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EDITORIAL

High density lipoproteins and type 2 diabetes: Emerging concepts in their relationship

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Abstract

Patients with type 2 diabetes mellitus (T2DM) frequently exhibit macrovascular complications of atherosclerotic cardiovascular (CV) disease. High density lipoproteins (HDL) are protective against atherosclerosis. Low levels of HDL cholesterol (HDL-C) independently contribute to CV risk. Patients with T2DM not only exhibit low HDL-C, but also dysfunctional HDL. Furthermore, low concentration of HDL may increase the risk for the development of T2DM through a decreased β cell survival and secretory function. In this paper, we discuss emerging concepts in the relationship of T2DM with HDL.

Key words: Type 2 diabetes; High density lipoproteins; Insulin secretion; β cells; Paraoxonase-1

Core tip: Patients with type 2 diabetes mellitus (T2DM) not only exhibit low high density lipoprotein (HDL) cholesterol, but also dysfunctional HDL. Furthermore, low concentration of HDL may increase the risk for the development of T2DM through a decreased β cell survival and secretory function. In this paper, we discuss emerging concepts in the relationship of T2DM with HDL.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) affects approximately 12 million people in the United States[1]. Atherosclerotic cardiovascular (CV) disease accounts for about 70% of overall mortality in patients with T2DM[2,3]. Various factors, modifiable or not, promote atherosclerosis in these patients[1]. These include metabolic abnormalities, such as hyperglycemia, hyperinsulinemia, albuminuria and atherogenic dyslipidemia [low high density lipoprotein cholesterol (HDL-C) together with increased triglycerides (TG) levels, as well as raised cholesterol concentration of the small dense low density lipoprotein (sdLDL) particles][1,4-7].

Atherogenic dyslipidemia is characterized by the imbalance between pro-atherogenic apolipoprotein (apo)B-containing and anti-atherogenic apoA1-containing lipoprotein particles[8]. In this context, sdLDL particles predominate[9-13]. The small size of LDL particles has been recognized as a risk predictor of CV events[10,11,14].

Interestingly, the risk of coronary heart disease (CHD) associated with atherogenic dyslipidemia may exceed the risk from raised low density lipoprotein cholesterol (LDL-C) levels of 150-220 mg/dL[1,7]. Furthermore, even statin-treated patients with T2DM within LDL-C goals exhibit residual CV risk, which is partially associated with the presence of atherogenic dyslipidemia[15,16]. A *post hoc* analysis of the United Kingdom Prospective Diabetes Study (UKPDS) assessed the CV risk across quintiles of log(TG)/HDL-C in 585 men with T2DM[17]. The risk for CHD or cerebrovascular events was augmented at the highest compared with the lowest quintile (28% *vs* 52%,

respectively, $P = 0.001$)[17].

Except for the predominance of sdLDL particles, low HDL-C levels comprise an independent risk factor of CV events[18,19]. In the Framingham Heart Study, HDL-C was a more potent predictor of CHD than total cholesterol, LDL-C or TG[18]. It was suggested that for every 1 mg/dL decrease in HDL-C levels, the risk for CHD increases by 2% in men and 3% in women[20].

HDL is responsible for the process of reverse cholesterol transport from peripheral tissues, including arterial wall, to the liver[21]. Furthermore, HDL exhibits multiple anti-atherogenic actions[21,22]. These include anti-inflammatory, anti-oxidant and anti-thrombotic effects together with an HDL-associated restoration of endothelial function[21,22]. These actions are mediated at least in part by the enrichment of HDL with apoA1 or enzymes [*e.g.,* paraoxonase-1 (PON1) and HDL-associated lipoprotein-associated phospholipase A_2 (Lp-PLA_2)][21,23,24]. In this paper, we discuss the relationship between T2DM and HDL.

LOW LEVELS OF HDL-C IN T2DM

Patients with T2DM exhibit low HDL-C levels[12]. Among 7692 outpatients with T2DM, the prevalence of low HDL-C levels (< 40 and 50 mg/dL for men and women, respectively) was 49.5%[25]. Several mechanisms have been described to explain this abnormality mostly associated with the predominance of TG-rich lipoproteins[12,23,26]. Briefly, very low density lipoproteins (VLDL) are overproduced in insulin resistant states[12,23,26]. Furthermore, insulin resistance is associated with a defective clearance of TG-rich lipoproteins (*i.e.,* VLDL, chylomicrons and their remnants) *via* lipoprotein lipase (LPL)[23]. These lipoproteins exchange their core lipids with HDL through cholesterol ester transfer protein (CETP) resulting in TG-enriched HDL particles[27]. The activity of CETP is enhanced in insulin resistant states (*e.g.,* T2DM)[27]. The enrichment of HDL particles with TG decreases the stability and plasma residence time of these lipoproteins[23,28,29]. Namely, apoA1 is easily removed from circulating TG-rich HDL particles following lipolysis[23,28]. Furthermore, the lipolysis of these lipoproteins by hepatic lipase gives rise to small HDL particles, which are rapidly cleared[23,28]. Also, hypertriglyceridemic states are characterized by reduced availability of the lipolytic surface fragments derived from TG-rich lipoproteins. These components are necessary for the formation of HDL[23,28].

