World Journal of Diabetes

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4239/wjd.v6.i7.970

World J Diabetes 2015 July 10; 6(7): 970-977
ISSN 1948-9358 (online)

MINIREVIEWS

Dyslipidaemia of diabetes and the intestine

Gerald H Tomkin, Daphne Owens

Gerald H Tomkin, Daphne Owens, Beacon Hospital Sandyford and Trinity College, Dublin 2, Ireland

Author contributions: Both authors contributed to this manuscript.

Conflict-of-interest statement: Neither Gerald H Tomkin nor Daphne Owens has any conflict of interest.

Correspondence to: Gerald H Tomkin, Professor, Beacon Hospital Sandyford and Trinity College, Clontra, Quinns Road, Shankill, Co Dublin, Dublin 2, Ireland. gerald.tomkin@tcd.ie
Telephone: +353-1-2390658
Fax: +353-1-2721395

Received: September 12, 2014
Peer-review started: September 13, 2014
First decision: December 12, 2014
Revised: February 11, 2015
Accepted: March 5, 2015
Article in press: March 9, 2015
Published online: July 10, 2015

Abstract

Atherosclerosis is the major complication of diabetes and has become a major issue in the provision of medical care. In particular the economic burden is growing at an alarming rate in parallel with the increasing world-wide prevalence of diabetes. The major disturbance of lipid metabolism in diabetes relates to the effect of insulin on fat metabolism. Raised triglycerides being the hallmark of uncontrolled diabetes, *i.e.*, in the presence of hyperglycaemia. The explosion of type 2 diabetes has generated increasing interest on the aetiology of atherosclerosis in diabetic patients. The importance of the atherogenic properties of triglyceride rich lipoproteins has only recently been recognised by the majority of diabetologists and cardiologists even though experimental evidence has been strong for many years. In the post-prandial phase 50% of triglyceride rich lipoproteins come from chylomicrons produced in the intestine. Recent evidence has secured the chylomicron as a major player in the atherogenic process. In diabetes chylomicron production is increased through disturbance in cholesterol absorption, in particular Neimann Pick C1-like1 activity is increased as is intestinal synthesis of cholesterol through 3-hydroxy-3-methyl glutaryl co enzyme A reductase. ATP binding cassette proteins G5 and G8 which regulate cholesterol in the intestine is reduced leading to chylomicronaemia. The chylomicron particle itself is atherogenic but the increase in the triglyceride-rich lipoproteins lead to an atherogenic low density lipoprotein and low high density lipoprotein. The various steps in the absorption process and the disturbance in chylomicron synthesis are discussed.

Key words: Triglyceride; Cholesterol chylomicrons; Microsomal triglyceride transfer protein; Niemann Pick C1-like1; Lipoproteins; Diabetes; ATP binding cassette proteins G5/G8

Core tip: The explosion of type 2 diabetes has generated increasing interest on the aetiology of atherosclerosis in diabetic patients. Evidence is mounting on the importance of the atherogenic properties of triglyceride rich lipoproteins. In the post-prandial phase 50% of triglyceride rich lipoproteins come from chylomicrons produced in the intestine. Recent evidence has secured the chylomicron as a major player in the atherogenic process. In diabetes chylomicron production is increased through disturbance in cholesterol absorption. This paper reviews recent literature in relation to diabetes, the intestine and dyslipidaemia with a view to understanding new targets for treatment.

Tomkin GH, Owens D. Dyslipidaemia of diabetes and the intestine. *World J Diabetes* 2015; 6(7): 970-977 Available from: URL: http://www.wjgnet.com/1948-9358/full/v6/i7/970.htm DOI: http://dx.doi.org/10.4239/wjd.v6.i7.970

INTRODUCTION

The increasing incidence and prevalence of diabetes is of concern to patients their relatives and the medical profession. Politicians who do not fit into the above groups are also concerned because of the health budget considerations. Management of chronic conditions is expensive! A major cost of diabetes care goes on the management of cardiovascular atherosclerotic complications which are so much more common in both diabetes and pre-diabetes. Although statins remain at the centre of dyslipidaemia treatment for diabetes, there is generally an unawareness of the importance of the chylomicron and triglyceride-rich proteins being atherogenic in their own right but also in forming atherogenic low density lipoprotein (LDL). This lack of appreciation of the importance of hypertriglyceridaemia has for example encouraged Tenenbaum *et al*[1] to write an article entitled "Hypertriglyceridaemia: too long an unfairly neglected major cardiovascular risk factor". Another important milestone in bringing the intestine to the notice of diabetologists and cardiologists has been the validation of ezetimibe, a drug that inhibits the absorption of intestinal cholesterol, which has been shown beyond doubt in the IMPROVE-IT study, demonstrating significantly lower primary combined endpoints in moderate to high risk patients who stabilise following acute coronary syndrome[2]. This article reviews dyslipidaemia in diabetes with a focus on the intestine as a dysfunctional regulator of cholesterol metabolism.

Insulin deficiency is associated with disturbance in both carbohydrate and fat metabolism. In fact even before diabetes becomes manifest, in the pre diabetes phase of the condition free fatty acids fail to be suppressed after a glucose load leading to the suggestion that diabetes should be defined as lipidus rather than mellitus[3]. Indeed, had the serum rather than the urine been easily available many centuries ago, post prandial chylomicronaemia, as demonstrated by the milky serum, would have been preferred to the sweet taste of the urine as the diagnostic tool of choice!

The chylomicron is a particle containing protein fat and cholesterol. The protein, which is mostly apolipoprotein (apo) B48, is the solubilising protein which facilitates the transport of fatty acids, triglycerides and cholesterol. The chylomicron is assembled in the intestinal mucosa under the influence of microsomal triglyceride transfer protein (MTP) which is the rate limiting enzyme. Very LDL (VLDL) is the major triglyceride-containing particle assembled in the liver and, in the postprandial state, about 50% of triglyceride is carried on the VLDL particle and 50% on the chylomicron. Although the chylomicron by definition is the triglyceride rich particle containing apo B48 and VLDL by definition is the triglyceride-rich particle containing apo B100, the term chylomicron is also used based on density following separation in the ultracentrifuge and thus is a mixture of both chylomicrons and large VLDL particles. Hence there is often confusion about what is meant by the term chylomicron.

