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Intensive LDL-cholesterol lowering therapy and neurocognitive function

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ABSTRACT

The key lipid-lowering target is to achieve guideline-recommended low-density lipoprotein cholesterol (LDL-C) levels, usually by using statins. The new treatment strategies for lipid-lowering therapy include using proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors as an exciting approach to reduce residual risk of cardiovascular diseases (CVD). However, concerns about possible adverse effects, including neurocognitive disorders, were issued by the Food and Drug Administration (FDA). The current disputable evidence does not allow definite conclusions as to whether statins contribute to, or cause, clinically meaningful cognitive impairment. Some evidence indicates a high rate of memory loss, while other evidence suggests a benefit in dementia prevention. This debate should not discourage appropriate statin and other lipid-lowering drug administration. However, prescribers should be aware of such potential drug-related side effects. Prospective controlled studies comparing the short- and long-term effects of different statins on cognitive function are warranted. The effects of intensive LDL-C lowering on neurocognition might be attributed to an off-target effect. It is also possible that pre-existing pathology and vascular risk may already be present outweighing any effect related to lipids. Gender, genetic, LDL-C-related genotypes and aging-related changes should also be considered. Some data indicate that carriers of apolipoprotein E (apoE) ε-4 allele, with low levels of apoA1 and high-density lipoprotein cholesterol have a distinct plasma lipid profile and may be more susceptible to neurocognitive dysfunction. Future research on lipid-lowering drugs and cognition is needed; careful study design and analysis will be critical.

Contents

Abbreviations: AD, Alzheimer's disease; Apo, Apolipoprotein; BP, Blood pressure; CHD, Coronary heart disease; CI, Confidence interval; CoQ10, Coenzyme Q10; CV, Cardiovascular; CVD, Cardiovascular disease; EBBINGHAUS, The Evaluating PCSK9 Binding antiBody Influence oN coGnitive HeAlth in High cardiovascUlar Risk Subjects; FDA, Food and Drug Administration; FOURIER, Further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk; GAUSS, Goal achievement after utilizing an anti-PCSK9 antibody in statin intolerant subjects; HDL-C, High density cholesterol; LDL-C, Low density lipoprotein cholesterol; LL, Lipid-lowering; LOAD, Late onset AD; MCI, Mild cognitive impairment; PCSK9, Proprotein convertase subtilisin/kexin type 9; Q2W, Every 2 weeks; RCTs, Randomized controlled trials; T2DM, Type 2 diabetes mellitus.

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1. Introduction

Lowering low density lipoprotein cholesterol (LDL-C) levels is the main aim of lipid-lowering therapy since this is associated with a reduction in cardiovascular disease (CVD) events (Hobbs, Banach, Mikhailidis, Malhotra, & Capewell, 2016). Because life expectancy has increased by >20 years since the 1970s, more and more patients with concomitant diseases are at high/very high cardiovascular risk, requiring intensive lipid-lowering (LL) therapy (Reiner et al., 2011; Stone et al., 2014a, 2014b). Statins are the first line drugs for the treatment of dyslipidaemia; they can be used alone or in combination with ezetimibe, as well as new drugs - proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Their use seems to be very safe and well tolerated, but they might also be associated with drug-related side effects (Banach, Rizzo, et al., 2015a, 2015b; Dragan, Serban, & Banach, 2015). Among these, neurocognitive disorders are of special interest due to the increasing proportion of elderly people worldwide (Yang, Sun, Lu, Leak, & Zhang, 2016). This adverse effect has been a matter of considerable debate, especially since February 28, 2012, when the Food and Drug Administration (FDA) raised concerns about possible statin-related adverse effects, such as neurocognitive disorders (Everett, Smith, & Hiatt, 2015; US Food and Drug Administration, 2012).

How to interpret any possible lipid-related effects on neurocognition, and whether there is a clear link and causality between LL therapies and cognitive disorders, remains a matter of debate (McGuinness, Craig, Bullock, & Passmore, 2016). Although some of the available data suggest a risk of adverse neurocognitive effects in those taking LL-drugs, it is still not known how relevant this finding might be; most experts do not consider it as an important problem, especially since there is no confirmed causality (Yang et al., 2016; Zanchetti et al., 2014). However, this issue cannot be completely dismissed. Any association with neurocognitive events has not been frequently reported with PCSK9 inhibitors [*e.g.* in the OSLER (Open-Label Study of Long-Term Evaluation against LDL Cholesterol) study including 4465 patients (Sabatine, Giugliano, Wiviott, Raal, Ballantyne, et al., 2015; Sabatine, Giugliano, Wiviott, Raal, Blom, et al., 2015)], and no direct link between such phenomenon and low LDL-C levels has been found. However, we need large outcome trials to definitively comment on the safety of these drugs (Zanchetti et al., 2014).

