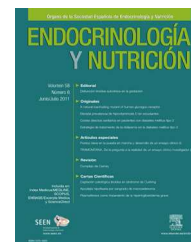


ENDOCRINOLOGÍA Y NUTRICIÓN

www.elsevier.es/endo



REVIEW ARTICLE

Role of enterocytes in dyslipidemia of insulin-resistant states[☆]

Juan Patricio Nogueira^{a,*}, Fernando Daniel Brites^b

^a Servicio de Endocrinología, Metabolismo y Medicina Nuclear, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

^b Laboratorio de Lípidos y Lipoproteínas, Departamento de Bioquímica Clínica, INFIBIOC, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, CONICET, Buenos Aires, Argentina

Received 20 February 2012; accepted 4 June 2012

KEYWORDS

Bowel;
Apolipoprotein-B48;
Type 2 diabetes;
Insulin resistance

PALABRAS CLAVE

Intestino;
Apolipoproteína-B48;
Diabetes tipo 2;
Resistencia insulínica

Abstract The increase in cardiovascular morbidity and mortality associated to insulin resistance (IR) states (obesity, metabolic syndrome, type 2 diabetes) represents a major public health problem. In IR, dyslipidemia typically include hypertriglyceridemia, low high density lipoprotein cholesterol, increased small and dense low density lipoprotein particles, and post-prandial hyperlipidemia, which play a direct or indirect role in the mechanisms of atherosclerosis. Dyslipidemia is mainly due to accumulation of circulating triglyceride-rich lipoproteins from the liver and bowel. The bowel has traditionally been seen as a passive organ, but current evidence confirms that it is an active organ subject to regulation by free fatty acids, insulin, incretins, and inflammation. Two new concepts have emerged: intestinal IR and overproduction of chylomicrons in hyperinsulinemic/IR states. A better understanding of intestinal IR may make the enterocyte a therapeutic target.

© 2012 SEEN. Published by Elsevier España, S.L. All rights reserved.

Rol del enterocito en la dislipemia de la resistencia insulínica

Resumen El aumento de la morbimortalidad cardiovascular en estados de resistencia insulínica (RI), como la obesidad, el síndrome metabólico, y la diabetes tipo 2, representa un problema mayor para la salud pública. La dislipemia de la RI comprende la hipertrigliceridemia, una disminución de colesterol de las lipoproteínas de alta densidad, aumento de las lipoproteínas de alta densidad pequeñas y densas e hiperlipemia posprandial, cumpliendo un papel directo e indirecto en la arteriosclerosis. Esta dislipemia es debida a la acumulación de lipopartículas ricas en triglicéridos de origen intestinal y hepático. El intestino ha sido considerado un órgano pasivo, pero la evidencia actual confirma al intestino como un órgano activo sometido a la regulación de: ácidos grasos libres, insulina, incretinas e inflamación. Dos conceptos han surgido,

[☆] Please cite this article as: Nogueira JP, Brites FD. Rol del enterocito en la dislipemia de la resistencia insulínica. Endocrinol Nutr. 2013;60:179–89.

* Corresponding author.

E-mail address: juanpnog@yahoo.com (J.P. Nogueira).

el de la RI intestinal y el de la sobreproducción de quilomicrones en los estados de hiperinsulinismo/RI. Una comprensión de la RI intestinal puede convertir al enterocito en una diana terapéutica.

© 2012 SEEN. Publicado por Elsevier España, S.L. Todos los derechos reservados.

Introduction

The alarming increase in the prevalence of insulin resistance (IR) in conditions such as type 2 diabetes, familial combined hyperlipidemia (FCHL), and metabolic syndrome, combined with the current obesity epidemic, represents a significant public health problem.¹ Atherosclerosis and its coronary, cerebral, and peripheral vascular complications represent the leading cause of morbidity and mortality in IR states, with a relative risk of 2–3 in males and 4–5 in females with type 2 diabetes mellitus.²

Lipid disorders play a predominant role in cardiovascular disease associated with IR states. The main lipid risk factor is low density lipoprotein cholesterol (LDL-C). This observation has been supported by epidemiological studies and fully concordant intervention studies.³ Dyslipidemia in IR is characterized by the following four manifestations: fasting hypertriglyceridemia, low levels of high density lipoprotein cholesterol (HDL-C), an increased number of small, dense LDL particles, and postprandial hyperlipidemia.⁴ Each of these parameters represents an independent cardiovascular risk marker.^{5–9} There are many arguments supporting the hypothesis that cardiovascular risk does not completely disappear with low LDL-C levels, particularly in conditions such as diabetes. This is now defined as residual cardiovascular risk.¹⁰

Some authors attribute part of the atherogenic process to an increased production of triglycerides (TG) in the bowel in the postprandial period.^{9,11} In fact, postprandial hyperlipidemia has been identified as a vascular risk factor in cohort and case-control studies.^{12,13} Recent studies suggest that type 2 diabetic patients experience an increase in triglyceride-rich lipoproteins (TRLs) of intestinal origin and in the postprandial state^{14,15}; a significant association has been found between postprandial lipid levels and coronary atherosclerosis.¹⁶ Unfailingly, intestinal TRL remnants are able to enter the subendothelial space of the vascular wall and to participate in the atherosclerosis process.¹⁷ The purpose of this study was to summarize recent findings referring to the new role of enterocytes in relation to the pathophysiology of dyslipidemia of IR states.

Role of triglyceride-rich lipoproteins in atherogenesis

Classical view

In humans, apolipoprotein (apo) B-48 is synthesized by the small bowel from the mRNA of apoB-100 by a post-transcriptional mechanism called mRNA editing, necessary for chylomicron (CM) synthesis, assembly, and secretion.^{18–20} There is a single apoB-48 molecule per CM²¹; it is therefore possible to differentiate in humans TRLs of hepatic origin

carrying apoB-100 (TRL-apoB-100) from TRLs of intestinal origin carrying apoB-48 (TRL-apoB-48). ApoB-48 content is determinant of the number of intestinal TRL particles and their remnants, of which the latter have greater atherogenic power. By contrast, TG content is a determinant of particle size; greater size decreases the atherogenic potential of TGs, as they cannot cross the subendothelial space.²²

In subjects with IR, dyslipidemia is due to a large extent to the accumulation of hepatic and intestinal TRLs in plasma. This accumulation is also secondary to hepatic hyperproduction of type 1 (big and rich in TG) very low density lipoproteins (VLDL),²³ to a defect in TRL clearance which may be attributed to decreased lipoprotein lipase (LPL) activity,^{24,25} to an abnormal apoprotein composition of lipoproteins,²⁶ to an increased circulating pool of plasma TRLs resulting from competition between hepatic and intestinal TRLs using the same saturable clearance route of LPL,²⁷ and to a defect in hepatic uptake.²⁸

The increased residence time in plasma of TRLs facilitates TG transfer from these particles to LDL and HDL by the action of the cholesteryl ester transfer protein (CETP); LDL and HDL enriched in TG are privileged substrates for hepatic lipase (HL), whose action is responsible for the formation of small, dense LDL and for increased HDL catabolism.²³ TRLs act indirectly in atherosclerotic events, promoting the occurrence of two atherogenic lipid abnormalities: an increase in the number of small, dense LDL, and a decrease in HDL-C levels (Fig. 1).

TRLs may act directly in the atherosclerosis process through an enrichment in circulating free fatty acids (FFAs), which are endogenous ligands of toll-like receptors present in leukocytes,²⁹ leading to the activation of nuclear transcription factor Kappa B (NFkB),²⁹ thus generating the synthesis of inflammatory and procoagulant cytokines and maintaining a proinflammatory, procoagulant, and proatherogenic microenvironment in the arterial wall, with its deleterious consequences¹¹ (Fig. 1).