CHYLOMICRON AS AN ATHEROGENIC PARTICLE

For many years triglycerides have taken a back seat in the perception and understanding of the aetiology of atherosclerosis. Part of the problem might have been that triglycerides have usually been taken fasting whereas the chylomicron is a post-prandial particle and the hepatic VLDL, the other major triglyceride containing particle, is also mostly produced in the postprandial state. Evidence that Apo B48 is found in the atherosclerotic plaque[4-7] has been around for years confirming the atherogenicity of the chylomicron particle. Trials such as the FIELD Study[8], failed to show cardiovascular benefit for reduction of triglycerides and had an adverse effect on the understanding of the atherosclerotic effect of the chylomicron. This has been rectified particularly by the Danish group who have shown that postprandial triglycerides are indeed associated with an increased in cardiovascular events[9]. Further analysis of the FIELD Study, and in particular understanding that too many people with normal triglycerides were included in the study, has resulted in a number of post hoc analysis of that study showing that reduction in triglycerides did have cardiovascular benefit. An evaluation of the effect of fenofibrate by sex in the FIELD Study was recently reported[10]. In that study the authors found that fenofibrate reduced LDL, non-high density lipoprotein (HDL) cholesterol and apo B more in women than in men irrespective of menopausal status. The prevention of total cardiovascular events was more in women (30% *viz* 13%). In Patients with high triglycerides and low HDL the cardiovascular reduction was less different between the sexes (30% *viz* 24%). In a recent review Varbo *et al*[11] conclude that post hoc subgroup analysis of randomised trials using fibrates in individuals with raised triglycerides show a benefit in lowering triglycerides. Conversely low non fasting triglycerides have been shown to be associated with reduced all cause mortality[12]. The authors examined individuals from the Copenhagen Heart study. Genetically derived low triglycerides were associated with a reduction in all cause mortality and the authors suggest probably due to a reduction in cholesterol in remnant particles. Apo C111 interferes with the uptake of triglyceride-rich apo E containing lipoproteins (both chylomicron and VLDL). Loss of function mutations are associated with lower triglycerides. The effect of these loss of function mutations on the risk of coronary heart disease (CHD) was examined[13]. An aggregate of rare mutations in the gene encoding apo C111 was associated with lower plasma triglycerides.

Levels were 39% lower in carriers when compared to non-carriers and circulating levels of apo C111 were 46% lower than in non-carriers. The study found that the risk of CHD among carriers of any apo C111 mutation was 40% lower than the risk among the non carriers. An other important boost to the importance of triglycerides in CHD. Fasting blood sugar is of course a recognised cause of increased cardiovascular risk[14] and it is very interesting to see that patients with polymorphisms of the various genes known to be associated with raised glucose such as the glucokinase gene (*GCK*) rs4607517 have been shown to be associated with an increased risk of ischaemic heart disease and myocardial infarction as compared to genotypes associated with lower levels[15]. It is likely that the raised glucose is associated with the failure to suppress triglyceride.

Inflammation is a key factor in atherosclerosis progression and obesity is associated with an increase in inflammatory proteins such as tumour necrosis factor alpha and interleucin 6 (IL6). A study genotyping for variants affecting levels of non fasting remnant cholesterol, LDL cholesterol and C-reactive protein (CRP) by both CRP alleles and IL6 receptor alleles found that increasing non-fasting remnant cholesterol was associated with significantly higher CRP. This was not the case for LDL, suggesting that remnant cholesterol may in part cause acceleration of atherosclerosis through an inflammatory process[16-18]. Endothelial dysfunction is a precursor of atherosclerosis. Post prandially, when triglycerides rise neutrophils increase with concomitant production of pro-inflammatory cytokines and oxidative stress suggesting a contributory cause of endothelial dysfunction[19,20]. Further triglycerides have also been shown to increase leucocyte activation markers[21,22].

The mechanisms whereby the postprandial lipoproteins might be pro-inflammatory and stimulate the progression of atherosclerosis has been investigated[23]. One mechanism is through the activation of neutrophils and Klop *et al*[24] have shown in healthy volunteers that post prandially changes occur in the white cell population which are similar to that shown in infection. A good review of post-prandial inflammation and the role of glucose and lipids has recently been published[25].

MTP

Since chylomicronaemia is such an important finding in diabetes it is of interest to examine MTP function in diabetes.

Biosynthesis of lipoproteins requires apo B and MTP. MTP binds and chaperones lipoproteins to the nascent apo B. MTP is an endoplasmic reticulum resident hetero dimeric complex. The liver and intestine are the major organs that express apo B and secrete apoB containing lipoproteins. There is good agreement between apoB levels and activity and in various animal models of diabetes in rats, rabbits and fructose fed hamsters diabetes MTP is up regulated[26-29].

In human studies in type 2 diabetes we demonstrated an increase in MTP mRNA in intestinal biopsies[30,31]. Diabetic patients who were on statin therapy had lower MTP mRNA compared to those not on statins[31]. We found positive correlations between MTP mRNA and chylomicron fraction cholesterol and apo B48[31]. A novel intestinal specific inhibitor of MTP has been shown to ameliorate impaired glucose and lipid metabolism in Zucker diabetic fatty rats but whether this effect was due to impairment of food intake or to inhibition of fat absorption is not clear[32]. The signals that upregulate chylomicron formation to cope with excess fat in the diet are slowly being elucidated. Another non-specific inhibitor of MTP, which reduced serum levels of triglycerides by more than 70%, was also associated with significant improvements in glucose tolerance and insulin sensitivity in Zucker fatty rats[33]. Hepatic MTP mRNA expression is negatively regulated by insulin and it is suggested that insulin might also directly inhibit apo B48 secretion independently of MTP even though it is probable that up-regulation of MTP stimulates apo B secretion[34]. The membrane glycoprotein CD36 binds long chain fatty acids. CD 36 deficiency reduces chylomicron production[35]. It has recently been shown that binding of lipid by CD36 upregulates apo B48 and MTP through CD 36 signalling *via* the ERK 1/2 pathway[36]. Interestingly polymorphisms of MTP which have been associated with differences in serum lipids appear to alter cholesterol absorption but not synthesis in women[37].

