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Review

Importance of Dyslipidaemia Treatment in Individuals with Type 2 Diabetes Mellitus—A Narrative Review

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Abstract: Type 2 diabetes mellitus (T2DM) is a common metabolic disease characterised by insulin resistance and elevated blood glucose levels, affecting millions of people worldwide. T2DM individuals with dyslipidaemia have an increased risk of cardiovascular disease (CVD). A complex interplay of risk factors such as hyperglycaemia, dyslipidaemia, hypertension, obesity, inflammation, and oxidative stress favour the development of atherosclerosis, a central mechanism in the pathogenesis of cardiovascular disease. Dyslipidaemia, a hallmark of T2DM, is characterised by elevated triglycerides, decreased high-density lipoprotein (HDL) cholesterol and the presence of small, dense low-density lipoprotein (LDL) particles, all of which promote atherosclerosis. In this article, we have attempted to present various treatment strategies that include pharmacological interventions such as statins, ezetimibe, PCSK9 inhibitors, fibrates, and omega-3 fatty acids. We have also tried to highlight the pivotal role of lifestyle modifications, including physical activity and dietary changes, in improving lipid profiles and overall cardiovascular health in T2DM individuals. We have also tried to present the latest clinical guidelines for the management of dyslipidaemia in T2DM individuals. In conclusion, the treatment of dyslipidaemia in T2DM individuals is of great importance as it lowers lipid particle levels, slows the progression of atherosclerosis, and ultimately reduces susceptibility to cardiovascular disease.

Keywords: type 2 diabetes mellitus; dyslipidaemia; metabolic disorder; pharmaceutical treatment; nonpharmaceutical treatment

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterised by insulin resistance and high blood glucose levels. It is estimated that 462 million people are affected by this disease, which corresponds to a prevalence rate of 6059 cases per 100,000. T2DM is more common in developed regions (Europe, North America) with equal gender distribution [1]. T2DM is a significant risk factor for cardiovascular disease including coronary artery disease, myocardial infarction, stroke, peripheral artery disease, and heart failure. Cardiovascular comorbidities in T2DM patients impose high costs on both the population and individuals. Cardiovascular expenditure accounts for between 20% and 49% of the total direct costs of treating T2DM at the population level. In the 2016 analysis of the economic burden of T2DM complications in Sweden, the cost per person was EUR 1317. This comprehensive figure encompasses a complex interplay of factors, with a notable 25% of the total costs being due to absenteeism. The main contributors to these costs were macrovascular complications such as angina, heart failure, and stroke, and microvascular

complications such as eye disease (e.g., retinopathy), kidney disease, and neuropathy. Furthermore, early mortality in the working-age population resulted in an additional cost of EUR 579 per person, while expenditure on drugs to treat risk factors amounted to EUR 418 per person [2]. The increased risk of CVD in individuals with T2DM is influenced by a complex interplay of risk factors that include hyperglycaemia, dyslipidaemia, hypertension, obesity, inflammation, and oxidative stress. These risk factors contribute to the development and progression of atherosclerosis, one of the major underlying processes in CVD [3,4]. The aim of this review is to shed light on the management of dyslipidaemia in people with type 2 diabetes mellitus, focusing on the underlying pathophysiology and the intricate web of interrelated metabolic disorders.

2. Pathophysiology

The pathophysiology of atherosclerosis in T2DM is a complex process, but it is important to understand its relationship to the increased risk of cardiovascular disease and mortality in people with T2DM. Atherosclerosis in T2DM is primarily caused by a combination of metabolic abnormalities, inflammation, oxidative stress, and endothelial dysfunction. The main pathophysiological mechanism is hyperglycaemia due to insulin resistance, which can damage blood vessels and increase the risk of atherosclerosis. People with T2DM have a significantly increased risk of developing cardiovascular disease, including coronary heart disease, stroke, and peripheral vascular disease. Cardiovascular disease is the leading cause of morbidity and mortality in this population, with T2D patients at similar risk to people who have already had a heart attack (coronary risk equivalent) [3,5,6]. The complicated pathophysiological processes described above contribute significantly to this increased risk. Dyslipidaemia, characterised by increased triglyceride levels, decreased high density lipoprotein (HDL) cholesterol levels and small, dense low-density lipoprotein (LDL) particles, is common in T2DM and promotes the development of atherosclerotic plaques. Chronic low-grade inflammation and oxidative stress are hallmarks of T2DM and play a critical role in the development and progression of atherosclerosis. These processes, in conjunction with endothelial dysfunction, lead to a proinflammatory and prothrombotic state in the blood vessels. The formation of atherosclerotic plaques with lipid deposits, inflammatory cells, smooth muscle cells, and fibrous tissue marks the beginning of the vicious circle [3,7,8]. Vulnerable plaques are prone to rupture, which can lead to thrombosis and cause acute cardiovascular events such as heart attacks and strokes. As atherosclerosis progresses, artery walls can remodel, leading to narrowing and reduced blood flow in the affected vessels. In summary, the pathophysiology of atherosclerosis in T2DM plays a critical role in the increased risk of cardiovascular disease and mortality in these patients. Understanding the intricate relationships between these factors is essential for effective management and risk reduction in people with T2DM [3,6,8].