A more direct action involves the retention of remnants of hepatic and intestinal TRLs in the arterial wall. In fact, a binding site of apoB-48 has been identified in proteoglycans in arterial intima.³⁰ Moreover, a specific receptor of apoB-48 was isolated and characterized in macrophages and monocytes.^{31,32} This receptor (apoB-48-R) differs from LDL receptors apoB/E, LRP (LDL-receptor related protein), and scavenger receptors in that it only captures TRL-apoB-48 from the bowel. This receptor is present at foam cell level in lipid streaks and atheroma plaques. Its capacity to bind and internalize intestinal TRL remnants is likely to be involved in the acquisition of the foam cell phenotype of macrophages and in the formation of atherosclerotic lesions (Fig. 1). ApoB-48 has recently been isolated from aortic atheroma plaques in humans.³³ The retention capacity of remnants of TRL-apoB-100 is ten times higher as compared to remnants of TRL-apoB-48 based on plasma levels,

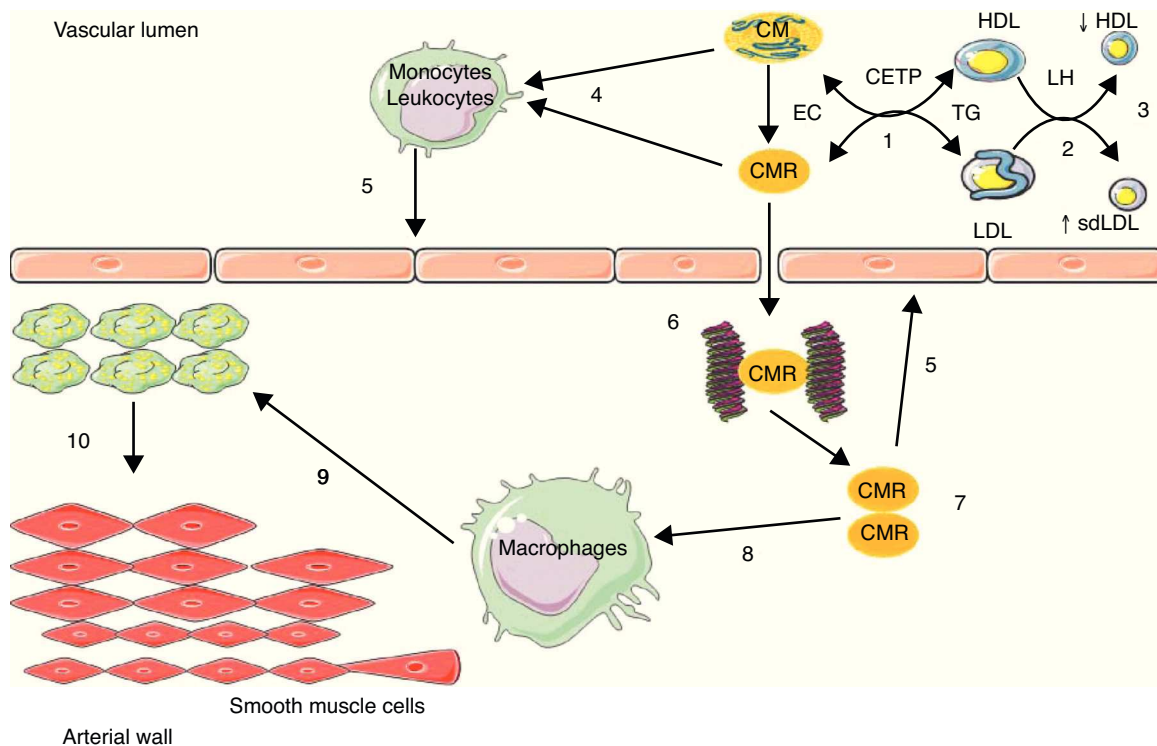


Figure 1 Implication of intestinal triglyceride-rich lipoparticles in atherosclerosis.

(1) Enrichment of low density lipoprotein (LDL) and high density lipoprotein (HDL) in triglycerides (TG) through the cholesteryl ester transfer protein (CETP); (2) TG hydrolysis by hepatic lipase (HL); (3) increase in small, dense LDL (sdLDL) and decrease in HDL by hypercatabolism; (4) enrichment of leukocytes/monocytes in free fatty acids; (5) activation of endothelium; (6) binding of chylomicron remnants (CMRs) to proteoglycans; (7) accumulation of CMRs; (8) binding of CMRs to apoB-48 receptors in macrophages; (9) conversion of macrophages into foam cells; (10) migration and proliferation of smooth muscle cells from the media. EC: esterified cholesterol.

but cholesterol levels are 40 times higher in TRL-apoB-48 as compared to TRL-apoB-100. This gives TRL-apoB-48 the possibility of releasing four times more cholesterol in the vascular wall than TRL-apoB-100.¹⁷

Based on all of these data, TRL-apoB-48 of dietary origin, CMs and their remnants appear to have atherogenic potential. Data from animal studies support this atherogenic role. In fact, there are transgenic mouse models (ApoCIII+/+ and ApoE-/-) characterized by a marked increase in lipoprotein particles carrying apoB-48 (although apoB-48 is not bowel-specific in mice). These animals experience accelerated atherosclerosis, particularly if lipid contents from their diet are increased.^{34,35}

It may be concluded from the foregoing that, apart from LDL (particularly the small, dense subfraction), there are other atherogenic lipid particles: CMs and their remnant of dietary origin, with apoB-48 having not only a role as a CM marker, but also an active role in atherosclerotic plaque formation. The classical view of the accumulation of intestinal TRLs in blood is secondary to decreased CM clearance in IR states.

Exploration of postprandial lipidemia

Metabolism of intestinal TRLs may be analyzed using two methods: the first method is the area under the curve (AUC)

of CM markers such as vitamin A and/or apoB-48 after an oral lipid overload (OLO),³⁶ and the second is the apoB-48 kinetic method using an infusion of stable isotopes under steady state conditions (plateau).³⁹

The first method uses a vitamin A metabolite, retinyl palmitate (RP), because it is incorporated into the CM and then recaptured by the liver and not secreted subsequently.³⁷ ApoB-48 is secreted in the bowel only and is not exchangeable with other lipid fractions, which makes it a helpful CM marker.³⁸ The differences lie in the fact that RP is 18–25% exchangeable with LDL and that it is only incorporated into mature CMs and does not integrate into newly formed CMs. These two differences are absent when apoB-48 is used as a specific intestinal marker.³⁶

The kinetic method represents the gold standard for the study of CM metabolism and consists of the administration every 30 or 60 min of nutritional products adapted to the daily calorie requirements of each patient to stimulate apoB-48 synthesis, obtaining stable apoB-48 plasma levels^{39,40} (plateau). In parallel to nutrition, a stable isotope such as the amino acid leucine labeled with deuterium (²H₃-leucine) or carbon 13 (1-¹³C-leucine) is infused in order to be incorporated into newly synthesized apoB-48. The goal is to obtain a ratio between the apoB-48 incorporating the stable isotope and the apoB-48 not incorporating the isotope. This ratio is expressed as a percentage, thus obtaining

an isotopic enrichment curve. These values are entered into a multicompartmental mathematic model to calculate the production rate (PR) and the catabolic rate (CR) of apoB-48.⁴¹ To sum up, the method estimating the AUC of apoB-48 after OLO is the simplest procedure, but also the least precise; by contrast, the kinetic method, in which the PR and CR of apoB-48 are calculated, is more accurate, although more complex.

