Chapter

Lipids Abnormality and Type 2 Diabetes Mellitus: Causes and Consequences

Kan Wang and Fariba Ahmadizar

Abstract

Dyslipidemia and diabetes both are important risk factors for cardiovascular disease. Emerging evidence suggests that these two are closely related to each other, the so-called "dyslipidemia-insulin resistance-hyperinsulinemia" cycle. Recently, several new lipid subfractions, such as apolipoprotein (Apo)B, and ApoJ, have been reported to associate with insulin resistance and incident diabetes, which further claim the role of lipid in the pathophysiology of diabetes. Besides, dyslipidemia is also one of the most prevalent diabetic complications. Clinical guidelines have widely recommended lipid management among diabetic patients through lifestyle intervention and lipid-lowering medications, especially statins, to prevent cardiovascular outcomes.

Keywords: Lipid, dyslipidemia, diabetes, cardiovascular disease, statins

1. Introduction

Type 2 diabetes mellitus (T2DM) is among the most prevalent chronic disease [1], affecting approximately 463 million people in 2019, and more than 690 million are expected to be diagnosed by 2045 [2]. People diagnosed with T2DM have a 2–4-fold higher risk of developing cardiovascular disease (CVD) [3]. Despite significant advantages in the prevention strategies that lessen related risk factors, CVD remains the leading cause of morbidity and mortality in patients with T2DM [4].

T2DM and CVD both have multi-factorial etiology, and disorders of lipid metabolism is one of the coexistence features sharing by them. For the development of CVD, the cumulation of ApoB-containing lipoproteins in the arterial wall would lead to lipid deposition and an atheroma initiation, resulting in the progression of atherosclerotic plaques, and eventually atherosclerotic vascular disease [5]. Therefore, lipid-lowering drugs, such as statins, have been recommended as front-line therapy for primary prevention of atherosclerotic CVD [6], and the state-of-the-art therapy in dyslipidemia in diabetic patients [3, 7, 8]. For the potential mechanism between lipid metabolism and diabetes, one meta-analysis reported that lipid parameters, such as triglyceride (TG), and low-density lipoprotein (LDL), can reflect the risk of T2DM [9]. Other lipid subfractions, such as high-density lipoprotein cholesterol (HDL) and lipid-free ApoA-I, could also benefit glycemic control by increasing glucose uptake in skeletal muscle, improving beta-cell function, and decreasing insulin resistance through inhibiting the proinflammatory signal transduction pathways [10].

Considering the rather complex components of lipid and different directions for the associations between different lipid components and diabetes [11], more efforts are needed to elucidate the relationships between lipid profile and diabetes.

2. Lipid abnormality and incident type 2 diabetes mellitus

There are six major lipoproteins exist in blood: chylomicrons, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL); lipoprotein(a) (Lp(a)), and high-density lipoprotein (HDL) [12]. Dyslipidemia represents a cluster of lipid and lipoprotein abnormalities, including elevation of both fasting and postprandial TG, apolipoprotein (Apo)A, or ApoB. The prevalence of dyslipidemia is getting severer worldwide. According to the 2015 Global Burden of Disease Study, the prevalence of elevated total cholesterol (TC) (≥200 mg/dL) was highest in the WHO European Region (54% for both sexes), followed by the WHO Region of the Americas (48% for both sexes). The WHO African Region and the WHO South-East Asia Region showed the lowest percentages (23% and 30%, respectively) [13]. In China, the prevalence of dyslipidemia was 42.8% overall [14], with 4.3%, 2.4%, 14.7%, and 17.4% for the age-standardized prevalence of high TC, LDL, TG, and HDL, respectively [15].