3. Type 2 Diabetes Mellitus and Dyslipidemia Interconnection

Dyslipidaemia is one of the most common findings in people with type 2 diabetes, affecting about 72–85% of those affected [9]. It additionally increases cardiovascular risk, especially the risk of developing coronary heart disease. The most important lipid abnormalities in diabetics are increased levels of triacylglycerols and decreased HDL cholesterol. In addition to quantitative changes in lipoproteins, there are also qualitative and kinetic changes in lipoprotein metabolism that contribute to the development of atherosclerosis [10]. Prior to the development of manifest type 2 diabetes, increased insulin resistance affects the accumulation of triglycerides and small, dense LDL particles. Starting from the chylomicron level, diabetics experience increased production of chylomicrons as a result of insulin resistance, leading to postprandial hyperlipidaemia, although the complex pathway that triggers this phenomenon is not yet fully understood [11,12]. On the other hand, the clearance of chylomicrons is impaired due to the decreased activity of lipoprotein lipase (LPL), an enzyme necessary for the degradation of chylomicrons [13]. In addition, the production of large VLDL particles is increased, leading to an increase in

plasma triacylglycerol levels. Studies have shown the link between VLDL production rates and fatty liver in people with type 2 diabetes [14]. Unlike other lipids, LDL cholesterol levels are not significantly increased in diabetics compared to the general population, but increased glycation of LDL leads to severe atherosclerosis. Glycated LDL cholesterol has a lower binding affinity to LDL receptors and is taken up by macrophages, leading to the formation of foam cells [15]. In addition, oxidised LDL particles increase the formation of cytokines (TNF-α, IL-1), adhesion molecules that promote the inflammatory atherosclerotic process. Diabetics also have reduced levels of HDL cholesterol, which plays a key role in the uptake and transport of lipoproteins. Studies have shown that HDL particles are more degraded in diabetics due to the accumulation of triacylglycerol [16]. HDL plays an important role in cardiovascular prevention due to its antioxidant and vasodilatory effects, so lower levels also increase overall cardiovascular risk. The most common quantitative changes in the lipid profile of diabetics are increased triglyceride levels, residual particles, and decreased HDL cholesterol levels. Qualitative and kinetic changes in the metabolism of LDL cholesterol have a major atherogenic effect, so that the treatment of dyslipidaemia should be taken very seriously.

4. Target Lipid Levels in Type 2 Diabetes Mellitus

The American Diabetes Association recently released updated guidelines for 2023 that include new recommendations for people with diabetes, including guidance on managing lipid levels. According to the current recommendations, it is advisable to prescribe high-intensity statin treatment for people with diabetes who are at increased risk for cardiovascular problems, especially those with one or more risk factors for atherosclerotic cardiovascular disease (ASCVD). The primary goal is to reduce LDL cholesterol levels by at least 50% from baseline, aiming for an LDL cholesterol level of less than 70 mg/dL (1.8 mmol/L) [17]. However, in clinical practise, it can be difficult to determine the exact baseline LDL cholesterol level before starting statin therapy. Therefore, for these individuals, it is recommended to focus on achieving a target LDL cholesterol of less than 70 mg/dL (1.8 mmol/L) rather than on the percentage reduction in LDL cholesterol. If appropriate, it may also be useful to supplement maximally tolerated statin therapy with ezetimibe or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor to achieve the desired LDL cholesterol reduction of at least 50% and reach the recommended LDL cholesterol target of below 70 mg/dL (1.8 mmol/L). Although primary prevention trials have typically involved limited numbers of older people with diabetes, they have not shown significant differences in the relative benefits of lipid-lowering therapy between age groups. However, because older age is associated with a higher risk profile, the absolute benefit of lipid-lowering therapy is greater. Therefore, it is advisable to recommend moderate-intensity statin therapy to people with diabetes aged 75 years or older. High-intensity statin therapy is recommended for all people with diabetes who have a history of ASCVD. The goal is to achieve a significant reduction in LDL cholesterol levels of at least 50% from baseline, with a specific goal of maintaining LDL cholesterol levels below 55 mg/dL (1.42 mmol/L) [17]. If these targets are not met despite administration of the maximally tolerated statin, it is advisable to consider additional administration of ezetimibe or a PCSK9 inhibitor. The new guidelines do not include precise target values for other lipoproteins. Therefore, it is advisable to consider the following target values: HDL cholesterol levels should be above 40 mg/dL (1.02 mmol/L) and triglyceride levels should be below 150 mg/dL (1.7 mmol/L) [18] (Table 1).