Regulation of the synthesis of intestinal triglyceride-rich lipoproteins

Modulation of diet

The production of intestinal TRLs has been considered for a long time to be regulated by dietary supply and, more specifically, by the total of lipids ingested. Many studies have addressed the relation between dietary supply and postprandial lipidemia without making any differentiation between abnormal production and/or clearance of CMs and their remnants. Lipid amounts of 20–50 g per meal dose-dependently increase postprandial lipidemia, and a constant increase is seen with amounts higher than 80 g per meal.⁴² The addition of sucrose and/or fructose or carbohydrates with a high glycemic index to a fat-rich meal increases postprandial lipidemia.⁴²

The other dietary factors that may play a mild to moderate role in the reduction of postprandial lipidemia include the administration of n-3 (omega-3) and n-6 (omega-6) polyunsaturated fatty acids or fiber-rich foods.⁴²

Increased postprandial lipidemia may also be secondary to a cholesterol-deficient or protein-rich meal.⁴³ Dietary provision contributes to a marked increase in TG content rather than apoB-48 content in the CM particle, with a resultant increase in the size, rather than the number, of TRL particles.²²

Overproduction of intestinal triglyceride-rich lipoproteins in insulin resistance states

Animal model

The Syrian golden hamster (fructose-fed hamster), made resistant to insulin through fructose-rich feeding, is a useful animal model for studying the role of the production of intestinal TRLs in the development of metabolic dyslipidemia.⁴⁴ As occurs in humans, the tissue-specific expression of apoB-100 in the liver only and of apoB-48 in the bowel only represents an advantage in the hamster model, allowing for *in vivo* studies of the production of intestinal versus hepatic TRLs.^{45,46} In this model, a 2–4-fold greater increase in TRL production was shown as compared to the hamster model with no IR. This acute secretion of intestinal TRLs has been confirmed *ex vivo* in cultures of enterocytes with IR. Similar to hepatic TRL overproduction,^{47–49} *ex vivo* and *in vitro* experiences on enterocytes have shown that chronic fructose feeding is associated with a greater stability of intracellular apoB-48, increased *de novo* lipogenesis, increased endogenous synthesis of TG and cholesterol esters, and increased expression of microsomal transfer protein (MTF), a key protein in the formation of intestinal

lipoproteins⁴⁴ (Fig. 2). A fructose-rich diet for only two days has no impact on intestinal TRL production, which suggests that this fructose-rich diet has a chronic effect.⁴⁴

This overproduction of intestinal TRLs has been confirmed *in vivo*, *ex vivo*, and *in vitro* in another IR model, the high fat-fed Syrian Golden hamster.⁵⁰ In these two animal models of hamster with IR, treatment with rosiglitazone (an agonist of the peroxisome proliferator-activated receptor gamma (PPAR- γ)) corrected elevated MTP levels and reduced the intestinal overproduction of TRLs, probably promoting insulin sensitivity.^{50,51} The results in this model were very similar to those in the model with IR/type 2 diabetes (the gerbil *Psammomys obesus*), which supports the association between IR and intestinal TRL overproduction. In this model, increases in monoacylglycerol transferase (MGAT), diacylglycerol transferase (DGAT), and the expression of fatty acid binding protein L (L-FABP) promoted *de novo* lipogenesis, without finding any abnormalities in MTP expression.⁵²

As regards insulin signaling pathways, *in vivo*, *ex vivo* and *in vitro* experiences in the hamster model with IR (fructose-fed hamster) showed defects at enterocyte level including a decrease in insulin receptor substrate-1 (IRS-1) and an inhibition of protein kinase B or Akt, and inversely, increased concentrations of subunit p110 of PI-3 kinase, tyrosine phosphatase 1-B, and the mitogen-activated protein kinase pathway (MAPK/ERK). These abnormalities suggest intestinal IR, which causes hyperactivation of the MAP/ERK pathway, leading to the increased expression of MTP, apoB, and a transcription factor, sterol response element binding protein 1c (SREBP-1c), which stimulates the synthesis of proteins involved in *de novo* lipogenesis.^{53,54} Overall, these abnormalities lead to the increased production and secretion of intestinal TRLs^{53,54} (Fig. 2).

Human model

The overproduction of intestinal TRLs is recognized as a new component of IR syndrome. This excess production was first documented in humans, in whom intestinal TRL production is increased as a function of the degree of hyperinsulinism and insulin sensitivity.⁴¹ Unlike animal models, rosiglitazone does not improve the production of intestinal TRLs in healthy subjects, but impairs it despite its insulin sensitizing effect, with a non-significant trend to an increased production and decreased clearance of intestinal TRLs⁵⁵ (Table 1). These results may explain the increase in coronary atherosclerosis in patients treated with rosiglitazone.⁵⁶ Observational studies in obese patients with IR have shown increased plasma levels of apoB-48 in fasting and postprandial conditions.^{57,58} In patients with type 2 diabetes, the overproduction of intestinal TRLs was found to be associated with a decrease in their clearance.¹⁴ FCHL is characterized by higher apoB-48 levels in fasting and postprandial conditions^{59,60} (Table 2). It is well known that the accumulation of apoB-48 is caused by a decreased LPL activity secondary to the increase in hepatic TRLs⁶⁰ associated in turn with apoC-III increase (a physiological inhibitor of LPL). ApoC-III in turn stimulates TRL production, participating in the final stage of TRL assembly at cell level.⁶¹ The presence of liver steatosis in type 2 diabetes and in FCHL is associated with increased production of apoB-48 production in the postprandial state.^{62,63} The IR

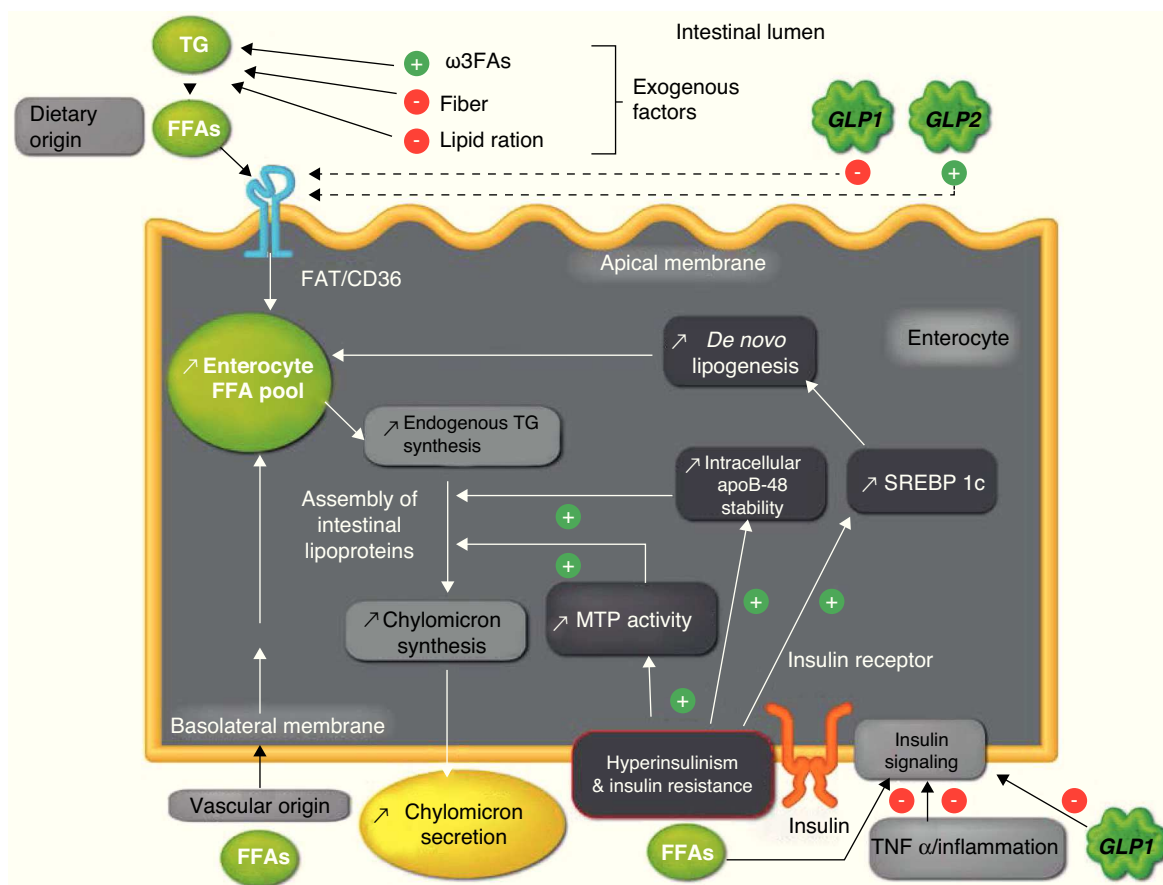


Figure 2 Mechanisms of overproduction of intestinal triglyceride-rich lipoparticles in the setting of hyperinsulinism and insulin resistance.

