

Effects of obesity on cholesterol metabolism and its implications for healthy ageing

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Abstract

The last few decades have witnessed a global rise in the number of older individuals. Despite this demographic shift, morbidity within this population group is high. Many factors influence healthspan; however, an obesity pandemic is emerging as a significant determinant of older people's health. It is well established that obesity adversely affects several metabolic systems. However, due to its close association with overall cardiometabolic health, the impact that obesity has on cholesterol metabolism needs to be recognised. The aim of the present review is to critically discuss the effects that obesity has on cholesterol metabolism and to reveal its significance for healthy ageing.

Key words: Ageing: Older individuals: Cholesterol metabolism: Obesity: Oldest old

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Introduction

In 2030 older people (individuals aged ≥ 60 years) are projected to account for almost 20 % of the global population⁽¹⁾. Despite this demographic shift in favour of older individuals, morbidity among this group is high⁽²⁾. Many factors make an impact on older people's health; however, an obesity pandemic is emerging as a significant global health concern^(3–7). Microcosmically, the UK illustrates the extent of the global obesity problem. Among females aged 65–74 years in the UK 30 % have a BMI ≥ 30 kg/m², and are categorised as obese⁽⁸⁾. The problem is even more pronounced among their male counterparts, as 33 % of males are categorised as obese within this age group⁽⁸⁾. The problem extends to those aged ≥ 75 years, as 28 % of females are obese, while 23 % of males are obese in this age group. From a public health perspective these figures are alarming because obesity adversely affects several metabolic systems, and is synonymous with many conditions including cancer, type 2 diabetes mellitus (T2DM), hypertension and dyslipidaemia^(9–11). However, due to its close association with overall cardiometabolic health, the impact that obesity has on cholesterol metabolism needs to be recognised^(12,13). The aim of the present review is to critically discuss the effects that obesity has on cholesterol metabolism and to reveal its significance for healthy ageing.

An overview of cholesterol metabolism

Fig. 1 outlines that cholesterol balance is maintained by the body responding to changes in ingestion, absorption, synthesis and excretion⁽¹⁴⁾. Humans ingest a modest amount of dietary cholesterol (DC), which mixes with intestinal cholesterol⁽¹⁵⁾. Absorption is controlled by cholesteryl ester (CE) hydrolase which liberates CE, facilitating the inclusion of free cholesterol (FC) into bile acid micelles⁽¹⁶⁾. The intestinal protein Niemann–Pick C1-like 1 (NPC1L1) mediates cholesterol absorption into the enterocyte by clathrin-mediated endocytosis⁽¹⁷⁾. ATP-binding cassette (ABC) transporters G5 and G8 (ABCG5/G8) control the efflux of cholesterol from the enterocytes to the lumen⁽¹⁸⁾. Within the enterocyte, acetyl CoA acetyltransferase 2 (ACAT2) re-esterifies cholesterol⁽¹⁹⁾, which is combined with apoB-48, TAG and phospholipids, to generate a chylomicron⁽²⁰⁾. Upon entering the bloodstream, chylomicrons are acted on by lipoprotein lipase (LPL), which catalyses their TAG, liberating NEFA⁽²¹⁾. Chylomicron remnants are removed from the circulation by hepatic remnant receptors⁽²²⁾.

The liver is the main site of cholesterol synthesis⁽²³⁾, providing cholesterol and TAG for the assembly of VLDL⁽²⁴⁾. In the plasma, LPL hydrolyses VLDL to LDL, via intermediate-density lipoproteins⁽²⁵⁾. LDL-cholesterol (LDL-C) is removed by the

Abbreviations: ABC, ATP-binding cassette; ACAT2, acetyl CoA acetyltransferase 2; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; DC, dietary cholesterol; FC, free cholesterol; FXR, farnesoid X receptor; HDL-C, HDL-cholesterol; HMGCR, HMG-CoA reductase; IR, insulin resistance; LCAT, lecithin-cholesterol acyltransferase; LDL-C, LDL-cholesterol; LDLr, LDL receptor; LPL, lipoprotein lipase; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NPC1L1, Niemann–Pick C1-like 1; PCSK9, proprotein convertase subtilisin/kexin type 9; RCT, reverse cholesterol transport; ROS, reactive oxygen species; SREBP, sterol regulatory element-binding protein; T2DM, type 2 diabetes mellitus.

