Hypertiglyceridemia in Diabetes Mellitus: Implications for Pediatric Care

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Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). It is estimated that the risk of CVD in diabetes mellitus (DM) is 2 to 10 times higher than in the general population. Much of this increased risk is thought to be related to the development of an atherogenic lipid profile, in which hypertriglyceridemia is an essential component. Recent studies suggest that dyslipidemia may be present in children and adolescents with DM, particularly in T2DM and in association with poor control in T1DM. However, the role of hypertiglyceridemia in the development of future CVD in youth with DM is unclear, as data are scarce. In this review, we will evaluate the pathophysiology of atherogenic hypertiglyceridemia in DM, the evidence regarding an independent role of triglycerides in the development of CVD, and the treatment of hypertiglyceridemia in patients with DM, highlighting the potential relevance to children and the need for more data in children and adolescents to guide clinical practice.

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) [1–3]. It is estimated that the risk of CVD in diabetes mellitus (DM) is 2 to 10 times higher than in the general population [4–6]. Much of this increased risk is thought to be related to the development of an atherogenic lipid profile, in which hypertiglyceridemia is an essential component [7]. Recent studies suggest that dyslipidemia may be present in children and adolescents with DM, particularly in T2DM and in association with poor control in T1DM [8, 9]. However, the role of hypertiglyceridemia in the development of future CVD in youth with DM is unclear as data are scarce. Current guidelines recommend a primary treatment goal to lower triglyceride levels, only in the prevention and treatment of triglyceride-induced pancreatitis [10–13]. Studies in childhood DM highlight the importance of understanding the relationship of triglycerides to CVD risk [4, 9]. In the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) trial, dyslipidemia worsened over the nearly 4 years of the study, including in those who were started on metformin; increasing hemoglobin A1c was associated with worsening dyslipidemia [9]. In the SEARCH for Diabetes in Youth Case-Control Study, patients with T1DM and T2DM who had excellent glucose control had lower triglyceride levels and higher high-density lipoprotein cholesterol (HDL-C) compared with those with poor control [14]. In this review, we will evaluate the pathophysiology of atherogenic hypertiglyceridemia in DM, the evidence regarding an independent role of triglycerides in the development of CVD, and the evidence regarding an independent role of triglycerides in the development of CVD.
CVD, and the treatment of hypertriglyceridemia in patients with DM, highlighting the potential relevance to children and the need for more data in children and adolescents to guide clinical practice.

Although this paper is not a systematic review, relevant literature was found by searching MEDLINE, Google Scholar, the Cochrane Library, and Web of Science for references published up to December 2017. In addition, we searched the references listed in the relevant publications. There were no language restrictions. The search terms were kept general and included hypertriglyceridemia, cardiovascular disease, diabetes mellitus, insulin resistance, diet, hyperglycemia, physical activity, statins, fibrates, omega-3 fatty acids, and combinations of these search terms.

1. Pathophysiology

Dyslipidemia is not an obligatory component of DM. In fact, in well-controlled T1DM, the lipid profile is often normal [14, 15]. However, in poorly controlled T1DM and T2DM, or in obese patients who develop T2DM, an atherogenic triad of lipid abnormalities consisting of elevated triglycerides, low levels of HDL-C, and an increased prevalence of small, dense low-density lipoprotein particles is often found [7, 16].

The link among these various components of dyslipidemia is likely secondary to the increase in circulating very low-density lipoprotein (VLDL) remnant particles and chylomicron remnants, which is often clinically estimated by measuring apolipoprotein B levels or by non-HDL-C [17]. Increased VLDL levels can be the result of increased VLDL production in the liver, reduced catabolism, or both [12, 18]. The mechanisms relating to this process are complex, but can be reduced to three pathways. First, in patients with insulin resistance, lipolysis of triglycerides in adipocytes and myocytes is unchecked, leading to a flood of fatty acids returning to the liver [19–21]. The increase in fatty acids returning to the liver stimulates increased VLDL production by the liver [15, 22]. Second, insulin resistance indirectly leads to an overproduction of both apolipoprotein B and VLDL, by failing to initiate degradation of apolipoprotein B in the liver [21, 23]. Thirdly, there is evidence that increased expression of apolipoprotein CIII in the setting of insulin resistance contributes to the overproduction of VLDL [24].