FFAs: free fatty acids; ω 3FAs: omega-3 fatty acids; FAT/CD36: fatty acid translocase; GLP-1: glucagon-like peptide-1; GLP-2: glucagon-like peptide-2; MTP: microsomal transfer protein; SREBP-1c: sterol response element binding protein 1c; TNF α : tumor necrosis factor alpha; TG: triglycerides.

state is the main determinant of apoB-48 overproduction, with active involvement in the coronary disease of these patients.⁶⁴

atherosclerosis, has justified the search for factors that modulate this production.

Intestinal lipid transporters

Passive diffusion was considered for a long time to be the main entry route of nutrients into the intestinal cell. This has changed with the demonstration of specific protein transporters on the microvillus membrane. The main protein transporters include fatty acid

Current view

Enterocyte involvement in lipid metabolism and intestinal TRL production, recognized as a new component of IR and as a significant element in the etiopathogenesis of

Table 1 Exploration of the metabolism of triglyceride-rich lipoproteins (TRLs)-apoB-48 in preserved insulin sensitivity states.

Subjects	Design	Methods	Results	References
Healthy	Intervention/RZG	Kinetics	↑ PR-apoB-48	Duez H et al., 2008 ⁵⁵
Healthy	Intervention/HIEC	OLO	↑ AUC-apoB-48	Harvis A et al., 2001 ⁷⁴
Healthy	Intervention/HIEC+I	Kinetics	↓ PR-apoB-48	Pavlic M et al., 2011 ⁷²
Healthy	Intervention/I	Kinetics	↑ PR-apoB-48	Duez H et al., 2008 ⁶⁸
Healthy	Intervention/GL	Kinetics	PR-apoB-48 (no change)	Xiao C et al., 2011 ⁸⁰
Healthy	Intervention/EX	Kinetics	↓ PR-apoB-48	Xiao C et al., 2012 ⁸⁶

AUC-apoB-48: area under the curve of apoprotein B48; HIEC: hyperinsulinemic-euglycemic clamp; EX: exenatide; GL: glucagon; I: Intralipid; RZG: rosiglitazone; no change: no significant change; OLO: oral lipid overload; PR-apoB-48: apoprotein B48 production rate.

Table 2 Exploration of the metabolism of triglyceride-rich lipoproteins (TRLs)-apoB-48 in insulin resistant states.

Subjects	Design	Methods	Results	References
Obese	Intervention/HIEC	OLO	AUC-apoB-48 (no change)	Allister EM et al., 2006 ⁵⁸
FCHL	Case/control	OLO	↑ AUC-apoB-48	Verseyden C et al., 2002 ⁶⁰
FCHL	Intervention/AT	OLO	↑ ApoB-48 clearance	Castro Cabezas M et al., 2008 ⁹⁷
T2D	Case/control	Kinetics	↑ PR/↓ CR-apoB-48	Hogue JC et al., 2007 ¹⁴
T2D	Intervention/AT/FB	Kinetics	↓ PR/↑ CR-apoB-48	Hogue JC et al., 2008 ⁹⁶
T2D	Intervention/VI	OLO	↓ AUC-apoB-48	Matikainen N et al., 2006 ⁸⁷
T2D	Intervention/SI	OLO	↓ AUC-apoB-48	Tremblay AJ et al., 2011 ⁸⁸
T2D	Intervention/HIEC/I	Kinetics	PR-apoB-48 (no change)	Nogueira JP et al., 2012 ⁴⁰

AUC-apoB-48: area under the curve of apoprotein B48; AT: atorvastatin; HIEC: hyperinsulinemic-euglycemic clamp; FB: fenofibrate; FCHL: familial combined hyperlipidemia; I: Intralipid; no change: no significant change; SI: sitagliptin; OLO: oral lipid overload; PR-apoB-48: apoprotein B48 production rate; VI: vildagliptin.

translocase (FAT/CD36), involved in the absorption of cholesterol and long-chain fatty acids; Niemann-Pick C1 like 1 (NPC1L1), involved in cholesterol and phytosterol absorption; ATP-binding-cassette transporter A1 (ABCA1), involved in cholesterol flow; and ATP-binding-cassette transporter G5/G8 (ABCG5/G8), involved in sterol flow. Enterocyte lipid content is a regulator of chylomicron production. The rat model deficient in the FAT/CD36 transporter, showing decreased lymphatic secretion of TG, illustrates this condition.⁶⁵ In rat models of diabetes (induced by streptozotocin), as compared to control rats, intestinal mRNAs of NPC1L1 and MTP increased, while those of ABCG5 and ABCG8 decreased, with a positive correlation with TG and cholesterol levels inside CMs and with apoB-48 levels.⁴

In a study conducted on type 2 diabetic patients and controls, duodenal biopsy was performed, and mRNAs of NPC1L1, MTP, and ABCG5/8 positively correlated to TG levels, showing an association between the expression of enterocyte levels and lipid abnormalities in type 2 diabetes.⁶⁶

Free fatty acids

Circulating FFAs are increased in type 2 diabetes, obesity, and FCHL.⁶³ These FFAs accumulate in non-adipocyte tissues, exerting different harmful effects collectively called lipocytotoxicity. FFA flow in the liver stimulates TRL production and secretion,⁶⁷ mainly in IR, because hepatic oxidation of fatty acids is reduced. Acute elevation of plasma FFA levels stimulates the production of intestinal and hepatic TRLs with no change in clearance in healthy subjects⁶⁸ (Table 1). This stimulating effect of FFAs on TRL production had previously been shown in the insulin-sensitive Syrian golden hamster model with no additive effect in the insulin-resistant hamster model, except when previously treated with insulin sensitizers such as rosiglitazone.⁵¹ The mechanisms accounting for this phenomenon are the blockade of the insulin signaling pathway, the stabilization of apoB-48, the direct incorporation of FFAs into lipoproteins, the stimulation of the mobilization and incorporation of reserve TG, and increased *de novo* TG synthesis⁵¹ (Fig. 2).

An *in vivo*, *ex vivo* and *in vitro* study in rats showed that the effect of FFAs in the liver is bimodal; FFAs at small concentrations and for a short time stimulate the secretion of hepatic TRLs, while FFAs at high concentrations

and for a long time decrease the production of hepatic TRLs.⁶⁹ This suppressive effect of FFAs on hepatic TRL production was confirmed in patients with type 2 diabetes under hyperinsulinemic-euglycemic clamp after the infusion of Intralipid and heparin.⁴⁰ This bimodal effect of FFAs was absent for apoB-48 in the animal model and in the population with type 2 diabetes.^{40,69}

Insulin

In contrast to the stimulating effect of hyperinsulinism associated with IR on the production of hepatic and intestinal TRLs,^{4,23} it is commonly accepted that acute elevation of insulin levels inhibits the secretion of hepatic and intestinal TRLs. This has been shown in humans both *in vivo*^{70–72} and *in vitro*.⁷³ In healthy humans, Malmström et al. showed that the inhibitory effect of insulin on hepatic TRL production was independent of the suppressive effect of insulin on FFAs⁷⁰; by contrast, Pavlic et al. showed that the inhibitory effect of insulin on intestinal TRL production was partly dependent on the effect of insulin on FFAs⁷² (Table 1).

In healthy humans, hyperinsulinism induced by foods with a high glycemic index or by a hyperinsulinemic-euglycemic clamp delays the appearance of intestinal TRLs in plasma after a fat-rich meal⁷⁴ (Table 1). An *in vitro* study showed that the acute addition of insulin to a culture medium of human fetal intestinal cells reduced chylomicron secretion.⁷⁵ Patients with type 2 diabetes, obese and with FCHL who have chronic hyperinsulinism secondary to IR do not respond to the acute inhibitory effect of insulin on the production of hepatic TRLs, probably secondary to the presence of liver steatosis.^{71,76,77} Similar checks have been performed in hepatocytes from rats with IR.⁷⁸ The suppressive action of insulin on CM production is absent in obese patients with IR subject to a hyperinsulinemic clamp.⁵⁸ We recently showed, in a previous study, that patients with type 2 diabetes under a hyperinsulinemic-euglycemic clamp are refractory to the acute inhibitory effect of insulin on intestinal TRL production⁴⁰ (Table 2).