Table 1. Statin treatment goal in T2DM individuals.

TD2M Individuals					
>40 years old					
>10 years T2DM					
At least one MACE					
T2DM end organ damage					
LDL-C >2.5					
<40 years old					
	>40 years old	>10 years T2DM	At least one MACE	T2DM end organ damage	LDL-C >2.5

Index	N/A	Moderate intensity statin treatment	High intensity statin treatment

5. Treatment of Dyslipidaemia in Type 2 Diabetes Mellitus

The treatment of dyslipidaemia in individuals with type 2 diabetes mellitus (T2DM) can be divided into two categories: nonpharmacological and pharmacological. If we talk about pharmacological therapeutic strategies with regard to elevated lipid levels in individuals who have already been diagnosed Type 2 DM, the most important approach is treatment with statins. Other options include cholesterol absorption inhibitors, fibrates, PCSK9 inhibitors, and omega-3 fatty acids [19].

Despite the significant benefits of treatment strategies that reduce CVD risk factors, CVD remains the major cause of morbidity and mortality in individuals with T2DM. The risk of MACE in T2DM is strongly determined by the presence of target organ damage, with risks increasing with the number of diseases present. In light of this information, the main focus of treatment for dyslipidaemia in individuals with T2DM is early initiation of treatment [19]. According to the latest guidelines, individuals who have had diabetes for at least 10 years or less but have known cardiovascular disease and/or at least one target organ damage and elevated lipid levels should start statin treatment immediately [19,20]. If an early 50% reduction is achieved, further supplementation is not required but continuation of pharmacological and nonpharmacological treatment is. However, if the desired reduction is not achieved, the additional administration of ezetimibe or PCSK9 inhibitor is suggested depending on the primary or secondary prevention setting [19,20] (Figure 1).

5.1. Statins

Statins are the first treatment option for individuals with T2DM. Management of LDL cholesterol is of paramount importance in these individuals. The Cholesterol Treatment Trialists (CTT) study performed a comprehensive analysis of the data and uncovered 3247 serious vascular events in the diabetic cohort [21]. Strikingly, each one millimole per litre (mmol/L) reduction in LDL cholesterol was associated with a remarkable 9% proportional reduction in all-cause mortality in participants with diabetes. Remarkably, this reduction paralleled the 13% decrease observed in individuals without diabetes, underscoring the importance of LDL-C modulation in preventing mortality [21]. This positive trend was underlined by a statistically significant reduction in vascular mortality in the diabetic cohort, while no discernible effect on non-vascular mortality was observed. In addition, a substantial proportional reduction in major vascular events of 21% per mmol/L reduction in LDL cholesterol was observed in participants with diabetes, mirroring the effects in participants without diabetes [21]. The discernible effects of statin therapy also extended to specific cardiovascular outcomes in the diabetes population, including reductions in myocardial infarction or coronary death, coronary revascularisation, and stroke. Notably, these results held true regardless of whether

participants had a history of vascular disease [22,23]. After 5 years, statin therapy had significant clinical benefit in the diabetic cohort, as evidenced by a reduction in major vascular events among participants receiving statin therapy [21]. Overall, these results highlight the compelling efficacy of statin therapy in reducing the burden of serious vascular events in people with diabetes mellitus and support the thesis that statins are a key therapeutic intervention for LDL-C management in the context of diabetes treatment. On the other hand, recent studies have brought to light a possible increase in the incidence of diabetes mellitus (DM) in individuals receiving statin therapy [24,25]. This trend has been supported by clinical trials, with the clearest effects observed in people who are already at increased risk of DM, such as those with prediabetes [26]. It is critical to emphasise that these results should not diminish our commitment to patient care, as the overarching benefits of reducing cardiovascular disease persist and far outweigh the increased incidence of DM. Conversely, a separate prospective study of T2DM individuals found no statistically significant difference in glycosylated haemoglobin (HbA1c) levels between statin-treated and non-statin-treated groups [27]. The safety profile of statins is well established, with adverse effects such as muscle pain and liver damage frequently reported [28]. These adverse effects may be the most important factor in the low adherence to statin treatment. However, newer approaches such as fixed-dose combination therapy with statins and other drugs such as antihypertensives or even antidiabetics are leading to better adherence and positive cardiovascular outcomes in individuals [29].

