International Journal of Scientific Advances
ISSN: 2708-7972
Volume: 5 | Issue: 6 | Nov – Dec 2024 Available Online: www.ijscia.com
DOI: 10.51542/ijscia.v5i6.94

Management of Dyslipidemia in Type 1 Diabetes Mellitus: Literature Review

Faya Maulida Qannia[1], Rimbun[2], Muhammad Faizi[3,4*], Abdul Khairul Rizki Purba[5,6]

[1]Medical Study Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

[2]Division of Histology, Departement of Anatomy, Histology and Pharmacology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

[3]Departement of Pediatrics, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

[4]Departement of Pediatrics, Dr. Soetomo General Hospital, Surabaya, Indonesia

[5]Division of Pharmacology, Department of Anatomy, Histology and Pharmacology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

[6]Department of Health Science, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

E-mail: r.a.faya.maulida.qannia-2021@fk.unair.ac.id; rimbun@fk.unair.ac.id; muhammad.faizi@fk.unair.ac.id; khairul_purba@fk.unair.ac.id

*Corresponding author details: Muhammad Faizi; muhammad.faizi@fk.unair.ac.id

ABSTRACT

Type 1 Diabetes Mellitus (T1DM) is a common chronic metabolic disease that alters insulin production by pancreatic beta cells. The prevalence of T1DM has been increasing by trend from 7.78 per 100,000 population in 1990 to 11.07 per 100,000 population in 2019. T1DM usually affects children, adolescents, and young adults. T1DM is an autoimmune disease characterized by autoantibody formation of pancreatic beta cells. The development of T1DM is associated with a multifactorial process, involving genetic, epigenetic, and environmental factors. One of the concerning conditions in patients with T1DM is dyslipidemia as it increases atherosclerotic cardiovascular disease (ASCVD) risk. Dyslipidemia in T1DM could be the result of poor glycemic control, hyperinsulinemia by subcutaneous insulin injection, and obesity in association with chronic inflammation. The management of dyslipidemia in pediatrics with T1DM has advanced lately. Distinct to adults, glucose control and LDL goals differ and drug therapy is indicated to those above 10 with specific criteria. Later guidelines show different management approaches, particularly the use of lipid-lowering drugs. Thus, this study aims to review the current management of dyslipidemia in Pediatrics with T1DM.

Keywords: type 1 diabetes mellitus; dyslipidemia; pediatrics; early diabetes diagnosis; quality treatment for children; increasing life expectancy.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic syndrome that is caused by the body's inability to produce sufficient amounts of insulin or the lack of adequate insulin action in the tissue [1]. This will result primarily in the alteration of glucose metabolism homeostasis leading to uncontrolled blood glucose. Type 1 diabetes mellitus (T1DM) is a type of DM that is categorized as an autoimmune disease, marked by autoantibody production to beta pancreatic cells resulting in the destruction of the body's main source of insulin production [2]. Thus, the hallmark of T1DM is the reduction of insulin available for use in the circulation.

This path mechanism severely disturbs body glucose metabolism and could spread to various pathologic conditions and complications if not managed closely. The incidence of T1DM has been increasing since 1990. The latest global burden study shows that 11.07 per 100.000 population globally suffer from T1DM in 2019 [3]. This number shows a significant increase in T1DM prevalence from 7.78 per 100.000 population in 1999. Even though management approaches have advanced in the past decades, the mortality rate of patients with T1DM continues to increase from 5,701.19 in 1999 to 6,123.04 in 2019 which shows a 7.40% increase in mortality [3].

This increasingly global burden trend has alerted physicians to the need for further research and more effective management in patients with T1DM.

With the disruption of glycemic control in T1DM, several metabolic conditions may emerge and further increase the risk of morbidity and mortality in T1DM. One of which is dyslipidemia, which is marked by abnormalities in the lipid profile, including triglyceride, cholesterol, and lipoprotein in T1DM [4]. This is caused by poor glycemic control and also partly due to the hyperinsulinemia which is caused by percutaneous insulin injection commonly used in T1DM [4]. The hazardous effect of dyslipidemia in T1DM is shown by the increased cardiovascular disease risk in T1DM with dyslipidemia compared to those without dyslipidemia. This shows the importance of both glycemic and lipid control in patients with T1DM.