ATP BINDING CASSETTE PROTEINS G5/G8

Once cholesterol has been transported across the brush border membrane it faces another regulatory process and may be excreted back into the intestinal lumen rather than being further processed for absorption into the lymphatic circulation. ATP binding cassette proteins G5/G8 (ABC G5/G8) are heterodimers which are mostly confined to the human small intestine and liver[38]. These two proteins act in tandem to re-excrete both cholesterol, and in particular non-cholesterol sterols from the body. Much of the understanding of ABC G5/G8 comes from the rare mutations that cause a defect in ABC G5 and G8 and result in high levels of sitosterol in the blood. Sitosterolemia, is a condition which manifests itself in children as tendon xanthomas or in young adults as severe CHD with massive accumulation of sterols and stanols in monocyte derived macrophages[39]. Ma *et al*[40] found in an animal model, that dietary calcium had a beneficial effect on lipoprotein profile by up-regulating the mRNA levels of intestinal ABC G5/8 and cholesterol-7α-hydroxylase (CYP7A1), whereas it down-regulated the intestinal NPC1L1 and MTP due to enhanced biliary cholesterol excretion. Méndez-González *et al*[41] investigated the effect of ABC G5 and G8 deficiency on lipoproteins in mice. They found that postprandial triglycerides were 5 fold higher in the ABCG5/G8$^{-/-}$ mice due to a lower fractional catabolic rate with lower post heparin lipoprotein lipase activities. They also showed

that liver triglyceride secretion and intestinal triglyceride secretion were higher and there was a relationship between this and the HOMA index as a measure of insulin resistance. Rats with induced diabetes (streptozotosin) had impaired expression of ABC G5/8. Treatment with insulin partially reversed this effect[42]. This trend in impairment was found in Zucker diabetic rats[43,44] and the Psamonas Obesus (sand rat) was found to have the same intestinal impairment[45,46]. Intestinal G5/G8 mRNA in type 2 diabetic subjects produced similar findings[30].

ABC 5/8 genetic variants have been associated with susceptibility to CHD. One polymorphism in particular was shown to be associated with increased triglycerides with a significant gene - tobacco smoking interaction[47]. Another study has shown that ABC G5/8 regulate cholesterol available for chylomicron production. It is interesting to read that ABC G5/8 genotypes that are associated with low LDL cholesterol are protective against myocardial infarction but increase risk of symptomatic gall stone disease[48].

NIEMANN PICK C1-LIKE1

The first step in cholesterol absorption in the intestine appears to be through the multi transmembrane protein Niemann Pick C1-like1 (NPC1L1) which is highly expressed in the jejunum[49]. In humans it is localised to the brush borders of the enterocytes and acts as a unidirectional transporter of cholesterol and non-cholesterol sterols[50]. Zhang *et al*[51] discovered that it is the N-terminal domain of NPC1L1 that binds cholesterol. Twenty rare NCP1L1 alleles have been found in the low cholesterol absorbers and appear to impair NPC1L1 cholesterol uptake through various mechanism[52,53], for review see Calandera[54]. It has been shown that the effectiveness of ezetimibe, which blocks NPC1L1 and inhibits cholesterol absorption, depends on the NPC1L1 genotype.

Cholesterol absorption has been shown to be increased in both animal and human diabetes[55] due to an increase in NPC1-L1[43,44,55]. In an animal model of type 2 diabetes, Sammomas Obesus, the opposite was found even though these animals have an increase in apo B48[45,46]. Ezetimibe inhibits cholesterol absorbtion through inhibition of NPCILI (for review see[56]). NPC1L1 activity appears to be governed by dietary cholesterol[57]. The mechanism of this control is through the nuclear receptor, peroxisome proliferator-activated receptor (PPAR)δ/β[58]. Fenofibrate, a PPARα agonist has been shown to inhibit cholesterol absorption, the mechanism has been shown to be through NCP1L1 transcription by binding to a PPARα response element upstream of the human *NPC1L1* gene[59]. In a human construct Iwayanagi *et al*[60] showed that PPARα positively regulated human NPC1L1 transcription and Valasek *et al*[59] showed that Fenofibrate reduced intestinal cholesterol absorption by PPARα modulation of NPC1L1. HMGCoA reductase inhibition (Atorvastatin) has been shown to increase cholesterol absorption in the intestine and downregulation of NPC1L1[61] in the intestine. Ezetimibe has been shown to improve biomarkers of inflammation and platelet activity[62] as stated above the IMPROVE-IT trial has been presented at the American Heart 2014 but not yet published. Ciriacks *et al*[63] have examined the addition of Ezetimibe to simvastatin in type 1 and type 2 diabetes. The study demonstrated that ezetimibe was at least as effective in lowering cholesterol as simvastatin among type 1 diabetics. Some studies have suggested that there may be a difference in cholesterol absorption rates between type 1 and type 2 diabetic patients[64].

OTHER TRANSPORTERS OF CHOLESTEROL

There are other transporters of cholesterol for example scavenger receptor class B type 1 (SR-B1) which is located both in the apical and basolateral membranes of the enterocyte[65]. SR are cell surface proteins that can bind and internalise modified lipoproteins. SR-B1, which is involved in cholesterol uptake in the intestine, may play an important part in intestinal chylomicron production[66]. The fatty acid transporter CD36 which is also involved in the uptake of oxidised LDL, is another member of the class B scavenger receptor family[66]. Hayashi *et al*[67] investigated gene expression of key proteins involved in the active absorption of dietary fat and cholesterol in response to the development of insulin resistance. They used 2 models of diet induced insulin resistance, the fructose fed hamster and the high fat fed mouse. Expression of SR-B1 was increased in both the fructose fed hamster and the high fat fed mouse models of insulin resistance. In CaCo2 cells SR-B1 over expression increased apo B100 and apo B48 secretion. The authors conclude that apical or basolateral SR-B1 may have an important role in cholesterol absorption and may play a part in cholesterol over absorption in insulin resistant states. SR-B1 in the intestine may play an important role in chylomicron production. CdC42, a member of the Rho family of small Guanidine triphosphotases with numerous functions, has been shown by Xie *et al*[68] to interact with NPC1L1 and to control its movement from endocytic recycling compartment to plasma membrane in a cholesterol dependent manner. Glucose stimulated CDc42 signalling appears to be essential for second stage insulin secretion[69]. It is probable that in insulin resistance the signalling of NPC1L1 is disturbed through this pathway but we have been unable to find any studies in the intestine that have explored the pathway in diabetes/insulin resistance.

