Apolipoproteins C-II and C-III and small dense low density lipoprotein: novel risk factors in metabolic syndrome?

Commentary on

Small dense LDL cholesterol and apolipoproteins C-II and C-III in non-diabetic obese subjects with metabolic syndrome

Theodosios D. Filippatos, Vasilis Tsimihodimos, Michalis Kostapanos, Christina Kostara, Eleni T. Bairaktari, Dimitrios N. Kiortsis, Alexandros D. Tselepis, Moses S. Elisaf

Arch Med Sci 2008; 4, 3: 263–269

Konstantinos Tziomalos[1], Vasilios G. Athyros[2], Asterios Karagiannis[2], Dimitri P. Mikhailidis[1]

[1]Department of Clinical Biochemistry (Vascular Prevention Clinic), Royal Free Hospital Campus, University College Medical School, University College London, London, United Kingdom
[2]Second Propedeutic Department of Internal Medicine, Aristotle University, Hippokration Hospital, Thessaloniki, Greece

Submitted: 23 September 2008
Accepted: 4 October 2008

Arch Med Sci 2008; 4, 3: 270–273

Corresponding author:
Dimitri P. Mikhailidis, MD, FFPM, FRCP, FRCPath
Academic Head, Department of Clinical Biochemistry
Royal Free Hospital Campus
University College Medical School
University College London
Pond Street, London NW3 2QG, United Kingdom
Phone: +44 20 7830 2258
Fax: +44 20 7830 2235
E-mail: MIKHAILIDIS@aol.com

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities, including dyslipidemia, abdominal obesity and elevated blood pressure levels [1]. MetS represents an important public health problem for 2 reasons. First, its prevalence is reaching epidemic proportions worldwide [1-6]. Second, most studies showed that MetS is associated with increased risk of developing type 2 diabetes mellitus (T2DM) and vascular disease [7, 8]. However, others argued that the presence of MetS does not confer more risk than the sum of its components [9]. One explanation for these discrepant findings may be that MetS is not a uniform condition [10]. Thus, some forms of MetS may carry a greater risk than others [10]. In this context, there is evidence that vascular risk rises as the number of diagnostic risk factors increases [1, 11]. Furthermore, patients with MetS might have additional vascular risk factors, including activation of pro-inflammatory and pro-thrombotic cascades [7, 12, 13], impaired renal function [14], as well as elevated uric acid levels [15].

Other potentially harmful lipid abnormalities may be present in MetS in addition to the diagnostic criteria of decreased high density lipoprotein cholesterol (HDL-C) and elevated triglyceride (TG) levels [1, 16]. These include elevated apolipoprotein (apo) C-II and C-III levels and a predominance of small dense low density lipoprotein cholesterol (sdLDL-C) [12, 16-18]. Apo C-II exerts a biphasic effect on lipoprotein lipase (LPL), the enzyme catabolizing TG-rich lipoproteins [19]. Physiologically, apo C-II activates LPL whereas elevated apo C-II levels inhibit LPL and might lead to hypertiglyceridemia [19]. Apo C-III inhibits LPL and down-regulates the catabolism of TGs [19, 20]. In turn, elevated TG levels not only might represent an independent vascular risk factor [21] but also predispose to an increased proportion of sdLDL particles [18]. Besides its role in TG regulation,

apo C-II was identified in atherosclerotic lesions where it colocalizes with macrophages and forms amyloid fibrils [22]. The latter have been assigned pro-inflammatory properties and might be implicated in the pathogenesis of atherosclerosis [23]. Apo C-III also appears to exert pro-inflammatory actions and to induce endothelial dysfunction [20], the early stage in the pathogenesis of atherosclerosis [24]. Some studies showed that elevated apo C-II levels [25] and apo C-III [26, 27], as well as a predominance of sdLDL particles might be associated with vascular risk [18].