Individuals with T1DM need strict monitoring and comprehensive lipid control to prevent complications, particularly cardiovascular disease risk. Several guidelines show some different approaches in the lipid management of T1DM [5]. Newer therapies with promising have also emerged in lifestyle, pharmacological, and immunotherapy [6]. Thus, a comprehensive review consisting of the current management of dyslipidemia in T1DM is needed. This review aims to understand the current and novel management of dyslipidemia in T1DM.

REVIEW CONTENT

Epidemiology of Type 1 Diabetes Mellitus

Type 1 Diabetes Mellitus (T1DM) is a common chronic disease that alters the ability of the human body to produce insulin. Around 8.4 million people were estimated to be diagnosed with T1DM in 2021 with a 0.34% increase in prevalence annually [7,8]. Based on the age affected, T1DM usually affects children, adolescents, and young adults. One study stated an increased incidence of T1DM in adolescents and young adults from 7.78 per 100,000 population in 1990 to 11.07 per 100,000 population in 2019 [3]. With its nature, this disease is normally diagnosed at the age of under 14 years old, however in recent years with more advanced technology, the mean age at diagnosis has decreased from 12 - 14 years in 1969 - 1990 to 10 - 11.9 years in 1990 - 1999 and an even lower mean age during 2000 - 2019 (4 - 5.9 years) [9]. With the increased prevalence of T1DM, it was even projected that in the year 2040, approximately 13.5 - 17.4 million people would be affected by this disease [7]. T1DM as a chronic disease leads to many complications, with 30% of the patients developing end-stage kidney disease [7]. This disease also presented a 7.40% increased mortality rate from 1990 to 2019 [9].

One study mentioned the risk factors of T1DM include age, sex, race, genotype, and location on geographic and seasonality [10]. As age has been mentioned before, for the geographic location itself the region Europe leads the number of T1DM cases. However, based on the patient's gender, the region with a high incidence of T1DM reported a male dominant, meanwhile, it is female dominant in regions with low incidence [11,12]. Agarwal et al, conducted a study mainly focused on the race-ethnicity affected by this disease and mentioned that non-Hispanic black leads in the T1DM growth compared to others [13].

Pathophysiology of Type 1 Diabetes Mellitus

The classic process of T1DM involves an autoimmune process that is characterized by insulin deficiency [1]. T1DM is an autoimmune disease with autoimmunity towards pancreatic beta cells, characterized by anti-islet autoantibodies, and is usually associated with multiple autoimmune diseases [14]. From this recent review in 2023, we can see how closely T1DM is related to various other autoimmune diseases, showing one of the major features of most autoimmune diseases, which proves individuals with other autoimmune diseases [14]. This shows that the pathophysiology of T1DM is far more complex, which includes a complex multifactorial process orchestrated by genetic, epigenetic, and environmental components [15].

One of the genetic factors that has been widely researched is the association of human leukocyte antigen (HLA), which is known as the major histocompatibility factor in humans, with the autoimmune risk of T1DM. HLA has roles in almost every other autoimmune disease [16]. One of the earliest studies of T1DM shows that a specific type of HLA, which corresponds to HLA-DRB1*04 has observed the association of this HLA subtype with lymphotoxicity towards pancreatic beta cells which causes the destruction of these cells [17]. Later studies in 2006 have further proven this type of HLA, shown by a positive correlation between HLA-A1-B8-DR3, a newer nomenclature of the same HLA haplotype, with T1DM [18]. A further large clinical trial has discovered several other haplotypes of HLA, including HLA-DRB1, HLA-DQA1, HLA-DPA1, and several others, which all have an association with T1DM, proving a genetical process in T1DM pathophysiology [14]. This provides the genuinity of T1DM as an autoimmune process by the proven HLA association with the development of the disease.