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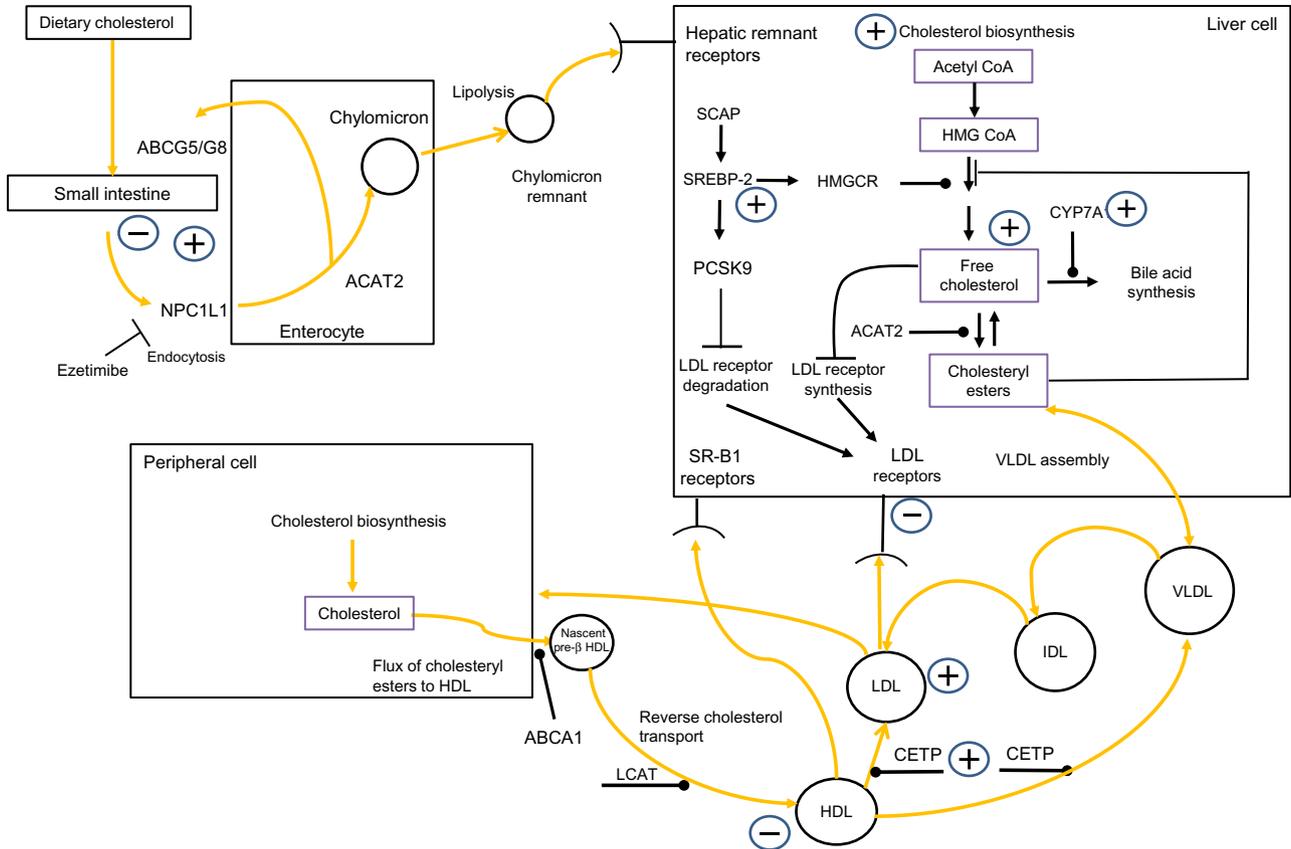


Fig. 1. Overview of whole-body cholesterol metabolism. Cholesterol metabolism is maintained by an array of regulatory processes which control absorption, synthesis, hepatic lipoprotein production, lipoprotein uptake and reverse cholesterol transport. The signs indicate where obesity has been shown to have an impact on cholesterol metabolism. Note: cholesterol absorption has both positive and negative signs associated with it, to indicate that certain studies have found that obesity decreases cholesterol absorption while other have found the opposite effect. ABCA1, ATP-binding cassette transporter; acetyl-CoA, acetyl coenzyme A; ABCG5/G8, ATP-binding cassette (ABC) transporters G5 and G8; ACAT2, acetyl CoA acetyltransferase 2; CETP, cholesteryl ester transfer protein; CYP7A1, cholesterol 7 α -hydroxylase; IDL, intermediate-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; HMGCR, HMG-CoA reductase; LCAT, lecithin-cholesterol acyltransferase; NPC1L1, Niemann-Pick C1-like 1; PCSK9, proprotein convertase subtilisin/kexin type 9; SCAP, sterol regulatory element-binding protein cleavage-activating protein; SREBP-2, sterol regulatory element-binding protein 2; SR-B1, scavenger receptor, class B type 1. For a colour figure, see the online version of the paper.

LDL receptor (LDLr)⁽²⁶⁾ and LDLr-related protein 1⁽²⁷⁾. This process is governed by intracellular sterol levels⁽²⁸⁾. Increasing intracellular cholesterol activates insulin-induced genes (Insigs) proteins. Insig-1 and Insig-2 bind to sterol regulatory element-binding protein (SREBP) cleavage-activating protein (SCAP) in the endoplasmic reticulum, restricting the migration of the SCAP/SREBP complex to the Golgi^(29,30). When sterol levels drop, SREBP-2 migrates to the Golgi where it is cleaved by subtilisin kexin isozyme/site-1 protease (SKI-1/S1P), and the intramembranous metalloprotease site-2 protease (S2P)⁽³¹⁾. This releases the NH-terminal domain of SREBP-2 from the membrane. Two N-terminal fragments dimerise, then interact with importin- β , before entering the nucleus, to activate SREBP-2-regulated gene promoters⁽³²⁾. A further regulatory point involves LDLr synthesis. Nuclear SREBP-2 increases the transcription of proprotein convertase subtilisin/kexin type 9 (PCSK9)⁽³³⁾. PCSK9 reduces the number of LDLr by increasing their metabolism, and subsequent degradation, restricting LDL uptake⁽³³⁾. High cellular cholesterol levels suppress SREBP-2 release from the endoplasmic reticulum, thus PCSK9 transcription is reduced, which subsequently increases LDLr levels⁽³⁴⁾. The synchronised interplay of SREBP-2-induced transcription

of both LDLr and PCSK9 regulates circulating LDL-C levels. Additionally, cholesterol entering a hepatic cell as part of LDL triggers ACAT2⁽²⁶⁾, which catalyses FC to CE⁽¹⁹⁾, and this cholesterol also activates cholesterol 7 α -hydroxylase (CYP7A1), the rate-limiting enzyme of bile acid synthesis⁽³⁵⁾.

By disrupting any of the mechanisms discussed above, obesity has the potential to provoke a rise in plasma LDL-C. Elevated LDL-C levels are inexorably linked to an increased risk of atherosclerotic CVD⁽³⁶⁻³⁸⁾. Moreover, emerging evidence suggests that suboptimal LDL-C levels, in tandem with elevated serum uric acid, could present an increased risk of developing hypertension or the metabolic syndrome^(39,40).