Higher insulin levels contribute to the decreased uptake up of VLDL particles, leading to prolonged circulation of these atherogenic particles [15, 17]. As VLDL and chylomicron remnants are cleared by the same mechanisms, the persistence of VLDL remnants prevents efficient clearance of chylomicron remnants, leading to the characteristic postprandial hyperlipidemia seen in patients with DM [17, 24]. Another mechanism of reduced catabolism of triglycerides is through the reduced function of lipoprotein lipase in muscle and adipose, leading to decreased uptake of free fatty acids by these cells and thus increased free fatty acids contributing to the cycle of VLDL overproduction [24].

2. Role of Triglycerides in CVD, Adult Studies

Hypertriglyceridemia is generally defined by fasting levels (Table 1). According to the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [11], a normal fasting triglyceride level is less than 150 mg/dL, but an optimal level is considered to be less than 100 mg/dL. Triglyceride levels from 150 to 199 mg/dL are defined as borderline, whereas levels from 200 to 499 mg/dL are defined as high, and levels greater than 500 mg/dL are considered very high [15].

In most studies assessing the role of triglycerides in the development of CVD in patients with DM, triglyceride levels are obtained following an 8- to 12-hour fast. A possibly more convenient measurement is to obtain a nonfasting triglyceride level. Nonfasting lipid profiles, on average, result in an increase in triglycerides of 26 mg/dL above fasting levels, increased total cholesterol of 8 mg/dL, and a decrease of 8 mg/dL for both low-density lipoprotein cholesterol (LDL-C) and HDL-C [25]. Evidence suggests that postprandial (nonfasting) triglyceride levels may have a stronger association with CVD than fasting levels [26]. For instance, in
the Women’s Health Study, nonfasting triglyceride levels were found to be independently associated with CVD events, but fasting triglycerides were not [27]. This finding is especially relevant to those with DM as deranged postprandial lipid metabolism is more common in those with insulin resistance [28]. Although there is concern that nonfasting levels may misclassify some patients, updated LDL-C modeling using nonfasting samples may actually perform better in predicting future CVD events and have been the standard in Denmark since 2009 [6, 29, 30].

Although an atherogenic triad composed of hypertriglyceridemia, low HDL-C, and increased prevalence of small, dense low-density lipoprotein particles is associated with an increased risk of CVD [31], the independent role of hypertriglyceridemia in CVD has been controversial. The independent association between triglycerides and CVD often is muted once models control for HDL-C and LDL-C [5, 15, 26, 32]. For example, for patients being treated with statins, triglyceride level was not associated with CVD risk in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) [33] nor were they predictive of CVD events in the Department of Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) [34]. In addition, the risk of CVD does not appear to be elevated in patients with inherited forms of severe hypertriglyceridemia, unless the inherited form is associated with increased apolipoprotein production or associated with an increase in triglyceride-rich remnant particles [6, 15]. In fact, the 2013 American College of Cardiology/American Heart Association Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults does not suggest targeting triglycerides with the goal to reduce CVD risk, only to reduce the risk of triglyceride-induced pancreatitis [10].

However, there is also increasing evidence of an independent role of hypertriglyceridemia in the development of CVD [26, 32, 35–39]. For instance, in the Long-Term Intervention With Pravastatin in Ischemic Disease (LIPID), each 89 mg/dL decrease in triglycerides reduced the risk of CVD by 11% in those taking pravastatin [40]. Similarly, a 2016 study that controlled for body mass index demonstrated that an elevated triglyceride level was associated with increased coronary plaque development in patients whose LDL-C was well controlled with lipid-lowering therapy [41]. Further, there is evidence that triglycerides are independent markers of risk of recurrent disease after myocardial infarctions, even in those with well-controlled LDL-C and controlling for body mass index [42, 43]. In a large Mendelian randomization study, a technique that can help inform decisions on causality, nonfasting triglycerides were associated with an increased risk of CVD of 2.8 times for each 1 mmol/L (89 mg/dL) increase in triglyceride levels [44, 45].