Glucagon

This pancreatic hormone may be involved in oxidative FFA metabolism in the liver.⁷⁹ In rats, glucagon decreased TG synthesis and secretion, and activated β -oxidation through

the activation of PPAR- α .⁷⁹ In healthy humans, acute glucagon administration decreased secretion and catabolism of VLDL type 1, with no changes in their plasma levels; by contrast, no significant changes were seen in CM secretion and catabolism⁸⁰ (Table 1). The lack of effect of glucagon on enterocytes may be due to the decrease in glucagon receptors in the bowel as compared to the liver.⁸¹

Incretins

Glucagon-like peptide-1 (GLP-1) and glucagon-like peptide-2 (GLP-2) are secreted in response to the oral intake of food, particularly food rich in fat and carbohydrates. In humans, GLP-1 secretion may be stimulated by oleic acid,⁸² which suggests an association between lipid metabolism and GLP-1. The concept that incretins modulate the metabolism of chylomicrons emerged in 2005, when the administration of recombinant GLP-1 to healthy rats was shown to decrease intestinal TG secretion.⁸³ The administration of a dipeptidyl peptidase IV (DPP-IV) inhibitor, such as sitagliptin, decreases TG secretion in the Syrian golden hamster model. This model has made it possible to explain the link between insulin signaling and the effect of GLP-1.⁸⁴

The administration of GLP-1 to healthy subjects decreased postprandial lipidemia (absence of TG elevation and decrease in plasma FFAs).⁸⁵ A recent study showed that treatment of healthy men with exenatide (a GLP-1 analog) for 4 weeks decreased PR-apoB-48 without changing PR-apoB-100, suggesting that the bowel is the site of action of GLP-1 in lipid metabolism⁸⁶ (Table 1).

The use of vildagliptin (a DPP-IV inhibitor) for 4 weeks improved postprandial lipidemia (decreasing plasma TG, chylomicron TG, and intestinal TRL levels) in patients with type 2 diabetes⁸⁷ (Table 2). Treatment with sitagliptin for 6 weeks decreased postprandial apoB-48 levels with a concomitant improvement in insulin sensitivity in patients with type 2 diabetes⁸⁸ (Table 2). In addition, the use of exenatide for 2 weeks in patients with type 2 diabetes decreased postprandial TG secretion.⁸⁹

By contrast, GLP-2 secreted together with GLP-1 exacerbates postprandial lipidemia. GLP-2 is elevated in the streptozotocin-induced rat model of diabetes, and could be implicated in the intestinal hyperplasia associated with diabetes.⁹⁰ Beyond its intestinotrophic effects, the acute administration of GLP-2 to humans stimulates postprandial lipidemia, probably increasing the intestinal absorption of lipids.⁹¹ Recent data in hamsters and mice support the role of GLP-2 in postprandial hyperlipidemia (increased assembly and secretion of intestinal TRLs) due to increased lipid absorption through expression of the glycosylated form of CD36/fatty acid translocase at the enterocyte apical membrane⁹² (Fig. 2).

Inflammation

IR is associated with a chronic inflammatory state. However, few studies have addressed the link between inflammation and IR at enterocyte level. In the Syrian golden hamster model, inflammation induced by the infusion of tumor necrosis factor alpha (TNF- α) was shown to induce intestinal IR by decreasing the insulin signaling cascade (Fig. 2). On the one

hand, TNF- α decreases the phosphorylation of subunit α of insulin receptor, IRS-1, and Akt, and, on the other hand, increases the MAPK/ERK-1/2 pathway in the postprandial period. This intestinal IR is associated with the overproduction of intestinal TRLs in fasting and postprandial conditions associated with the increased expression of MTP and transporters such as CD36, without modifying the transcription factors involved in *de novo* lipogenesis, such as SREBP-1c.⁹³

Intervention studies

Several nutritional or pharmacological intervention studies have been conducted with the aim of reducing postprandial lipidemia. This review will only focus on clinical trials evaluating the effect of treatment on intestinal TRL production. These studies usually had small sample sizes and modest statistical power.

Effect of circulating free fatty acids

In an animal model of metabolic syndrome (the gerbil *Psammomys obesus*), a diet rich in n-3 fatty acids (omega-3) decreased the synthesis of apo-B-48 and the assembly and secretion of intestinal TRLs.⁹⁴ The addition of treatment with omega-3 fatty acids (3–4 g/day) to a high-calorie diet and treatment with a statin (fluvastatin 80 mg/day) significantly decreased fasting levels of apoB-48 in a group of 8 with type 2 diabetes with mixed hyperlipidemia.⁹⁵

Effect of statins, fibrates, and ezetimibe

Statin treatment (atorvastatin 20 mg/day for 6 weeks) decreased intestinal TRL production in a group of 6 patients with type 2 diabetes and hypertriglyceridemia. A similar but not significant trend was seen with fibrate treatment (fenofibrate 200 mg/day for 6 weeks). However, treatment with fenofibrate increased catabolism of TRL-apoB-48, which does not occur with atorvastatin⁹⁶ (Table 2). Treatment with atorvastatin (10–80 mg/day for 16 weeks) decreased TRL-apoB-48 levels by stimulating clearance in the postprandial state in patients with FCHL⁹⁷ (Table 2). The use of fenofibrate (200 mg/day for 6 months) decreased levels of intestinal TRL remnants in patients with FCHL.⁹⁸

In a group of 8 patients with hypercholesterolemia, treatment with ezetimibe for 8 weeks did not change the metabolism of intestinal TRLs.⁹⁹ However, when simvastatin (40 mg/day for 6 weeks) was combined with ezetimibe in a group of 16 patients with mixed hyperlipidemia, a significant reduction occurred in the production of intestinal TRLs. This reduction is not achieved with simvastatin or ezetimibe alone.¹⁰⁰

Evaluation of triglyceride-rich lipoproteins of intestinal origin in clinical practice

The intestinal overproduction of TRLs represents a new component of IR which contributes to increased plasma TG levels in both the postprandial and postabsorptive states. Enterocytes are resistant to the suppressive action of insulin on CM production in type 2 diabetes and obesity.^{40,56} The

assessment of postprandial lipidemia in IR states ought to be an additional component of routine examinations, in an attempt to detect more marked subclinical hyperlipidemia in the postprandial state as compared to under fasting conditions. The standardization of the amount of fat needed to stimulate CM metabolism continues to be controversial.⁴² A recent meta-analysis of 113 clinical trials of postprandial lipidemia proposed the use of a new index, the so-called lipemic index (LI), for which 50–70 g of fat per meal are given and postprandial lipidemia is assessed through the AUC 4 h after the end of OLO.^{101,102}

Testing of fasting and postprandial apoB-48 levels should be a part of annual examinations in IR states such as type 2 diabetes, obesity, FCHL, and coronary disease due to their association with atherosclerosis.^{59,103} ApoB-48 would also be helpful for follow-up in treatments with statins, fibrates, and omega-3.^{95,97} The value of apoB-48 in the clinical and research areas is clearly evident.

Conclusions

There are many arguments suggesting that the bowel is not a passive organ, but rather a metabolically active organ that receives information from the periphery and is able to modulate its own lipid synthesis and secretion processes in relation to substrates, hormones, and other endogenous or exogenous substances. Functional kinships exist between the bowel and liver. The direct and/or indirect role(s) of enterocyte IR, as well as the cellular and molecular mechanisms of action of these different regulatory factors, have not been elucidated yet. Testing of apoB-48 as a marker of postprandial lipidemia and atheromatosis should be used in the clinical practice of endocrinology.

The atherogenic potential of chylomicrons makes understanding their overproduction in the bowel and their accumulation in plasma in type 2 diabetes, and also in IR syndromes mandatory.

Conflicts of interest

The authors state that they have no conflicts of interest.

Acknowledgement

Authors thank Dr. León Litwak for his reading and corrections on this study.