A further important aspect of cholesterol metabolism is reverse cholesterol transport (RCT). RCT removes excess cholesterol from peripheral tissue⁽⁴¹⁾. HDL are central to this. HDL 'mop up' excess cholesterol, generating HDL-cholesterol (HDL-C)⁽⁴²⁾. Central to RCT is the ferrying of FC and phospholipids to lipid-free apoA-I to form nascent pre- β HDL particles, in a process primarily regulated by ABCA1^(43,44). Nascent HDL progress to mature HDL due to the esterification of cholesterol by lecithin-cholesterol acyltransferase (LCAT)⁽⁴⁵⁾. Cholesterol within HDL can follow one of two routes to the liver. HDL can go directly

to the liver and deposit their cholesterol by interacting with scavenger receptor class B, type 1 receptors⁽⁴⁶⁾. Second, cholesterol can be transferred to the liver via the action of CE transfer protein (CETP), which redistributes cholesterol to LDL and VLDL⁽⁴⁷⁾. Regardless of the route, HDL transfer cholesterol to the liver, where it can be effluxed directly as cholesterol or converted to bile salts⁽⁴⁸⁾. It can then be excreted during enterohepatic circulation. Consequently, RCT is regarded as antiatherogenic⁽⁴⁹⁾; this is underscored by studies which have revealed an inverse relationship between HDL-C levels and the onset of premature CVD^(50,51). Intriguingly, HDL's antiatherogenic role is thought to be enhanced further by possessing antioxidant properties⁽⁵²⁾. As with the mechanisms which regulate LDL-C levels, if obesity interferes with the processes underpinning RCT, this has the potential to modulate an individual's risk of CVD.

Obesity and cholesterol metabolism

Cholesterol absorption

In pioneering work, Miettinen & Kesäniemi⁽⁵³⁾ identified a negative correlation between the fractional absorption of DC and obesity in middle-aged men; however, a mechanistic explanation for this result was not immediately apparent. In a follow-up investigation cholesterol absorption was also found to be inhibited in obese middle-aged males (BMI >31 kg/m²)⁽⁵⁴⁾. On this occasion two explanations were proposed for this finding. It was posited that labelled DC could have contributed to sub-normal cholesterol absorption. Second, it was suggested that cholesterol absorption was inhibited by expanded biliary secretion. However, the precise reason why obesity inhibited cholesterol absorption remained unclear. More recent studies have added further intrigue to this puzzle. It has been found that treatment of obese hypercholesterolaemic subjects with the NPC1L1 inhibitor, ezetimibe, improved the lipid profile and insulin resistance (IR) in these subjects^(55,56). This suggests that obesity could in fact increase cholesterol absorption in obese subjects rather than inhibiting it, and an arbiter of this change could be NPC1L1. If obesity does increase cholesterol absorption, this effect could also be induced by provoking a rise in circulating bile acids. For example, Vincent *et al.*⁽⁵⁷⁾ found that the postprandial bile acid response is increased in obese male and female patients with T2DM compared with age-matched normoglycaemic individuals. Further evidence that obesity influences bile acid metabolism comes from studies of the gut microbiome⁽⁵⁸⁾. For instance, in one study it was found that bile salt hydrolase is the arbiter of host-microbiome interactions which modulated weight gain, and lipid metabolism in a murine model⁽⁵⁹⁾. Specifically, the expression of cloned bile salt hydrolase enzymes in the gastrointestinal tract of gnotobiotic or conventionally raised mice significantly modified plasma bile acid signatures and regulated the transcription of important genes involved in cholesterol metabolism (*Abcg5/8*) both hepatically and intestinally. Moreover, high-level expression of bile salt hydrolase in conventionally raised mice resulted in a significant drop in host weight gain, plasma cholesterol levels, and hepatic TAG. As an adjunct to this finding it has been shown that the

farnesoid X receptor (FXR) has a central role to play in modulating host-microbiome dialogue. For instance, mouse models of diet-induced obesity have shown that both the microbiome and FXR signalling are required for weight gain^(60,61).

Cholesterol synthesis

Cholesterol synthesis is also affected by obesity; sterol-balance studies have shown that increased weight gain results in a higher rate of cholesterol synthesis^(62,63). It is uncertain how weight gain induces a higher rate of cholesterol synthesis. However, it is important to acknowledge that hepatic HMGCR increases in obese subjects⁽⁶⁴⁾. This would naturally result in an increase in hepatic cholesterol production, something which has been observed in obese subjects⁽⁶⁵⁾. For example, in a study involving seventeen morbidly obese middle-aged males, it was found that the activity, and mRNA levels of HMGCR, was higher in the obese subjects, when compared with a lean control group⁽⁶⁶⁾. Moreover, the activity and mRNA level of cholesterol 7 α -hydroxylase (CYP7A1) also increased compared with controls. The activity of ACAT2, and LDLr mRNA levels were elevated in these subjects. Such alterations have the potential to make an impact on the normal functioning of hepatic LDLr. For example, it was also found in this study that the binding of LDL to the LDLr was reduced by 50 % when compared with controls⁽⁶⁶⁾.