Some antipsychotics are associated with metabolic dysregulation such as dyslipidaemia, hyperglycaemia and weight gain, which raise CV risk and it has been reported that antipsychotic-induced hypercholesterolemia may be associated with cognitive improvement (Krakowski & Czobor, 2011). Thus, increased cholesterol and triglyceride levels were associated with better cognitive function in patients with schizophrenia in the Clinical Antipsychotic Trial of Interventional Effectiveness (CATIE) study. One explanation might be that the brain is 85% "lipids" (Krakowski & Czobor, 2011). However, we still do not know whether the circulating levels of lipids can influence cognitive function.

In this review we aimed to summarize available data on neurocognitive side effects caused by LL agents. We highlighted such effects related to statins and PCSK9 inhibitors. We also attempt to consider all the possible underlying mechanisms.

2. Search strategy

We searched the electronic databases [MEDLINE (1966–1 June 2016), EMBASE and SCOPUS (1965–1 June 2016), DARE (1966–1 June 2016)], and Web of Science Core Collection (up to 1 June 2016). Additionally, abstracts from national and international meetings were searched. Where necessary, the relevant authors were contacted to obtain further data. The main search terms were: 'low-density lipoprotein cholesterol', 'LDL', 'LDL-C', 'proprotein convertase subtilisin/kexin type 9', 'PCSK9', 'ezetimibe', 'lipid-lowering drug(s)', 'neurocognitive function', 'cognitive function', 'neurocognition', 'cognition', 'neurocognitive disorder(s)', 'cognitive disorder(s)', and 'statin(s)'. The main inclusion criterion was data from studies, trials and meta-analyses on the association between lipid-lowering therapy and neurocognitive disorders.

3. Potential pathomechanisms involved in neurocognition

Cholesterol synthesis is essential for neurons to function normally, is an important component of the cellular membrane and serves as a precursor molecule for steroid hormones (Ikonen, 2008). Therefore, it is theoretically possible that excessive inhibition of cholesterol synthesis may result in neurocognitive adverse effects and that lipid metabolism may play a role in neurodegeneration (Sato & Morishita, 2015; Wagstaff, Mitton, Arvik, & Doraiswamy, 2003). Given that there was no correlation between neurocognitive events and reduction in LDL-C, very low levels of LDL-C *per se* may not lead to neurocognitive problems. Therefore, one hypothesis would be that intense LDL-C lowering is associated with total cholesterol and other lipoproteins reduction, and taking into account their functions, this might be a cause of neurocognition (Fig. 1). However, this might also mean that the neurocognitive events are caused by unknown off-target effects (Yang et al., 2016). In a large sample of generally healthy adults individual serum lipoproteins and triglycerides were differentially related to neuropsychological function and together with age emerged as significant predictors of the memory factor. While higher triglycerides were associated with poorer performance, higher LDL-C levels were associated with better performance on neuropsychological measures of memory (Leritz, McGlinchey, Salat, & Milberg, 2016). The only predictor of both the executive and memory/language factors was education, where higher education was associated with better performance, while high density cholesterol (HDL-C) did not emerge as a significant predictor of any cognitive factor (Leritz et al., 2016). The authors suggest that LDL and triglycerides may have differential effects on neuropsychological performance that may reflect both beneficial and deleterious properties of cholesterol in relation to the brain and cognitive health. These results were independent of HDL, as well as of use of lipid lowering agents, apolipoprotein (Apo) E status and additional CVD risk factors. Thus, the consideration of individual variables may be important in future studies. However, it remains to be determined if the direction of these associations persist over time (Leritz et al., 2016).

Transient impairment of cognitive function by statins may also be in part due to cholesterol's modulation of *N*-methyl-D-aspartate receptor function (Korinek et al., 2015) (Fig. 1). In addition, activation of A_{β} cascade in ApoE ε-4 transgenic mice induces lysosomal activation and neurodegeneration resulting in marked cognitive deficits (Belinson, Lev, Masliah, & Michaelson, 2008). Recent large, long-term, randomized controlled trials (RCTs) suggest that a multidisciplinary intervention, including exercise and diet, could improve or maintain cognitive function in at-risk elderly people (Ngandu et al., 2015), and it is known that exercise and diet also alter lipid and glucose metabolism in these subjects. Further, disruption of homeostasis of lipid and glucose metabolism affects production and clearance of β-amyloid and *tau* phosphorylation, and induces neurodegeneration (Sato & Morishita, 2015) (Fig. 1). Therefore, a more integrated understanding of the interactions among lipid, glucose, and protein metabolism might also be required to elucidate the pathogenesis of Alzheimer's disease (AD) (Sato & Morishita, 2015). In a cohort consisting of 193 participants from the Keys to Optimal Cognitive Aging (KOCOA) Project, a prospective cohort study in Okinawa, Japan, higher LDL-C levels and lower triglyceride/HDL-C ratios were associated with higher scores in memory performance after controlling for confounders (Katsumata et al., 2013). On the other hand, the results from an African American sample suggested that attentional processes were associated with diastolic blood pressure (BP) levels, verbal learning processes with diastolic BP and triglyceride levels, and the ability to shift the cognitive set of variables with HDL-C levels (Sims, Madhere, Callender, & Campbell, 2008).