Evidence suggests that the development of T2DM was closely associated with lipid abnormality [16–26]. A study based on the 2010–2012 China National Nutrition and Health Survey (CNNHS) reported that the prevalence of dyslipidemia was 39.9%, 46.8%, and 59.3% in participants with normal glucose, prediabetes, and T2DM [16]. Zhu et al. 's meta-analysis reported that there were positive associations between different lipid parameters and T2DM. Moreover, the standardized mean difference for the Atherogenic index of plasma (AIP, lg(TG/HDL)) is 1.78 (95% confidence interval (CI): 1.04–2.52), which is higher than for other parameters (TG: 0.93, 95% CI: 0.78–1.09; TC: 0.46, 95% CI: 0.21–0.71; HDL-C: −0.89, 95%CI: −1.18 to −0.60; and LDL-C: 0.44, 95% CI: 0.11–0.77), suggesting AIP may be more closely associated with the risk of T2DM [9]. Results from the prospective cohort study (Multi-Ethnic Study of Atherosclerosis) found that elevated total ApoC-III concentrations were associated with a higher rate of diabetes, while ApoC-III-defined HDL subspecies displayed opposing associations: HDL lacking ApoC-III was inversely associated with incident diabetes, while no association was found for HDL containing ApoC-III. Further adjustment for plasma TG as a potential intermediate attenuated these associations [17]. Besides, not only baseline cross-sectional estimated or abnormal lipid level is related, Zheng et al. found that time-dependent TG/HDL ratios were also positively associated with future incident T2DM, which supports the change patterns for these parameters during the follow-up could intricate the development of diabetes [18]. Beshars et al. evaluated the relationship between diabetes and the increment in triglyceride levels within the normal range. Their results suggest that sustained increments in rising triglyceride levels, even within the accepted normal range, might pose a cumulative risk for the development of diabetes and impaired fasting glucose [19].

Despite the aforementioned epidemiologic evidence, the precise mechanisms of the associations are complex and remain unclear. Since the hallmark of T2DM is the inability of pancreatic beta-cells to produce adequate amounts of insulin, accompanied by reduced tissue responsiveness to insulin, also known as insulin resistance. Lipotoxicity caused by dyslipidemia plays an important role in the development and progression of insulin resistance [10]. It can disturb the utilization of insulin in peripheral target tissues (such as the liver), thus affecting the amount of lipids synthesis in the liver. So, elevated blood lipid can lead to insulin resistance,

which in turn aggravates the generation of lipid metabolism disorder [27–29]. More recently, Seo et al. found that ApoJ is a novel hepatokine targeting muscle glucose metabolism and insulin sensitivity through low-density lipoprotein receptor-related protein-2 (LRP2)-dependent mechanism, coupled with the insulin receptor signaling cascade. In muscle, LRP2 is necessary for insulin receptor internalization, an initial trigger for insulin signaling, that is crucial in regulating downstream signaling and glucose uptake. Of physiologic significance, deletion of hepatic ApoJ or muscle LRP2 causes insulin resistance and glucose intolerance [30].

3. Lipid-lowering medication and incident type 2 diabetes mellitus

Lipid-lowering medication plays an essential role in the current healthcare system, not only for the optimization of the lipid profile but also to reduce cardiovascular risk [6, 12]. Recently, there is increased awareness of the possibility that lipid-lowering medications may affect glucose control and insulin resistance [31–33]. This phenomenon is reported in all classes of lipid-modifying agents, with differential effects of distinct drugs.

Some insights into this question emerged from some recent studies. Barak et al. systematically reviewed the related evidence and reported that both statins and niacin are associated with increased risk of impaired glucose control and development of new-onset diabetes, as opposed to bile-acid sequestrants which display concomitant moderate lipid and glucose-lowering effects, and fibrates (particularly the pan-PPAR agonist bezafibrate) which may produce beneficial effects on glucose metabolism and insulin sensitivity [34]. Another recently published meta-analysis, which included 163,688 nondiabetic patients from thirty-three randomized controlled trials, reported no significant association between 1-mmol/L reduction in LDL cholesterol and incident diabetes for statins or PCSK9 inhibitors. More intensive lipid-lowering therapy (defined as the more potent pharmacological strategy, such as PCSK9 inhibitors, higher intensity statins, or statins) was associated with a higher risk of incident diabetes compared with less intensive therapy (active control group or placebo/usual care of the trial). Meta-regression analysis suggested that these results were mainly driven by a higher risk of incident diabetes with statins, whereas PCSK9 inhibitors were not associated with incident diabetes ($P = 0.02$ for interaction). Thus, among intensive lipid-lowering therapies, there was no independent association between reduction in LDL cholesterol and incident diabetes [32].