Hepatic free cholesterol/bile acid accumulation and non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) encompasses a number of hepatic pathologies, from fatty liver disease to non-alcoholic steatohepatitis (NASH), a condition which can progress to cirrhosis⁽⁶⁷⁻⁷¹⁾. NAFLD has a higher occurrence in males than females, and its prevalence increases with age^(72,73). NAFLD is closely associated with IR and hyperinsulinaemia and is prevalent in 70-80 % of obese individuals⁽⁷⁴⁾. Moreover, it has recently been associated with key parameters of cardiovascular health, including arterial stiffness⁽⁷⁵⁾. Traditionally, NAFLD has been associated with increased hepatic TAG; however, in recent years there has been growing evidence linking altered cholesterol metabolism with the aetiology of NAFLD⁽⁷⁶⁻⁷⁸⁾. For instance, hepatic FC accumulates in obese diabetic mice and results in steatohepatitis⁽⁷⁹⁾. Most recently in mice it has been found that hepatic cholesterol, but not hepatic TAG, increased with age⁽⁸⁰⁾. Focusing on human subjects, the intake of high levels of DC has been associated with NASH^(81,82). Mechanistically, it would appear that cholesterol synthesis is up-regulated in NAFLD. This was demonstrated by a study which examined the expression of an array of genes associated with cholesterol metabolism⁽⁸³⁾. In the investigation, twenty middle-aged subjects with NAFLD (mean BMI 34.1 kg/m²) and NASH (mean BMI 34.2 kg/m²) were compared with twenty obese controls (33.2 kg/m²) and six lean normal controls (mean BMI 21.4 kg/m²). It was found that NAFLD was associated with increased SREBP-2 maturation, HMGCR expression and decreased phosphorylation of HMGCR. Additionally, CE hydrolase was increased, while ACAT2 remained unchanged. Moreover, LDLr expression decreased significantly. Also, HMGCR expression was correlated with FC, histologic severity of NAFLD

and LDL-C levels. Bile acid homeostasis is also affected as a result of NAFLD⁽⁸⁴⁾. Individuals with NASH have elevated levels of bile acids which can accumulate hepatically⁽⁸⁵⁾. Bile acid signalling is regulated by the FXR, which contributes to overall cholesterol metabolism⁽⁸⁴⁾. Interestingly, it has been shown in mice that the gut microbiota can modulate obesity via this receptor. The gut microbiota promoted weight gain and hepatic steatosis in an FXR-dependent manner between *Fxr*^{-/-} and wild-type mice⁽⁶⁰⁾. Moreover, bile acid profiles and the composition of faecal microbiota differed between *Fxr*^{-/-} and wild-type mice. The finding that the gut microbiota induced liver steatosis in an FXR-dependent manner was suggested to be due to increased expression of CD36, apoC2 and VLDL receptor, all of which are involved in lipoprotein uptake. Thus, increased steatosis was thought to be attributed to the augmented expression of lipogenic genes or diminished expression of genes associated with fatty acid oxidation. In terms of promoting obesity mechanistically the authors showed that the gut microbiota of *Fxr*-deficient mice was defined by a phylum-wide rise in Bacteroidetes and phylum-wide reduction of Firmicutes. Thus, the gut microbiota changes in response to diet and is associated with an obesity phenotype, which is mediated by FXR signalling.

Lipoprotein dynamics and reverse cholesterol transport

Lipoprotein processing is significantly impaired due to obesity. Morbidly obese middle-aged patients have been found to have lower expression of LPL and LDLr-related protein 1 in their visceral tissue⁽⁸⁶⁾. LPL expression was also lower in the subcutaneous adipose tissue of these subjects. The decrease in the expression of LDLr-related protein 1 is probably a contributing factor to the increase in plasma LDL-C, which often, but not always, accompanies obesity⁽⁸⁷⁾. More strikingly, obesity has regularly been associated with an increase in atherogenic small dense LDL^(88–90). Obesity also lowers HDL-C regardless of age, sex or ethnic background, while an inverse association between HDL-C levels and BMI has also been observed^(91–93). Intriguingly, in the Framingham Offspring Study, the effect of increased BMI on total cholesterol and LDL-C was not as strong as it was for HDL-C⁽⁹⁴⁾. More recently, an inverse association has been found between LDL-C and BMI in morbidly obese subjects⁽⁹⁵⁾. Low levels of the major apolipoprotein component of HDL (apoA-I) have also been found to be associated with obesity in the Framingham Offspring Study in men and women⁽⁹⁶⁾. Moreover, it has been revealed in a mouse model that increased apoA-I could have an anti-obesity effect. Increased energy expenditure and up-regulation of uncoupling protein 1 in brown fat were associated with high levels of apoA-I⁽⁹⁷⁾. In addition, other apolipoproteins have been shown to be influenced by obesity. Elevated levels of fasting and postprandial apoB-48 have been measured in obese human subjects⁽⁶⁶⁾. Obesity could also have an impact on the functional capacity of HDL-C. For example, the antioxidant capacity of HDL appears to be compromised in obese subjects⁽⁹⁸⁾. Obesity interferes with other components of RCT, for example, obesity causes impairment in RCT due to reduced plasma cholesterol uptake and efflux by hepatocytes and adipocytes in *ob/ob* mice⁽⁹⁹⁾. Plasma CETP levels have also been positively correlated with obesity⁽¹⁰⁰⁾. The likely reason for this finding is that adipose tissue is a significant source of

CETP⁽¹⁰¹⁾. Intriguingly, LCAT deficiency has been suggested to confer a degree of protection from the development of obesity. Tentative evidence for this finding comes from a study of LCAT-null mice which appeared to be protected from diet-induced obesity⁽¹⁰²⁾.

