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The Relationship Between Cholesterol And Aging In Patients With Type 2 Diabetes

Ibrahim Mohammed Alshahrani[1] , Musaad Alhassan Ahmed Al khayrat[2] , Abdulmajeed Rubayyi M Alharbi[3]

[1]Lab technician.
[2,3]lab specialist.

Abstract:

Although lipid-lowering medications (LLDs) are protective against cerebrovascular disease (CVD) and coronary artery disease (CAD), a paradoxical correlation between cholesterol and a number of illnesses, including atrial fibrillation, diabetes, and dementia, has been found. In older adults with type 2 diabetes mellitus (T2DM), we sought to examine the relationship between LLDs and cholesterol levels. Three Taiwanese centers recruited consecutive patients aged ≥50 years for this cross-sectional study. Age, triglyceride level, sex, comorbidities, and medication were taken into account when calculating odds ratios (ORs) for various levels of total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C) in comparison to the highest level using a multiple logistic regression model. Of the 3688 participants, 676 did not have type 2 diabetes and 572 did. Regardless of LLD use, the non-T2DM group outperformed the T2DM group in terms of daily functioning, medical conditions, and cognition after controlling for age and sex. As TC levels declined, ORs increased significantly in comparison to the maximum TC level (≥240 mg/dL). LDL-C levels showed a similar pattern of T2DM prevalence. T2DM in older adults was associated with poor cognitive and everyday functioning. Regardless of LLD use, a higher prevalence of T2DM in older adults was linked to significantly lower TC and LDL levels. Cognitive and everyday functioning impairment was linked to type 2 diabetes. When the "lower is better" approach is used for the secondary prevention of type 2 diabetes, a higher prevalence of the disease in older adults with low cholesterol levels raises concerns about how cognition and everyday functioning may be compromised.

Keywords: Cholesterol, Type 2 Diabetes Mellitus, Lipid-Lowering Drugs.

Introduction

For clinically regulating low-density-lipoprotein cholesterol (LDL-C) levels in individuals at risk of coronary artery disease (CAD) or cerebrovascular disease (CVD), the "lower is better" approach has grown in popularity. Nonetheless, cholesterol is one of the most important nutrients for preserving health, and it is necessary for many physiological processes, including hormone synthesis, cell membrane structure, myelin synthesis or repair, defense against viruses or bacterial endotoxins, and many more (Krause , 2014).

Randomized controlled trials (RCTs) have produced strong evidence in recent decades that lowering LDL-C levels can prevent CAD or CVD either primary or secondary. Furthermore, even at very low or ultralow LDL-C levels, a larger decrease in LDL-C might have a stronger protective effect. Consequently, reducing LDL-C levels has emerged as the most widely accepted tactic. However, as the U.S. Food and Drug Administration has warned, based on evidence showing that LLD use or low cholesterol levels are not beneficial or may be harmful, controversial results are often mentioned in the subgroup analysis of these RCTs or real-world studies on the association of total cholesterol (TC), LDL-C levels, or lipid-lowering drugs (LLDs) with many other diseases, such as new-onset diabetes and cognitive impairment (Hu, 2010; Saherm 2005).

Numerous RCTs and real-world studies have documented the contradictory relationship between cholesterol, including TC and LDL-C, and diabetes. Several RCTs showed a significant percentage of new-onset diabetes, which is regarded as an adverse event. For instance, the Jupiter study showed that rosuvastatin had a promising protective effect against CAD/CVD events; however, as LDL-C levels dropped, the risk of developing diabetes increased, and the hazard increased as well. In patients with hypertension, a real-world study has shown a U-shaped correlation between LDL-C levels and diabetes mellitus (Ravnskov , 2003).

Nunes defined the "LDL cholesterol paradox" as a decrease in CAD/CVD risk associated with a decrease in LDL-C blood levels that does not coincide with a decrease in overall mortality in order to explain these contradictory findings. Other research, however, has found a paradoxical link between low cholesterol and atrial fibrillation (AF) that develops suddenly (Karalis, 2009; Grundy, 2008).

Thus, this study suggested that diabetes is strongly correlated with both age and low cholesterol levels. With the hypothesis that lower cholesterol levels, including TC and LDL-C, may be linked to diabetes in older adults, and that LLDs may amplify this effect if

TC/LDL-C levels are ultralow, we chose older adults and examined the relationship between TC or LDL-C levels and the prevalence of diabetes.