5.2. Ezetimibe

Ezetimibe, a lipid-lowering agent that acts as a cholesterol absorption inhibitor, is associated with a 19% reduction in LDL-C levels [30]. Although ezetimibe alone has no positive results in risk reduction MACE, when added to statin therapy, ezetimibe has shown remarkable ability to reduce the risk of serious vascular events. It is important to note that the magnitude of relative risk reduction in MACE is directly proportional to the absolute degree of LDL-C reduction, a relationship consistent with the observed effects of statins [31]. In the study IMPROVE-IT, which included a subgroup of individuals diagnosed with T2DM, it was expected that this subgroup would have a higher rate of major vascular events than individuals without DM. In fact, the placebo arm of the study showed that individuals with DM had a significantly increased rate of MACE, with a 7-year Kaplan–Meier rate of 46% compared to 31% in individuals without DM [32]. Of particular importance is the observation that ezetimibe proved to be particularly effective in individuals with DM in the IMPROVE-IT study. When ezetimibe was added to their treatment regimen, individuals with DM experienced a relative risk reduction of 15% in MACE, which corresponds to a substantial absolute risk reduction of 5.5% [32]. However, it is worth noting that the IMPROVE-IT study did not demonstrate a significant reduction in MACE with single-use ezetimibe [33]. The reduction in major vascular events was most notable when ezetimibe was used in conjunction with statin therapy, highlighting the synergy between these therapies in achieving significant clinical benefits in cardiovascular risk management. Importantly, the safety profile of the combined statin-ezetimibe treatment remained consistent regardless of the presence of DM, underscoring the tolerability of this therapeutic approach [32,33] (Table 2) Based on the observed results, ezetimibe is used as a second treatment option in combination with statins in individuals in whom LDL-C lowering cannot be achieved with statin treatment alone [19,20].