Commonality between obesity and ageing

It is possible that obesity superimposed on ageing could expedite the age-associated dysregulation of cholesterol metabolism^(103–105). Taking LDL-C as an example, increasing age is associated with a rise in LDL-C in males and females, in both cross-sectional^(106,107) and prospective studies^(108,109). It is not known how ageing contributes to a rise in LDL-C; however, there are solid reasons to believe that a decline in the hepatic clearance rate of LDL-C is a factor^(110,111). For example, human ageing is associated with a drop in the number of hepatic LDLr⁽¹¹²⁾. Obesity can also result in a rise in LDL-C^(87,94), although in some observational studies it is only weakly associated^(113,114), or not associated at all⁽¹¹⁵⁾. An obesity-induced rise in LDL-C could have the same mechanistic underpinning as ageing, because it is also associated with a decline in hepatic LDLr numbers. Also similar to obesity, HDL-C levels decrease with age in human subjects in certain studies⁽¹¹⁶⁾. For instance, HDL-C levels have been observed to decrease with age in both men and women in prospective studies^(109,117). Although HDL-C levels do not change with age in most cross-sectional studies^(118,119), they have been shown to decrease in others⁽¹²⁰⁾. A decline in HDL-C with age could be due to disrupted CETP activity. If this is the case it would be mechanistically similar to the putative effect that obesity has on RCT⁽¹⁰⁰⁾. Ageing also makes an impact on lipoprotein processing by reducing the activity of plasma LPL by as much as 55–60%^(121,122). This is similar to the metabolic affect that obesity has on LPL⁽¹²³⁾. In rodents it has been found that bile acid synthesis diminishes with age⁽¹²⁴⁾. This is also similar to obesity because in men and women a decrease in the conversion of cholesterol to bile acids has been identified in certain studies^(125,126). However, other studies conflict with this and suggest that obesity results in an increase in bile acid synthesis⁽¹²⁷⁾.

The landscape of an obese state also resonates with the free radical theory of ageing⁽¹²⁸⁾. For example, obesity is associated with oxidative stress via increased generation of reactive oxygen species (ROS)⁽¹²⁹⁾. As visceral fat stores increase, adipocytes generate increasing levels of ROS⁽¹³⁰⁾. Consequently, oxidative stress results in IR within adipose and peripheral tissue⁽¹³¹⁾. It has been suggested that high levels of ROS impinge on intracellular cholesterol homeostasis⁽¹³²⁾. ROS have been found to up-regulate the activity of hepatic HMGCR in rodent hepatic tissue, leading to an increase in cholesterol synthesis^(80,133–135). ROS are also implicated in the pathogenesis of atherosclerosis, where oxidation of LDL is regarded as a key event in the initial stages of atherosclerosis formation⁽¹³⁶⁾. Despite the many parallels between obesity and ageing, a number of differences do exist. In contrast to obesity it has been revealed that cholesterol absorption efficiently increases with age; however, there is a paucity of evidence for this in human subjects and findings are confined to rodent studies⁽¹³⁷⁾. Mechanistically it appears that ageing

suppresses the expression of *Abcg5* and *Abcg8*, and up-regulates the expression of *Npc1l1* in murine models⁽¹³⁸⁾. In rodents it has been found that bile acid synthesis declines with age⁽¹²⁴⁾. This contrasts with obesity. Also, unlike obesity, it has been found that hepatic ACAT2 activity decreases with age in Watanabe heritable hyperlipidaemic rabbits⁽¹³⁹⁾.

Diet: a key modulator of obesity and cholesterol metabolism

An obese state is the result of an imbalance between the amount of energy consumed by an individual and the amount of energy they expend⁽¹⁴⁰⁾. Moreover, it is generally regarded that excess consumption of dietary fat plays a role in the development of obesity⁽¹⁴¹⁾. Taking this a step further, a clear link between diet, cholesterol metabolism and obesity centres on the excessive intake of DC. For instance, DC has been shown to exacerbate hepatic steatosis and inflammation in obese LDLr-deficient mice⁽¹⁴²⁾. Moreover, in this study, the consumption of DC exacerbated hepatic macrophage infiltration, apoptosis and oxidative stress. Excessive intake of DC has also been shown to result in the accumulation of hepatic cholesterol in obese diabetic mice⁽⁷⁹⁾. The accumulation of cholesterol was attributed to changes in some of the regulator mechanisms discussed previously, including the up-regulation of LDLr, via activation of SREBP-2, a drop in the conversion of cholesterol to bile acids, and suppression of bile acid excretion in bile.

In addition to the intake of fat/DC, high intakes of dietary sugars have been associated with obesity and unfavourable lipid levels in both men and women^(125,126). In particular, dietary fructose has emerged as an important dietary factor which contributes to the hepatic dysregulation of cholesterol metabolism^(69,143). For instance, high fructose consumption increases serum PCSK9 concentrations and reduces liver LDLr protein levels in hyperlipidaemic hamsters⁽¹⁴⁴⁾. In human subjects, it has been found that the consumption of fructose and high-fructose maize syrup increases LDL-C, and apo-B in both men and women⁽¹⁴⁵⁾. Moreover, NASH is associated with animal models fed a high-fat, high-fructose diet^(146,147). Consumption of excessive dietary fructose has also been associated with cognitive decline in older adults⁽¹⁴⁸⁾. This is intriguing because obesity can be correlated with poor cognitive performance in older adults⁽¹⁴⁹⁾. Taking this a step further, it is possible that fructose makes a mechanistic contribution to the pathogenesis of Alzheimer's disease by interfering with lipid metabolism. For example, animal models of dementia suggest that excessive consumption of fructose induces IR and promotes dementia pathogenesis^(150–152). This is thought to occur as follows: IR is associated with elevated plasma ceramides which interfere with lipoprotein metabolism and amyloidogenic processing, resulting in the deposition of β -amyloid peptides, which is a hallmark of Alzheimer's disease⁽¹⁵³⁾.

In certain circumstances age could potentially offer a degree of protection against diet-induced obesity. In a recent study which compared the response of young and old mice to a Western diet, it was found that old mice did not show a higher body weight or adipose tissue mass, when compared with their young counterparts⁽¹⁵⁴⁾. Significantly, and of direct relevance to the underlying hepatic health of older individuals, it was found

that the aged mice did have a build up of hepatic lipid on the Western diet. As well as the type and amounts of nutrients consumed, it has been found that meal frequency, timing and regularity are also associated with obesity⁽¹⁵⁵⁾. Recently this has been shown to have important implications for cholesterol metabolism. In a cross-sectional study of non-institutionalised and non-pregnant healthy Taiwanese adults (aged ≥ 19 years old), it was found that higher energy intake at night time is associated with elevated total cholesterol and LDL-C levels⁽¹⁵⁶⁾. This was an interesting finding, although a mechanistic explanation for this discovery was not posited. Regardless, the study presents the possibility that meal timing and frequency could make an impact on both obesity and cholesterol metabolism, which is an intriguing prospect.