The precise mechanisms for statin-induced diabetes remain unclear. However, several mechanisms have been proposed, including impaired insulin sensitivity, impaired insulin secretion, and compromised beta-cell function via enhanced intracellular cholesterol uptake due to inhibition of intracellular cholesterol synthesis by statins [34]. Recently, genetic studies have added more evidence to this. LDL-lowering alleles in *HMGCR*, which encodes the statins' molecular target, were associated with a higher risk of T2DM and higher body mass index [35]. A further larger-scale individual meta-analysis concluded that other LDL-lowering alleles, such as *NPC1L1*, *PCSK9*, *ABCG5/G8*, were also associated with a higher risk T2DM [31]. Nevertheless, it has to be stressed here that the cardiovascular benefits of statins far outweigh diabetes risk [3].

4. Type 2 diabetic dyslipidemia

Diabetic dyslipidemia is a cluster of plasma lipid and lipoprotein abnormalities that are metabolically interrelated among diabetic patients. It is mainly

characterized by increased TG levels, low HDL levels, and postprandial lipemia and contributes to the development of vascular complications [36]. Results from the 2010–2012 China National Nutrition and Health Survey (CNNHS) shown that the prevalence of dyslipidemia was 39.9%, 46.8%, and 59.3% in participants with normal glucose, prediabetes, and T2DM [16]. Another study using data from the 2010–2014 Diabetes Mellitus/Hypertension (DM/HT) study, which included 140,557 Thai adults with diabetes, reported that the dyslipidemia prevalence of 88.9% [37]. Despite the heterogeneity between different studies, the prevalence of diabetic dyslipidemia has grown gradually worldwide [4].

The pathophysiology of diabetic dyslipidemia is intricate and has not been fully understood [38]. Briefly speaking, changes in plasma lipoproteins among diabetic patients are affected by insufficient insulin function and hyperglycemia [39]. During the postprandial state, dietary fatty acids (FA) and cholesterol absorbed by the intestinal cells are incorporated as TG and cholesteryl esters into chylomicrons. In the capillary beds of adipocytes (especially in the fed state) and muscle, chylomicrons are the substrate for lipoprotein lipase (LPL), promoting lipolysis of chylomicrons TG and the release of FA. Insulin regulates LPL activity at several levels, including gene expression, protein synthesis, and secretion, and LPL is reduced in insulin-resistant individuals with T2DM with a consequent increase in plasma TG and decrease in HDL [40].

5. Type 2 diabetic dyslipidemia and cardiovascular disease

Both diabetes and dyslipidemia are important risk factors for CVD development, powered by the dyslipidemia-insulin resistance-hyperinsulinemia cycle [41]. This makes patients with diabetes dyslipidemia much more vulnerable to CVD outcomes. Results from the Multiple Risk Factor Intervention Trial (MRFIT) reported that among men who had diabetes at baseline, the absolute risk of coronary mortality at each level of blood cholesterol (for 20 mg/dL increments in TC starting from 180 mg/dL to >280 mg/dL), was 3–5 times higher in the presence of diabetes [42]. The United Kingdom Prospective Diabetes Study (UKPDS) has provided further evidence of a similarly direct and continuous association of coronary disease risk with LDL concentration. Among newly diagnosed T2DM, one mmol/L increase in LDL was associated with a 57% increased risk of myocardial infarction [43].

Many former studies have widely reported the causal association between dyslipidemia and CVD. Due to the rather complex components of lipid profile, diagnosis of diabetic dyslipidemia is not always revealed by the lipid measures used in clinical practice, as LDL levels may remain within the normal range. Therefore, it is suggested to use non-HDL levels to reflect the whole lipid spectrum [12]. The 2019 ESC/EAS Guidelines stated that ApoB analysis is recommended for risk assessment, particularly in people with high TG, diabetes, obesity, or metabolic syndrome. ApoB can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management [6].