DYSFUNCTIONAL HDL IN T2DM

It was suggested that HDL is dysfunctional in T2DM. Experimental *in vivo* and *in vitro* studies showed that HDL-associated reverse cholesterol transport is impaired in T2DM[30-32]. Several mechanisms were suggested to mediate this abnormality. These include a reduced expression of the ATP-binding cassette (ABC) transporters. The members A1 and G1 of this family facilitate the efflux of cellular free cholesterol and phospholipid to assemble with apoA1 and form nascent HDL[33]. The gene expression and protein levels of ABC-A1 were reduced in T2DM in parallel with poor glycemic control[32]. This may increase risk for CHD[34]. Furthermore, insulin decreased the *in vitro* protein expression and activity of ABC-G1[35]. This finding suggests a role of hyperinsulinemia (*e.g.,* in T2DM) in defective HDL-mediated reverse cholesterol transport.

The oxidative modification of HDL (especially of apoA1) by glycated hemoglobin may be another mechanism explaining HDL dysfunctionality in T2DM[30,31]. This could be related to the presence of the haptoglobin Hp2 allele, which increases the oxidative modification of circulating lipoproteins[31]. Experimental data showed that HDL dysfunctionality in T2DM may be ameliorated by the use of antioxidants (*e.g.,* vitamin E) *in vivo*[36]. Furthermore, the anti-oxidant defense of HDL is decreased in T2DM. This could be associated with a reduced PON1 activity mediated by the glycation of this enzyme[37-39]. Of interest, postprandial glycemia and impaired catabolism of TG-rich lipoproteins was associated with decreased PON1 activity in T2DM[40-42]. Several polymorphisms of *PON1* gene favor the defective action of PON1 in T2DM[43]. Reduced PON1 activity was an independent predictor of CV events in patients with T2DM[44].

We have previously shown that patients with metabolic syndrome exhibit decreased activity of HDL-associated Lp-PLA_2 compared with age and sex-matched controls[45,46]. HDL-associated Lp-PLA_2 contributes significantly to the anti-inflammatory and anti-atherogenic potential of HDL[47,48]. Despite low activity of this enzyme in pre-diabetic insulin resistant states, data are insufficient for patients with T2DM.

PROTECTIVE ROLE OF HDL IN THE PATHOGENESIS OF T2DM

The gradual deterioration of pancreatic β cell function following persistent insulin resistance is the main pathophysiological event in T2DM[49,50]. At the time of T2DM diagnosis, the secretory function of β cells is declined by approximately 50% of normal[51]. It was suggested that lipoproteins may regulate glucose homeostasis by affecting both peripheral insulin resistance and pancreatic islet secretion[52]. For example, high circulating levels of free fatty acids impair insulin sensitivity[53-55]. The emerging concept is that atherogenic dyslipidemia may precede T2DM and favor its development by promoting the dysfunction and apoptosis of β cells[56]. In the UKPDS, the log(TG)/HDL-C ratio, as a surrogate of atherogenic dyslipidemia, was associated with decreased insulin sensitivity and impaired β cell function in 585 male patients with T2DM[17].

Low HDL-C levels independently predict the development of T2DM[57]. A recent observational study investigated the association of HDL-C and β cell function in 1087 subjects at risk of T2DM[58]. Low HDL-C levels

were independently associated with indices of β cell dysfunction in patients with impaired either fasting glucose or glucose tolerance[58].

Pancreatic β cells express receptors that participate in the binding and processing of plasma lipoproteins[53,59]. These include the LDL-receptor and the LDL-receptor related protein[60]. Both circulating and endogenous cholesterol of β cells can affect insulin secretion[60]. In this context, VLDL and LDL particles reduce insulin mRNA expression and proliferation, while inducing apoptosis of β cells[53]. Furthermore, cholesterol accumulation in pancreatic β cells may impair their secretory function[52,60,61]. In contrast, HDL exerts a protective role by improving β cell secretory function and antagonizing the apoptosis of these cells[53]. The lipid-free apoA1 and apoA2 or HDL increased insulin secretion by up to 5-fold *in vitro*[62]. Furthermore, the administration of reconstituted HDL in patients with T2DM improved the glycemic control by increasing β cell insulin secretory function[63].