References

- Seshasai SR, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med*. 2011;364:829–41.
- Grimaldi A, Heurtier A. Epidemiology of cardio-vascular complications of diabetes. *Diabetes Metab*. 1999;25 Suppl. 3:12–20.
- Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–81.
- Adeli K, Lewis GF. Intestinal lipoprotein overproduction in insulin-resistant states. *Curr Opin Lipidol*. 2008;19:221–8.
- Barter P, Gotto AM, LaRosa JC, Maroni J, Szarek M, Grundy SM, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N Engl J Med*. 2007;357:1301–10.
- Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk*. 1996;3:213–9.
- Miller M, Cannon CP, Murphy SA, Qin J, Ray KK, Braunwald E. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol*. 2008;51:724–30.
- Packard CJ. Small dense low-density lipoprotein and its role as an independent predictor of cardiovascular disease. *Curr Opin Lipidol*. 2006;17:412–7.
- 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.
- LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352:1425–35.
- Alipour A, Elte JW, van Zaanen HC, Rietveld AP, Castro Cabezas M. Novel aspects of postprandial lipemia in relation to atherosclerosis. *Atheroscler Suppl*. 2008;9:39–44.
- Curtin A, Deegan P, Owens D, Collins P, Johnson A, Tomkin GH. Elevated triglyceride-rich lipoproteins in diabetes. A study of apolipoprotein b-48. *Acta Diabetol*. 1996;33:205–10.
- Pal S, Semorine K, Watts GF, Mamo J. Identification of lipoproteins of intestinal origin in human atherosclerotic plaque. *Clin Chem Lab Med*. 2003;41:792–5.
- Hogue JC, Lamarche B, Tremblay AJ, Bergeron J, Gagne C, Couture P. Evidence of increased secretion of apolipoprotein b-48-containing lipoproteins in subjects with type 2 diabetes. *J Lipid Res*. 2007;48:1336–42.
- Schaefer EJ, McNamara JR, Shah PK, Nakajima K, Cupples LA, Ordovas JM, et al. Elevated remnant-like particle cholesterol and triglyceride levels in diabetic men and women in the framingham offspring study. *Diabetes Care*. 2002;25:989–94.
- Karpe F, Steiner G, Uffelman K, Olivecrona T, Hamsten A. Postprandial lipoproteins and progression of coronary atherosclerosis. *Atherosclerosis*. 1994;106:83–97.
- Proctor SD, Vine DF, Mamo JC. Arterial retention of apolipoprotein b(48)- and b(100)-containing lipoproteins in atherogenesis. *Curr Opin Lipidol*. 2002;13:461–70.
- Innerarity TL, Boren J, Yamanaka S, Olofsson SO. Biosynthesis of apolipoprotein b48-containing lipoproteins. Regulation by novel post-transcriptional mechanisms. *J Biol Chem*. 1996;271:2353–6.
- van Greevenbroek MM, de Bruin TW. Chylomicron synthesis by intestinal cells in vitro and in vivo. *Atherosclerosis*. 1998;141 Suppl. 1:59–16.
- Kendrick JS, Chan L, Higgins JA. Superior role of apolipoprotein b48 over apolipoprotein b100 in chylomicron assembly and fat absorption: an investigation of apobec-1 knock-out and wild-type mice. *Biochem J*. 2001;356:821–7.
- Gleeson A, Anderton K, Owens D, Bennett A, Collins P, Johnson A, et al. The role of microsomal triglyceride transfer protein and dietary cholesterol in chylomicron production in diabetes. *Diabetologia*. 1999;42:944–8.
- Cohn JS, Johnson EJ, Millar JS, Cohn SD, Milne RW, Marcel YL, et al. Contribution of apob-48 and apob-100 triglyceride-rich lipoproteins (TRL) to postprandial increases in the plasma concentration of TRL triglycerides and retinyl esters. *J Lipid Res*. 1993;34:2033–40.
- Adiels M, Olofsson SO, Taskiran MR, Boren J. Overproduction of very low-density lipoproteins is the hallmark of the dyslipidemia in the metabolic syndrome. *Arterioscler Thromb Vasc Biol*. 2008;28:1225–36.

24. Haffner SM, Foster DM, Kushwaha RS, Hazzard WR. Retarded chylomicron apolipoprotein-b catabolism in type 2 (non-insulin-dependent) diabetic subjects with lipaemia. *Diabetologia*. 1984;26:349–54.
25. Mamo JC, Hirano T, Sainsbury A, Fitzgerald AK, Redgrave TG. Hypertriglyceridemia is exacerbated by slow lipolysis of triacylglycerol-rich lipoproteins in fed but not fasted streptozotocin diabetic rats. *Biochim Biophys Acta*. 1992;1128:132–8.
26. Bar-on H, Levy E, Oschry Y, Ziv E, Shafir E. Removal defect of very-low-density lipoproteins from diabetic rats. *Biochim Biophys Acta*. 1984;793:115–8.
27. Brunzell JD, Hazzard WR, Porte Jr D, Bierman EL. Evidence for a common, saturable, triglyceride removal mechanism for chylomicrons and very low density lipoproteins in man. *J Clin Invest*. 1973;52:1578–85.
28. Chan DC, Watts GF, Redgrave TG, Mori TA, Barrett PH. Apolipoprotein b-100 kinetics in visceral obesity: Associations with plasma apolipoprotein c-iii concentration. *Metabolism*. 2002;51:1041–6.
29. Dasu MR, Jialal I. Free fatty acids in the presence of high glucose amplify monocyte inflammation via toll-like receptors. *Am J Physiol Endocrinol Metab*. 2011;300:E145–54.
30. Flood C, Gustafsson M, Richardson PE, Harvey SC, Segrest JP, Boren J. Identification of the proteoglycan binding site in apolipoprotein b48. *J Biol Chem*. 2002;277:32228–33.
31. Varela LM, Ortega A, Bermudez B, Lopez S, Pacheco YM, Villar J, et al. A high-fat meal promotes lipid-load and apolipoprotein b-48 receptor transcriptional activity in circulating monocytes. *Am J Clin Nutr*. 2011;93:918–25.
32. Brown ML, Ramprasad MP, Umeda PK, Tanaka A, Kobayashi Y, Watanabe T, et al. A macrophage receptor for apolipoprotein b48: cloning, expression, and atherosclerosis. *Proc Natl Acad Sci USA*. 2000;97:7488–93.
33. Nakano T, Nakajima K, Niimi M, Fujita MQ, Nakajima Y, Takeichi S, et al. 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.
34. de Silva HV, Lauer SJ, Wang J, Simonet WS, Weisgraber KH, Mahley RW, et al. Overexpression of human apolipoprotein c-iii in transgenic mice results in an accumulation of apolipoprotein b48 remnants that is corrected by excess apolipoprotein e. *J Biol Chem*. 1994;269:2324–35.
35. Zhang SH, Reddick RL, Piedrahita JA, Maeda N. Spontaneous hypercholesterolemia and arterial lesions in mice lacking apolipoprotein e. *Science*. 1992;258:468–71.
36. Lemieux S, Fontani R, Uffelman KD, Lewis GF, Steiner G. Apolipoprotein b-48 and retinyl palmitate are not equivalent markers of postprandial intestinal lipoproteins. *J Lipid Res*. 1998;39:1964–71.
37. Lenich CM, Ross AC. Chylomicron remnant-vitamin a metabolism by the human hepatoma cell line hepg2. *J Lipid Res*. 1987;28:183–94.
38. Phillips ML, Pullinger C, Kroes I, Kroes J, Hardman DA, Chen G, et al. A single copy of apolipoprotein b-48 is present on the human chylomicron remnant. *J Lipid Res*. 1997;38:1170–7.
39. Welty FK, Lichtenstein AH, Barrett PH, Dolnikowski GG, Schaefer EJ. Interrelationships between human apolipoprotein a-i and apolipoproteins b-48 and b-100 kinetics using stable isotopes. *Arterioscler Thromb Vasc Biol*. 2004;24:1703–7.
40. Nogueira JP, Maraninchi M, Beliard S, Padilla N, Duvillard L, Mancini J, et al. Absence of acute inhibitory effect of insulin on chylomicron production in type 2 diabetes. *Arterioscler Thromb Vasc Biol*. 2012;32:1039–44.
41. Duez H, Lamarche B, Uffelman KD, Valero R, Cohn JS, Lewis GF. Hyperinsulinemia is associated with increased production rate of intestinal apolipoprotein b-48-containing lipoproteins in humans. *Arterioscler Thromb Vasc Biol*. 2006;26:1357–63.
42. Lopez-Miranda J, Williams C, Lairon D. Dietary, physiological, genetic and pathological influences on postprandial lipid metabolism. *Br J Nutr*. 2007;98:458–73.
43. Lairon D. Macronutrient intake and modulation on chylomicron production and clearance. *Atheroscler Suppl*. 2008;9:45–8.
44. Haidari M, Leung N, Mahbub F, Uffelman KD, Kohen-Avraroglu R, Lewis GF, et al. Fasting and postprandial overproduction of intestinally derived lipoproteins in an animal model of insulin resistance. Evidence that chronic fructose feeding in the hamster is accompanied by enhanced intestinal de novo lipogenesis and apob48-containing lipoprotein overproduction. *J Biol Chem*. 2002;277:31646–55.
45. Arbeeney CM, Meyers DS, Bergquist KE, Gregg RE. Inhibition of fatty acid synthesis decreases very low density lipoprotein secretion in the hamster. *J Lipid Res*. 1992;33:843–51.
46. Liu GL, Fan LM, Redinger RN. The association of hepatic apoprotein and lipid metabolism in hamsters and rats. *Comp Biochem Physiol A Comp Physiol*. 1991;99:223–8.
47. Taghibiglou C, Carpentier A, Van Iderstine SC, Chen B, Rudy D, Aiton A, et al. Mechanisms of hepatic very low density lipoprotein overproduction in insulin resistance. Evidence for enhanced lipoprotein assembly, reduced intracellular apob degradation, and increased microsomal triglyceride transfer protein in a fructose-fed hamster model. *J Biol Chem*. 2000;275:8416–25.
48. Taghibiglou C, Rashid-Kolvear F, Van Iderstine SC, Le-Tien H, Fantus IG, Lewis GF, et al. Hepatic very low density lipoprotein-apob overproduction is associated with attenuated hepatic insulin signaling and overexpression of protein-tyrosine phosphatase 1b in a fructose-fed hamster model of insulin resistance. *J Biol Chem*. 2002;277:793–803.
49. Carpentier A, Taghibiglou C, Leung N, Szeto L, van Iderstine SC, Uffelman KD, et al. Ameliorated hepatic insulin resistance is associated with normalization of microsomal triglyceride transfer protein expression and reduction in very low density lipoprotein assembly and secretion in the fructose-fed hamster. *J Biol Chem*. 2002;277:28795–802.
50. Leung N, Naples M, Uffelman K, Szeto L, Adeli K, Lewis GF. Rosiglitazone improves intestinal lipoprotein overproduction in the fat-fed syrian golden hamster, an animal model of nutritionally-induced insulin resistance. *Atherosclerosis*. 2004;174:235–41.
51. Lewis GF, Uffelman K, Naples M, Szeto L, Haidari M, Adeli K. Intestinal lipoprotein overproduction, a newly recognized component of insulin resistance, is ameliorated by the insulin sensitizer rosiglitazone: studies in the fructose-fed syrian golden hamster. *Endocrinology*. 2005;146:247–55.
52. Zoltowska M, Ziv E, Delvin E, Sinnett D, Kalman R, Garofalo C, et al. Cellular aspects of intestinal lipoprotein assembly in psammomys obesus: a model of insulin resistance and type 2 diabetes. *Diabetes*. 2003;52:2539–45.
53. Federico LM, Naples M, Taylor D, Adeli K. Intestinal insulin resistance and aberrant production of apolipoprotein b48 lipoproteins in an animal model of insulin resistance and metabolic dyslipidemia: evidence for activation of protein tyrosine phosphatase-1b, extracellular signal-related kinase, and sterol regulatory element-binding protein-1c in the fructose-fed hamster intestine. *Diabetes*. 2006;55:1316–26.
54. Avramoglu RK, Basciano H, Adeli K. Lipid and lipoprotein dysregulation in insulin resistant states. *Clin Chim Acta*. 2006;368:1–19.
55. Duez H, Lamarche B, Uffelman KD, Valero R, Szeto L, Lemieux S, et al. Dissociation between the insulin-sensitizing effect of rosiglitazone and its effect on hepatic and intestinal lipoprotein production. *J Clin Endocrinol Metab*. 2008;93:1722–9.
56. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med*. 2007;356:2457–71.