THE EFFECT OF HIGH GLUCOSE ON CHOLESTEROL ABSORPTION

Ravid *et al*[70] have shown that high glucose increases intestinal absorption of cholesterol through an increase in the protein expression of NPC1L1. The same group later showed that the effect was through the basolateral

domain suggesting glucose in the circulation rather than in the lumen to be the stimulus[71]. The reason for the up-regulation of cholesterol through NPC1L1 in diabetes has been explored by Malhotra *et al*[72]. Using CaCo2 cells they showed that removal of glucose from the culture medium significantly decreased NPC1L1 mRNA protein expression as well as pro-motor activity. Glucose replenishment significantly increased the promoter activity of NPC1L1 in a dose dependant manner. The authors concluded their experiments by examining mouse jejunum after 24 h fasting which confirmed the CaCo2 cell results.

The role of cholecystokinin on intestinal absorption has been reported by Zhou *et al*[73]. They found that in mice cholecystokinin (CCK) increased cholesterol absorption and increased cell surface associated NPC1L1. Previously Irwin *et al*[74] have shown that an CCK-8 analogue improves insulin sensitivity and triglyceride deposition in liver and muscle but with reduction in weight gain and food intake. The effect therefore on lipid metabolism might be very dependant on dietary intake and the inhibition of apatite and improvement in insulin sensitivity with improvement in glucose tolerance with CCK makes analogues of CCK of interest as a possible treatment in diabetes and the metabolic syndrome.

Interest in bile salt binding drugs for treatment of dyslipidaemia, such as cholestyramine, went out of fashion because of their poor cholesterol lowering effects and their unacceptable side effects. A new formulation colsevelam, is interesting in that not only that it lowers cholesterol and apo B but also lowers blood sugar. A recent study in type 2 diabetic patients demonstrated a 0.32 drop in HbA1c *vs* placebo at 24 wk and a reduction of cholesterol of 6.5%[75,76]. The majority of adverse effects were mild or moderate, the authors concluding that the drug was well tolerated. Thus another option for patients who are near to but not on target with current medication.

CHOLESTEROL SYNTHESIS AND 3-HYDROXY-3-METHYLGLUTARYL CO-ENZYME A REDUCTASE

Cholesterol synthesis in the intestine makes up 25% of *de novo* cholesterol synthesis. Cholesterol synthesis is regulated by 3-hydroxy-3-methylglutaryl co-enzyme A (HMGCo A) reductase the rate limiting enzyme in the synthetic pathway. HMGCo A reductase activity has been shown to be reduced by insulin in the rat hepatocyte[77]. It has been suggested that in type 1 diabetes improved glycaemic control will increase cholesterol synthesis. HMGCoA reductase inhibition has been shown to increase cholesterol absorption through a lowering of ABC G5/G8 and an increase in NPC1L1[78].

HEPATIC STEATOSIS

Hepatic steatosis is common in diabetes, insulin resistance and obesity. Inflammatory stress is present in these conditions and is also associated with obesity insulin resistance and diabetes. It is therefore of interest to read that Zhao *et al*[79] demonstrated that IL1b and IL6 stimulation in Hep G2 cells increased SREBP2 and HMGCoA mRNA. Further high fat loading in mice or LDL loading in HepG2 cells suppressed the above genes but this suppression could be over ridden by the above inflammatory proteins. Severe calorie restriction in patients with steatosis results in rapid reduction of liver fat, insulin resistance and improvement in diabetes control[80]. On the other side of the coin insulin resistance and the accompanying hyperinsulinaemia are associated with an upregulation of SREPB-2 through extracellular signal regulated pathways involving the kinases ERK-1 and 2 another example of the interaction between fat and carbohydrate metabolism, for review see Van Rooyen *et al*[81].

In conclusion, vascular disease in diabetes is complex as would be expected with a condition that impacts on so many metabolic pathways. Examination of the intestine in the search for abnormalities in cholesterol absorption and chylomicron formation has been rewarding. Statins have been very effective in reducing the burden of atherosclerosis in patients with diabetes but even so a large proportion of patients still succumb to events. Reduction in triglycerides is now accepted as being important in those patients who have raised triglycerides and in particular the importance of postprandial disturbance in triglyceride metabolism and its impact on atherosclerosis is now accepted as being an important issue in management of diabetes and in the prevention of macrovascular complications.

REFERENCES

1 **Tenenbaum A**, Klempfner R, Fisman EZ. Hypertriglyceridemia: a too long unfairly neglected major cardiovascular risk factor. *Cardiovasc Diabetol* 2014; **13**: 159 [PMID: 25471221]
2 **Kohno T**. Report of the American Heart Association (AHA) Scientific Sessions 2014, Chicago. *Circ J* 2015; **79**: 34-40 [PMID: 25502168]
3 **Shafrir E**, Raz I. Diabetes: mellitus or lipidus? *Diabetologia* 2003; **46**: 433-440 [PMID: 12687345]
4 **Elsegood CL**, Mamo JC. An investigation by electron microscopy of chylomicron remnant uptake by human monocyte-derived macrophages. *Atherosclerosis* 2006; **188**: 251-259 [PMID: 16310792]
5 **Proctor SD**, Mamo JC. Intimal retention of cholesterol derived from apolipoprotein B100- and apolipoprotein B48-containing lipoproteins in carotid arteries of Watanabe heritable hyperlipidemic rabbits. *Arterioscler Thromb Vasc Biol* 2003; **23**: 1595-1600 [PMID: 12842838]
6 **Pal S**, Semorine K, Watts GF, Mamo J. Identification of lipoproteins of intestinal origin in human atherosclerotic plaque. *Clin Chem Lab Med* 2003; **41**: 792-795 [PMID: 12880143]
7 **Nakano T**, Nakajima K, Niimi M, Fujita MQ, Nakajima Y, Takeichi S, Kinoshita M, Matsushima T, Teramoto T, Tanaka A. Detection of apolipoproteins B-48 and B-100 carrying particles in lipoprotein fractions extracted from human aortic atherosclerotic plaques in sudden cardiac death cases. *Clin Chim Acta* 2008; **390**: 38-43 [PMID: 18206113 DOI: 10.1016/j.cca.2007.12.012]
8 **Scott R**, Best J, Forder P, Taskinen MR, Simes J, Barter P, Keech A. Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)

study: baseline characteristics and short-term effects of fenofibrate [ISRCTN64783481]. *Cardiovasc Diabetol* 2005; **4**: 13 [PMID: 16111499]