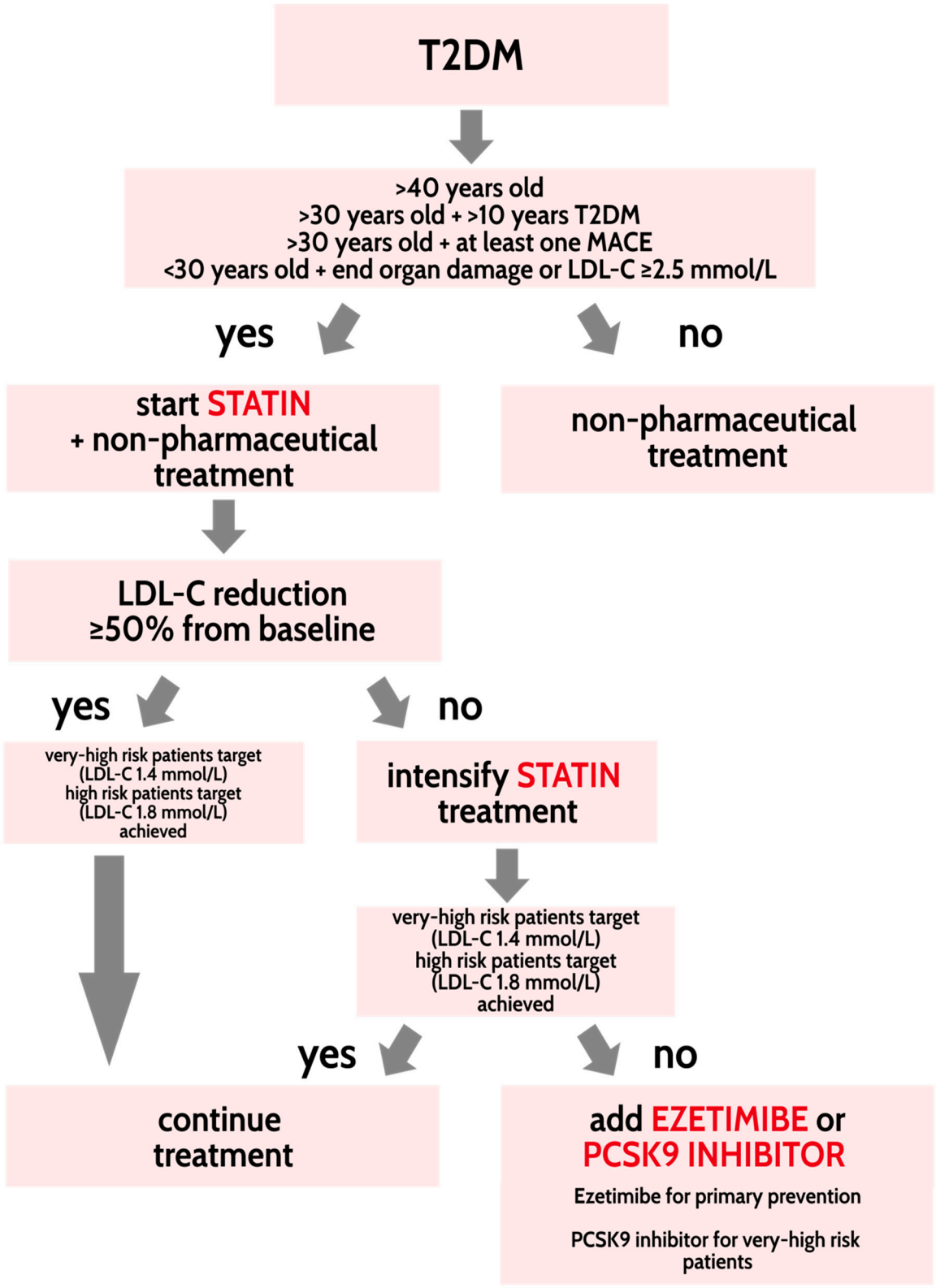

Figure 1. Recommendations for the treatment of dyslipidaemia in T2DM.

Table 2. Overview of the pharmacological approaches to dyslipidaemia in T2DM individuals.

Pharmacological Approach to Dyslipidaemia in T2DM Individuals				
Drug	**Dosage**	**Mechanism of Action**	**Common Adverse Events**	**Monitoring (Except Lipid Profile)**
Statins	10–80 mg Oral use/daily	HMG-3-CoA reductase antagonist	Statin-associated muscle disease Fatigue Hepatic dysfunction	Serum aminotransferases Serum creatine-kinase Regular blood count
Ezetimibe	10 mg Oral use/daily	NPC1L1 transporter inhibitor	Hepatic dysfunction Muscle-related effects	Serum aminotransferases Serum creatine-kinase
Alirocumab Evolocumab	140 mg 75–300 mg Subcutaneous injections/2–4 weeks	PCSK9 inhibitors—monoclonal antibodies	Local injection reactions	-
Fibrates	145–215 mg Oral use/daily	PPARs activators	Hepatic dysfunction Muscle-related effects Renal dysfunction	Serum aminotransferases Serum creatine-kinase Serum renal function tests Regular blood count

5.3. PCSK9 Inhibitors

PCSK9 monoclonal antibodies such as evolocumab and alirocumab have attracted considerable attention due to their efficacy in lowering LDL-C levels, which is around 60% [33,34]. In the FOURIER study, the relative risk reduction for MACE was consistent in all patient groups with and without diabetes mellitus. However, the baseline risk profile of individuals with DM, characterised by an inherently higher cardiovascular risk, resulted in a more pronounced absolute risk reduction of 2.7% in MACE over 3 years [34]. These outstanding results are consistent with those of the ODYSSEY study, which demonstrated a consistent benefit of PCSK9 inhibitors, particularly in diabetic individuals after an acute coronary syndrome [35]. These studies highlight the potent LDL-C lowering effect of PCSK9 monoclonal antibody inhibitors and their potential to reduce the risk of MACE in both diabetics and non-diabetics [34,35]. A recent study that deepened our understanding of the effects of PCSK9 inhibitor therapy examined the effect of alirocumab in individuals of different glycaemic categories [34]. Importantly, alirocumab resulted in similar relative reductions in the incidence of primary cardiovascular endpoints in all glycaemic categories. However, in individuals with diabetes, there was a greater absolute reduction of 2.3% in the incidence of primary endpoints than in individuals with prediabetes (1.2%) or normoglycaemia (1.2%) [36]. Furthermore, in individuals without diabetes, the risk of new-onset diabetes was not increased by alirocumab therapy. These results highlight the safety profile of alirocumab with respect to new-onset diabetes [36,37]. Similar observations were made with evolocumab in a study that included individuals with and without diabetes. Evolocumab reduced cardiovascular outcomes in both patient groups [34,37]. These results suggest that the benefit of evolocumab is not dependent on diabetes status. Importantly, evolocumab did not increase the risk of new-onset diabetes in individuals without diabetes. In addition, haemoglobin A1c (HbA1c) and fasting plasma glucose (FPG) levels remained constant over time in all glycaemic categories between the evolocumab and placebo groups [38]. In addition, the frequency of adverse events was comparable between the evolocumab and placebo groups, further underscoring the safety profile of this PCSK9

inhibitor therapy regardless of diabetes status [34,35]. Overall, these comprehensive results highlight the robust efficacy and safety of monoclonal antibody PCSK9 inhibitors in both diabetic and non-diabetic individuals, supporting their role in controlling LDL-C levels and lowering MACE. However, the elephant in the room needs to be addressed, as the cost–benefit analysis of PCSK9 inhibitors is still ongoing. While some countries report further price reductions to increase cost-effectiveness, inclusion in T2DM treatment may justify their cost [39].