Even though genetics plays a major role in T1DM pathophysiology, it seems that environmental factors also play a role in balance with genetics. The first factor is the exposure of microorganisms. Viral infections such as Coxsackievirus B, an enterovirus, cytomegalovirus, adenovirus, mumps, and rubella, have shown a positive link in T1DM [19]. Viruses can trigger T1DM following antigenic mimicry, although the process is closely related to genetic predisposition at first [20]. Another thing involving microorganisms in relation to T1DM is the disruption of the gut microbiome. This theory is proven in rats which shows that a disrupted gut microbiome is associated with a higher risk of developing T1DM than in healthy gut microbiome rats [21]. In humans, particularly in children with T1DM, a similar association was also found [22].

Deficiencies of specific micronutrients have also been linked to T1DM. Vitamin deficiencies, for example, have been shown to affect pancreatic function and contribute to the destruction of pancreatic beta cells, together with other enzymatic and oxidative stress catastrophes [22]. Mineral deficiency results in the same fashion. One of which is zinc, which is involved in various cell functions and cytokine production, if chronically deficient, could impair immunological function and increase autoimmunity by damaging signaling pathways of an immune response [23]. Furthermore, epigenetic changes are closely related to environmental triggers in the development of T1DM. One study shows that DNA methylation, together with histone modification and RNA gene silencing shows a mediating response for T1DM caused by exposure to environmental triggers [24]. In conclusion, T1DM is a multifactorial disease, far from the classical theory of solitary autoimmune process, which requires several factors together in the development and progression of the disease.

Dyslipidemia in Type 1 Diabetes Mellitus

Dyslipidemia is concerning in patients with T1DM as it is associated with a higher risk of atherosclerotic cardiovascular disease (ASCVD) risk compared to T1DM without dyslipidemia [5]. Lipid abnormalities in patients with diabetes have distinct characteristics compared to the general dyslipidemia population [25]. In patients with T1DM, good glycemic control usually prevents abnormalities in lipid profile, in contrast with T2DM, which shows abnormalities in lipid profiles from patients even with appropriate glycemic control [26]. High-density lipoprotein cholesterol (HDL-C) in T1DM is slightly increased, accompanied by an increase in low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein (VLDL), and increased cholesterol-to-triglyceride ratios [4]. The changes in lipid profile in T1DM do not affect the quantities alone but affect the function of each component in the cellular cholesterol and lipid metabolism.

The development of dyslipidemia is known by several mechanisms. The most popular one is caused by poor glycemic control itself in patients with T1DM. The prevalence of dyslipidemia was found to be significantly higher in patients with T1DM with poor glycemic control compared to patients with adequate glycemic control [27]. Another study done in Egypt also found similar findings in adolescents with T1Dm [28]. One of the reasons is that poor glycemic control, which is indicated by high HbA1c levels, could alter the metabolism of apolipoprotein, especially Apolipoprotein-B (ApoB) [29]. The in-depth mechanism of this is still poorly understood, but some have linked high HbA1c levels with oxidative stress and lipid peroxidation that could alter lipid metabolism [20]. The harmful effect of poor glycemic control also extends to the development and progression of atherosclerosis with dyslipidemia as a mediator [30].

Another mechanism is mediated by insulin administration. Insulin is administered subcutaneously, producing transient peripheral hyperinsulinemia which acts as an important factor in dyslipidemia [31]. It has been widely known that hyperinsulinemia, particularly in T2DM, promotes atherosclerosis through the alteration of vascular smooth muscle and enhancing LDL-C levels in circulation [31]. Insulin also enhances the lipid storage mechanism by inhibiting lipolysis and stimulating triacylglycerol synthesis which will be stored in lipid cells [32]. Furthermore, insulin could also increase the synthesis of cholesterol while decreasing cholesterol absorption further increasing cholesterol levels in the blood [33]. A newer method of the administration of insulin using the insulin pump shows a better lipid profile compared to conventional insulin subcutaneous injection because of better insulin level control [34]. This proves that hyperinsulinemia may contribute to worse lipid profiles in T1DM with routine insulin injection administration.

