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Restenosis after PCI with Intensive Lowing Density Lipoprotein Cholesterol Reduction: A Case Report

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1. Abstract

Intra-stent restenosis is an important cause of angina pectoris, and hyperlipidemia has long been considered as the main factor of coronary stent restenosis. However, the patient we report had intensive lowing density lipoprotein cholesterol level, which in turn led to recurrent episodes of angina and severely affected the quality of life. A 66-year-old woman with Hypertension and Type 2 diabetes was admitted to our hospital, who had suffered intermittent chest pain for more than 4 years. She regularly took secondary prevention drugs for coronary heart disease. From 2016 to 2020, the level of blood lipids, especially low density lipoprotein cholesterol (LDL-C) decreased gradually, with a minimum of 0.64mmol/L. She had experienced 10 times of coronary angiographies, 8 stents were implanted, 2 coronary artery bypass grafts were grafted, and multiple drug balloon dilations were performed. There was no significant abnormality in ANA spectrum, coagulation and anticoagulant test, electrolyte detection, immune indexes of lupus and cardiac ultrasonography. In this case, there was no clear family history, and no abnormality of related auxiliary examinations, only the LDL-C was decreasing gradually. This leads to the debate that whether intensive lowing density lipoprotein cholesterol level is related to repeated restenosis after interventional operations.

2. Introduction

Intra - stent restenosis is one of the important causes of angina pectoris after revascularization and is closely related to high LDL-C levels. There is an evidence that lowering LDL-C benefits patients with both stable and acute coronary heart disease [1]. Therefore, LDL-C lowering therapy is one of a primary therapies to improve the prognosis of CHD. However, LDL-C also plays an important role in human physiological process, such as maintaining the integrity of cell membrane and regulating lipid metabolism, therefore, too low level of LDL-C may be harmful, even increases the danger of breast cancer [2]. Whether the low level of LDL-C is related to repeated restenosis after percutaneous coronary intervention has not been systematically studied, and this study is just a case report rather than a systematical study. In this paper, we analyzed a patient who underwent multiple interventional therapies, including implantation of 7 drug-eluting stents and 1 biodegradable stent, and concurrent coronary artery bypass therapy, but still suffered from repeated stent stenosis and recurrent angina pectoris, accompanied by continuous reduction of LDL-C. From the case, we raise a presumption that low level of LDL-C may be associated with repeated restenosis after interventional surgery.

3. Details of The Case

The patient, with 8 years of Hyperlipidemia, 8 years of hypertension, 3years type 2 diabetes and reflux esophagitis, who was admitted to Xiyuan Hospital of China Academy of Chinese Medical Sciences in January 2021 because of intermittent chest distress and chest pain. The patient had a sudden chest distress and chest pain after returning home from a trip in August 2016, which could be relieved after rest. The coronary angiography in local hospital showed 95% stenosis in the anterior descending branch (LAD) ,40-50% stenosis in the distal branch, 80-90% stenosis in the opening of the first diagonal branch from the proximal segment, the circumflex branch (LCX) was normal, the intima of the right coronary artery (RCA) was not smooth, and a stent was placed

