesis, and accelerate reverse cholesterol transport, secretion of bile acids and cholesterol excretion. With these potential mechanisms, CD36 is a substantial factor and more studies are needed to elucidate the mechanisms including *n*-3 PUFA and CD36-signalling pathways.

n-6 PUFA and CD36-mediated cholesterol metabolism

Cholesterol absorption. The effects of *n*-6 PUFA on dietary cholesterol homeostasis still need to be clarified because *n*-6 PUFA might improve or impair cholesterol homeostasis with different metabolic processes involved in absorption, synthesis, transport and excretion of cholesterol[133]. An *in vitro* study reported that Caco-2 cells incubated with linoleic acid and arachidonic acid did not affect the level of NPC1L1[66,89] and SR-BI[89], whereas arachidonic acid decreased ABCA1 expression (Table 4)[66,89]. Nevertheless, there is limited knowledge about the effects of dietary *n*-6 PUFA on cholesterol absorption in the intestine.

Cholesterol synthesis. CD36 might induce PPARγ and therefore inhibit cholesterol biosynthesis. A decrease in the *n*-3:*n*-6 PUFA ratio of the diet (1:10) may increase the expression of CD36, PPARγ, LXR and ACAT1 in macrophages[134]. In literature,

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Table 4. Potential effects of *n*-6 PUFA on CD36-related cholesterol homeostasis

	Species	Cells/tissues	Fat component*		Main outcomes	References
			Total fat/*n*-6 PUFA (% energy)	*n*-6 PUFA (mM)		
Cholesterol absorption	F1B hamster	Intestine	26·7/17·9		NPC1L1, ABCA1/G5/G8 =	(67)
	Cell line	Caco-2		1	NPC1L1 and ABCA1 ↓	(66)
				0·5	MTTP ↑ ABCA1 ↓ NPC1L1 and SR-BI =	(89)
Cholesterol synthesis	F1B hamster	Liver	26·7/17·9		HMGCR, ACAT2, LDLR, PPARα and SR-BI ↑	(67,119)
	Cell line	THP1 cells	*n*-3:*n*-6 PUFA: 1:10	–	CD36, ACAT2, PPARγ and LXRα ↑	(134)
Cholesterol transport	C57BL/6 mouse	Serum and liver	42/11·8		Serum TC and free TC ↑ Liver TC, plasma HDL, oxLDL and oxHDL =	(15)
	Sprague–Dawley rat	Serum	33·5/10·4		TC, LDL-C, non-HDL-C, HDL-C and oxLDL ↑	(125)
	Cell line	THP1	*n*-3:*n*-6 PUFA: 1:10	–	TC and cholesteryl ester ↑	(134)
Cholesterol excretion	C57BL/6 mouse	Liver	40/10		CD36, CYP7A1 and CYP27A1 ↑	(136)
		Liver and intestine	42/11·8		Liver ABCG5/G8 ↑ Intestine ABCG5/G8 =	(15)
	Golden hamster	Liver	26·7/17·9		CYP7A1 =	(67)

↑, Increase; ↓, decrease; =, no change; ABC, ATP binding cassette transporter; ACAT, acetyl-CoA acetyltransferase; CD36, cluster of differentiation 36; CYP7A1, cholesterol 7α hydroxylase; CYP27A1, sterol 27 hydroxylase; HDL-C, HDL-cholesterol; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; LDL-C, LDL-cholesterol; LDLR, LDL receptor; LXR, liver X receptor; MTTP, microsomal TAG transfer protein; NPC1L1, Niemann–Pick C1-like 1; oxHDL, oxidised HDL; oxLDL, oxidised LDL; SR-BI, scavenger receptor class B type I; TC, total cholesterol.

* The molarity or percentage of the energy for total fat/*n*-6 PUFA is recorded or calculated from the diets in the reference studies.

it was concluded that CD36 expression was up-regulated by dietary sunflower-seed oil in mice and suppressed the endogenous synthesis of cholesterol[69]. However, high dietary *n*-6 PUFA might decrease SREBP2 expression[66] and might not have a significant effect on HMGCR enzyme[119]. *n*-6 PUFA might also induce cholesterol accumulation in the liver by elevating the level of ACAT2 and esterification of cholesterol in the hepatocytes (Table 4)[119].

Cholesterol transport. As a result of studies investigating the effects of high dietary *n*-6 PUFA on the lipoprotein profile, *n*-6 PUFA might elevate blood LDL-C, VLDL-C[6,72,135], HDL-C and apo-A1 levels and might decrease apo-B by accelerating its catabolism[6,72]. An increase in *n*-6 PUFA in the diet may increase plasma oxLDL[125], but decrease the formation of oxLDL and oxHDL compared with a high SFA intake[15]. Furthermore, it has been reported that a dietary *n*-3:*n*-6 PUFA ratio of 1:20 increases the levels of reactive oxygen species and oxLDL in the blood[125], but that the *n*-3:*n*-6 ratio of higher than 1:5 decreases the total cholesterol content in macrophages in atherosclerosis (Table 4)[134].

Cholesterol excretion. In cholesterol excretion in the form of bile acids, it has been pointed out that consumption of high amounts of soyabean oil elevate the expression of CD36 and decrease the expression of bile acid synthesis-related enzymes such as CYP7A1 and CYP27A1 in mouse liver[136]. On the other hand, linoleic acid and arachidonic acid did not affect the expression of ABCG5 and ABCG8, transporters related to excretion and reabsorption of cholesterol in the form of bile acids, in the small intestine (Table 4)[66].

It was been suggested that both *n*-6 PUFA amount and the *n*-3:*n*-6 ratio of the diet affect CD36 and other endogenous factors related to cholesterol homeostasis. However, studies on how *n*-6 PUFA influence CD36-mediated cholesterol homeostasis are limited in the literature and, therefore, the influences of *n*-6 PUFA intake on cholesterol metabolism with underlying mechanisms should be clarified.

Conclusion

Hypercholesterolaemia and dyslipidaemia, which are CVD risk factors, are known to be influenced by dietary fat and the fatty acid pattern determined in the current literature. As part of a healthy diet, international nutrition committees recommend that 25–35 % of total energy intake should be from fats to prevent CVD and to regulate cholesterol homeostasis in the body. Furthermore, lowering the intakes of SFA (5–10 % of the total energy intake) and TFA (less than 1 % of the total energy intake), while replacing them with unsaturated fatty acids (MUFA and PUFA), and additionally reducing industrial *trans*-fats as much as possible are recommended. The literature includes mainly animal and cell culture studies, with a limited number of human studies. Extrapolation of the dose from the animals, relatively high doses, to humans needs consideration of body surface area and metabolic differences.

To combine the dietary recommendations and the novel nutrient-sensitive biomarkers related to CVD is a global focus. Thus, the current literature indicates that the type of dietary fatty acids might alter CD36 levels associated with cholesterol homeostasis. Additionally, CD36 is also a potential risk factor for hyperlipidaemia/dyslipidaemia in CD36 deficiency, relatively frequent in Asian and African populations. Nevertheless, further studies investigating cholesterol metabolism with the underlying mechanisms including CD36 and possible effects of dietary fatty acids are essential. Thus, since the CD36 receptor is suggested to

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be a novel nutrient-sensitive biomarker, the role of CD36 and dietary fatty acids on cholesterol metabolism might be considered in the future approving the importance in individualised medical nutrition therapy.

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