Another mechanism is associated with a high prevalence of obesity in patients with T1DM. Obesity is associated with an inflammatory state due to the cytokines produced by macrophages in the adipose tissue [35]. The cytokines, mainly TNF and IL-1 decrease the expression of an important lipid metabolism enzyme, lipoprotein lipase, which reduces the body's ability to break lipoprotein and decreases lipid clearance. Obesity may also decrease HDL-C levels by the inhibition of ApoA1 which is the main component of HDL-C [36]. Obesity also decreases the activity of lecithin-cholesterol acyltransferase (LCAT), which is an important enzyme in the formation of HDL-C, further decreasing HDL-C levels. Furthermore, low HDL-C, which has an anti-oxidative profile could increase oxidative stress even more which could also increase LDL-C level [37].

Management of Dyslipidemia in Pediatrics Type 1 Diabetes Mellitus

Diabetes mellitus is considered a high-risk condition for atherosclerotic cardiovascular disease (ASCVD) based on the new American Heart Association guidelines [38]. In pediatric patients, based on the guidelines the management of dyslipidemia in T1DM does not differ from normal dyslipidemia in children, however, there are a few differences in terms of glucose control and LDL goal [39]. In patients with T1DM, cardiovascular disease (CVD) remains the leading mortality source [40]. The management of dyslipidemia in T1DM starts at an early age, > 2 years if there is a positive family history, or at the age of 12 [39]. The first necessary step is taking on dietary therapy with cholesterol less than 200 mg/day and saturated fat <7 % of total calories, drug therapy is only recommended if the children age are >10 years old with the criteria of: 1) LDL level ≥ 190 mg/dl with no CVD risk or 2) LDL ≥ 160 mg in those with CVD. The difference lies in the end goal where dyslipidemia in T1DM Pediatrics targets LDL lower than 100 mg/dl, meanwhile < 130 in dyslipidemia only.

Based on the American Heart Association, Type 1 Diabetes with dyslipidemia is categorized as high-risk/tier I patients with an aggressive end goal of BMI ≤ 85% and LDL-c ≤ 100 mg/dl [41]. The recommendations are intensification of glucose management, dietary evaluation with nutritionists including monitoring of body mass index (BMI), fasting lipids, and balance between weight and lipids. If the dietary approach does not reach a favorable response within 6 months, a higher level of weight loss and exercise program is recommended prior to pharmacologic treatment. One study assessing the effect of exercise on T1DM demonstrated a significantly improving dyslipidemia profile with reduced requirements of insulin [42].

Currently, there are a lot of guidelines regarding the management of dyslipidemia in Type 1 diabetes mellitus. The International Society of Pediatrics and Adolescent Diabetes (ISPAD) suggests that screening should be taken every 5 years if initial screening at 2 years of age is normal, with ADA recommending a three-year repeat [43,44]. However, both guidelines recommended the initiation of statins to help lower the level of lipids. Other guidelines, the European Atherosclerosis Society/ European Society of Cardiology (EAS/ESC) recommends the starting of statin straight after the diagnosis of T1DM patients especially in the high or very high-risk category [45]. Heading into the pharmacologic treatment of Dyslipidemia in T1DM, statin is still the preferred type of drug to use [45]. In spite of that, the use of statin in the age under 10 years old is still not to be confirmed yet except in those who suffer from familial hypercholesterolemia. With a lot of conflict around the use of statins at an early age, a few trials conducted revealed that the use of statins benefits the individual lipid profile by lowering the LDL-C without worsening insulin resistance and increasing the cardiac function in children [46,47]. These conflicts around the use of statin came from the speculation of teratogenicity with some trials in animals supporting the claim [45,48]. Nevertheless, future clinical trials assessing the safety should be prioritized alongside its efficacy.

CONCLUSION

Poor glycemic control of T1DM leads to dyslipidemia occurring in the individual. To summarize the management of dyslipidemia in T1DM, screening to diagnose the patient should be done earlier with age in order to prevent the risk of ASCVD. Management of both sides including glycemic control for diabetes and improving lipid profile in dyslipidemia are equally important.