Individuals With Diabetes:

People who have diabetes are more likely to use medications and have other health issues, such as vascular disorders. Furthermore, with the exception of TC and LDL-C levels, which were higher in the non-T2DM group, nearly all of the medical parameters of participants with diabetes were worse than those of participants without the disease. These results were noted irrespective of the use of LLD. As a result, queries like whether it is true that "lower LDL-C is better" and why individuals with diabetes have lower LDL-C levels rather than higher levels come up. Our results on the contradictory relationship between TC/LDL-C levels and diabetes in the elderly are in line with RCTs or empirical research that has indicated a higher risk of type 2 diabetes in adults with or without CAD/CVD who use LLDs for an extended period of time (Cybulska , 2021).

Although the pathophysiology of this phenomenon is still unknown, one possible mechanism is impaired β-cell function. The down-regulation of GLUT-4 in adipocytes, impaired Ca2+ signaling in pancreatic β-cells, and compromised insulin signaling are possible additional mechanisms that contribute to the association between LLDs and incident diabetes. Furthermore, it has been reported that statins' effects on epigenetics may contribute to statin-induced type 2 diabetes by altering the expression of miRNAs. The drug-naive group showed a stronger correlation with diabetes than with LLD use. Numerous studies have proposed beta cell-specific mechanisms, such as modifications in ion channels, signaling pathway modulation, inflammation/oxidative stress, and insulin secretion. A PCSK9 deficiency increases glucose intolerance and decreases insulin secretion. Additionally, LDL-C, elevated plasma glucose levels, and a higher risk of type 2 diabetes are linked to genetic variants of PCSK9 loss of function (Burger , 2022; Jukema , 2012).

Increases Cholesterol levels:

Human cholesterol levels naturally rise after birth and fall during the 50th and 60th decades of life. Since LDL-C is the so-called bad cholesterol, some researchers or clinicians may contend that, particularly in people with a high risk of CVD, its level should be as low as it was in infancy. However, normal and adequate cholesterol levels, either LDL or HDL, are necessary for many physiological processes, such as hormone production, cell membrane structure,

myelination or neurotransmission in the brain and nerves, beta cell functions, and many more. As a result, cholesterol levels continue to rise until the latter half of life(Navarese , 2013).

As a result, the infant's LDL-C level might not be high enough to support additional physiological processes or address pathological conditions. Lastly, the results of our study and a number of others suggest that older adults may be more vulnerable to the negative consequences of LLDs and low TC or LDL-C levels. The cholesterol paradox is widespread and not just present in people with diabetes or atrial fibrillation, according to solid evidence. More research is necessary to examine the balance between lowering and maintaining LDL-C in managing illnesses like cardiovascular disease, coronary artery disease, dementia, diabetes, atrial fibrillation, infection, and many more. Bad cholesterol isn't always bad (Corrao, 2014).

Recommendations:

In order to control medical conditions like cardiovascular disease, coronary artery disease, dementia, diabetes, atrial fibrillation, infection, and many other diseases, more research is necessary to examine the balance between lowering and maintaining LDL-C.

There were certain restrictions on this study. First, a causal relationship could not be established because the comparison of the relationship between cholesterol levels and type 2 diabetes was cross-sectional. It is necessary to conduct additional longitudinal follow-up on a cohort that can track new-onset diabetes across various cholesterol levels. Consequently, TC, LDL-C, or LLDs may be able to contribute. Second, only two hospitals in Central Taiwan and one in Southern Taiwan were used for our study. Selection bias was therefore unavoidable. In order to lessen selection bias in subsequent research, patients should be gathered from several locations. Third, even though this study looked into the relationship between diabetes and cognitive function, it was unclear how much diabetes and cholesterol contribute to cognitive decline. The causal connections between diabetes, cholesterol, and dementia or cognitive impairment need to be further examined.

Conclusion:

In conclusion, regardless of LLD use, a higher prevalence of T2DM in older adults was linked to significantly lower TC or LDL-C levels. The "lower is better" approach to secondary prevention of CAD or CVD is controversial because people who have never used LLDs with low cholesterol levels have a higher prevalence of T2DM.

Additionally, older T2DM patients showed reduced cognitive and everyday functioning. When the "lower is better" approach is used to prevent cognitive impairment or dementia, a higher prevalence of type 2 diabetes in older adults with low cholesterol levels will also raise concerns about how cognition and everyday functioning may be compromised.

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