The results of the study from Elisaf's group [28] provide novel insight in this topic. They studied 73 obese patients with MetS but without established vascular disease and evaluated the role of apo C-II and C-III plasma levels as determinants of the concentration of sdLDL-C. When patients were divided according to sdLDL-C tertiles, there was a progressive increase in TG, apo C-II and C-III plasma levels in parallel with the increase in sdLDL-C concentration ($P<0.001$ for all 3 trends). Interestingly, the apo C-III/C-II ratio was relatively constant across the tertiles of sdLDL-C levels, suggesting that common determinants of apo C-II and C-III levels might exist or that there is an interaction between these apolipoproteins. In multivariate analysis, apo C-II and C-III levels did not correlate with sdLDL-C concentration. The only independent predictors of sdLDL-C concentration were TG and apo B levels. However, apo C-III was independently correlated with TG levels and, more importantly, explained approximately 76.8% of the variation in TG levels.

The findings of this study [28] raise several issues of potential interest. Could apo C-II, apo C-III and sdLDL-C represent novel targets in patients with MetS? Several lipid-modifying agents (statins, fibrates, nicotinic acid and ezetimibe) and pioglitazone appear to reduce apo C-III levels and increase LDL particle size [18, 29-36]. In patients with MetS, statin and fibrate combination treatment improved the lipid profile more than either monotherapy [37]. Another study in patients with MetS showed that adding fenofibrate to simvastatin resulted in a further increase in LDL particle size [38]. Data on the effects of cardiovascular agents on apo C-II levels are more limited. Fibrates, statins and nicotinic acid appear to reduce apo C-II levels [39-41]. However, the addition of fenofibrate to simvastatin in patients with MetS did not induce any further fall in apo C-II levels [38].

Another issue is the role of apo C-II, apo C-III and sdLDL in risk stratification. Even though apo C-II and C-III are determinants of TG catabolism they appear to predict vascular risk independently of TG levels [25-27]. In addition, a decline in apo C-II levels and a rise in apo C-III levels were reported in the prostprandial state and might play a role in the increase in TG levels after a meal [42, 43]. The association between apo C-II, C-III and postprandial TG levels was not evaluated in the Elisaf study. However, postprandial hypertriglyceridaemia is present in patients with MetS [16, 44, 45], is associated with vascular risk [44] and might be improved by both statins and fibrates [30, 31, 45, 46]. Regarding sdLDL, studies showed an incremental predictive value of evaluating not only the quantity but also the quality of LDL-C [18]. Since elevated apo C-II, apo C-III and sdLDL levels appear to be harmful and are frequently present in patients with MetS, would it be helpful to include them in the diagnostic criteria of MetS? The definition of MetS is still in progress [10, 47]. Should other risk factors, including C-reactive protein or elevated uric acid levels, be included in a more holistic definition of MetS? Even though this approach might improve risk stratification, it would also render the diagnosis of MetS rather cumbersome in every day clinical practice. Current methods used to determine LDL particle size are expensive and time-consuming [18, 48]. However, the LDL-C/apoB and TG/HDL-c ratios appear to provide a reliable estimate of sdLDL size and are widely available [18]. It is clear that more work is required in this field and the Elisaf study [28] is an important contribution.

Despite the criticism on the usefulness of the concept of MetS, this construct is attractive because it draws the attention to abnormalities that would often not be individually noticeable. In addition, a diagnosis of MetS should stimulate screening for other risk factors. However, awareness of MetS is low and effective management of its components is infrequent [3, 49-52]. A multitargeted approach appears to be necessary to reduce vascular risk in patients with MetS [1, 7]. Whether the routine assessment and aggressive management of apo C-II, apo C-III and sdLDL levels will improve the prognosis of this population remains to be established.

Declaration of interest

This commentary was written independently; no company or institution supported it financially. Some of the authors have attended conferences, given lectures and participated in advisory boards or trials sponsored by various pharmaceutical companies.

Konstantinos Tziomalos is supported by a grant from the Hellenic Atherosclerosis Society.

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