REFERENCE

[1] Goldenberg R, Punthakee Z. Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome Canadian. 2013;37:8–11.

[2] Holt RIG, Devries HJ, Hess-Fischl A, Ludwig B, Pettus J, Skyler JS. Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2022;65(12):1925–66.

[3] Gong B, Yang W, Xing Y, Lai Y, Shan Z. Global, regional, and national burden of type 1 diabetes in adolescents and young adults. Pediatr Res. 2024;(January).

[4] Vergès B. Lipid disorders in type 1 diabetes. Diabetes Metab. November 2009;35(5):353–60.

[5] Tell S, Nadeau KJ, Eckel RH, Campus M, Campus AM. Lipid management for cardiovascular risk reduction in type 1 diabetes. 2020;27(4):1–16.

[6] Jialal I, Singh G. Management of diabetic dyslipidemia: An update. World J Diabetes. 2019;10(5):280–90.

[7] Ogrotis I, Koufakis T, Kotsa K. Changes in the Global Epidemiology of Type 1 Diabetes in an Evolving Landscape of Environmental Factors: Causes, Challenges, and Opportunities. Med. 2023;59(4).

[8] Liu J, Ren ZH, Qiang H, Wu J, Shen M, Zhang L, et al. Trends in the incidence of diabetes mellitus: results from the Global Burden of Disease Study 2017 and implications for diabetes mellitus prevention. BMC Public Health. 2020;20(1):1–12.

[9] Kandemir N, Vuralli D, Ozon A, Gonc N, Ardicli D, Jalilova L, et al. Epidemiology of type 1 diabetes mellitus in children and adolescents: A 50-year, single-center experience. J Diabetes. 2024;16(5).

[10] Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of type 1 diabetes. Endocrinol Metab Clin North Am. 2010;39(3):481–97.

[11] Karvonen M, Pitkäniemi M, Pitkäniemi J, Kohtamäki K, Tajima N, Tuomilehto J. Sex difference in the incidence of insulin-dependent diabetes mellitus: an analysis of the recent epidemiological data. Diabetes Metab Rev. 1997;13(4):275–91.

[12] Green A, Gale EAM, Patterson CC. Incidence of childhood-onset insulin-dependent diabetes mellitus: the EURODIAB ACE Study. Lancet. 1992;339(8798):905–9.

[13] Agarwal S, Kanapka LG, Raymond JK, Walker A, Gerard-Gonzalez A, Kruger D, et al. Racial-Ethnic Inequity in Young Adults with Type 1 Diabetes. J Clin Endocrinol Metab. Agustus 2020;105(8):e2960-9.

[14] Popoviciu MS, Kaka N, Sethi Y, Patel N, Chopra H, Cavalu S. Type 1 Diabetes Mellitus and Autoimmune Diseases: A Critical Review of the Association and the Application of Personalized Medicine. J Pers Med. 2023;13(3):1–20.

[15] DiMeglio LA, Ford L, McClintock C, Peacock M. Intravenous pamidronate treatment of children under 36 months of age with osteogenesis imperfecta. Bone. November 2004;35(5):1038–45.

[16] Bodis G, Toth V, Schwarting A. Role of Human Leukocyte Antigens (HLA) in Autoimmune Diseases. Rheumatol Ther [Internet]. 2018;5(1):5–20. Tersedia pada: https://doi.org/10.1007/s40744-018-0100-z

[17] Singal DP, Blajchman MA. Lymphocytotoxic Antibodies and Tissue Antibodies in Patients with Diabetes Mellitus. 1973.

[18] Aly TA, Eller E, Ide A, Gowan K, Babu SR, Erlich HA, et al. Multi-SNP analysis of MHC region: Remarkable conservation of HLA-A1-B8-DR3 haplotype. Diabetes. 2006;55(5):1265–9.