The ratio of triglycerides to HDL-C has been associated with an increased risk of CVD [46]. Various cutoff points have been used, varying from 2.5 for men and 2 for women [15] to 3.5 for both sexes [46]. A ratio as low as 2:1 has been used in children to identify risk factors for metabolic syndrome, with studies in children and adolescents indicating that a higher ratio is associated with increased number of markers of CVD [47, 48]. African Americans, both

| NCEP-ATP III [11] | Endocrine Society [12] | NHLBI Expert Panel in Children and Adolescents [13] |
|-------------------|------------------------|--------------------------------------------------|
| Normal 150–199 mg/dL | Normal <150 mg/dL | Acceptable 0–9 years <75 mg/dL |
| Moderate 200–999 mg/dL | Moderate 200–999 mg/dL | Borderline high 0–9 years 75–99 mg/dL |
| High >500 mg/dL | Severe 1000–1999 mg/dL | Borderline high 10–19 years 130–190 mg/dL |
| Very high >2000 mg/dL | Very severe >2000 mg/dL | High 0–9 years ≥100 mg/dL |

Fasting is defined as having a sample drawn after a patient has fasted for 8 to 12 hours.

Abbreviations: NCEP-ATP, Third Report of the National Cholesterol Education Program-Adult Treatment Panel; NHLBI, National Heart Lung and Blood Institute.
adolescents and adults, tend to have a higher HDL-C and lower triglycerides than whites, but a higher rate of CVD. It appears that the ratio in which an atherogenic dyslipidemia develops is lower in African Americans and closer to 2:1. After controlling for the triglyceride-to-HDL-C ratio, adolescents and adults have similar levels of obesity and inflammatory markers, suggesting a similar atherogenic substrate related to high triglycerides at a much younger age [49, 50].

The Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial [51] and the Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS-2 THRIVE) [52] suggest the association between HDL-C and CVD is much less than previously thought and strengthens the argument that hypertriglyceridemia has a causal role in atherosclerosis [6, 52]. Similarly, only one trial investigating cholesteryl ester transfer protein inhibitors has demonstrated reduction in CVD risk, even with meaningful elevations in HDL-C [53–55]. Non-HDL-C appears to improve risk prediction and progression of atherosclerosis than LDL-C. Non-HDL-C measures all lipoproteins containing apolipoprotein B, including the triglyceride-rich lipoproteins. In a study of adults on statins, non-HDL-C had a stronger association with plaque progression than LDL-C [41]. This is further supported by the Mendelian randomization studies on triglycerides that help control for the very high day-to-day variability of triglycerides in the general population, a factor that can confound traditional epidemiologic analysis [45, 56].

Another factor increasing the relevance of hypertriglyceridemia in DM is a better understanding of the role of triglycerides in the development of atherosclerosis. Although triglycerides are absent in atherosclerotic plaques, remnant particles, which are triglyceride rich, likely contribute to the inflammatory component of atherosclerosis and do enter developing plaques similar to LDL-C [45]. For example, in patients with genetically high LDL-C, this inflammation is absent, suggesting the inflammation is not primarily a result of LDL-C [57].

To summarize, the role of triglycerides in the development of CVD remains unresolved, but recent evidence using more sophisticated methods suggests that triglycerides may have a more important role in the development of CVD in patients with DM.

3. Treatment Recommendations for Adults

Treatment of hypertriglyceridemia in T1DM and T2DM depends on the degree of elevation of triglycerides. For those with less than very high hypertriglyceridemia (<500 mg/dL) [15], the focus of treatment has been on reducing CVD risk, rather than the triglyceride level. However, for those with significantly higher levels, triglyceride-induced pancreatitis is a potentially serious complication. Although it can occur at lower levels, patients with triglyceride levels greater than 800 mg/dL are thought to be at the highest risk. In one study, 15% of patients with a triglyceride level >20 mmol/L (1770 mg/dL) had triglyceride-induced pancreatitis, whereas the prevalence dropped to 3% when the triglyceride level ranged from 10 to 20 mmol/L (885 to 1770 mg/dL) [58]. For patients with triglycerides levels in this range, the goal of treatment should be to lower the triglyceride level quickly. In the prevention and treatment of triglyceride-induced pancreatitis, fat should be eliminated or severely restricted. For those with symptoms of pancreatitis, patients should fast until they improve. After improvement, a nonfat diet should be implemented slowly.