5.4. Fibrates

Fibrates are drugs used primarily to treat abnormal lipid profiles and conditions such as hypertriglyceridaemia and low levels of high-density lipoprotein cholesterol (HDL-C). These drugs work by activating peroxisome proliferator-activated receptors (PPARs), which regulate lipid metabolism [40]. The therapeutic efficacy of treating elevated triglyceride levels (TG) and low high-density lipoprotein cholesterol (HDL-C) levels, which are common in people with diabetes mellitus (DM), remains controversial. This debate arises from observations in studies such as FIELD and ACCORD, conducted in the context of T2DM cohorts, in which the effects of fenofibrate therapy on MACE did not yield positive results. In the FIELD study, fenofibrate showed a 27% reduction in CVD in individuals with elevated TG levels and elevated HDL-C levels [41]. Similarly, the ACCORD study confirmed that participants with both elevated TG and low HDL-C levels appeared to benefit from taking fenofibrate and statin at the same time [42]. The available evidence suggests that diabetics with dyslipidaemia may derive clinical benefits from TG -lowering therapy when administered concurrently with statin treatment.

5.5. Omega-3 Fatty Acids

Omega-3 fatty acids are essential polyunsaturated fats that provide a number of health benefits. These fats are abundant in certain fish such as salmon, mackerel, and sardines, as well as in flaxseeds, chia seeds, and walnuts [43]. They have the benefit of lowering triglyceride levels, improving blood vessel function and possibly reducing inflammation [44,45]. Omega-3 supplements are widely available in various forms such as fish oil capsules, krill oil, and algae-based supplements, so it is extremely difficult to regulate them and determine the exact dosage. There are limited data on the effects of adding omega-3 fatty acids to statin therapy in individuals with elevated plasma levels TG. The study REDUCE-IT sought to fill this gap by investigating the effects of icosapent ethyl at a dose of 2 grammes twice daily in high-risk HTG individuals taking statins concomitantly. The results showed a 25% reduction in the composite primary outcome, which includes cardiovascular death (CV), non-fatal myocardial infarction (MI), non-fatal stroke, coronary revascularisation, or unstable angina. This decrease corresponded to an absolute decrease of 4.8% [45]. Contrastingly, the ASCEND trial revealed that omega-3 fatty acids did not demonstrate a reduction in MACE [46] Although more research is needed, omega-3 fatty acids have an excellent safety profile. The most commonly reported adverse effects are gastrointestinal discomfort, increased risk of bleeding, and allergic reactions. While certain observations suggest the potential benefits of omega-3 fatty acids for individuals with T2DM, it is crucial to recognize that they cannot replace standard recommended treatments and are not in the guidelines for dyslipidaemia treatment. Both individuals and healthcare professionals should remain mindful of the potential impacts that supplements may have on patients [47].

