

The Zero-LDL Hypothesis. Towards Extremely Low LDL Concentrations



La hipótesis del LDL cero. Hacia concentraciones de LDL extremadamente bajas

To the Editor,

Recent clinical data show that very low low-density lipoprotein (LDL) cholesterol (LDL-C) levels are associated with an even lower incidence of arteriosclerosis-related diseases. The Cholesterol Treatment Trialists' Collaboration meta-analyses have shown a continuous linear correlation between LDL reduction and cardiovascular benefit.¹ The IMPROVE-IT trial provided scientific evidence of incremental benefits down to an LDL-C concentration of 1.3 mmol/L (50 mg/dL).² Proprotein convertase subtilisin kexin type 9 inhibitors have quickly been adopted in this field and have provided physicians with new scenarios. Patients with LDL-C values < 0.4 mmol/L (15 mg/dL) are occasionally seen, while concentrations below 1.3 mmol/L (50 mg/dL) are common. The LDL-C concentrations < 0.4 mmol/L (15 mg/dL) show no concerns in safety analyses; on the contrary, these concentrations are associated with even higher cardiovascular benefit. The recently reported GLAGOV trial data confirm a benefit to atherosclerotic plaque level by lowering LDL concentrations closer to 0.52 mmol/L (20 mg/dL).³

Can we live with these extremely low LDL-C levels? In other words, what is the physiological function of LDL?

Low-density lipoprotein is the final step of the lipoprotein metabolism cascade and is considered the vehicle by which cholesterol is delivered to peripheral tissues through LDL receptors (LDL-R). However, a few points must be taken into consideration. First, all mammalian cells have the capacity to synthesize their own cholesterol. Additionally, in the adrenal glands, where cholesterol is needed for hormone synthesis, the cells capture external cholesterol from high-density lipoprotein (HDL), rather than LDL, through scavenger receptor B1. Interestingly, the main organ receiving LDL particles is the liver. Approximately 3 out of 4 LDL particles finish their metabolic life in the liver. The hepatic LDL/LDL-R system is, along with HDL, the main pathway to excrete cholesterol with bile into the feces, which is almost the only mechanism to get rid of cholesterol. When the LDL-LDL-R pathway is not efficient enough, LDL accumulates and infiltrates the artery wall, inducing *atheroma* plaque formation. Familial hypercholesterolemia patients, who are characterized by an abnormally low number of LDL-R, are an example of this process.

Low LDL-C plasma concentrations due to an increased catabolic rate are the result of a highly efficient LDL/LDL-R pathway. For the first time in history, we are facing the impact of highly efficient therapies that increase the activity of this pathway, thereby leading to extremely low LDL-C levels.

Do we need LDL-C at all? The question is a provocative one.

Low LDL levels due to increased catabolism should not be compared with those due to low production rates, as in hypobeta- and abetalipoproteinemia, which are diseases characterized by severe symptoms because of apolipoprotein B deficiency.

Which other functions could be altered by very low LDL-C concentrations? LDL proteomic studies show that, in contrast to

HDL, this particle carries—almost exclusively—proteins linked to its own metabolism (apolipoprotein B:100 [85%] and other apolipoproteins).⁴ Some vitamins, such as vitamin E, are associated with the lipoprotein system. LDL-vitamin E has 2 functions: accessing peripheral tissues through the LDL/LDL-R system, and protecting the LDL particle itself from oxidation. An increased LDL-R activity results in a more efficient delivery of vitamin E. On the other hand, the vitamin E:LDL-C ratio is not modified by proprotein convertase subtilisin kexin type 9 inhibitors, thereby maintaining its antioxidant function.

LDL transports toxic substances, such as endotoxin lipopolysaccharide, in special situations such as septicemia. By increasing LDL-R activity, LDL-associated lipopolysaccharide plasma clearance is accelerated, which has been associated with a better prognosis.⁵

Regarding LDL-mediated peripheral delivery, we should take into account lessons from homozygous familial hypercholesterolemia patients. Homozygous familial hypercholesterolemia is a zero-LDL/LDL-R functional pathway situation; however, no clinical effects due to impaired LDL-mediated peripheral delivery have been reported. There have been no reports of metabolic or immune alterations, either during fetal development or in patients achieving advanced ages⁶ and normal pregnancies have been described. This suggests a negligible effect of the LDL/LDL-R system on molecular transport to peripheral tissues.