The process of reverse cholesterol transport can help explain these benefits. Several experimental studies highlighted the protective role of ABC-A1 against T2DM[60]. In contrast, ABC-A1 knockout mice exhibited impaired glucose tolerance due to a decreased insulin secretion upon glucose stimulation[64]. This effect was not accompanied by any changes in insulin mRNA expression, suggesting that cholesterol accumulation in β cells interferes with insulin exocytosis[52,64]. Furthermore, human carriers of loss-of-function ABC-A1 mutations exhibited reduced not only HDL-C levels, but also insulin secretion[63,65]. On the other hand, rosiglitazone improved glucose tolerance by upregulating the expression of ABC-A1 gene[64].

Several *in vitro* studies suggested a beneficial role of HDL on the survival of β cells[53,56,66]. This benefit may be mediated by the anti-oxidant effects of HDL. For example, oxidized LDL (oxLDL) decreased insulin secretion at the transcriptional level and promoted apoptosis of β cells *in vitro*[66]. This was associated with an activation of the Jun N-terminal kinase pathway[66,67]. HDL reversed these actions of oxLDL[66]. To this extent, experimental studies showed that PON1 increases insulin secretion, thereby reducing the incidence of T2DM *in vivo*[68,69]. PON1 was also associated with increased survival of β cells[69]. Furthermore, not only PON1 but also HDL-associated Lp-PLA$_2$ inhibits the oxidation of LDL[70]. Lp-PLA$_2$ is produced in the arterial wall by macrophages[70]. It is associated with lipoproteins, primarily LDL and secondarily HDL, and degrades bioactive phospholipids[70]. Both PON1 and HDL-associated Lp-PLA$_2$ protected hypercholesterolemic mice from atherosclerosis[71,72]. OxLDL inhibit these enzymes[72]. Therefore, oxLDL and HDL are considered antagonists in the development of atherosclerotic vascular disease[72].

CONCLUSION

Interest is increasing on the protective role of HDL against atherosclerotic CV disease. CV risk is high even in patients with T2DM who exhibit LDL-C levels within normal range. Low HDL-C is an independent contributor of this residual risk. The increased concentration of circulating TG-rich lipoproteins mostly accounts for low HDL-C levels in patients with T2DM. Considerable evidence suggests that HDL is dysfunctional in T2DM. Indeed, decreased ABC-A1 and/or -G1 expression reduces biosynthesis of HDL in T2DM through reduced availability of cholesterol for loading to apoA1. This results in impaired reverse cholesterol transport. Furthermore, the oxidative modification of HDL (especially of apoA1) in T2DM impairs its functionality. This is in part associated with a reduced anti-oxidant defense of these lipoproteins *via* PON1. The emerging concept is that low HDL-C may be involved in the pathogenesis of T2DM. The abundance of circulating atherogenic particles together with the increased intracellular cholesterol concentration in β cells have been associated with impaired secretory function of pancreatic islets. HDL by removing cholesterol from these cells may increase insulin secretion. Furthermore, these lipoproteins increase the survival of β cells by mechanisms which are under investigation. The anti-oxidant actions of HDL *via* PON1 may play a key role in this benefit.

REFERENCES

1 **Garber AJ**. Attenuating cardiovascular risk factors in patients with type 2 diabetes. *Am Fam Physician* 2000; **62**: 2633-2642, 2633-2642 [PMID: 11142470]

2 **Leal J**, Gray AM, Clarke PM. Development of life-expectancy tables for people with type 2 diabetes. *Eur Heart J* 2009; **30**: 834-839 [PMID: 19109355 DOI: 10.1093/eurheartj/ehn567]

3 **Grundy SM**, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, Mitch W, Smith SC, Sowers JR. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation* 1999; **100**: 1134-1146 [PMID: 10477542 DOI: 10.1161/01.CIR.100.10.1134]

4 **Wanner C**, Krane V. Recent advances in the treatment of atherogenic dyslipidemia in type 2 diabetes mellitus. *Kidney Blood Press Res* 2011; **34**: 209-217 [PMID: 21691123 DOI: 10.1159/000326849]

5 **Austin MA**, King MC, Vranizan KM, Krauss RM. Atherogenic lipoprotein phenotype. A proposed genetic marker for coronary heart disease risk. *Circulation* 1990; **82**: 495-506 [PMID: 2372896 DOI: 10.1161/01.CIR.82.2.495]