For many patients with DM, poor glucose control will be the primary driver of hypertriglyceridemia and may actually be a presenting symptom at diagnosis of DM [59]. In these patients, insulin can rapidly lower triglyceride levels in concert with stabilizing blood glucose levels, particularly in patients presenting concurrently with triglyceride-induced pancreatitis and diabetic ketoacidosis (DKA) [60, 61]. In one of the largest studies of triglyceride-induced pancreatitis in patients with DKA, at least 11% of patients with DKA had evidence of pancreatitis, with the risk of pancreatitis being associated with the severity of acidosis and hyperglycemia [62].
Once patients are able to tolerate oral intake, fibrates and/or omega-3 fatty acid supplements can be useful in reducing triglyceride levels in the long term (Table 2). The American Heart Association states it is reasonable to start triglyceride-lowering medications once triglyceride levels are over 500 mg/dL [15]. If the pancreatitis or hypertriglyceridemia persist, despite medical management, plasmapheresis is one potential option. Plasmapheresis is preferred over more selective forms of apheresis because filtering of triglycerides often leads to clogging of apheresis filters. Of note, intravenous heparin was once used in the treatment of very high triglyceride levels but should now be avoided. Although heparin is able to release lipoprotein lipase from the endothelium and therefore increases triglyceride hydrolysis, this effect is temporary and increases the risk of rebound hypertriglyceridemia [63, 64].

4. Moderately Increased Triglycerides

A. Role of Glucose Control

Poor glucose control is central to many of the consequences of T1DM and T2DM. However, tightly controlling glucose will likely be insufficient to reduce all CVD risk and may actually increase risk, as was demonstrated in Action to Control Cardiovascular Risk in Diabetes (ACCORD) [4, 65, 66]. One potential explanation for this counterintuitive finding is that tight glucose control is most important in the early stages of T1DM and T2DM and that the increased possibility of hypoglycemia with tight glucose regulation in older adults is associated with excessive risk. Only in the Diabetes Control and Complications Trial (DCCT) and its follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC) trial, in which tight glucose control was started early in the course of the illness, did a reduction in CVD risk occur [4, 67, 68]. Glucose control appears to be of most importance in the prevention and treatment of triglyceride-induced pancreatitis, rather than in reducing CVD risk factors [65].

B. Role of Diet and Physical Activity

A healthy diet, sufficient physical activity, smoking cessation, and moderation in the use of alcohol remain first-line treatments for hypertriglyceridemia, particularly for patients with DM (Table 3) [2, 4, 12, 69]. In adult trials, a modest reduction in weight by 5% to 10% can lead to a decrease of triglyceride levels by approximately 20% [70]. For patients with DM and hypertriglyceridemia, reducing carbohydrates may be the most effective strategy to reduce triglycerides and improve the atherogenic triad [26]. Substantial reduction in calories from carbohydrates, especially those from foods and beverages with added sugar, can lead to a 10% to 20% reduction in triglyceride levels [4]. In the large Primary Prevention of Cardiovascular Disease With a Mediterranean Diet (PREDIMED), a diet high in nuts and polyunsaturated fatty acids reduced hypertriglyceridemia and the risk of CVD in adults [71]. A subgroup analysis of patients with DM also showed an improvement in hypertriglyceridemia [71]. However, in comprehensive review of diets with different macronutrient compositions, the

| Medication          | Triglyceride Reduction |
|---------------------|------------------------|
| Fibrates            | 30%–50%                |
| Niacin              | 20%–50%                |
| Omega-3 supplements | 20%–50%                |
| Statins             | 10%–30%                |
| Ezetimibe           | 5%–10%                 |