57. Chan DC, Watts GF, Barrett PH, Mamo JC, Redgrave TG. Markers of triglyceride-rich lipoprotein remnant metabolism in visceral obesity. *Clin Chem*. 2002;48:278–83.
58. Allister EM, James AP, Watts GF, Barrett PH, Mamo JC. Effect of an acute hyperinsulinaemic clamp on post-prandial lipaemia in subjects with insulin resistance. *Eur J Clin Invest*. 2006;36:489–96.
59. Alipour A, Valdivielso P, Elte JW, Janssen HW, Rioja J, van der Meulen N, et al. Exploring the value of apob48 as a marker for atherosclerosis in clinical practice. *Eur J Clin Invest*. 2011;41:1365–71.
60. Verseyden C, Meijssen S, Castro Cabezas M. Postprandial changes of apob-100 and apob-48 in tg rich lipoproteins in familial combined hyperlipidemia. *J Lipid Res*. 2002;43:274–80.
61. Sundaram M, Zhong S, Bou Khalil M, Links PH, Zhao Y, Iqbal J, et al. Expression of apolipoprotein c-iii in mca-rh7777 cells enhances vldl assembly and secretion under lipid-rich conditions. *J Lipid Res*. 2010;51:150–61.
62. Evans K, Burdge GC, Wootton SA, Collins JM, Clark ML, Tan GD, et al. Tissue-specific stable isotope measurements of postprandial lipid metabolism in familial combined hyperlipidaemia. *Atherosclerosis*. 2008;197:164–70.
63. Brouwers MC, de Graaf J, van Greevenbroek MM, Schaper N, Stehouwer CD, Stalenhoef AF. Novel drugs in familial combined hyperlipidemia: lessons from type 2 diabetes mellitus. *Curr Opin Lipidol*. 2010;21:530–8.
64. Duez H, Pavlic M, Lewis GF. Mechanism of intestinal lipoprotein overproduction in insulin resistant humans. *Atheroscler Suppl*. 2008;9:33–8.
65. Drover VA, Ajmal M, Nassir F, Davidson NO, Nauli AM, Sahoo D, et al. Cd36 deficiency impairs intestinal lipid secretion and clearance of chylomicrons from the blood. *J Clin Invest*. 2005;115:1290–7.
66. 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;49:1008–16.
67. Lewis GF, Carpentier A, Adeli K, Giacca A. Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. *Endocr Rev*. 2002;23:201–29.
68. Duez H, Lamarche B, Valero R, Pavlic M, Proctor S, Xiao C, et al. Both intestinal and hepatic lipoprotein production are stimulated by an acute elevation of plasma free fatty acids in humans. *Circulation*. 2008;117:2369–76.
69. Ota T, Gayet C, Ginsberg HN. Inhibition of apolipoprotein b100 secretion by lipid-induced hepatic endoplasmic reticulum stress in rodents. *J Clin Invest*. 2008;118:316–32.
70. Malmstrom R, Packard CJ, Caslake M, Bedford D, Stewart P, Yki-Jarvinen H, et al. Effects of insulin and acipimox on vldl1 and vldl2 apolipoprotein b production in normal subjects. *Diabetes*. 1998;47:779–87.
71. Malmstrom R, Packard CJ, Caslake M, Bedford D, Stewart P, Yki-Jarvinen H, et al. Defective regulation of triglyceride metabolism by insulin in the liver in niddm. *Diabetologia*. 1997;40:454–62.
72. Pavlic M, Xiao C, Szeto L, Patterson BW, Lewis GF. Insulin acutely inhibits intestinal lipoprotein secretion in humans in part by suppressing plasma free fatty acids. *Diabetes*. 2010;59:580–7.
73. Theriault A, Cheung R, Adeli K. Expression of apolipoprotein b in vitro in cell-free lysates of hepg2 cells: evidence that insulin modulates apob synthesis at the translational level. *Clin Biochem*. 1992;25:321–3.
74. Harbis A, Defoort C, Narbonne H, Juhel C, Senft M, Latge C, et al. Acute hyperinsulinism modulates plasma apolipoprotein b-48 triglyceride-rich lipoproteins in healthy subjects during the postprandial period. *Diabetes*. 2001;50:462–9.
75. Loidighi N, Menard D, Levy E. Insulin decreases chylomicron production in human fetal small intestine. *Biochim Biophys Acta*. 1992;1175:100–6.
76. Lewis GF, Uffelman KD, Szeto LW, Steiner G. Effects of acute hyperinsulinemia on vldl triglyceride and vldl apob production in normal weight and obese individuals. *Diabetes*. 1993;42:833–42.
77. Aitman TJ, Godsland IF, Farren B, Crook D, Wong HJ, Scott J. Defects of insulin action on fatty acid and carbohydrate metabolism in familial combined hyperlipidemia. *Arterioscler Thromb Vasc Biol*. 1997;17:748–54.
78. Bourgeois CS, Wiggins D, Hems R, Gibbons GF. Vldl output by hepatocytes from obese Zucker rats is resistant to the inhibitory effect of insulin. *Am J Physiol*. 1995;269:E208–15.
79. Longuet C, Sinclair EM, Maida A, Baggio LL, Maziarz M, Charron MJ, et al. The glucagon receptor is required for the adaptive metabolic response to fasting. *Cell Metab*. 2008;8:359–71.
80. Xiao C, Pavlic M, Szeto L, Patterson BW, Lewis GF. Effects of acute hyperglucagonemia on hepatic and intestinal lipoprotein production and clearance in healthy humans. *Diabetes*. 2011;60:383–90.
81. Hansen LH, Abrahamsen N, Nishimura E. Glucagon receptor mRNA distribution in rat tissues. *Peptides*. 1995;16:1163–6.
82. Thomsen C, Rasmussen O, Lousen T, Holst JJ, Fenselau S, Schrezenmeier J, et al. Differential effects of saturated and monounsaturated fatty acids on postprandial lipemia and incretin responses in healthy subjects. *Am J Clin Nutr*. 1999;69:1135–43.
83. Qin X, Shen H, Liu M, Yang Q, Zheng S, Sabo M, et al. Glp-1 reduces intestinal lymph flow, triglyceride absorption, and apolipoprotein production in rats. *Am J Physiol Gastrointest Liver Physiol*. 2005;288:G943–9.
84. Hsieh JLC, Baker CL, Qin B, Federico LM, Drucker DJ, Adeli K. The glucagon-like peptide 1 receptor is essential for postprandial lipoprotein synthesis and secretion in hamsters and mice. *Diabetologia*. 2010;53:552–61.
85. Meier JJ, Gethmann A, Gotze O, Gallwitz B, Holst JJ, Schmidt WE, et al. Glucagon-like peptide 1 abolishes the postprandial rise in triglyceride concentrations and lowers levels of non-esterified fatty acids in humans. *Diabetologia*. 2006;49:452–8.
86. Xiao C, Bandsma RH, Dash S, Szeto L, Lewis GF. Exenatide, a glucagon-like peptide-1 receptor agonist, acutely inhibits intestinal lipoprotein production in healthy humans. *Arterioscler Thromb Vasc Biol*. 2012;32:1513–9.
87. Matikainen N, Manttari S, Schweizer A, Ulvestad A, Mills D, Dunning BE, et al. Vildagliptin therapy reduces postprandial intestinal triglyceride-rich lipoprotein particles in patients with type 2 diabetes. *Diabetologia*. 2006;49:2049–57.
88. Tremblay AJ, Lamarche B, Deacon CF, Weisnagel SJ, Couture P. Effect of sitagliptin therapy on postprandial lipoprotein levels in patients with type 2 diabetes. *Diabetes Obes Metab*. 2011;13:366–73.
89. DeFronzo RA, Okerson T, Viswanathan P, Guan X, Holcombe JH, MacConell L. Effects of exenatide versus sitagliptin on postprandial glucose, insulin and glucagon secretion, gastric emptying, and caloric intake: a randomized, cross-over study. *Curr Med Res Opin*. 2008;24:2943–52.
90. Hartmann B, Thulesen J, Hare KJ, Kissow H, Orskov C, Poulsen SS, et al. Immunoneutralization of endogenous glucagon-like peptide-2 reduces adaptive intestinal growth in diabetic rats. *Regul Pept*. 2002;105:173–9.
91. Meier JJ, Nauck MA, Pott A, Heinze K, Goetze O, Bulut K, et al. Glucagon-like peptide 2 stimulates glucagon secretion, enhances lipid absorption, and inhibits gastric acid secretion in humans. *Gastroenterology*. 2006;130:44–54.