Alcohol consumption also affects cholesterol metabolism. Evidence suggests that moderate to low alcohol consumption increases levels of HDL-C and decreases levels of LDL-C⁽¹⁵⁷⁾. However, it is important to be cautious as alcohol has a limited therapeutic range and only modest drinking appears to be beneficial. This is partly due to the energy richness of alcohol, as its excessive consumption can result in increased weight gain in certain individuals⁽¹⁵⁸⁾. Moreover, chronic alcohol intake affects lipid metabolism broadly by provoking the increased synthesis of TAG and subsequent hypertriglycerolaemia⁽¹⁵⁹⁾. In addition, it has been observed that alcohol consumption decreases the activity of LPL, which is also associated with hypertriglycerolaemia⁽¹⁶⁰⁾. From the perspective of HDL metabolism, in individuals with alcohol dependence syndrome no association between plasma HDL-C and the number of drinks consumed per d has been observed in these individuals, indicating that only low-level consumption of alcohol is beneficial⁽¹⁶¹⁾. Furthermore, in a longitudinal study of alcohol consumption, the long-term effect of total alcohol consumption on the change in HDL-C was observed to be a non-linear relationship⁽¹⁶²⁾. The mechanistic explanation for this is thought to centre on the pathophysiological effect of alcohol on the liver which results in a decrease in the hepatic production of HDL in these subjects⁽¹⁶³⁾.

Alarmingly, the excessive intake of alcohol has been increasing among older individuals in certain populations⁽¹⁶⁴⁾. In a recent study involving a cohort of Australian males (aged ≥ 65 years), which explored the association between alcohol intake and body composition, it was found that participants who consumed ≥ 5 alcoholic drinks/d had a greater BMI, fat mass index, waist circumference, percentage body fat and lower lean mass than non-drinkers⁽¹⁶⁵⁾. This has metabolic consequences for older individuals because alcohol consumption augments lipid synthesis via sterol SREBP-1⁽¹⁶⁶⁾. This is possibly mediated by acetaldehyde, which contributes to an increase in the synthesis of SREBP-1, which in turn augments cholesterol and fat synthesis⁽¹⁶⁶⁾. Alcohol consumption has also been shown to dysregulate hepatic fatty acid oxidation⁽¹⁶⁷⁾ and decrease the secretion of VLDL⁽¹⁶⁸⁾. A drop in VLDL secretion could result in a decrease in the conversion of VLDL-C to LDL-C, and be responsible for the decrease in LDL-C associated with low to moderate alcohol intake⁽¹⁶⁹⁾. Furthermore, this mechanism could explain the decreased risk of alcohol dependence with increased LDL-C levels identified among some of the participants of a recent case-control study investigating alcohol consumption and obesity⁽¹⁷⁰⁾.

On the flip side of the coin, emerging research has revealed that certain novel dietary components improve both cholesterol metabolism and have anti-obesity effects. For example, a diet high in fruit and vegetables is associated with a lower risk of obesity/body adiposity^(171–173). Moreover, certain components of fruits and vegetables have a favourable effect on cholesterol metabolism. For instance, soluble fibre exerts a favourable effect by decreasing LDL-C levels⁽¹⁷⁴⁾. It has been found that 3 g/d of soluble fibre can lower total cholesterol and LDL-C by about 0.13 mmol/l⁽¹⁷⁵⁾. Several mechanisms have been suggested to account for this effect, including the inhibition of bile salt intestinal re-absorption, and a diminished glycaemic response, which results in a drop in insulin-stimulated hepatic cholesterol synthesis⁽¹⁷⁶⁾. The gut is also thought to be the site of action of plant sterols. Plant sterols are naturally occurring compounds found in fruit and vegetables which are structurally related to cholesterol, differing only in the structure of their side chains⁽¹⁷⁷⁾. Consumption of 1.8–2.0 g/d of plant sterols has been shown to lower both total cholesterol and LDL-C concentrations by 10–15 % in different population groups^(178,179). Although the precise mechanism by which LDL-C is lowered is uncertain, it is generally regarded that plant sterols inhibit intestinal cholesterol absorption⁽¹⁸⁰⁾. Not only have plant sterols been associated with decreased LDL-C. More recently, the consumption of high levels of phytosterols, which includes plants sterols, have been associated with decreased rates of obesity. For example, a recent cross-sectional study of Chinese adults (aged 18–60 years) revealed that higher consumption of phytosterols was associated with lower BMI, waist circumference, and a lower prevalence of overweight/obesity/abdominal obesity in this population group⁽¹⁸¹⁾. Intriguingly the administration of both phytosterols and red rice was recently studied in mildly hypercholesterolaemic subjects⁽¹⁸²⁾. In tandem these two nutraceuticals had a more significant impact on LDL-C levels, when compared with either phytosterols or red rice on their own. Diet also has an important role to play in terms of alleviating the metabolic consequence of obesity. Most recently, it has been shown that medium-chain SFA could illicit a degree of protection against obesity-induced co-morbidities such as diabetes in obesogenic mice⁽¹⁸³⁾. Moreover, in a rat model it has been found that medium-chain SFA could help prevent NAFLD⁽¹⁸⁴⁾. Mechanistically, it is thought the beneficial effects of medium-chain SFA consumption could be induced via their preferential β -oxidation over long-chain SFA⁽¹⁸⁵⁾. A further way that diet has been suggested to provide a means of treating obesity is by modulating the gut microbiome. For instance, in an obese population which adhered to a Mediterranean diet for 1 year, it was found that the Mediterranean diet exerted a protective effect against T2DM development by modulating specific changes in the gut microbiota. Specifically, this involved increasing the abundance of *Faecalibacterium prausnitzii* and *Roseburia* species.