in the proximal middle segment of the LAD. Postoperatively, she regularly took oral drugs for anticoagulation, lipid-lowering, ventricular rate controlling and coronary expansioning. Auxiliary examination showed the LDL-C was 1.06mmol/L. There was no significant abnormality in ANA spectrum, coagulation test, anticoagulant test, ions and immune indexes of lupus. Cardiac ultrasonography: ejection fraction 57%, secondary and tricuspid regurgitation (small amount), aortic regurgitation (medium amount), and left atrial enlargement after Coronary-artery-bypass-grafting and Percutaneous coronary intervention. From 2016 to 2020, her lesion scope gradually increased, from simple type A lesion of the anterior descending branch to diffuse long lesion of the anterior descending branch, then involved the circumferential branch, right coronary artery and bridging vessels. The degree of vascular stenosis gradually worsened, the vascular lesion changed from simple to complex, and the symptoms of angina pectoris gradually worsened (Figure 1). The patient experienced 10 times of coronary angiographies. 7 alloy drug-coated stents and 1 biodegradable stent were implanted in LAD, RCA and LCX, 2 coronary artery bypass grafts were grafted, and multiple drug balloon dilations were performed. The 6 LAD stents occluded successively, the RCA stent occluded successively and the bridging vessel occluded successively, and the proximal segment of the LCX degradable stent occluded for several times, leaving only the Lima-LAD bridging vessel and the repeated stenosis LCX to provide blood flow. But the efficacy was still weak and the angina pectoris had repeated attacks. Interestingly, in this case, there was no clear family history, no abnormality of immune system indexes, and no obvious abnormality was found in platelet activity, aggregation rate, thromboelastic map, coagulation function, immunity, inflammatory factors and other indexes as well as cardiac ultrasound during hospitalization. However, the patient's LDL-C levels showed significant and persistent decrease, with it dropping from 3.16 to 0.64mmol/L (Table 1). With the continuous decrease of LDL-C, the chest pain showed gradually worsened. The most serious symptom was from September to December 2020, when she had persistent chest pain, accompanied by palpitation and chest tiredness, could not sleep at night due to pain, and the pain could not be relieved even after taking nitroglycerins. The patient was treated with rosuvastatin and ezetimibe for long periods, and the gradually lower LDL-C was neglected. Later, in March 2021, the latest follow-up of the patient showed that the patient had discontinued the Ezemibe Tablet, and the LDL-C level is now 1.44mmol/L. The patient's symptoms of chest distress and pain were significantly relieved, without radiating pain, sweating, fatigue relief, and no special discomfort.

Date	Coronary angiography results	Treatments	Stent type	Bypass type	LDL-C（mmol/L）
Sep,2016	LAD 95% stenosis,D1 opening to proximal 80-90% stenosis, LCX is normal, RCA intima is not smooth。	1 stent implanted in the middle of the LAD	FIREBIRD 2 3.0mm*18mm		0.95
Jun,2017	The proximal segment of the LAD stent was 100% occlusion.	2 stents implanted in the middle of the LAD	FIREBIRD2 2.25mm*33m， 3.0mm*23mm		0.89
Jan,2019	LM is normal, LAD proximal segment original stent is 100% occluded, LCX is normal, RCA proximal segment stenosis is 98%.	1 stents implanted in the middle of the RCA	XIENCE PRIME 3.5mm*28mm		0.9
Apr,2019	The proximal segment of the LAD stent is 100% occlusion, and the LCX opening is 30% narrow. The distal end of RCA provides level 1 collateral circulation to the LAD.	3 stents implanted in the distal of the LAD	XIENCE PRIME 2.25mm*28mm 2.75mm*33mm 3.0mm*38mm		0.96

Jun,2019	LM is normal, 99-100% restenosis in the proximal and distal segments of the LAD stent, 50% stenosis in the LCX stent, 95% restenosis in the proximal segment of the RCA stent, and collateral circulation to the diagonal branches is provided distally.	LAD and RCA bypass graft		LIMA-LAD AO-SVG-PDA	0.79
Sep,2019	99% stenosis in the LCX proximal stent.	LCX drug balloon dilation			0.9
Dec,2019	Lima-LAD bridge is unobstructed, AO-SVG-PDA is occluded.	None			0.79
Jun,2020	LM is 80% stenosis, LAD stent is 100% occlusion, LCX opening is 99% stenosis, RCA proximal segment is 100% occlusion, AO-PDA proximal segment is 100% occlusion. IVUS: the minimum lumen area of LM-LCX was 4.22mm^2, and the plaque load is 81%.	1 stents implanted in the proximal of the LAD	NieoVas 3.5*18mm		0.9
Sep,2020	LAD-LCX is 99% severely stenosis.	LCX drug balloon dilation			0.64
Jan,2021	LAD-LCX is 95% severely stenosis.	None			1.06