Since a higher risk of atherosclerotic vascular disease in diabetic patients, lipid management has been recommended by diabetes-related clinical guidelines [3, 7, 8, 44, 45]. Consistent data have demonstrated the efficacy of statins, the first-choice lipid-lowering treatment, in preventing cardiovascular events and reducing cardiovascular mortality in patients with diabetes. A meta-analysis including 18,686 diabetic patients demonstrated that a statin-induced reduction of LDL by 1.0 mmol/L was associated with a 9% reduction in all-cause mortality and a 21% reduction in the incidence of major CV events [46]. The newly released ADA's Standards of Medical Care in Diabetes-2020 has stated that statins should be used

	Density (g/mL)	Diameter (nm)	TGs (%)	Cholesteryl esters (%)	PLs (%)	Cholesterol (%)	Apolipoproteins	
							Major	Others
Chylomicrons	<0.95	80–100	90–95	2–4	2–6	1	ApoB-48	ApoA-I, A-II, A-IV, A-V
VLDL	0.95–1.006	30–80	50–65	8–14	12–16	4–7	ApoB-100	ApoA-I, C-II, C-III, E, A-V
IDL	1.006–1.019	25–30	25–40	20–35	16–24	7–11	ApoB-100	ApoC-II, C-III, E
LDL	1.019–1.063	20–25	4–6	34–35	22–26	6–15	ApoB-100	
HDL	1.063–1.210	8–13	7	10–20	55	5	ApoA-I	ApoC-II, C-III, E, M
Lp(a)	1.006–1.125	25–30	4–8	35–46	17–24	6–9	Apo(a)	ApoB-100

Apo: apolipoprotein; HDL: high-density lipoprotein; IDL: intermediate-density lipoprotein; LDL: low-density lipoprotein; Lp(a): lipoprotein(a); PLs: phospholipids; TGs: triglycerides; VLDL: very-low-density lipoprotein.

**Adapted from: "2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk." By Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. Eur Heart J. 2020;41 [1]:111–88.*

Table 1.
Physical and chemical characteristics of human plasma lipoproteins.*

Target	Statin treatment
ADA	
For patients with diabetes aged 40–75 years without atherosclerotic cardiovascular disease, use moderate-intensity statin therapy in addition to lifestyle therapy.	
For patients with diabetes aged 20–39 years with additional atherosclerotic cardiovascular disease risk factors, it may be reasonable to initiate statin therapy in addition to lifestyle therapy.	
In patients with diabetes at higher risk, especially those with multiple atherosclerotic cardiovascular disease risk factors or aged 50–70 years, it is reasonable to use high-intensity statin therapy.	
In adults with diabetes and a 10-year atherosclerotic cardiovascular disease risk of 20% or higher, it may be reasonable to add ezetimibe to maximally tolerated statin therapy to reduce LDL cholesterol levels by 50% or more.	
ESC/EASD	
In patients with T2D at moderate CV risk, an LDL-C target of <2.6 mmol/L (<100 mg/dL) is recommended.	Statins are recommended as the first-choice lipid-lowering treatment in patients with DM and high LDL-C levels: administration of statins is defined based on the CV risk profile of the patient and the recommended LDL-C (or non-HDL-C) target levels.
In patients with T2D at high CV risk, an LDL-C target of <1.8 mmol/L (<70 mg/dL) and LDL-C reduction of at least 50% is recommended.	
In patients with T2D at very high CV risk, an LDL-C target of <1.4 mmol/L (<55 mg/dL) and LDL-C reduction of at least 50% is recommended.	
CDS	
The primary goal is to reduce LDL-C to the target (very high risk of ASCVD: <1.8 mmol/L, high risk of ASCVD: <2.6 mmol/L).	Statins are the preferred lipid-lowering drugs. Lipid-lowering therapy should start with a moderate-intensity statin, and the dose should be adjusted according to individual response to medication and tolerability.
LDL-C reduction by ≥50% may be used as an alternative target in the event of high baseline LDL-C and failure to reduce LDL-C to the target after 3 months of standard lipid-lowering therapy.	
JDS	
The primary goal of antidyslipidemic therapy is to control the LDL-C level to <120 mg/dL in patients without a history of coronary artery disease.	Statins are the agents of choice for hyper-LDL-C in patients with diabetes.
The control goal for fasting triglyceride (TG) is <150 mg/dL.	
The control goal for HDL-C is ≥40 mg/dL.	

