

 **DYSLIPIDAEMIA**

Effect of hypercholesterolaemia on HDL particle remodelling

Hypercholesterolaemia induces lipidomic and proteomic changes in HDL particles, which impair the functionality of the HDL particles and reduce their cardioprotective properties. This finding comes from a study on ischaemia–reperfusion injury in pigs, in which the beneficial effects of HDL were abolished by hypercholesterolaemia.

Pigs received a normocholesterolaemic or hypercholesterolaemic diet for 10 days, resulting in non-HDL-cholesterol concentrations of 38.2 mg/dl and 218.6 mg/dl, respectively. HDLs were isolated from the animals and underwent lipidomic and proteomic analysis to investigate the molecular remodelling, and NMR analysis to assess HDL particle size.

Compared with HDLs from normocholesterolaemic pigs, HDLs from

hypercholesterolaemic animals had a core enriched in cholesteryl esters and a surface depleted of phosphatidylcholine species containing polyunsaturated and long-chain fatty acids. These changes are indicative of mature HDL particles with low surface fluidity. HDL particle size was bigger with hypercholesterolaemia than with normocholesterolaemia.

Changes were also observed in levels of HDL-transported proteins. HDLs from hypercholesterolaemic pigs contained reduced levels of two lipocalins: retinol-binding protein 4 and apolipoprotein M (a sphingosine 1-phosphate carrier). The level of cellular retinoic acid-binding protein 1 was also reduced in hypercholesterolaemia. Of note, no changes were observed in apolipoprotein A-I profile or content. Functionally, HDLs from hypercholesterolaemic pigs had lower antioxidant



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activity (–35%) and cholesterol efflux capacity (–60%).

“Our data indicated that hyperlipidaemia induced quantitative and qualitative changes in the HDL lipidome and proteome that shift HDL particles toward a dysfunctional state,” conclude the investigators. “These findings may partly explain the inability of these particles to protect against the deleterious effects of [ischaemia–reperfusion].” Research should be conducted into whether HDL particles from hypercholesterolaemic animals can recover their protective functions when hyperlipidaemia is reversed. These findings might be relevant to the failure of HDL-raising therapies to improve outcomes in clinical trials.

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ORIGINAL ARTICLE Padró, T. *et al.* Detrimental effect of hypercholesterolemia on high-density lipoprotein particle remodeling in pigs. *J. Am. Coll. Cardiol.* **70**, 165–178 (2017)

FURTHER READING Rosenson, R. S. *et al.* Dysfunctional HDL and atherosclerotic cardiovascular disease. *Nat. Rev. Cardiol.* **13**, 48–60 (2016)



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