5.6. Non-Pharmaceutical Treatment

A healthy lifestyle is a key element in the prevention of adverse cardiovascular events. A healthy lifestyle includes not only physical activity, but also improving dietary habits, reducing environmental risk factors, and maintaining mental health [48]. People who have type 2 diabetes mellitus have a higher risk of developing severe cardiovascular events. Expected lifestyle changes for these people therefore include improving dietary habits, increasing physical activity, and even taking medication to prevent further complications [49]. Added fats, sugars, or processed meats and sweetened beverages can significantly increase the risk of developing diabetes mellitus and cardiovascular disease. For example, drinking a single sweetened beverage per day can increase the risk of developing diabetes mellitus by up to 20% [50]. Physical activity and balanced dietary habits lead to weight loss in overweight individuals. Weight loss has a significant impact on lipid levels as well as on the treatment of type II diabetes mellitus, thus improving overall health. The effects of increased physical activity on lowering HbA1c levels have been known for several decades and point to the importance of a healthy lifestyle for blood glucose levels and cardiovascular-related morbidity and mortality in people with diabetes mellitus [51]. Exercise and increased physical activity have the greatest impact on HDL and triglyceride levels. In the study by Coillard and et al., participants were divided into four subgroups based on baseline HDL and triglyceride levels: The first consisted of people with normal levels (high HDL and low triglycerides), the second consisted of people with isolated low HDL and normal triglycerides, the third consisted of people with isolated high triglycerides and normal HDL levels, and the fourth subgroup included people with elevated triglycerides and low HDL. Among those with a combination of initially low HDL and elevated triglycerides, increased physical activity had the most significant effect, with a 4.9% increase in HDL levels, compared with a slight increase of 0.4% among those with isolated low HDL levels [52]. In addition, some studies suggest that not only physical activity but also its intensity has an impact on lipid management. In the STRRIDE study, changes in serum lipoproteins were monitored in participants with dyslipidaemia who took part in a range of physical activities. After eight months, HDL cholesterol levels and concentrations of large HDL particles were higher in those who engaged in intensive and vigorous physical activity than in the other groups. The STRIDDE-PD study included people with prediabetes, and global radiolabelled efflux capacity increased significantly (6.2%) in the high-volume/high-intensity group compared with all other STRRIDE-PD groups [53,54]. A combination of physical activity and healthy diet has shown a greater impact on lipid management. In a study of 22 obese men with metabolic syndrome, 3 weeks of physical activity combined with dietary changes resulted in an increase in platelet-activating factor acetylhydrolase activity [55]. Some diets tend to have a positive effect on the lipid profile of people with diabetes mellitus. For example, a ketogenic diet with 70% fat, 20% protein, and only 10% carbohydrate has been shown to reduce body mass, lower triglycerides and increase HDL levels in people with diabetes mellitus. In one study, no significant differences were found in the values for total cholesterol and LDL cholesterol. Another important outcome of the ketogenic diet is a reduction in waist circumference, which leads to a further reduction in the risk of complications of diabetes mellitus and the development of cardiovascular complications. In addition, in the same study, there is a significant improvement in blood glucose regulation due to a decrease in HbA1c [56]. Although there are studies that point to negative effects of the ketogenic diet on lipid levels, most studies report a reduction in weight and a resulting improvement in the lipid profile [57]. The Mediterranean diet, characterised by ingredients such as olive oil, seeds, whole grains, nuts, and fruits, is usually recommended as a golden model for the prevention of metabolic syndrome and its components. There are data indicating a significant impact of this diet on LDL cholesterol levels and triglyceride levels, especially in people suffering from type 2 diabetes mellitus. In a study by Elhayany and et al.

three different dietary approaches were compared during a one-year follow-up period. All participants had diabetes mellitus and were followed in a community-based setting. During this period, participants strictly followed the dietary recommendations for the low-carbohydrate Mediterranean diet, the classic Mediterranean diet, or the diet recommended by the American Diabetic Association in 2003. The low-carbohydrate Mediterranean diet has been shown to be particularly beneficial in lowering HbA1c and has been the only one associated with an increase in HDL cholesterol. The classic Mediterranean diet and the low-carbohydrate diet resulted in a greater reduction in triglyceride levels [58] (Figure 2). Olive oil, a major component of the Mediterranean diet, has shown positive effects on regulating lipid profiles, improving HDL functions such as cholesterol metabolism and cholesterol efflux capacity, and promoting an anti-inflammatory effect [59]. Consumption of phenol-containing olive oil increased HDL cholesterol and lowered total cholesterol and LDL cholesterol, resulting in a reduction in the ratio of total cholesterol/HDL cholesterol and LDL cholesterol/HDL cholesterol [60]. The CORDIOPREV (Coronary Diet Intervention with Olive Oil and Cardiovascular Prevention) trial showed that a 1.5-year intervention with a Mediterranean diet resulted in improved flow-mediated vasodilation and endothelial function and reduced overall cardiovascular risk in participants with diabetes mellitus and dyslipidaemia [61]. According to some studies, taking probiotics has also been shown to be beneficial. There is data to suggest that probiotics can lead to a reduction in total cholesterol and LDL cholesterol. The combination of probiotics and fermented dairy products can lead to an even greater reduction in LDL cholesterol than when probiotics are taken in capsule form [62]. Certain probiotic species such as Lactobacillus acidophilus and Lactobacillus plantarum have been shown to have more lipid-lowering effects and have been successful in lowering LDL cholesterol and total cholesterol [63]. The decrease in lipid levels varies from study to study and needs further investigation. On the other hand, in patients with dyslipidaemia and type 2 diabetes mellitus, synbiotics have shown an effect of significantly lowering fasting blood glucose levels and increasing HDL [64]. Probiotics have been shown to be beneficial in lowering liver enzymes and total cholesterol in patients with non-alcoholic fatty liver disease (NAFLD) [65]. In one study, NAFLD was induced in Iberian pigs fed a high-fat diet, as opposed to the control group, with or without probiotic supplementation. The high-fat diet caused inflammation and ectopic lipid accumulation in skeletal muscle, with no significant difference found between the groups with and without probiotic addition [66]. The full potential of probiotic supplementation in patients with metabolic syndrome and its components is often controversial, but it is certainly an interesting field waiting to be explored and used in the nonpharmacological treatment of patients. The microbiome diet, a new dietary trend, focuses on consuming less processed foods and increasing the intake of foods rich in prebiotics. Prebiotics are dietary fibres that promote beneficial gut bacteria. By promoting a healthier gut balance, this diet aims to improve metabolic function and reduce inflammation. Research has shown that a high-fat diet can disrupt the balance of the gut microbiome, leading to metabolic problems such as insulin resistance and inflammation. It is thought that by promoting a diverse and balanced gut microbiome community, the microbiome diet can positively influence conditions such as T2DM and dyslipidaemia [67]. The exact model of dietary habits and physical activity that will lead to adequate control of the risk of major cardiovascular events has yet to be found, but research to date may lead to a new answer to this dilemma.