92. Hsieh J, Longuet C, Maida A, Bahrami J, Xu E, Baker CL, et al. Glucagon-like peptide-2 increases intestinal lipid absorption and chylomicron production via cd36. *Gastroenterology*. 2009;137:1005, e1001–1004.
93. Qin B, Qiu W, Avramoglu RK, Adeli K. Tumor necrosis factor- α induces intestinal insulin resistance and stimulates the overproduction of intestinal apolipoprotein b48-containing lipoproteins. *Diabetes*. 2007;56:450–61.
94. Levy E, Spahis S, Ziv E, Marette A, Elchebly M, Lambert M, et al. Overproduction of intestinal lipoprotein containing apolipoprotein b-48 in psammomys obesus: Impact of dietary n-3 fatty acids. *Diabetologia*. 2006;49:1937–45.
95. Valdivielso P, Rioja J, Garcia-Arias C, Sanchez-Chaparro MA, Gonzalez-Santos P. Omega 3 fatty acids induce a marked reduction of apolipoprotein b48 when added to fluvastatin in patients with type 2 diabetes and mixed hyperlipidemia: A preliminary report. *Cardiovasc Diabetol*. 2009;8:1–6.
96. Hogue JC, Lamarche B, Deshaies Y, Tremblay AJ, Bergeron J, Gagne C, et al. Differential effect of fenofibrate and atorvastatin on in vivo kinetics of apolipoproteins b-100 and b-48 in subjects with type 2 diabetes mellitus with marked hypertriglyceridemia. *Metabolism*. 2008;57:246–54.
97. Castro Cabezas M, Verseyden C, Meijssen S, Jansen H, Erkelens DW. Effects of atorvastatin on the clearance of triglyceride-rich lipoproteins in familial combined hyperlipidemia. *J Clin Endocrinol Metab*. 2004;89:5972–80.
98. Ooi TC, Cousins M, Ooi DS, Nakajima K, Edwards AL. Effect of fibrates on postprandial remnant-like particles in patients with combined hyperlipidemia. *Atherosclerosis*. 2004;172:375–82.
99. Tremblay AJ, Lamarche B, Cohn JS, Hogue JC, Couture P. Effect of ezetimibe on the in vivo kinetics of apob-48 and apob-100 in men with primary hypercholesterolemia. *Arterioscler Thromb Vasc Biol*. 2006;26:1101–6.
100. Tremblay AJ, Lamarche B, Hogue JC, Couture P. Effects of ezetimibe and simvastatin on apolipoprotein b metabolism in males with mixed hyperlipidemia. *J Lipid Res*. 2009;50:1463–71.
101. Mihos C, Kolovou GD, Mikhailidis DP, Kovar J, Lairon D, Nordestgaard BG, et al. Diagnostic value of postprandial triglyceride testing in healthy subjects: a meta-analysis. *Curr Vasc Pharmacol*. 2011;9:271–80.
102. Ooi TC, Robinson L, Graham T, Kolovou GD, Mikhailidis DP, Lairon D. Proposing a “Lipemic index” as a nutritional and research tool. *Curr Vasc Pharmacol*. 2011;9:313–7.
103. Masuda D, Sugimoto T, Tsujii KI, Inagaki M, Nakatani K, Yuasa-Kawase M, et al. Correlation of fasting serum apolipoprotein b-48 with coronary artery disease prevalence. *Eur J Clin Invest*. 2012. In press.