Table 2.
Guidelines for the management of diabetic dyslipidemia using statin.

for both primary and secondary CVD prevention among diabetes. The detailed guideline are listed according to age groups: for 20–39 years-old diabetic patients with atherosclerotic cardiovascular disease risk factors, statin therapy is highly recommended in addition to lifestyle therapy; for patients with diabetes aged 40–75 years without atherosclerotic cardiovascular disease, use moderate-intensity statin therapy (lowers LDL by 30–49%) in addition to lifestyle therapy; while for patients aged 50–70 years with diabetes, high-intensity statin therapy (lowers LDL by ≥50%) is recommended [8]. The 2013 ACC/AHA guideline emphasized statin therapy recommended for all patients with diabetes 40 to 75 years of age-independent of baseline cholesterol [47].

Despite the CVD protective effect among diabetic patients, statin therapy has been associated with new-onset T2DM [31, 32]. A former study reported that for every 40 mmol/L reduction of LDL by statins, conversion to T2DM is increased by 10% [48, 49]. Nevertheless, the benefits in terms of cardiovascular event reduction

greatly exceed the risks of statin therapy, and this has been confirmed in patients at low cardiovascular risk [46] (**Tables 1** and **2**).

6. Conclusion

Complex lipoprotein metabolism abnormalities could present both in the development and progression of type 2 diabetes, which indicates that lipid management can prevent cardiovascular complications among diabetic patients and involve in the prevention of diabetes. Epidemiological studies suggest that lipid components could be a marker for diabetes prediction, though it is still uncertain which lipid markers are of the most clinical value. Lipid control using a lipid-lowering medication, such as statins, could reduce CVD risk among the general population also diabetic people. However, it is necessary to consider statin diabetogenicity in clinical practice when the statin is indicated.

Conflict of interest

The authors declare no conflict of interest.

Author details

Kan Wang and Fariba Ahmadizar*
Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands

*Address all correspondence to: f.ahmadizar@erasmusmc.nl

References

[1] Diseases GBD, Injuries C. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1204-22.

[2] Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. Diabetes Res Clin Pract. 2019;157:107843.

[3] Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020;41(2):255-323.

[4] Harding JL, Pavkov ME, Magliano DJ, Shaw JE, Gregg EW. Global trends in diabetes complications: a review of current evidence. Diabetologia. 2019;62(1):3-16.

[5] Boren J, Williams KJ. The central role of arterial retention of cholesterol-rich apolipoprotein-B-containing lipoproteins in the pathogenesis of atherosclerosis: a triumph of simplicity. Curr Opin Lipidol. 2016;27(5):473-83.

[6] Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111-88.

[7] Jia W, Weng J, Zhu D, Ji L, Lu J, Zhou Z, et al. Standards of medical care for type 2 diabetes in China 2019. Diabetes Metab Res Rev. 2019;35(6):e3158.

[8] American Diabetes A. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020;43(Suppl 1):S111-S34.

[9] Zhu XW, Deng FY, Lei SF. Meta-analysis of Atherogenic Index of Plasma and other lipid parameters in relation to risk of type 2 diabetes mellitus. Prim Care Diabetes. 2015;9(1):60-7.

[10] Manandhar B, Cochran BJ, Rye KA. Role of High-Density Lipoproteins in Cholesterol Homeostasis and Glycemic Control. J Am Heart Assoc. 2020;9(1):e013531.

[11] Guasch-Ferre M, Hruby A, Toledo E, Clish CB, Martinez-Gonzalez MA, Salas-Salvado J, et al. Metabolomics in Prediabetes and Diabetes: A Systematic Review and Meta-analysis. Diabetes Care. 2016;39(5):833-46.