6 **Musunuru K**. Atherogenic dyslipidemia: cardiovascular risk and dietary intervention. *Lipids* 2010; **45**: 907-914 [PMID: 20524075 DOI: 10.1007/s11745-010-3408-1]

7 **Grundy SM**. Small LDL, atherogenic dyslipidemia, and the metabolic syndrome. *Circulation* 1997; **95**: 1-4 [PMID: 8994405 DOI: 10.1161/01.CIR.95.1.1]

8 **Walldius G**, Jungner I, Aastveit AH, Holme I, Furberg CD, Sniderman AD. The apoB/apoA-I ratio is better than the cholesterol ratios to estimate the balance between plasma proatherogenic and antiatherogenic lipoproteins and to predict coronary risk. *Clin Chem Lab Med* 2004; **42**: 1355-1363 [PMID: 15576296 DOI: 10.1515/CCLM.2004.254]

9 **Austin MA**. Triglyceride, small, dense low-density lipoprotein, and the atherogenic lipoprotein phenotype. *Curr Atheroscler Rep* 2000; **2**: 200-207 [PMID: 11122745]

10 **Mikhailidis DP**, Elisaf M, Rizzo M, Berneis K, Griffin B, Zambon A, Athyros V, de Graaf J, März W, Parhofer KG, Rini GB, Spinas GA, Tomkin GH, Tselepis AD, Wierzbicki AS, Winkler K, Florentin M, Liberopoulos E. "European panel on low density lipoprotein (LDL) subclasses": a state-