We are not recommending achieving a zero-LDL level, but are rather advising that extremely low LDL plasma concentrations due to increased LDL-R activity should not be considered harmful. This is not a science fiction statement, as LDL concentrations < 0.4 mmol/L (15 mg/dL) are frequently seen, and no adverse effects have been reported, only benefits.

In summary, by increasing LDL-R activity, the LDL/LDL-R system is improved, and thus, very low LDL-C levels must be considered a marker of optimal LDL/LDL-R system efficiency. Although extremely low LDL-C concentrations secondary to increased LDL-R activity should not be viewed with concern, extreme caution should be taken before extrapolating these data to the overall population until more extensive safety data are available.

CONFLICTS OF INTEREST

Lectures and advisory fees from Amgen, Sanofi, and MSD.

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Infective Endocarditis Due to *Leuconostoc* Species



Endocarditis infecciosa por *Leuconostoc* species

To the Editor,

We present a case of infective endocarditis due to *Leuconostoc* species and *Staphylococcus hominis* in a patient with no underlying disease and complaining of gastrointestinal symptoms. A systematic review of the literature identified only 2 other cases of infective endocarditis due to *Leuconostoc* species,^{1,2} neither of them occurring in combination with coagulase-negative *Staphylococci*, which is quite common in other clinical scenarios.³ The main findings of the 3 episodes are summarized in the Table.

Our patient was an 80 year-old man, with a personal history of colon cancer surgery in 2001. He was admitted because of

unspecified abdominal pain, nausea, vomiting, constitutional syndrome, and episodic fever (39 °C) for the last 2 months, despite antacid treatment and with negative gastric and colorectal endoscopic studies. Hematologic analysis showed leukocytosis (12 300/μL), neutrophilia (82%), and C-reactive protein 169 mg/L. Acute cholecystitis was initially suspected but, despite the presence of lithiasis in an enlarged gall bladder, there were no signs of inflammation, and this diagnosis was ruled out by general surgeons. Blood cultures were obtained and empirical antibiotic therapy was initiated. However, the presence of a systolic and diastolic aortic murmur required an echocardiographic evaluation, which was performed 72 hours after admission. A vegetation (17 x 14 mm) above the aortic native valve with severe regurgitation and a pseudoaneurysm (19 x 15 mm) in the anterior leaflet of the mitral valve were detected (Figure). *Leuconostoc* species and *Staphylococcus hominis* grew in 2 out of 2 blood cultures. Antibiotic treatment was adapted to the antibiogram with amoxicillin-clavulanic acid and gentamicin. There were no signs of heart

Table
Main Findings of Patient With *Leuconostoc* Species Infective Endocarditis

	Episode 1 ¹	Episode 2 ²	Episode 3
Age, y	72	55	80
Sex	Female	Male	Male
Comorbidities	Aortic and mitral prostheses Mitral prosthesis IE due to <i>Streptococcus sanguis</i>	Not significant	Past colon cancer
Risk factors	Oral endoscopy Colonoscopy	No	No
Fever	Yes	No	Yes
Heart failure	No	No	No
Septic shock	No	No	No
Abdominal symptoms	No	No	Yes
Septic emboli	No	Central nervous system	Central nervous system
Empirical antibiotic treatment	Unknown	Ceftriaxone Vancomycin	Levofloxacin
Blood cultures	Positive	Positive	Positive
Microorganism	<i>Leuconostoc mesenteroides</i>	<i>Leuconostoc</i> species	<i>Leuconostoc</i> species <i>Staphylococcus hominis</i>
Vancomycin sensitivity	Resistant	Sensitive	Resistant
Echocardiogram			
Vegetation, mm	11	> 10	17 x 14
Periannular complication	No	No	Mitral pseudoaneurysm
Location	Mitral prosthesis	Native aortic valve	Native aortic and mitral valves
Valvular insufficiency	No	Not specified	Severe
Treatment	Penicillin G 6 weeks Gentamicin 10 d	Penicillin G 6 wk Gentamicin 2 wk	Amoxicillin-clavulanic acid 4 wk Gentamicin 2 wk
Cardiac surgery	No	Elective	Elective
In-hospital mortality	No	No	No
Long-term follow-up	Died (possible reinfection) (3 mo)	Asymptomatic (6 wk)	Asymptomatic (6 mo)

IE, infective endocarditis.