9 **Varbo A**, Benn M, Nordestgaard BG. Remnant cholesterol as a cause of ischemic heart disease: evidence, definition, measurement, atherogenicity, high risk patients, and present and future treatment. *Pharmacol Ther* 2014; **141**: 358-367 [PMID: 24287311]

10 **d'Emden MC**, Jenkins AJ, Li L, Zannino D, Mann KP, Best JD, Stuckey BG, Park K, Saltevo J, Keech AC. Favourable effects of fenofibrate on lipids and cardiovascular disease in women with type 2 diabetes: results from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Diabetologia* 2014; **57**: 2296-2303 [PMID: 25149070]

11 **Varbo A**, Nordestgaard BG. Remnant cholesterol and ischemic heart disease. *Curr Opin Lipidol* 2014; **25**: 266-273 [PMID: 24977981]

12 **Thomsen M**, Varbo A, Tybjærg-Hansen A, Nordestgaard BG. Low nonfasting triglycerides and reduced all-cause mortality: a mendelian randomization study. *Clin Chem* 2014; **60**: 737-746 [PMID: 24436475]

13 **Crosby J**, Peloso GM, Auer PL, Crosslin DR, Stitziel NO, Lange LA, Lu Y, Tang ZZ, Zhang H, Hindy G, Masca N, Stirrups K, Kanoni S, Do R, Jun G, Hu Y, Kang HM, Xue C, Goel A, Farrall M, Duga S, Merlini PA, Asselta R, Girelli D, Olivieri O, Martinelli N, Yin W, Reilly D, Speliotes E, Fox CS, Hveem K, Holmen OL, Nikpay M, Farlow DN, Assimes TL, Franceschini N, Robinson J, North KE, Martin LW, DePristo M, Gupta N, Escher SA, Jansson JH, Van Zuydam N, Palmer CN, Wareham N, Koch W, Meitinger T, Peters A, Lieb W, Erbel R, Konig IR, Kruppa J, Degenhardt F, Gottesman O, Bottinger EP, O'Donnell CJ, Psaty BM, Ballantyne CM, Abecasis G, Ordovas JM, Melander O, Watkins H, Orho-Melander M, Ardissino D, Loos RJ, McPherson R, Willer CJ, Erdmann J, Hall AS, Samani NJ, Deloukas P, Schunkert H, Wilson JG, Kooperberg C, Rich SS, Tracy RP, Lin DY, Altshuler D, Gabriel S, Nickerson DA, Jarvik GP, Cupples LA, Reiner AP, Boerwinkle E, Kathiresan S. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. *N Engl J Med* 2014; **371**: 22-31 [PMID: 24941081 DOI: 10.1056/NEJMoa1307095]

14 **Sarwar N**, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CD, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010; **375**: 2215-2222 [PMID: 20609967 DOI: 10.1016/S0140-6736(10)]

15 **Benn M**, Tybjaerg-Hansen A, McCarthy MI, Jensen GB, Grande P, Nordestgaard BG. Nonfasting glucose, ischemic heart disease, and myocardial infarction: a Mendelian randomization study. *J Am Coll Cardiol* 2012; **59**: 2356-2365 [PMID: 22698489 DOI: 10.1016/j.jacc.2012.02.043]

16 **Bansal S**, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. *JAMA* 2007; **298**: 309-316 [PMID: 17635891]

17 **Mora S**, Rifai N, Buring JE, Ridker PM. Fasting compared with nonfasting lipids and apolipoproteins for predicting incident cardiovascular events. *Circulation* 2008; **118**: 993-1001 [PMID: 18711012 DOI: 10.1161/CIRCULATIONAHA.108.777334]

18 **Nordestgaard BG**, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA* 2007; **298**: 299-308 [PMID: 17635890]

19 **van Oostrom AJ**, Sijmonsma TP, Verseyden C, Jansen EH, de Koning EJ, Rabelink TJ, Castro Cabezas M. Postprandial recruitment of neutrophils may contribute to endothelial dysfunction. *J Lipid Res* 2003; **44**: 576-583 [PMID: 12562833]

20 **Van Oostrom AJ**, Sijmonsma TP, Rabelink TJ, Van Asbeck BS, Cabezas MC. Postprandial leukocyte increase in healthy subjects. *Metabolism* 2003; **52**: 199-202 [PMID: 12601632]

21 **van Oostrom AJ**, Plokker HW, van Asbeck BS, Rabelink TJ, van Kessel KP, Jansen EH, Stehouwer CD, Cabezas MC. Effects of rosuvastatin on postprandial leukocytes in mildly hyperlipidemic patients with premature coronary sclerosis. *Atherosclerosis* 2006; **185**: 331-339 [PMID: 16098531]

22 **van Oostrom AJ**, Rabelink TJ, Verseyden C, Sijmonsma TP, Plokker HW, De Jaegere PP, Cabezas MC. Activation of leukocytes by postprandial lipemia in healthy volunteers. *Atherosclerosis* 2004; **177**: 175-182 [PMID: 15488881]

23 **Klop B**, Proctor SD, Mamo JC, Botham KM, Castro Cabezas M. Understanding postprandial inflammation and its relationship to lifestyle behaviour and metabolic diseases. *Int J Vasc Med* 2012; **2012**: 947417 [PMID: 21961070 DOI: 10.1155/2012/947417]

24 **Klop B**, van de Geijn GJ, Njo TL, Janssen HW, Rietveld AP, van Miltenburg A, Fernández-Sender L, Elte JW, Castro Cabezas M. Leukocyte cell population data (volume conductivity scatter) in postprandial leukocyte activation. *Int J Lab Hematol* 2013; **35**: 644-651 [PMID: 23663689 DOI: 10.1111/ijlh.12103]

25 **de Vries MA**, Alipour A, Klop B, van de Geijn GJ, Janssen HW, Njo TL, van der Meulen N, Rietveld AP, Liem AH, Westerman EM, de Herder WW, Cabezas MC. Glucose-dependent leukocyte activation in patients with type 2 diabetes mellitus, familial combined hyperlipidemia and healthy controls. *Metabolism* 2015; **64**: 213-217 [PMID: 25456098 DOI: 10.1016/j.metabol]

26 **Phillips C**, Bennett A, Anderton K, Owens D, Collins P, White D, Tomkin GH. Intestinal rather than hepatic microsomal triglyceride transfer protein as a cause of postprandial dyslipidemia in diabetes. *Metabolism* 2002; **51**: 847-852 [PMID: 12077729]