*In children, 4 g per day lowers triglycerides by approximately 50 mg/dL [84, 85] and by 15% to 30% in adults [86–88].
primary driver for improved triglyceride levels was caloric restriction, rather than the macronutrient content [72]. In adults, aerobic exercise also can reduce triglycerides by 20% if a low-calorie diet is followed [70]. Taken together, reductions of 50% or more in triglyceride levels could potentially be attained through intensive therapeutic lifestyle change [15, 73]. However, the role of lifestyle interventions in patients with DM is not conclusive. Findings from the 2013 Look Action for HEAlth in Diabetes (Look AHEAD) did not find that moderate weight loss in obese patients with T2DM led to a reduction in CVD risk factors [74]. Similarly, an intensive lifestyle intervention in patients with DM did not result in reduced risk of CVD and was stopped prematurely, with average follow-up of over 8 years [75]. A systematic review by Nield et al. [76] did not find evidence of a benefit of nutrition interventions in adults with DM, although the lack of high-quality studies was noted. In the absence of long-term results, it is difficult to determine the impact of lifestyle interventions if they are started at young age.

C. Statins

Statins are the most effective of the lipid-lowering medications in reducing the risk of CVD in patients with DM and hypertriglyceridemia [15]. Statins generally reduce triglycerides by 10% to 15%, depending on baseline triglyceride level, specific statin, and its dose [12, 70]. In LIPID, each 89 mg/dL decrease in triglycerides reduced the risk of CVD by 11% in those taking pravastatin [40]. However, much of the risk reduction in CVD is related to statin’s ability to lower LDL-C and the triglyceride-lowering effect remains modest. As a result, the 2013 ACC/AHA guidelines on reducing CVD and the Endocrine Society guidelines on hypertriglyceridemia in DM do not suggest the use of statins to reduce triglycerides and only recommend statins for reducing CVD [10, 12]. There is a growing body of literature suggesting statins should be first line to reduce CVD in patients with hypertriglyceridemia, especially if the apolipoprotein B level is high [15]. Unfortunately, patients with hypertriglyceridemia are typically excluded from statin trials; in addition, no clinical trial has evaluated the use of non-HDL-C or apolipoprotein b as primary risk factors for CVD, and the evidence to use these markers as therapy targets is limited to secondary analysis [6, 45].

D. Fibrates

Fibrates are the most potent of the lipid-lowering therapies with regard to triglycerides. They reduce triglycerides by decreasing VLDL production and increase the activity of lipoprotein lipase [12]. Studies suggest fibrates decrease triglyceride levels by 30% to 50% and lead to small increases in HDL-C, but generally have no effect on LDL-C [12]. Fibrates have been demonstrated to reduce microvascular complications of DM, such as retinopathy,
nephropathy, and amputations [77]. The efficacy of fibrates in reducing CVD in patients with DM has been disappointing, and fibrates likely do not lower all-cause mortality [12, 78]. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, there was no effect of fenofibrate on CVD events [79]. Similar results were reported by the ACCORD trial, which added a fenofibrate to statin therapy [65]. However, in ACCORD, fibrates reduced CVD events in the subgroup with triglyceride levels greater than 204 mg/dL and HDL-C less than 35 mg/dL [80, 81]. In summary, there is scant evidence that fibrates used in patients with DM have worse outcomes compared with statins [82].

E. Omega-3 Fatty Acids

Omega-3 fatty acids lower triglycerides primarily through reducing triglyceride synthesis in the liver, inhibiting VLDL production, and increasing clearance of triglycerides [83]. Omega-3 fatty acid supplements are well tolerated, but only have a modest effect on triglyceride levels. Triglycerides are usually lowered between 15% to 30%, and LDL-C usually remains unchanged, or even slightly increases [84–88]. In a systematic review, omega-3 fatty acids decreased triglycerides in patients with DM and had no effect on glucose control [89, 90]. The effect of reducing atherosclerotic events, though, is mixed. In JELIS, a study of the effectiveness of omega-3 fatty acids in Japanese adults who were already prescribed a statin, the risk of major cardiac events was reduced by 19% [91]. However, these results were not replicated in the Outcome Reduction With Initial Glargine Intervention trial, Age-Related Eye Disease Study 2, or in the Risk Prevention Study of Omega-3 Fatty Acids [92–94]. The variability of results may depend on several factors, including dose and formulation of supplement, baseline triglyceride level, and baseline omega-3 fatty acid level in the subject of interest. Based on the available evidence, a 2017 statement from the American Heart Association found no evidence that omega-3 fatty acid supplementations reduce CVD in patients with DM [95].