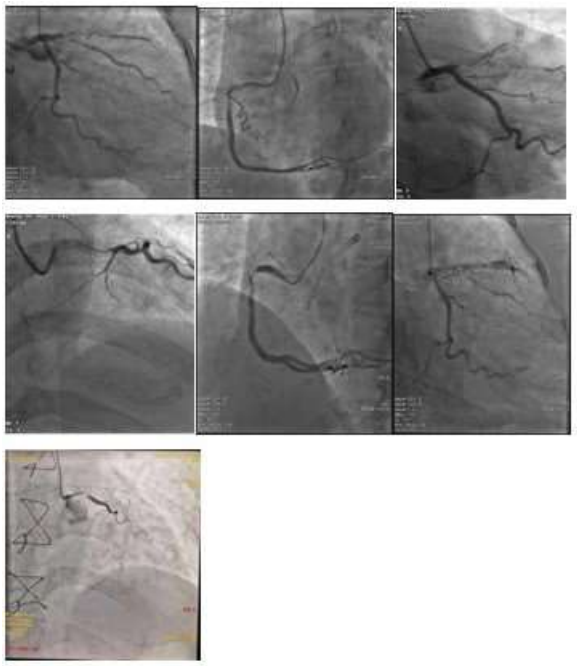

Figure 1. Coronary artery angiography of the patient.（a: June 2017,LAD near segment 100% occluded；b: January2019, RCA near segment 98% occluded；c,d: April 2019, the leading edge of the proximal LAD original stent was 100% occlusion, and the LCX was 30% narrow；e,f: June 2019, 99-100% restenosis in the proximal and distal stents of the LAD, 50% stenosis in the LCX, and 95% restenosis in the proximal segment of the RCA stent. g: The opening in the near section of LCX was 95% narrow）.

4. Discussion

Stent restenosis refers to the pathological process in which stent coronary artery lesions gradually rearrange from artery injury, followed by the proliferation of new intimal tissue. Drug delivery at the fracture point of the stent was reduced, leading to blood flow changes and stent overlap, further damage to the vascular endothelial proliferation, and increased restenosis risks [3]. Inflammation and platelet activation is one of the important pathophysiological basis of stent restenosis, lead to neointimal hyperplasia and sclerosis of arterial congee appearance, then intra-stent restenosis occurred [4]. Therefore, down-regulation or inhibition of the expression of inflammatory factors can improve coronary inflammation, and optimized antiplatelet drugs can reduce the risk of in-stent thrombosis, thus significantly reducing the incidence of in-stent restenosis [5]. It is evidenced that statins reduce lipid and plaque stability, and reduce cardiovascular risks by reducing neutrophilic/lymphocyte ratio (NLR) and mean platelet volume (MPV) levels [6]. LDL-C could produce interleukin (IL)-1, IL-6 and tumor necrosis factor α, trigger inflammation and increased risk of atherosclerosis [7]. LDL-C-mediated inflammation is also associated with arterial thrombosis, which increases the risks of myocardial infarction, stroke, and pulmonary embolism, etc [8]. As a recognized risk factor for cardiovascular diseases, LDL-C is recommended as the main target of lipid-regulating therapy in China Cholesterol Education Program Expert Recommendations for Reducing Cardiovascular Events (2019) [9]. According to the 2019 ESC/EAS guidelines for the treatment of dyslipidemia, the targets for LDL-C control are <1.8mmol/L for those at high risk of cardiovascular disease, <2.6mmol/L for those at moderate risk, and <3.0mmol/L for those at low risk [10]. But on this basis, we can find that further reduced LDL-C, which even below 1mmol/L might be harmful to cardiovascular system. Futhermore, we assumed that severely reduced LDL-C might be associated with repeated restenosis after interventional surgery. However, these questions have not been proved by large-scale clinical studies yet. For a long time, the standard of LDL-C has been widely controversal. LDL-C is an important component of lipids and one of the main sources of energy, an indispensable substance in human and animal tissues and cells [11]. LDL-C is not only involved in the formation of cell membrane, but also the raw material for the synthesis of bile acid, vitamin D and steroid hormones [12]. LDL-C can meet the needs of extra-hepatic tissue cells for cholesterol, supply the body with nutrition, and has a protective effect on human body to a certain extent [13]. A study has shown that there is an interaction between lipid metabolism and cellular immune activation [14]. High plasma neopterin is associated with LDL-C. Alterations in lipid metabolism may affect interferon-γ-mediated cellular immune activation, leading to immune dysregulation, activation of inflammatory response, and increased risk of coronary heart disease [15]. Lower-than-median LDL-C levels were linearly positively correlated with acute myocardial infarction(AMI) events, which is known as the "lipid paradox" theory [16]. According to a study by the Korean National Registry, 840 of the 9,571 patients with AMI in the study had low LDL-C levels (<1.8mmol/L), and their mortality rate (7.7%) was three times higher than that of the normal LDL-C group [17]. In addition, it is known that the choles-