ment on the pathophysiology, atherogenicity and clinical significance of LDL subclasses. *Curr Vasc Pharmacol* 2011; **9**: 533-571 [PMID: 21595628]
11 **Mikhailidis DP**, Elisaf M, Rizzo M, Berneis K, Griffin B, Zambon A, Athyros V, de Graaf J, März W, Parhofer KG, Rini GB, Spinas GA, Tomkin GH, Tselepis AD, Wierzbicki AS, Winkler K, Florentin M, Liberopoulos E. "European panel on low density lipoprotein (LDL) subclasses": a statement on the pathophysiology, atherogenicity and clinical significance of LDL subclasses: executive summary. *Curr Vasc Pharmacol* 2011; **9**: 531-532 [PMID: 21595629]
12 **Kreisberg RA**. Diabetic dyslipidemia. *Am J Cardiol* 1998; **82**: 67U-73U; discussion 85U-86U [PMID: 9915665]
13 **Hepp P**, Osterhoff G, Engel T, Marquass B, Klink T, Josten C. Biomechanical evaluation of knotless anatomical double-layer double-row rotator cuff repair: a comparative ex vivo study. *Am J Sports Med* 2009; **37**: 1363-1369 [PMID: 19307331 DOI: 10.1242/dmm.001180]
14 **St-Pierre AC**, Cantin B, Dagenais GR, Mauriège P, Bernard PM, Després JP, Lamarche B. Low-density lipoprotein subfractions and the long-term risk of ischemic heart disease in men: 13-year follow-up data from the Québec Cardiovascular Study. *Arterioscler Thromb Vasc Biol* 2005; **25**: 553-559 [PMID: 15618542 DOI: 10.1161/01.ATV.0000154144.73236.f4]
15 **Chapman MJ**, Ginsberg HN, Amarenco P, Andreotti F, Borén J, Catapano AL, Descamps OS, Fisher E, Kovanen PT, Kuivenhoven JA, Lesnik P, Masana L, Nordestgaard BG, Ray KK, Reiner Z, Taskinen MR, Tokgözoglu L, Tybjærg-Hansen A, Watts GF. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. *Eur Heart J* 2011; **32**: 1345-1361 [PMID: 21531743 DOI: 10.1093/eurheartj/ehr112]
16 **Kostapanos MS**, Katsiki N, Elisaf MS, Mikhailidis DP. Editorial: reducing cardiovascular risk: is low-density lipoprotein-cholesterol (LDL-C) lowering enough? *Curr Vasc Pharmacol* 2012; **10**: 173-177 [PMID: 22250844]
17 **Hermans MP**, Ahn SA, Rousseau MF. log(TG)/HDL-C is related to both residual cardiometabolic risk and β-cell function loss in type 2 diabetes males. *Cardiovasc Diabetol* 2010; **9**: 88 [PMID: 21156040 DOI: 10.1186/1475-2840-9-88]
18 **Link JJ**, Rohatgi A, de Lemos JA. HDL cholesterol: physiology, pathophysiology, and management. *Curr Probl Cardiol* 2007; **32**: 268-314 [PMID: 17481993]
19 **Cziraky MJ**, Watson KE, Talbert RL. Targeting low HDL-cholesterol to decrease residual cardiovascular risk in the managed care setting. *J Manag Care Pharm* 2008; **14**: S3-S28; quiz S30-S31 [PMID: 19891279]
20 **Chapman MJ**, Assmann G, Fruchart JC, Shepherd J, Sirtori C. Raising high-density lipoprotein cholesterol with reduction of cardiovascular risk: the role of nicotinic acid--a position paper developed by the European Consensus Panel on HDL-C. *Curr Med Res Opin* 2004; **20**: 1253-1268 [PMID: 15324528]
21 **Florentin M**, Liberopoulos EN, Wierzbicki AS, Mikhailidis DP. Multiple actions of high-density lipoprotein. *Curr Opin Cardiol* 2008; **23**: 370-378 [PMID: 18520722 DOI: 10.1097/HCO.0b013e3283043806]
22 **Besler C**, Heinrich K, Riwanto M, Lüscher TF, Landmesser U. High-density lipoprotein-mediated anti-atherosclerotic and endothelial-protective effects: a potential novel therapeutic target in cardiovascular disease. *Curr Pharm Des* 2010; **16**: 1480-1493 [PMID: 20196740]
23 **Kontush A**, Chapman MJ. Antiatherogenic small, dense HDL--guardian angel of the arterial wall? *Nat Clin Pract Cardiovasc Med* 2006; **3**: 144-153 [PMID: 16505860 DOI: 10.1038/ncpcardio0500]
24 **Kostapanos MS**, Milionis HJ, Filippatos TD, Christogiannis LG, Bairaktari ET, Tselepis AD, Elisaf MS. Dose-dependent effect of rosuvastatin treatment on HDL-subfraction phenotype in patients with primary hyperlipidemia. *J Cardiovasc Pharmacol Ther* 2009; **14**: 5-13 [PMID: 19246334 DOI: 10.1177/1074248408331031]
25 **Grant RW**, Meigs JB. Prevalence and treatment of low HDL cholesterol among primary care patients with type 2 diabetes: an unmet challenge for cardiovascular risk reduction. *Diabetes Care* 2007; **30**: 479-484 [PMID: 17327308 DOI: 10.2337/dc06-1961]
26 **Ginsberg HN**. Diabetic dyslipidemia: basic mechanisms underlying the common hypertriglyceridemia and low HDL cholesterol levels. *Diabetes* 1996; **45** Suppl 3: S27-S30 [PMID: 8674885]
27 **Kolovou GD**, Anagnostopoulou KK, Kostakou PM, Mikhailidis DP. Cholesterol ester transfer protein (CETP), postprandial lipemia and hypolipidemic drugs. *Curr Med Chem* 2009; **16**: 4345-4360 [PMID: 19835569]
28 **Lamarche B**, Rashid S, Lewis GF. HDL metabolism in hypertriglyceridemic states: an overview. *Clin Chim Acta* 1999; **286**: 145-161 [PMID: 10511289]
29 **Sparks DL**, Davidson WS, Lund-Katz S, Phillips MC. Effects of the neutral lipid content of high density lipoprotein on apolipoprotein A-I structure and particle stability. *J Biol Chem* 1995; **270**: 26910-26917 [PMID: 7592936 DOI: 10.1074/jbc.270.45.26910]
30 **Asleh R**, Levy AP. Divergent effects of alpha-tocopherol and vitamin C on the generation of dysfunctional HDL associated with diabetes and the Hp 2-2 genotype. *Antioxid Redox Signal* 2010; **12**: 209-217 [PMID: 19769483 DOI: 10.1089/ars.2009.2829]
31 **Asleh R**, Miller-Lotan R, Aviram M, Hayek T, Yulish M, Levy JE, Miller B, Blum S, Milman U, Shapira C, Levy AP. Haptoglobin genotype is a regulator of reverse cholesterol transport in diabetes in vitro and in vivo. *Circ Res* 2006; **99**: 1419-1425 [PMID: 17082477 DOI: 10.1161/01.RES.0000251741.65179.56]
32 **Patel DC**, Albrecht C, Pavitt D, Paul V, Pourreyron C, Newman SP, Godsland IF, Valabhji J, Johnston DG. Type 2 diabetes is associated with reduced ATP-binding cassette transporter A1 gene expression, protein and function. *PLoS One* 2011; **6**: e22142 [PMID: 21829447 DOI: 10.2459/JCM.0b013e3283522422]
33 **Oram JF**, Vaughan AM. ATP-Binding cassette cholesterol transporters and cardiovascular disease. *Circ Res* 2006; **99**: 1031-1043 [PMID: 17095732 DOI: 10.1161/01.RES.0000250171.54048.5c]
34 **Frikke-Schmidt R**, Nordestgaard BG, Schnohr P, Steffensen R, Tybjaerg-Hansen A. Mutation in ABCA1 predicted risk of ischemic heart disease in the Copenhagen City Heart Study Population. *J Am Coll Cardiol* 2005; **46**: 1516-1520 [PMID: 16226177 DOI: 10.1016/j.jacc.2005.06.066]
35 **Yamashita M**, Tamasawa N, Matsuki K, Tanabe J, Murakami H, Matsui J, Suda T. Insulin suppresses HDL-mediated cholesterol efflux from macrophages through inhibition of neutral cholesteryl ester hydrolase and ATP-binding cassette transporter G1 expressions. *J Atheroscler Thromb* 2010; **17**: 1183-1189 [PMID: 20733269 DOI: 10.5551/jat.4721]
36 **Asleh R**, Blum S, Kalet-Litman S, Alshiek J, Miller-Lotan R, Asaf R, Rock W, Aviram M, Milman U, Shapira C, Abassi Z, Levy AP. Correction of HDL dysfunction in individuals with diabetes and the haptoglobin 2-2 genotype. *Diabetes* 2008; **57**: 2794-2800 [PMID: 18599520 DOI: 10.2337/db08-0450]
37 **Stefanović A**, Kotur-Stevuljević J, Spasić S, Vekić J, Zeljković A, Spasojević-Kalimanovska V, Jelić-Ivanović Z. HDL 2 particles are associated with hyperglycaemia, lower PON1 activity and oxidative stress in type 2 diabetes mellitus patients. *Clin Biochem* 2010; **43**: 1230-1235 [PMID: 20709049 DOI: 10.1016/j.clinbiochem.2010.08.005]
38 **Mastorikou M**, Mackness B, Liu Y, Mackness M. Glycation of paraoxonase-1 inhibits its activity and impairs the ability of high-density lipoprotein to metabolize membrane lipid hydroperoxides. *Diabet Med* 2008; **25**: 1049-1055 [PMID: 18937674 DOI: 10.1111/j.1464-5491.2008.02546.x]
39 **Nobécourt E**, Jacqueminet S, Hansel B, Chantepie S, Grimal-