27 **Gleeson A**, Anderton K, Owens D, Bennett A, Collins P, Johnson A, White D, Tomkin GH. The role of microsomal triglyceride transfer protein and dietary cholesterol in chylomicron production in diabetes. *Diabetologia* 1999; **42**: 944-948 [PMID: 10491754]

28 **Qin B**, Qiu W, Avramoglu RK, Adeli K. Tumor necrosis factor-alpha induces intestinal insulin resistance and stimulates the overproduction of intestinal apolipoprotein B48-containing lipoproteins. *Diabetes* 2007; **56**: 450-461 [PMID: 17259391]

29 **Zoltowska M**, Ziv E, Delvin E, Sinnett D, Kalman R, Garofalo C, Seidman E, Levy E. Cellular aspects of intestinal lipoprotein assembly in Psammomys obesus: a model of insulin resistance and type 2 diabetes. *Diabetes* 2003; **52**: 2539-2545 [PMID: 14514638]

30 **Lally S**, Tan CY, Owens D, Tomkin GH. Messenger RNA levels of genes involved in dysregulation of postprandial lipoproteins in type 2 diabetes: the role of Niemann-Pick C1-like 1, ATP-binding cassette, transporters G5 and G8, and of microsomal triglyceride transfer protein. *Diabetologia* 2006; **49**: 1008-1016 [PMID: 16518588]

31 **Phillips C**, Mullan K, Owens D, Tomkin GH. Intestinal microsomal triglyceride transfer protein in type 2 diabetic and non-diabetic subjects: the relationship to triglyceride-rich postprandial lipoprotein composition. *Atherosclerosis* 2006; **187**: 57-64 [PMID: 16183064]

32 **Hata T**, Mera Y, Kawai T, Ishii Y, Kuroki Y, Kakimoto K, Ohta T, Kakutani M. JTT-130, a novel intestine-specific inhibitor of microsomal triglyceride transfer protein, ameliorates impaired glucose and lipid metabolism in Zucker diabetic fatty rats. *Diabetes Obes Metab* 2011; **13**: 629-638 [PMID: 21362121 DOI: 10.1111/j.1463-1326.2011.01387.x]

33 **Dhote V**, Joharapurkar A, Kshirsagar S, Dhanesha N, Patel V, Patel A, Raval S, Jain M. Inhibition of microsomal triglyceride transfer protein improves insulin sensitivity and reduces atherogenic risk in Zucker fatty rats. *Clin Exp Pharmacol Physiol* 2011; **38**: 338-344 [PMID: 21401695 DOI: 10.1111/j.1440-1681.2011.05513.x]

34 **Sparks JD**, Chamberlain JM, O'Dell C, Khatun I, Hussain MM, Sparks CE. Acute suppression of apo B secretion by insulin occurs independently of MTP. *Biochem Biophys Res Commun* 2011; **406**: 252-256 [PMID: 21316344 DOI: 10.1016/j.bbrc.2011.02.028]

35 **Tran TT**, Poirier H, Clément L, Nassir F, Pelsers MM, Petit V, Degrace P, Monnot MC, Glatz JF, Abumrad NA, Besnard P, Niot I. Luminal lipid regulates CD36 levels and downstream signaling to stimulate chylomicron synthesis. *J Biol Chem* 2011; **286**: 25201-25210 [PMID: 21610069 DOI: 10.1074/jbc.M111.233551]

36 **Buttet M**, Traynard V, Tran TT, Besnard P, Poirier H, Niot I. From fatty-acid sensing to chylomicron synthesis: role of intestinal lipid-binding proteins. *Biochimie* 2014; **96**: 37-47 [PMID: 23958439 DOI: 10.1016/j.biochi.2013.08.011]

37 **Wolff E**, Vergnes MF, Defoort C, Planells R, Portugal H, Nicolay A, Lairon D. Cholesterol absorption status and fasting plasma cholesterol are modulated by the microsomal triacylglycerol transfer protein -493 G/T polymorphism and the usual diet in women. *Genes Nutr* 2011; **6**: 71-79 [PMID: 21437032 DOI: 10.1007/s12263-010-0174-x]

38 **Berge KE**, Tian H, Graf GA, Yu L, Grishin NV, Schultz J, Kwiterovich P, Shan B, Barnes R, Hobbs HH. Accumulation of dietary cholesterol in sitosterolemia caused by mutations in adjacent ABC transporters. *Science* 2000; **290**: 1771-1775 [PMID: 11099417]

39 **Silbernagel G**, Fauler G, Renner W, Landl EM, Hoffmann MM, Winkelmann BR, Boehm BO, März W. The relationships of cholesterol metabolism and plasma plant sterols with the severity of coronary artery disease. *J Lipid Res* 2009; **50**: 334-341 [PMID: 18769018 DOI: 10.1194/jlr.P800013-JLR200]

40 **Ma KY**, Yang N, Jiao R, Peng C, Guan L, Huang Y, Chen ZY. Dietary calcium decreases plasma cholesterol by down-regulation of intestinal Niemann-Pick C1 like 1 and microsomal triacylglycerol transport protein and up-regulation of CYP7A1 and ABCG 5/8 in hamsters. *Mol Nutr Food Res* 2011; **55**: 247-258 [PMID: 20715096]

41 **Méndez-González J**, Julve J, Rotllan N, Llaverias G, Blanco-Vaca F, Escolà-Gil JC. ATP-binding cassette G5/G8 deficiency causes hypertriglyceridemia by affecting multiple metabolic pathways. *Biochim Biophys Acta* 2011; **1811**: 1186-1193 [PMID: 21855652 DOI: 10.1016/j.bbalip]

42 **Bloks VW**, Bakker-Van Waarde WM, Verkade HJ, Kema IP, Wolters H, Vink E, Groen AK, Kuipers F. Down-regulation of hepatic and intestinal Abcg5 and Abcg8 expression associated with altered sterol fluxes in rats with streptozotocin-induced diabetes. *Diabetologia* 2004; **47**: 104-112 [PMID: 14618236]

43 **Lally S**, Owens D, Tomkin GH. The different effect of pioglitazone as compared to insulin on expression of hepatic and intestinal genes regulating post-prandial lipoproteins in diabetes. *Atherosclerosis* 2007; **193**: 343-351 [PMID: 17109865]

44 **Lally S**, Owens D, Tomkin GH. Genes that affect cholesterol synthesis, cholesterol absorption, and chylomicron assembly: the relationship between the liver and intestine in control and streptozotosin diabetic rats. *Metabolism* 2007; **56**: 430-438 [PMID: 17292734]