[12] Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139(25):e1082-e143.

[13] Collaborators GBDRF. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1659-724.

[14] Song P, Zha M, Yang X, Xu Y, Wang H, Fang Z, et al. Socioeconomic and geographic variations in the prevalence, awareness, treatment and control of dyslipidemia in middle-aged and older Chinese. Atherosclerosis. 2019;282:57-66.

[15] Xi Y, Niu L, Cao N, Bao H, Xu X, Zhu H, et al. Prevalence of dyslipidemia and associated risk factors among adults aged >/=35 years in northern China: a cross-sectional study. BMC Public Health. 2020;20(1):1068.

[16] Li Y, Zhao L, Yu D, Ding G. The prevalence and risk factors of dyslipidemia in different diabetic progression stages among middle-aged and elderly populations in China. PLoS One. 2018;13(10):e0205709.

[17] Aroner SA, Furtado JD, Sacks FM, Tsai MY, Mukamal KJ, McClelland RL, et al. Apolipoprotein C-III and its defined lipoprotein subspecies in relation to incident diabetes: the Multi-Ethnic Study of Atherosclerosis. Diabetologia. 2019;62(6):981-92.

[18] Zheng D, Li H, Ai F, Sun F, Singh M, Cao X, et al. Association between the triglyceride to high-density lipoprotein cholesterol ratio and the risk of type 2 diabetes mellitus among Chinese elderly: the Beijing Longitudinal Study of Aging. BMJ Open Diabetes Res Care. 2020;8(1).

[19] Beshara A, Cohen E, Goldberg E, Lilos P, Garty M, Krause I. Triglyceride levels and risk of type 2 diabetes mellitus: a longitudinal large study. J Investig Med. 2016;64(2):383-7.

[20] Brahimaj A, Ligthart S, Ikram MA, Hofman A, Franco OH, Sijbrands EJ, et al. Serum Levels of Apolipoproteins and Incident Type 2 Diabetes: A Prospective Cohort Study. Diabetes Care. 2017;40(3):346-51.

[21] Qin H, Chen Z, Zhang Y, Wang L, Ouyang P, Cheng L, et al. Triglyceride to high-density lipoprotein cholesterol ratio is associated with incident diabetes in men: A retrospective study of Chinese individuals. J Diabetes Investig. 2020;11(1):192-8.

[22] Lim TK, Lee HS, Lee YJ. Triglyceride to HDL-cholesterol ratio and the incidence risk of type 2 diabetes in community dwelling adults: A longitudinal 12-year analysis of the Korean Genome and Epidemiology Study. Diabetes Res Clin Pract. 2020;163:108150.

[23] Huth C, von Toerne C, Schederecker F, de Las Heras Gala T, Herder C, Kronenberg F, et al. Protein markers and risk of type 2 diabetes and prediabetes: a targeted proteomics approach in the KORA F4/FF4 study. Eur J Epidemiol. 2019;34(4):409-22.

[24] Razquin C, Toledo E, Clish CB, Ruiz-Canela M, Dennis C, Corella D, et al. Plasma Lipidomic Profiling and Risk of Type 2 Diabetes in the PREDIMED Trial. Diabetes Care. 2018;41(12):2617-24.

[25] von Toerne C, Huth C, de Las Heras Gala T, Kronenberg F, Herder C, Koenig W, et al. MASP1, THBS1, GPLD1 and ApoA-IV are novel biomarkers associated with prediabetes: the KORA F4 study. Diabetologia. 2016;59(9):1882-92.

[26] Gudbjartsson DF, Thorgeirsson G, Sulem P, Helgadottir A, Gylfason A, Saemundsdottir J, et al. Lipoprotein(a) Concentration and Risks of Cardiovascular Disease and Diabetes. J Am Coll Cardiol. 2019;74(24):2982-94.

[27] Rye KA, Barter PJ, Cochran BJ. Apolipoprotein A-I interactions with insulin secretion and production. Curr Opin Lipidol. 2016;27(1):8-13.