di A, Chapman MJ, Kontush A. Defective antioxidative activity of small dense HDL3 particles in type 2 diabetes: relationship to elevated oxidative stress and hyperglycaemia. *Diabetologia* 2005; **48**: 529-538 [PMID: 15729582 DOI: 10.1007/s00125-004-1655-5]

40 **Duncan MD**, Tihan T, Donovan DM, Phung QH, Rowley DL, Harmon JW, Gearhart PJ, Duncan KL. Esophagogastric adenocarcinoma in an E1A/E1B transgenic model involves p53 disruption. *J Gastrointest Surg* 2000; **4**: 290-297 [PMID: 10769092 DOI: 10.1016/S1091-255X(00)80078-5]

41 **Serin O**, Konukoglu D, Firtina S, Mavis O. Serum oxidized low density lipoprotein, paraoxonase 1 and lipid peroxidation levels during oral glucose tolerance test. *Horm Metab Res* 2007; **39**: 207-211 [PMID: 17373636 DOI: 10.1055/s-2007-970419]

42 **Kalmár T**, Seres I, Balogh Z, Káplár M, Winkler G, Paragh G. Correlation between the activities of lipoprotein lipase and paraoxonase in type 2 diabetes mellitus. *Diabetes Metab* 2005; **31**: 574-580 [PMID: 16357806 DOI: 10.1016/S1262-3636(07)70233-1]

43 **Flekac M**, Skrha J, Zídková K, Lacinová Z, Hilgertová J. Paraoxonase 1 gene polymorphisms and enzyme activities in diabetes mellitus. *Physiol Res* 2008; **57**: 717-726 [PMID: 17949258]

44 **Ikeda Y**, Inoue M, Suehiro T, Arii K, Kumon Y, Hashimoto K. Low human paraoxonase predicts cardiovascular events in Japanese patients with type 2 diabetes. *Acta Diabetol* 2009; **46**: 239-242 [PMID: 18830558 DOI: 10.1007/s00592-008-0066-3]

45 **Rizos E**, Tambaki AP, Gazi I, Tselepis AD, Elisaf M. Lipoprotein-associated PAF-acetylhydrolase activity in subjects with the metabolic syndrome. *Prostaglandins Leukot Essent Fatty Acids* 2005; **72**: 203-209 [PMID: 15664305 DOI: 10.1016/j.plefa.2004.10.021]

