

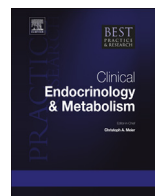


ELSEVIER

Contents lists available at [ScienceDirect](#)

Best Practice & Research Clinical Endocrinology & Metabolism

Journal homepage: www.elsevier.com/locate/beem



7

The metabolic and pharmacologic bases for treating atherogenic dyslipidaemia



Dick C. Chan, PhD, FRCPATH, Research Assistant Professor in
Medicine and Pharmacology^a,
P. Hugh R. Barrett, PhD, Professor of Systems Biology^{a,b},
Gerald F. Watts, DSc, PhD, DM, FRACP, FRCP, Professor of
Cardiometabolic Medicine^{a,c,*}

^a *Metabolic Research Centre, School of Medicine and Pharmacology, University of Western Australia, Perth, Australia*

^b *Faculty of Engineering, Computing and Mathematics, University of Western Australia, Perth, Australia*

^c *Lipid Disorders Clinic, Royal Perth Hospital, Perth, Australia*

Keywords:

Metabolic syndrome
Hypertriglyceridaemia
Low-HDL-cholesterol
Lifestyle modification
Pharmacological treatment
Cardiovascular disease
Treatment target

Dyslipoproteinaemia is a cardinal feature of the metabolic syndrome that accelerates atherosclerosis. It is characterized by high plasma concentrations of triglyceride-rich and apolipoprotein (apo) B-containing lipoproteins, with depressed high-density lipoprotein (HDL) and increased small dense low-density lipoprotein (LDL) particle concentrations. Dysregulation of lipoprotein metabolism in the metabolic syndrome may be due to a combination of overproduction of very-low density lipoprotein (VLDL) apoB, decreased catabolism of apoB-containing particles, and increased catabolism of HDL apoA-I particles. These abnormalities are due to a global metabolic effect of insulin resistance and visceral obesity. Lifestyle modifications (dietary restriction and increased exercise) and pharmacological treatments favourably alter lipoprotein transport by decreasing the hepatic secretion of VLDL-apoB and the catabolism of HDL apoA-I, as well as by increasing the clearance of LDL-apoB. The safety and tolerability of combination drug therapy based on statins is important and merits further investigation. There are several pipeline therapies for correcting

* Corresponding author. School of Medicine and Pharmacology University of Western Australia, GPO Box X2213, Perth, WA 6847, Australia. Tel.: +61 8 92240252; Fax: +61 8 92240246.

E-mail address: gerald.watts@uwa.edu.au (G.F. Watts).

triglyceride-rich lipoprotein and HDL metabolism. However, their clinical efficacy, safety and cost-effectiveness remain to be demonstrated.

© 2014 Elsevier Ltd. All rights reserved.

Practice points

- Dysregulation of VLDL is integral to atherogenic dyslipidaemia, which results from hepatic insulin resistance due to ectopic fat accumulation in visceral adipose tissue and liver.
- Dysregulation of lipoprotein metabolism in these subjects is due to a combination of overproduction of VLDL-apoB, decreased catabolism of apoB-containing particles, and increased catabolism of HDL-apoA-I particles.
- LDL-cholesterol, non-HDL-cholesterol and apoB have been identified as the primary target of lipid-regulating therapy in patients at increased risk of CVD.
- Management of obesity should initially focus on lifestyle modifications including weight loss, dietary modifications and exercise. Lipid-regulating agents may be used as second-line strategy to optimize the regulation of dyslipoproteinaemia.
- Statins are recommended first-line lipid-regulating agent. The use of statin in combination with other lipid-regulating agents is considered to improve lipid treatment efficacy but safety and tolerability must be considered carefully.

Research agenda

- Continued research into the underlying mechanisms responsible for atherogenic dyslipidaemia in subjects with obesity and type 2 diabetes.
- Understanding mechanisms of action of lipid-regulating agents on TRL and HDL metabolism.
- More evidence for the use of combination therapies from cardiovascular disease outcome studies.
- Development of pipeline agents that regulate TRL and/or HDL metabolism.

Introduction

Dysregulation of lipoprotein metabolism is central to the development of atherosclerosis [1]. Prospective epidemiological studies consistently demonstrate that elevated plasma low-density lipoprotein-cholesterol (LDL-C) is associated with increased risk of cardiovascular disease (CVD) [2–5]. Although the causal role of LDL-C in the development of atherosclerosis is well established, it does not fully account for the increase in risk of CVD [6]. Residual risk may partly be due to atherogenic dyslipidaemia, which clusters with hypertension, central obesity and insulin resistance, collectively known as metabolic syndrome (MetS) [7]. We review the metabolic and pharmacologic bases for the treatment of the atherogenic lipid phenotype.

Atherogenic dyslipidaemia: biochemical features and cardiovascular risk

Definition and prevalence

Atherogenic dyslipidaemia is characterized by high plasma triglycerides, low high-density lipoprotein-cholesterol (HDL-C) and a high concentration of apolipoprotein (apo) B-containing lipoproteins, particularly elevated small, dense LDL particles [8–10]. More than 85% of Caucasian adults (age >35 yr) with a mild-to-moderate elevation in plasma triglyceride and low HDL-C phenotype have the MetS [11]. Fig. 1 compares the lipid and lipoprotein profiles between normal and MetS individuals.

Download English Version:

<https://daneshyari.com/en/article/2791627>

Download Persian Version:

<https://daneshyari.com/article/2791627>

[Daneshyari.com](https://daneshyari.com)