[28] Martin SS, Qasim AN, Wolfe M, St Clair C, Schwartz S, Iqbal N, et al. Comparison of high-density lipoprotein cholesterol to apolipoprotein A-I and A-II to predict coronary calcium and the effect of insulin resistance. Am J Cardiol. 2011;107(3):393-8.

[29] Waldman B, Jenkins AJ, Davis TM, Taskinen MR, Scott R, O'Connell RL, et al. HDL-C and HDL-C/ApoA-I

predict long-term progression of glycemia in established type 2 diabetes. Diabetes Care. 2014;37(8):2351-8.

[30] Seo JA, Kang MC, Yang WM, Hwang WM, Kim SS, Hong SH, et al. Apolipoprotein J is a hepatokine regulating muscle glucose metabolism and insulin sensitivity. Nat Commun. 2020;11(1):2024.

[31] Lotta LA, Sharp SJ, Burgess S, Perry JRB, Stewart ID, Willems SM, et al. Association Between Low-Density Lipoprotein Cholesterol-Lowering Genetic Variants and Risk of Type 2 Diabetes: A Meta-analysis. JAMA. 2016;316(13):1383-91.

[32] Khan SU, Rahman H, Okunrintemi V, Riaz H, Khan MS, Sattur S, et al. Association of Lowering Low-Density Lipoprotein Cholesterol With Contemporary Lipid-Lowering Therapies and Risk of Diabetes Mellitus: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2019;8(7):e011581.

[33] Ahmadizar F, Ochoa-Rosales C, Glisic M, Franco OH, Muka T, Stricker BH. Associations of statin use with glycaemic traits and incident type 2 diabetes. Br J Clin Pharmacol. 2019;85(5):993-1002.

[34] Zafrir B, Jain M. Lipid-lowering therapies, glucose control and incident diabetes: evidence, mechanisms and clinical implications. Cardiovasc Drugs Ther. 2014;28(4):361-77.

[35] Swerdlow DI, Preiss D, Kuchenbaecker KB, Holmes MV, Engmann JE, Shah T, et al. HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials. Lancet. 2015;385(9965):351-61.

[36] Mooradian AD. Dyslipidemia in type 2 diabetes mellitus. Nat Clin Pract Endocrinol Metab. 2009;5(3):150-9.

[37] Narindrarangkura P, Bosl W, Rangsin R, Hatthachote P. Prevalence of dyslipidemia associated with complications in diabetic patients: a nationwide study in Thailand. Lipids Health Dis. 2019;18(1):90.

[38] Verges B. Pathophysiology of diabetic dyslipidaemia: where are we? Diabetologia. 2015;58(5):886-99.

[39] Lewis GF, Steiner G. Acute effects of insulin in the control of VLDL production in humans. Implications for the insulin-resistant state. Diabetes Care. 1996;19(4):390-3.

[40] Jaiswal M, Schinske A, Pop-Busui R. Lipids and lipid management in diabetes. Best Pract Res Clin Endocrinol Metab. 2014;28(3):325-38.

[41] Steiner G, Vranic M. Hyperinsulinemia and hypertriglyceridemia, a vicious cycle with atherogenic potential. Int J Obes. 1982;6 Suppl 1:117-24.

[42] Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care. 1993;16(2):434-44.

[43] Turner RC, Millns H, Neil HA, Stratton IM, Manley SE, Matthews DR, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). BMJ. 1998;316(7134):823-8.

[44] Araki E, Goto A, Kondo T, Noda M, Noto H, Origasa H, et al. Japanese Clinical Practice Guideline for Diabetes 2019. Diabetol Int. 2020;11(3):165-223.

[45] Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics-2019 Update: A Report

From the American Heart Association. Circulation. 2019;139(10):e56-e528.

[46] Cholesterol Treatment Trialists C, Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380(9841):581-90.

[47] Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2889-934.

[48] Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet. 2010;375(9716):735-42.

[49] Preiss D, Seshasai SR, Welsh P, Murphy SA, Ho JE, Waters DD, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA. 2011;305(24):2556-64.