46 **Lagos KG**, Filippatos TD, Tsimihodimos V, Gazi IF, Rizos C, Tselepis AD, Mikhailidis DP, Elisaf MS. Alterations in the high density lipoprotein phenotype and HDL-associated enzymes in subjects with metabolic syndrome. *Lipids* 2009; **44**: 9-16 [PMID: 18956219 DOI: 10.1007/s11745-008-3251-9]

47 **Tellis CC**, Tselepis AD. The role of lipoprotein-associated phospholipase A2 in atherosclerosis may depend on its lipoprotein carrier in plasma. *Biochim Biophys Acta* 2009; **1791**: 327-338 [PMID: 19272461 DOI: 10.1016/j.bbalip.2009.02.015]

48 **Saougos VG**, Tambaki AP, Kalogirou M, Kostapanos M, Gazi IF, Wolfert RL, Elisaf M, Tselepis AD. Differential effect of hypolipidemic drugs on lipoprotein-associated phospholipase A2. *Arterioscler Thromb Vasc Biol* 2007; **27**: 2236-2243 [PMID: 17656665 DOI: 10.1161/ATVBAHA.107.147280]

49 **Unger J**, Parkin CG. Type 2 diabetes: an expanded view of pathophysiology and therapy. *Postgrad Med* 2010; **122**: 145-157 [PMID: 20463424 DOI: 10.3810/pgm.2010.05.2152]

50 **Scheen AJ**. Pathophysiology of type 2 diabetes. *Acta Clin Belg* 2003; **58**: 335-341 [PMID: 15068125]

51 U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. U.K. Prospective Diabetes Study Group. *Diabetes* 1995; **44**: 1249-1258 [PMID: 7589820]

52 **Getz GS**, Reardon CA. High-density lipoprotein function in regulating insulin secretion: possible relevance to metabolic syndrome. *Arterioscler Thromb Vasc Biol* 2010; **30**: 1497-1499 [PMID: 20631346 DOI: 10.1161/ATVBAHA.110.210583]

53 **Roehrich ME**, Mooser V, Lenain V, Herz J, Nimpf J, Azhar S, Bideau M, Capponi A, Nicod P, Haefliger JA, Waeber G. Insulin-secreting beta-cell dysfunction induced by human lipoproteins. *J Biol Chem* 2003; **278**: 18368-18375 [PMID: 12594227 DOI: 10.1074/jbc.M300102200]

54 **Griffin ME**, Marcucci MJ, Cline GW, Bell K, Barucci N, Lee D, Goodyear LJ, Kraegen EW, White MF, Shulman GI. Free fatty acid-induced insulin resistance is associated with activation of protein kinase C theta and alterations in the insulin signaling cascade. *Diabetes* 1999; **48**: 1270-1274 [PMID: 10342815 DOI: 10.2337/diabetes.48.6.1270]

55 **Kraegen EW**, Cooney GJ. Free fatty acids and skeletal muscle insulin resistance. *Curr Opin Lipidol* 2008; **19**: 235-241 [PMID: 18460913 DOI: 10.1097/01.mol.0000319118.44995.9a]

56 **Rütti S**, Ehses JA, Sibler RA, Prazak R, Rohrer L, Georgopoulos S, Meier DT, Niclauss N, Berney T, Donath MY, von Eckardstein A. Low- and high-density lipoproteins modulate function, apoptosis, and proliferation of primary human and murine pancreatic beta-cells. *Endocrinology* 2009; **150**: 4521-4530 [PMID: 19628574 DOI: 10.1210/en.2009-0252]

57 **von Eckardstein A**, Schulte H, Assmann G. Risk for diabetes mellitus in middle-aged Caucasian male participants of the PROCAM study: implications for the definition of impaired fasting glucose by the American Diabetes Association. Prospective Cardiovascular Münster. *J Clin Endocrinol Metab* 2000; **85**: 3101-3108 [PMID: 10999793 DOI: 10.1210/jc.85.9.3101]

58 **Bardini G**, Dicembrini I, Rotella CM, Giannini S. Correlation between HDL cholesterol levels and beta-cell function in subjects with various degree of glucose tolerance. *Acta Diabetol* 2013; **50**: 277-281 [PMID: 21997326 DOI: 10.1007/s00592-011-0339-0]

59 **Cnop M**, Grupping A, Hoorens A, Bouwens L, Pipeleers-Marichal M, Pipeleers D. Endocytosis of low-density lipoprotein by human pancreatic beta cells and uptake in lipid-storing vesicles, which increase with age. *Am J Pathol* 2000; **156**: 237-244 [PMID: 10623672 DOI: 10.1016/S0002-9440(10)64724-4]