Supplemental omega-3 fatty acids are available as either over-the-counter formulations or in a prescription formulation. Omega-3 fatty acid preparations typically include docosahexaenoic acid and eicosapentaenoic acid (EPA), either alone or in combination. Lovaza, Epanova, and Omtryg, which include both DHA and EPA, are approved by the Federal Drug Administration. Vascepa, a formulation of EPA only, is also approved by the Federal Drug Administration. Omega-3 fatty acids also can be obtained from the diet, such as from fish and vegetables [96].

F. Niacin

Niacin was the first drug to be approved to treat dyslipidemia. Depending on dose and formulation, Niacin typically leads to a 15% to 30% reduction in triglycerides in patients with and without DM [90, 97–99]. The reduction in triglycerides is a result of inhibition of lipolysis in adipose tissue, which reduces the return of free fatty acids to the liver [70]. Despite the decrease in triglycerides, niacin does not appear to reduce the risk of CVD as was demonstrated in AIM-HIGH [50]. In fact, in some populations, it may also increase the risk of stroke and worsen glucose control in patients with DM [100–103].

5. Treatment Recommendations for Children

Data in children and adolescents is much less robust than it is in adults with DM. Current pediatric guidelines focus on treating hypertriglyceridemia as the primary treatment goal only in regards to prevention and treatment of triglyceride-induced pancreatitis (Table 4) [13]. It should be noted, though, that non-HDL-C is recommended as a secondary target for those with elevated triglycerides despite reaching LDL-C goals. For all degrees of hypertriglyceridemia, treatment in children and adolescents is based on small studies and/or extrapolated from trials in adults. The 2011 Expert Panel on Integrated Guidelines for
Cardiovascular Health and Risk Reduction in Children and Adolescents (2011 Expert Panel) has different thresholds for hypertriglyceridemia for those <10 years old and for those ≥10 years old (Table 1) [13]. To ensure an accurate diagnosis, classification of hypertriglyceridemia should be based on at least two fasting lipid panels, unless the initial value is >1000 mg/dL [13]. Except in patients at risk for triglyceride-induced pancreatitis, the initial treatment of patients with DM and hypertriglyceridemia is a 6-month trial of lifestyle modifications. The 2011 Expert Panel [13] suggests using the Cardiovascular Health Integrated Lifestyle Diet (CHILD-1) if the triglyceride level is ≥100 mg/dL for children less than 10 years old or ≥130 mg/dL for those ≥10 years old [13]. In contrast, the American Diabetes Association Standards of Medical Care in Diabetes-2018 recommends the Step 2 American Heart Association diet [104]. Both the CHILD-1 and Step 2 American Heart Association diets recommend that total fat intake be <30% of total calories, trans fatty acids be eliminated, and saturated fat limited to 8% to 10% of total calories. If the CHILD-1 diet is insufficient, or the initial triglyceride level is ≥500 mg/dL, the more restrictive CHILD-2 diet is recommended. Although the CHILD-1 and CHILD-2 diets are very similar, the CHILD-2 diet restricts saturated fat to <7% of total calories and specifically recommends that 10% of total calories are from monounsaturated fat [13]. Per the 2011 Expert Panel, sufficient physical activity is defined as having at least 1 hour each day of moderate-to-vigorous activity and at least 3 days per week with 1 hour of vigorous-intensity physical activity [13]. In one study, a reduction in sugar-sweetened beverages coupled with increased physical activity levels was associated with lower triglyceride levels and reduced insulin resistance in boys, but not girls [105].

For most children and adolescents, weight loss, increased physical activity, and following the CHILD-1 or CHILD-2 diets should be effective in improving triglyceride levels. However, dietary intervention trials have failed to find that diet alone is adequate [106, 107]. In those in whom it fails, guidelines recommend medication referral to a lipid specialist, intensifying glucose control, and consideration of lipid-lowering therapy. In children and adolescents with DM, poor glucose control is associated with a more atherogenic lipid profile [8, 108]. Although adequate glucose control is of the utmost importance in DM, it often is insufficient to normalize the lipid profile [108].