Cholesterol metabolism and obesity in older individuals

Certain individuals have a metabolic profile which does not appear to be overtly affected by obesity. Such individuals are known as 'metabolically healthy obese'⁽¹⁸⁶⁾. In a study which investigated obesity in the US population, it was found that

31.7 % of obese adults (about 19.5 million) were metabolically healthy obese⁽¹⁸⁷⁾. The prevalence of metabolically healthy older individuals was 14.3 % among those aged 65–79 years, and 22.1 % among those aged ≥ 80 years. Healthy participants were defined by having 0 or 1 cardiometabolic abnormality. Unhealthy individuals were defined as having ≥ 2 cardiometabolic abnormalities. Among individuals with ≥ 2 metabolic abnormalities, the two most common cardiometabolic risk factor combinations were high TAG level/low HDL-C level and high blood pressure/high glucose level. In a similar investigation it was found that among participants with ≤ 1 metabolic abnormality, obesity was associated with a greater risk of developing multiple metabolic abnormalities⁽¹⁸⁸⁾. Significantly, lipid metabolism was also key, as TAG and HDL-C levels predicted an individual's progression to a metabolically unhealthy obese state. Within obesity research, a further puzzle exists; there are situations where being overweight/mildly obese appears to be beneficial. This is known as the 'obesity paradox'⁽¹⁸⁹⁾. In an ageing context, the obesity paradox appears to confer a survival advantage in older patients (generally those aged > 50 years) who have conditions such as CVD, arthritis and kidney disease⁽¹⁹⁰⁾. Focusing specifically on cholesterol metabolism, and its intersection with the obesity paradox, normal total serum cholesterol levels have been reported in morbidly obese individuals. In a study of 3312 women (aged ≥ 18 years) it was found that the percentage of individuals with normal total serum cholesterol levels (< 200 mg/dl; < 5.18 mmol/l) decreased with increasing BMI, from 55 % in those with a BMI < 20 kg/m² to 28 % in women with a BMI of 30–35 kg/m²⁽¹⁹¹⁾. Total serum cholesterol > 7.75 mmol/l was found in 2 % of individuals with a BMI < 20 kg/m², but in 6 % of the group with a BMI between 30 and 35 kg/m². Among morbidly obese women (BMI > 40 kg/m²), 39 % had total serum cholesterol levels < 5 mmol/l. Thus, it would appear in morbidly obese women that there is a significant number of individuals with normal total serum cholesterol levels. Such findings were also identified in a study which examined individuals (aged 20–64 years) with a BMI in the range 34–77 kg/m²⁽¹⁹²⁾. It was found that mean total cholesterol levels in the obese group fell with increasing BMI. Moreover, LDL-C levels were lower in obese men (3.65 mmol/l *v.* the control group, 4.17 mmol/l).

The association between obesity and cholesterol metabolism has been studied to a limited extent in the oldest old (individuals aged ≥ 80 years). Despite this, the oldest old who are obese have a higher prevalence of morbidity⁽¹⁹³⁾. In a study which examined the oldest old among a group aged 60–85 years, it was reported that obesity was associated with shorter survival plus a higher incidence of CHD and T2DM⁽¹⁹⁴⁾. When cholesterol metabolism has been examined in the oldest old some intriguing findings have been revealed. In the Leiden 85-Plus Study it was observed that both high and low levels of LDL-C had a similar impact on mortality risk⁽¹⁹⁵⁾. Interestingly, this finding occurred despite CVD being the main cause of mortality in these subjects. Similar observations have been identified in several other studies which have examined the lipoprotein profile of the oldest old^(196,197). Interestingly, during a 3-year follow-up study involving the Chinese oldest old it was found that for each 1 mmol/l increase of LDL-C concentration there was a corresponding 19 % decrease in 3-year all-cause mortality⁽¹⁹⁸⁾. These findings