[19] Filippi CM, Von Herrath MG. Viral trigger for type 1 diabetes: Pros and cons. Diabetes. 2008;57(11):2863–71.

[20] Yahaya TO, Yusuf ARB, Danjuma JK, Usman BM, Ishiaku YM. Mechanistic links between vitamin deficiencies and diabetes mellitus: a review. Egypt J Basic Appl Sci [Internet]. 2021;8(1):189–202. Tersedia pada: https://doi.org/10.1080/2314808X.2021.1945395

[21] Brugman S, Klatter FA, Visser JTJ, Wildeboer-Veloo ACM, Harmsen HJM, Rozing J, et al. Antibiotic treatment partially protects against type 1 diabetes in the Bio-Breeding diabetes-prone rat. Is the gut flora involved in the development of type 1 diabetes? Diabetologia. 2006;49(9):2105–8.

[22] Murri M, Leiva I, Gomez-Zumaquero JM, Tinahones FJ, Cardona F, Soriguer F, et al. Gut microbiota in children with type 1 diabetes differs from that in healthy children: A case-control study. BMC Med [Internet]. 2013;11(1):46. Tersedia pada: http://www.biomedcentral.com/1741-7015/11/46

[23] Pallavi Dubey, Vikram Thakur MC. Role of Minerals and Trace Elements in Diabetes and Insulin Resistance. Role Miner Trace Elem Diabetes Insul Resist. 2020;1–17.

[24] Yahaya T, Shemishere U. Association between Bioactive Molecules in Breast Milk and Type 1 Diabetes Mellitus. 2020;20(February):5–12.

[25] de Ferranti SD, de Boer IH, Fonseca V, Fox CS, Golden SH, Lavie CJ, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Circulation. September 2014;130(13):1110– 30.

[26] Ginsberg NH, MacCallum RP. The Obesity Metabolic Syndrome and Type 2 Diabetes Mellitus Pandemic. J cardiometabolic Syndr. 2010;4(2):113–9.

[27] Zabeen B, Balsa AM, Islam N, Parveen M, Nahar J, Aza, K. Lipid Profile in Relation to Glycemic Control in Type 1 Diabetes Children and Adolescents in Bangladesh. 2018;89–92.

[28] Homma TK, Endo CM, Saruhashi T, Mori APl, Noronha RM de, Monte O, et al. Dyslipidemia in young patients with type 1 diabetes mellitus. Arch Endocrinol Metab. Juni 2015;59(3):215–9.

[29] Fagundes Melo R, Laurindo LF, Sloan KP, Sloan LA, Cressoni Araújo A, Bitelli P, et al. Investigating the Incidence of Dyslipidemia among Brazilian Children and Adolescents Diagnosed with Type 1 Diabetes Mellitus: A Cross-Sectional Study. Diseases. 2024;12(3):1–16.

[30] Corpeleijn WE, de Waal WJ, Schipper HS, Wiegman A. Dyslipidemia as a target for atherosclerotic cardiovascular disease prevention in children with type 1 diabetes: lessons learned from familial hypercholesterolaemia. Diabetologia. Januari 2024;67(1):19–26.

[31] Sowers JR. Insulin resistance, hyperinsulinemia, dyslipidemia, hypertension, and accelerated atherosclerosis. J Clin Pharmacol. Juni 1992;32(6):529–35.

[32] Choi SM, Tucker DF, Gross DN, Easton RM, DiPilato LM, Dean AS, et al. Insulin Regulates Adipocyte Lipolysis via an Akt-Independent Signaling Pathway. Mol Cell Biol. 2010;30(21):5009–20.

[33] Pihlajamäki J, Gylling H, Miettinen TA, Laakso M. Insulin resistance is associated with increased cholesterol synthesis and decreased cholesterol absorption in normoglycemic men. 2004;45:507–12.