60 **Brunham LR**, Kruit JK, Verchere CB, Hayden MR. Cholesterol in islet dysfunction and type 2 diabetes. *J Clin Invest* 2008; **118**: 403-408 [PMID: 18246189 DOI: 10.1172/JCI33296]

61 **Fryirs M**, Barter PJ, Rye KA. Cholesterol metabolism and pancreatic beta-cell function. *Curr Opin Lipidol* 2009; **20**: 159-164 [PMID: 19417651 DOI: 10.1097/MOL.0b013e32832ac180]

62 **Fryirs MA**, Barter PJ, Appavoo M, Tuch BE, Tabet F, Heather AK, Rye KA. Effects of high-density lipoproteins on pancreatic beta-cell insulin secretion. *Arterioscler Thromb Vasc Biol* 2010; **30**: 1642-1648 [PMID: 20466975 DOI: 10.1161/ATVBAHA.110.207373]

63 **Kruit JK**, Brunham LR, Verchere CB, Hayden MR. HDL and LDL cholesterol significantly influence beta-cell function in type 2 diabetes mellitus. *Curr Opin Lipidol* 2010; **21**: 178-185 [PMID: 20463468 DOI: 10.1097/MOL.0b013e328339387b]

64 **Brunham LR**, Kruit JK, Pape TD, Timmins JM, Reuwer AQ, Vasanji Z, Marsh BJ, Rodrigues B, Johnson JD, Parks JS, Verchere CB, Hayden MR. Beta-cell ABCA1 influences insulin secretion, glucose homeostasis and response to thiazolidinedione treatment. *Nat Med* 2007; **13**: 340-347 [PMID: 17322896 DOI: 10.1038/nm1546]

65 **Vergeer M**, Brunham LR, Koetsveld J, Kruit JK, Verchere CB, Kastelein JJ, Hayden MR, Stroes ES. Carriers of loss-of-function mutations in ABCA1 display pancreatic beta-cell dysfunction. *Diabetes Care* 2010; **33**: 869-874 [PMID: 20067955 DOI: 10.2337/dc09-1562]

66 **Abderrahmani A**, Niederhauser G, Favre D, Abdelli S, Ferdaoussi M, Yang JY, Regazzi R, Widmann C, Waeber G. Human high-density lipoprotein particles prevent activation of the JNK pathway induced by human oxidised low-density lipoprotein particles in pancreatic beta cells. *Diabetologia* 2007; **50**: 1304-1314 [PMID: 17437081 DOI: 10.1007/s00125-007-0642-z]

67 **Nofer JR**, Levkau B, Wolinska I, Junker R, Fobker M, von Eckardstein A, Seedorf U, Assmann G. Suppression of endothelial cell apoptosis by high density lipoproteins (HDL) and HDL-associated lysosphingolipids. *J Biol Chem* 2001; **276**: 34480-34485 [PMID: 11432865 DOI: 10.1074/jbc.M103782200]

68 **Rozenberg O**, Shiner M, Aviram M, Hayek T. Paraoxonase 1 (PON1) attenuates diabetes development in mice through its antioxidative properties. *Free Radic Biol Med* 2008; **44**: 1951-1959 [PMID: 18358245 DOI: 10.1016/j.freeradbiomed.2008.02.012]

69 **Koren-Gluzer M**, Aviram M, Meilin E, Hayek T. The anti-

oxidant HDL-associated paraoxonase-1 (PON1) attenuates diabetes development and stimulates β-cell insulin release. *Atherosclerosis* 2011; **219**: 510-518 [PMID: 21862013]

70 **Dada N**, Kim NW, Wolfert RL. Lp-PLA2: an emerging biomarker of coronary heart disease. *Expert Rev Mol Diagn* 2002; **2**: 17-22 [PMID: 11963798 DOI: 10.1586/4737159.2.1.17]

71 **Zhang C**, Peng W, Wang M, Zhu J, Zang Y, Shi W, Zhang J, Qin J. Studies on protective effects of human paraoxonases 1 and 3 on atherosclerosis in apolipoprotein E knockout mice. *Gene Ther* 2010; **17**: 626-633 [PMID: 20182519 DOI: 10.1038/gt.2010.11]

72 **Mertens A**, Holvoet P. Oxidized LDL and HDL: antagonists in atherothrombosis. *FASEB J* 2001; **15**: 2073-2084 [PMID: 11641234 DOI: 10.1096/fj.01-0273rev]

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Organization as author

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

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Issue with no volume

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Books

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Chapter in a book (list all authors)

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Conference proceedings

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Conference paper

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Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and position-

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