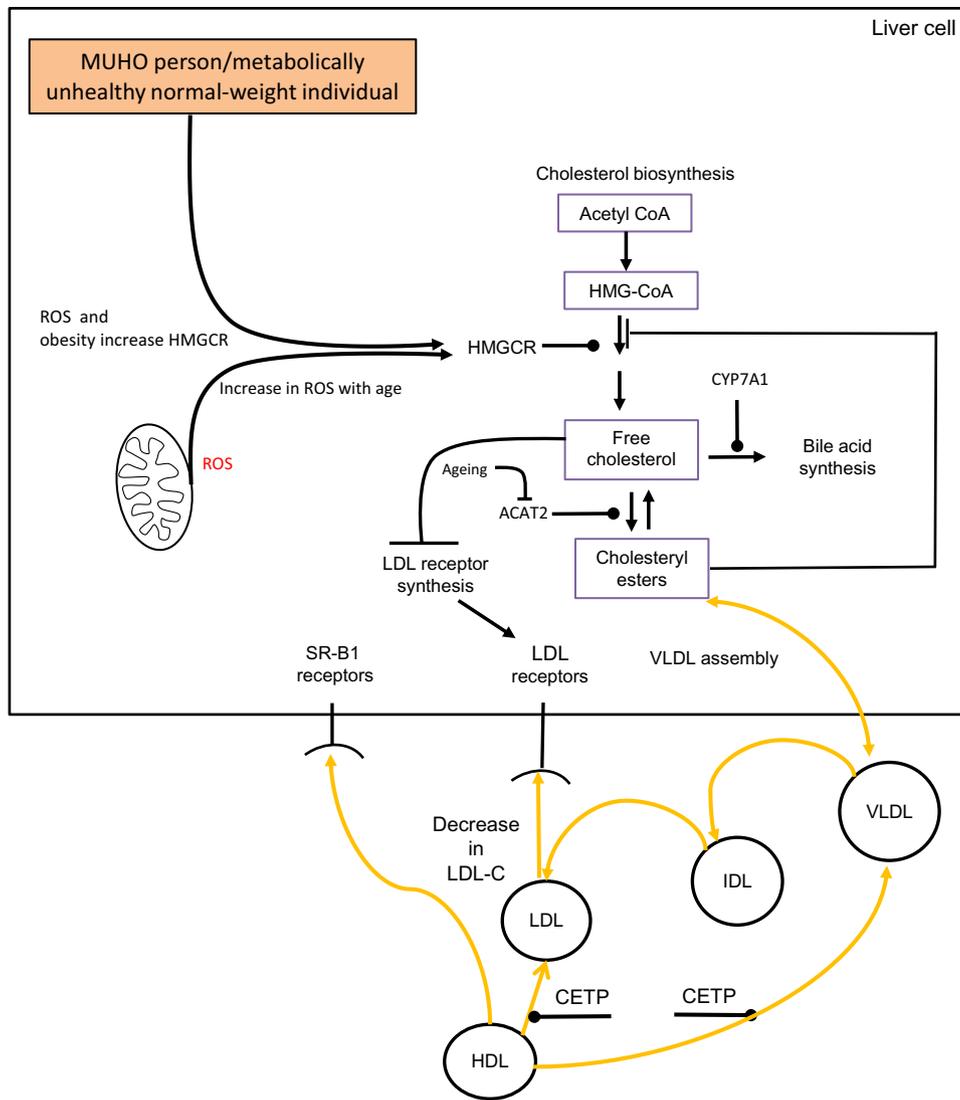


Fig. 2. Conceptual model of obesity/ageing-induced changes to hepatic cholesterol metabolism which could result in low levels of LDL-cholesterol (LDL-C), a metabolic feature which has been observed in a number of studies involving the oldest old. Acetyl-CoA, acetyl coenzyme A; ACAT2, acetyl CoA acetyltransferase 2; CETP, cholesteryl ester transfer protein; CYP7A1, cholesterol 7 α -hydroxylase; IDL, intermediate-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; HMGCR, HMG-CoA reductase; MUHO, metabolically unhealthy obese; ROS, reactive oxygen species; SR-B1, scavenger receptor, class B type 1. For a colour figure, see the online version of the paper.

are intriguing and require a biological explanation. The oldest old in general are in a state of multi-morbidity⁽¹⁹⁹⁾. Based on this premise it is logical that low levels of LDL-C could be one particular clinical manifestation of underlying multi-morbidity. Ageing superimposed on cholesterol metabolism in a metabolically unhealthy obese individual or a metabolically unhealthy normal-weight individual could theoretically contribute to a drop in LDL-C. The conceptual framework outlined in Fig. 2 suggests that an obese state/poor metabolic health combined with an age-associated rise in hepatic ROS levels results in a rise in HMGCR activity^(200,201). In a normolipidaemic individual this would result in a rise in LDL-C due to the homeostatic down-regulation of LDLr synthesis. However, if there is also an age-associated decrease in ACAT2 activity, this reduces the conversion of FC to CE. Consequently, VLDL-C production would drop and there would be a concomitant reduction in

LDL-C. As intracellular levels of FC accumulate and oxidative stress progresses, this state could advance to NAFLD⁽²⁰²⁾. As there is a strong association between NAFLD⁽²⁰³⁾ and CVD⁽²⁰⁴⁾, this in theory could increase an older individual's risk of mortality, and help to account for the association between low levels of LDL-C and increased risk of mortality, which has been observed in certain studies involving the oldest old.

Conclusions

Obesity among older individuals has increased significantly. The present review has revealed that obesity has a pleiotropic effect on cholesterol metabolism. Obesity affects cholesterol absorption, synthesis, lipoprotein processing, and results in the accumulation of cholesterol hepatically. Many of the changes are similar to how ageing intersects with cholesterol metabolism,

and it can be suggested that an obese state superimposed on ageing has the potential to exacerbate the dysregulation of cholesterol metabolism, which occurs with advancing age. The present review also revealed diet as a key factor which links an obese state to important changes which occur in hepatic cholesterol metabolism. In particular, the excessive intakes of dietary lipids and fructose were highlighted as key factors which underpin conditions such as NAFLD. Careful attention needs to be placed on this association. This review also highlighted a number of anomalies which exist in this field. Firstly, there are certain individuals who, despite being in an obese state, appear to be normolipidaemic, and it is not immediately clear why this is the case. The second anomaly centres on the oldest old: in particular, the association between low levels of LDL-C and an increased risk of mortality, which has been observed in a number of studies. A tentative explanation for this association was presented, which centred on obesity/an unhealthy metabolic state and its intersection with ageing as important factors underpinning this anomaly. However, this is only one possible explanation and to fully elucidate this intriguing anomaly, it is necessary for the dynamics of cholesterol metabolism in the oldest old to be investigated to a much greater extent. To date there has been a paucity of research in this area. Finally, the present review has raised a broader question which relates to the public health challenge surrounding an ageing global population which is becoming increasingly obese. There is no straightforward solution to this problem. However, one possible strategy could involve adopting public health initiatives which target middle-aged individuals and educating them about the deleterious health implications of being overweight/obese. Increased awareness among this group could lead to better health in later life. To this end it is vital that public health interventions are initiated which make both younger and middle-aged individuals cognisant of appropriate lifestyle choices which optimise their chances of growing old healthily. If this issue is not addressed in coming years, more and more people will reach old age in poor metabolic health due to being obese.

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