[34] Kosteria I, Schwandt A, Davis E, Jali S, Prieto M, Rottembourg D, et al. Lipid profile is associated with treatment regimen in a large cohort of children and adolescents with Type 1 diabetes mellitus: a study from the international SWEET database. Diabet Med [Internet]. 1 Oktober 2019;36(10):1294–303. Tersedia pada: https://doi.org/10.1111/dme.13963

[35] Lara-Castro C, Fu Y, Chung BH, Garvey WT. Adiponectin and the metabolic syndrome: mechanisms mediating risk for metabolic and cardiovascular disease. Curr Opin Lipidol. Juni 2007;18(3):263–70.

[36] Feingold KR, Grunfeld C. Effect of inflammation on HDL structure and function. Curr Opin Lipidol. Oktober 2016;27(5):521–30.

[37] Rosenblat M, Karry R, Aviram M. Paraoxonase 1 (PON1) is a more potent antioxidant and stimulant of macrophage cholesterol efflux, when present in HDL than in lipoprotein-deficient serum: relevance to diabetes. Atherosclerosis. Juli 2006;187(1):74–81.

[38] 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. Juni 2019;139(25):e1082–143.

[39] AMERICAN DIABETES ASSOCIATION. Management of Dyslipidemia in Children LEVELS TRACK FROM CHILDHOOD TO ATHEROSCLEROSIS BEGIN IN CHILDHOOD ? IS THIS RELATED TO SPECIFIC LIPID ABNORMALITIES IN. Diabetes Care [Internet]. 2003;26(7):2194–7.Tersedia pada: http://care.diabetesjournals.org/content/26/7/2194.full. pdf+html?sid=8df709e6-8cba-42b5-80a8-ed515f88e65a

[40] Libby P, Nathan DM, Abraham K, Brunzell JD, Fradkin JE, Haffner SM, et al. Report of the National Heart, Lung, and Blood Institute-National Institute of Diabetes and Digestive and Kidney Diseases Working Group on Cardiovascular Complications of Type 1 Diabetes Mellitus. Circulation. Juni 2005;111(25):3489–93.

[41] Kavey R-EW, Allada V, Daniels SR, Hayman LL, McCrindle BW, Newburger JW, et al. Cardiovascular risk reduction in high-risk Pediatrics patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology, and Prevention, Circulation. Desember 2006;114(24):2710– 38.

[42] Salem MA, Aboelasrar MA, Elbarbary NS, Elhilaly RA, Refaat YM. Is exercise a therapeutic tool for the improvement of cardiovascular risk factors in adolescents with type 1 diabetes mellitus? A randomised controlled trial. Diabetol Metab Syndr. 2010;2(1):1–10.

[43] Donaghue KC, Marcovecchio ML, Wadwa RP, Chew EY, Wong TY, Calliari LE, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Microvascular and macrovascular complications in children and adolescents. Pediatr Diabetes. Oktober 2018;19 Suppl 2(Suppl 27):262– 74.

[44] AMERICAN DIABETES ASSOCIATION. Children and adolescents: Standards of medical care in diabetes—2021. Diabetes Care. 2021;44(January):S180–99.

[45] O'Brien ST, Neylon OM, O'Brien T. Dyslipidemia in Type 1 Diabetes: Molecular Mechanisms and Therapeutic Opportunities. Vol. 9, Biomedicines. 2021.

[46] Badreldeen A, El Razaky O, Erfan A, El-Bendary A, El Amrousy D. Comparative study of the efficacy of captopril, simvastatin, and L-carnitine as cardioprotective drugs in children with type 1 diabetes mellitus: a randomised controlled trial. Cardiol Young. Agustus 2021;31(8):1315– 22.

[47] Canas JA, Ross JL, Taboada M V, Sikes KM, Damaso LC, Hossain J, et al. A randomized, double blind, placebo- controlled pilot trial of the safety and efficacy of atorvastatin in children with elevated low-density lipoprotein cholesterol (LDL-C) and type 1 diabetes. Pediatr Diabetes. Maret 2015;16(2):79–89.

[48] Kazmin A, Garcia-Bournissen F, Koren G. Motherisk rounds: risks of statin use during pregnancy: a systematic review. J Obstet Gynaecol Canada. 2007;29(11):906–8