45 **Levy E**, Lalonde G, Delvin E, Elchebly M, Précourt LP, Seidah NG, Spahis S, Rabasa-Lhoret R, Ziv E. Intestinal and hepatic cholesterol carriers in diabetic Psammomys obesus. *Endocrinology* 2010; **151**: 958-970 [PMID: 20130116 DOI: 10.1210/en.2009-0866]

46 **Levy E**, Spahis S, Ziv E, Marette A, Elchebly M, Lambert M, Delvin E. Overproduction of intestinal lipoprotein containing apolipoprotein B-48 in Psammomys obesus: impact of dietary n-3 fatty acids. *Diabetologia* 2006; **49**: 1937-1945 [PMID: 16788801]

47 **Wu G**, Li GB, Yao M, Zhang DQ, Dai B, Ju CJ, Han M. ABCG5/8 variants are associated with susceptibility to coronary heart disease. *Mol Med Rep* 2014; **9**: 2512-2520 [PMID: 24691589 DOI: 10.3892/mmr]

48 **Stender S**, Frikke-Schmidt R, Nordestgaard BG, Tybjaerg-Hansen A. The ABCG5/8 cholesterol transporter and myocardial infarction versus gallstone disease. *J Am Coll Cardiol* 2014; **63**: 2121-2128 [PMID: 24657701 DOI: 10.1016/j.jacc.2013.12.055]

49 **Altmann SW**, Davis HR, Zhu LJ, Yao X, Hoos LM, Tetzloff G, Iyer SP, Maguire M, Golovko A, Zeng M, Wang L, Murgolo N, Graziano MP. Niemann-Pick C1 Like 1 protein is critical for intestinal cholesterol absorption. *Science* 2004; **303**: 1201-1204 [PMID: 14976318]

50 **Sané AT**, Sinnett D, Delvin E, Bendayan M, Marcil V, Ménard D, Beaulieu JF, Levy E. Localization and role of NPC1L1 in cholesterol absorption in human intestine. *J Lipid Res* 2006; **47**: 2112-2120 [PMID: 16829661]

51 **Zhang JH**, Ge L, Qi W, Zhang L, Miao HH, Li BL, Yang M, Song BL. The N-terminal domain of NPC1L1 protein binds cholesterol and plays essential roles in cholesterol uptake. *J Biol Chem* 2011; **286**: 25088-25097 [PMID: 21602275 DOI: 10.1074/jbc.M111.244475]

52 **Fahmi S**, Yang C, Esmail S, Hobbs HH, Cohen JC. Functional characterization of genetic variants in NPC1L1 supports the sequencing extremes strategy to identify complex trait genes. *Hum Mol Genet* 2008; **17**: 2101-2107 [PMID: 18413323 DOI: 10.1093/hmg/ddn108]

53 **Wang LJ**, Wang J, Li N, Ge L, Li BL, Song BL. Molecular characterization of the NPC1L1 variants identified from cholesterol low absorbers. *J Biol Chem* 2011; **286**: 7397-7408 [PMID: 21189420 DOI: 10.1074/jbc.M110.178368]

54 **Calandra S**, Tarugi P, Speedy HE, Dean AF, Bertolini S, Shoulders CC. Mechanisms and genetic determinants regulating sterol absorption, circulating LDL levels, and sterol elimination: implications for classification and disease risk. *J Lipid Res* 2011; **52**: 1885-1926 [PMID: 21862702 DOI: 10.1194/jlr.R017855]

55 **Gleeson A**, Owens D, Collins P, Johnson A, Tomkin GH. The relationship between cholesterol absorption and intestinal cholesterol synthesis in the diabetic rat model. *Int J Exp Diabetes Res* 2000; **1**: 203-210 [PMID: 11467411]

56 **Betters JL**, Yu L. NPC1L1 and cholesterol transport. *FEBS Lett* 2010; **584**: 2740-2747 [PMID: 20307540 DOI: 10.1016/j.febslet.2010.03.030]

57 **Huff MW**, Pollex RL, Hegele RA. NPC1L1: evolution from pharmacological target to physiological sterol transporter. *Arterioscler Thromb Vasc Biol* 2006; **26**: 2433-2438 [PMID: 16973966]

58 **van der Veen JN**, Kruit JK, Havinga R, Baller JF, Chimini G, Lestavel S, Staels B, Groot PH, Groen AK, Kuipers F. Reduced cholesterol absorption upon PPARdelta activation coincides with decreased intestinal expression of NPC1L1. *J Lipid Res* 2005; **46**: 526-534 [PMID: 15604518]

59 **Valasek MA**, Clarke SL, Repa JJ. Fenofibrate reduces intestinal cholesterol absorption via PPARalpha-dependent modulation of NPC1L1 expression in mouse. *J Lipid Res* 2007; **48**: 2725-2735 [PMID: 17726195]

60 **Iwayanagi Y**, Takada T, Tomura F, Yamanashi Y, Terada T, Inui K, Suzuki H. Human NPC1L1 expression is positively regulated by PPARα. *Pharm Res* 2011; **28**: 405-412 [PMID: 20953676 DOI: 10.1007/s11095-010-0294]

61 **Tremblay AJ**, Lamarche B, Lemelin V, Hoos L, Benjannet S, Seidah NG, Davis HR, Couture P. Atorvastatin increases intestinal expression of NPC1L1 in hyperlipidemic men. *J Lipid Res* 2011; **52**: 558-565 [PMID: 21123766 DOI: 10.1194/jlr.M011080]

62 **Miller M**, DiNicolantonio JJ, Can M, Grice R, Damoulakis A, Serebruany VL. The effects of ezetimibe/simvastatin versus simvastatin monotherapy on platelet and inflammatory biomarkers in patients with metabolic syndrome. *Cardiology* 2013; **125**: 74-77 [PMID: 23652826 DOI: 10.1159/000347134]

63 **Ciriacks K**, Coly G, Krishnaswami S, Patel SB, Kidambi S. Effects of simvastatin and ezetimibe in lowering low-density lipoprotein cholesterol in subjects with type 1 and type 2 diabetes mellitus. *Metab Syndr Relat Disord* 2015; **13**: 84-90 [PMID: 25490061]