Until the LDL-C is normalized, statins are recommended as the initial medication in patients with DM and dyslipidemia [13]. As opposed to adult guidelines that focus on reducing risk profiles, guidelines in pediatrics continue to use level-driven goals. As DM is considered a high-risk condition, statins are recommended if the LDL-C is ≥130 mg/dL and goal LDL-C levels are <100 mg/dL. Unfortunately, data on the long-term efficacy and safety of statins in reducing CVD risk in children and adolescents with DM is limited. However, studies of children and adolescents with familial hypercholesterolemia provide evidence that statins are safe and can effectively improve the lipid profile and markers of CVD risk [109–112]. Studies of the use of statins in children and adolescents with DM have found

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**Table 4. Treatment Recommendations for Hypertriglyceridemia in Children and Adolescents [13]**

| TG ≥130 mg/dL<sup>a</sup> | TG ≥100 mg/dL<sup>b</sup> | TG 200–499 mg/dL | TG ≥1000 mg/dL or Average TG ≥500 mg/dL |
|---------------------------|--------------------------|------------------|----------------------------------------|
| Step 1 CHILD-1            | CHILD-1                  |                  |                                        |
| Step 2 CHILD-2            | CHILD-2; consider omega-3; consider statin if non-HDL-C ≥145 mg/dL | CHILD-2; consider statin if non-HDL-C ≥145 mg/dL |                                        |
| Goal                      | TG < 130<sup>a</sup>     | Non-HDL-C <145 mg/dL | Acutely lower TG to prevent pancreatitis |
| TG < 100<sup>b</sup>     | TG < 130                 |                  |                                        |

Abbreviations: omega-3, omega-3 fatty acid supplement; TG, triglyceride level.

<sup>a</sup>10 to 19 years old.

<sup>b</sup><10 years old.
similar results, including benefits beyond LDL-C lowering [113–115]. Although there are concerns of worsening insulin sensitivity with the use of statins in adults, in a randomized control trial in adolescents with T1DM and elevated LDL-C, atorvastatin was not found to increase insulin resistance. Further, this pilot study found atorvastatin was associated with lower levels of LDL-C, apolipoprotein B, and atherogenic lipoprotein subparticles [106].

In the most recent guidelines, the use of fish oil supplements, fibrates, or niacin can be considered if triglycerides or non-HDL-C remains elevated. However, the guidelines do not provide specific recommendations in regards to treatment thresholds or doses [13]. As mentioned, fibrates are recommended in adults only to prevent triglyceride-induced pancreatitis. In children and adolescents, the safety and efficacy of fibrates is limited to a single study in youth with familial hypercholesterolemia, which demonstrated similar safety and efficacy for reducing CVD risk as in adults [116]. There also is limited data on omega-3 supplements. In two small studies, omega-3 supplements appear safe in children at a dose of 4 g/d, but only reduce the triglyceride level by about 50 mg/dL and were marginally significant compared with placebo [84, 85]. There is no data on the use of niacin in children with DM and hypertriglyceridemia.

6. Conclusion

There is an improved understanding of the role of hypertriglyceridemia in adult patients with DM in the development of CVD; however, specific treatments to prevent CVD continue to be directed toward statins. The implications of hypertriglyceridemia in children and adolescents with DM remain unknown and are of critical importance given the potential for lifelong exposure to elevated levels. Current pediatric guidelines consider DM as a major CVD risk factor and recommend focusing treatment on lowering LDL-C with statins and using lower LDL-C thresholds for initiating medication (130 to 160 mg/dL depending on the presence of other risk factors) [11–13]. Although fibrates, niacin, and supplemental omega-3 fatty acids are effective at lowering triglyceride levels, the data supporting their use in reducing CVD risk is rather weak and data on use in children is lacking. Specifically targeting triglyceride levels, however, remains important in the prevention and treatment of triglyceride-induced pancreatitis for both children and adults. Further research on hypertriglyceridemia in children and adolescents with DM is needed to sufficiently prevent future CVD in this population.

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