terol transport volume is reduced when LDL-C is too low, which is easy to cause malnutrition, chronic anemia, malignant tumors and other acute or chronic diseases, seriously affecting the quality of life of patients [18]. To maintain adequate cholesterol levels, cholesterol metabolism requires absorption of lipoprotein cholesterol from surrounding cells through surface protein receptors such as LDLR, storage of esterified cholesterol, and transfer and export of excess cholesterol to maintain lipid balance in the body [19]. Significant low LDL-C level is potentially risky. Studies have shown that some rare human genetic diseases, such as hereditary hypolipoproteemia, are at risk of severe systemic atherosclerosis, suggesting that excessively low levels of LDL-C are not protective of the cardiovascular system, but are associated with a variety of adverse outcomes [20]. In addition, when the human LDL-C level is too low, the plasma apolipoprotein level is relatively reduced, patients often have clinical conditions such as fat malabsorption and liver steatosis, and the prognosis of elderly patients is worse [21]. A Danish study showed a U-shaped correlation between LDL-C level and all-cause mortality, that is, both high LDL-C (> 3.8mmol/L) or low LDL-C (< 1.8mmol/L) increased the risk of all-cause mortality. In particular, low LDL-C level was significantly associated with increased all-cause mortality, cardiovascular mortality, and cancer mortality. And it was more pronounced in people under 65 years [22]. Faheem W found that too low LDL-C was positively correlated with the long-term incidence of community-acquired sepsis, the most common of which were renal complications and urinary tract infections [23]. LDL-C has been recognized to play a role in the removal of bacterial toxins, lipopolysaccharides from Gram-negative bacteria, and lipopolichoic acid from Gram-positive bacteria. Thus, a potential risk factor for the increased risk of sepsis caused by low LDL-C is the inability to remove bacterial toxins from the blood [24]. According to the above medical records, the risk factors for routine restenosis of this patient were not significantly abnormal, only the persistent decrease of LDL-C, with the lowest value being 0.85mmol/L. Combined with all the above studies, it can be seen that when the LDL-C level < 1.4mmol/L, the patient suffered from repeated restenosis and recurrent symptoms of chest distress and chest pain; When the LDL-C level≥1.4mmol/L, the symptoms were significantly relieved. This suggests that there may be an association between persistently reduced LDL-C and repeated restenosis after coronary interventional operations. However, this report is only a case report, and further multicenter, large-sample randomized controlled trials are needed to prove the causal relationship between LDL-C and repeated restenosis after interventional operations. Moreover, there is still a lack of more specific LDL-C control requirements for different populations, and future researches should be more targeted to scientifically develop lipid control indicators suitable for various populations, so as to reduce the incidence of cardiovascular events in different patients more accurately.

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