64 **Gylling H**, Laaksonen DE, Atalay M, Hallikainen M, Niskanen L, Miettinen TA. Markers of absorption and synthesis of cholesterol in men with type 1 diabetes. *Diabetes Metab Res Rev* 2007; **23**: 372-377 [PMID: 17080398]

65 **Wiersma H**, Nijstad N, Gautier T, Iqbal J, Kuipers F, Hussain MM, Tietge UJ. Scavenger receptor BI facilitates hepatic very low density lipoprotein production in mice. *J Lipid Res* 2010; **51**: 544-553 [PMID: 19723664 DOI: 10.1194/jlr.M000844]

66 **Iqbal J**, Hussain MM. Intestinal lipid absorption. *Am J Physiol Endocrinol Metab* 2009; **296**: E1183-E1194 [PMID: 19158321]

67 **Hayashi AA**, Webb J, Choi J, Baker C, Lino M, Trigatti B, Trajcevski KE, Hawke TJ, Adeli K. Intestinal SR-BI is upregulated in insulin-resistant states and is associated with overproduction of intestinal apoB48-containing lipoproteins. *Am J Physiol Gastrointest Liver*

Physiol 2011; **301**: G326-G337 [PMID: 21546579 DOI: 10.1152/ajpgi]

68 **Xie C**, Li N, Chen ZJ, Li BL, Song BL. The small GTPase Cdc42 interacts with Niemann-Pick C1-like 1 (NPC1L1) and controls its movement from endocytic recycling compartment to plasma membrane in a cholesterol-dependent manner. *J Biol Chem* 2011; **286**: 35933-35942 [PMID: 21844200 DOI: 10.1074/jbc.M111.270199]

69 **Wang Z**, Thurmond DC. Differential phosphorylation of RhoGDI mediates the distinct cycling of Cdc42 and Rac1 to regulate second-phase insulin secretion. *J Biol Chem* 2010; **285**: 6186-6197 [PMID: 20028975 DOI: 10.1074/jbc.M109.072421]

70 **Ravid Z**, Bendayan M, Delvin E, Sane AT, Elchebly M, Lafond J, Lambert M, Mailhot G, Levy E. Modulation of intestinal cholesterol absorption by high glucose levels: impact on cholesterol transporters, regulatory enzymes, and transcription factors. *Am J Physiol Gastrointest Liver Physiol* 2008; **295**: G873-G885 [PMID: 18772361 DOI: 10.1152/ajpgi.90376.2008]

71 **Grenier E**, Mailhot G, Dion D, Ravid Z, Spahis S, Bendayan M, Levy E. Role of the apical and basolateral domains of the enterocyte in the regulation of cholesterol transport by a high glucose concentration. *Biochem Cell Biol* 2013; **91**: 476-486 [PMID: 24219290 DOI: 10.1139/bcb-2013-0053]

72 **Malhotra P**, Boddy CS, Soni V, Saksena S, Dudeja PK, Gill RK, Alrefai WA. D-Glucose modulates intestinal Niemann-Pick C1-like 1 (NPC1L1) gene expression via transcriptional regulation. *Am J Physiol Gastrointest Liver Physiol* 2013; **304**: G203-G210 [PMID: 23139223 DOI: 10.1152/ajpgi.00288.2012]

73 **Zhou L**, Yang H, Okoro EU, Guo Z. Up-regulation of cholesterol absorption is a mechanism for cholecystokinin-induced hypercholesterolemia. *J Biol Chem* 2014; **289**: 12989-12999 [PMID: 24692543 DOI: 10.1074/jbc.M113.534388]

74 **Irwin N**, Frizelle P, O'Harte FP, Flatt PR. Metabolic effects of activation of CCK receptor signaling pathways by twice-daily administration of the enzyme-resistant CCK-8 analog, (pGlu-Gln)-CCK-8, in normal mice. *J Endocrinol* 2013; **216**: 53-59 [PMID: 23055535]

75 **Rosenstock J**, Truitt KE, Baz-Hecht M, Ford DM, Tao B, Chou HS. Efficacy and safety of colesevelam in combination with pioglitazone in patients with type 2 diabetes mellitus. *Horm Metab Res* 2014; **46**: 943-949 [PMID: 25054436 DOI: 10.1055/s-0034-1383648]

76 **Sonne DP**, Hansen M, Knop FK. Bile acid sequestrants in type 2 diabetes: potential effects on GLP1 secretion. *Eur J Endocrinol* 2014; **171**: R47-R65 [PMID: 24760535 DOI: 10.1530/EJE-14-0154]

77 **Devery RA**, O'Meara N, Collins PB, Johnson AH, Scott L, Tomkin GH. A comparative study of the rate-limiting enzymes of cholesterol synthesis, esterification and catabolism in the alloxan-induced diabetic rat and rabbit. *Comp Biochem Physiol B* 1987; **88**: 547-550 [PMID: 3427902]

78 **Sittiwet C**, Gylling H, Hallikainen M, Pihlajamäki J, Moilanen L, Laaksonen DE, Niskanen L, Agren JJ, Laakso M, Miettinen TA. Cholesterol metabolism and non-cholesterol sterol distribution in lipoproteins of type 1 diabetes: the effect of improved glycemic control. *Atherosclerosis* 2007; **194**: 465-472 [PMID: 16996519]

79 **Zhao L**, Chen Y, Tang R, Chen Y, Li Q, Gong J, Huang A, Varghese Z, Moorhead JF, Ruan XZ. Inflammatory stress exacerbates hepatic cholesterol accumulation via increasing cholesterol uptake and de novo synthesis. *J Gastroenterol Hepatol* 2011; **26**: 875-883 [PMID: 21488946 DOI: 10.1111/j.1440-1746.2010.06560.x]

80 **Xie X**, Liao H, Dang H, Pang W, Guan Y, Wang X, Shyy JY, Zhu Y, Sladek FM. Down-regulation of hepatic HNF4alpha gene expression during hyperinsulinemia via SREBPs. *Mol Endocrinol* 2009; **23**: 434-443 [PMID: 19179483 DOI: 10.1210/me.2007-0531]

81 **Van Rooyen DM**, Farrell GC. SREBP-2: a link between insulin resistance, hepatic cholesterol, and inflammation in NASH. *J Gastroenterol Hepatol* 2011; **26**: 789-792 [PMID: 21488942 DOI: 10.1111/j.1440]

P- Reviewer: Masaki T, Tamemoto H, Traub M **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Liu SQ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com