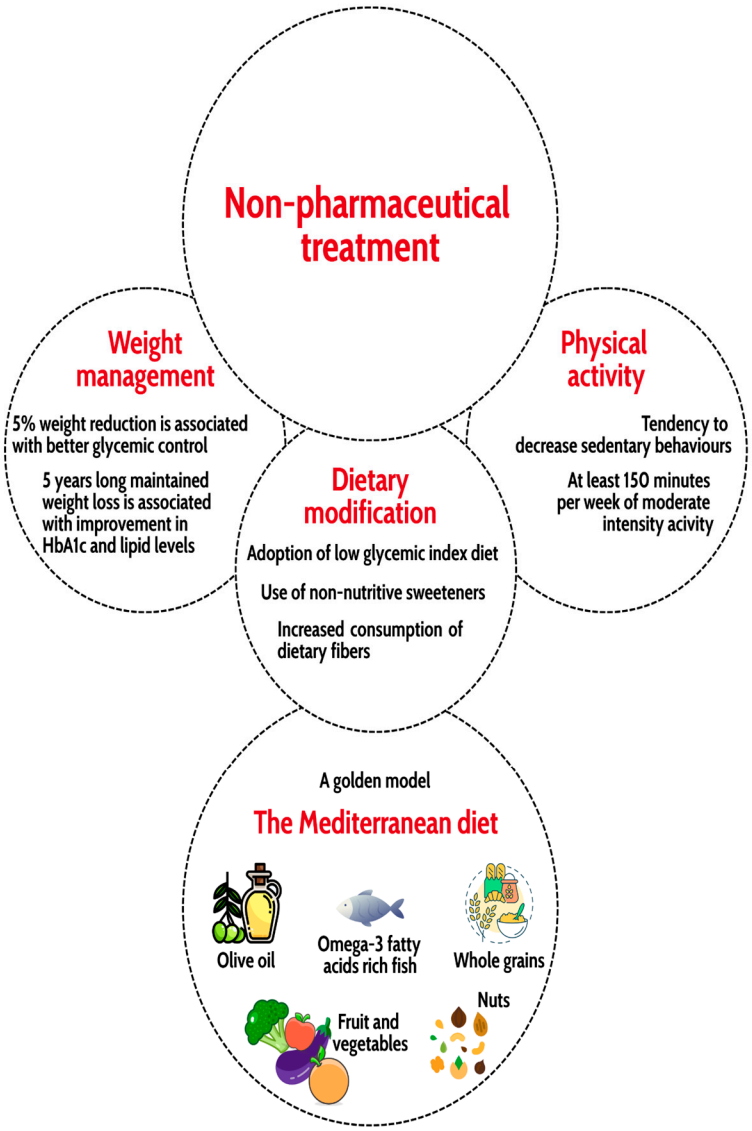

Figure 2. Overview of nonpharmaceutical treatment options in T2DM.

6. Conclusions

The treatment of dyslipidaemia in individuals with type 2 diabetes mellitus (T2DM) is of paramount importance because of the high risk of cardiovascular disease (CVD). T2DM is a complex metabolic disorder that not only affects glucose metabolism but also strongly influences lipid profiles, contributing to the development and progression of atherosclerosis—a key process underlying CVD. The pathophysiology of atherosclerosis in T2DM involves a complex interplay of metabolic abnormalities, inflammation, oxidative stress, and endothelial dysfunction. High glucose levels, a hallmark of T2DM, can damage blood vessels and lead to inflammation and oxidative stress that further increase CVD risk. Dyslipidaemia is common in T2DM. It is characterised by elevated triglycerides, reduced HDL cholesterol levels and the presence of small, dense low-density lipoprotein (LDL) particles. These lipid abnormalities contribute to the formation of atherosclerotic plaques. A comprehensive approach that includes pharmacological therapies, lifestyle modifications, and individualised treatment plans can significantly improve lipid profiles and reduce the risk of major cardiovascular events, ultimately improving the overall health and well-being of people with T2DM. While we have known therapeutical approaches to dyslipidaemia treatment in T2DM individuals, clear primary and secondary prevention

protocols are still up for debate. However, treatment initiation at the earliest moment is of the utmost importance.

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