Editorial

Managing the Cardiovascular Risk Associated with the Metabolic Syndrome

1. Introduction

The metabolic syndrome (MetS) is a cluster of abnormalities including abdominal obesity, glucose intolerance, hypertension, and dyslipidaemia, factors that are all associated with an increased cardiovascular (CV) risk [1]. Currently, there is a debate regarding the effective diagnosis, control and treatment of all the components of MetS, and in the consequences of the MetS itself [2]. In addition, in the past decade there has been a marked increase in the prevalence of the MetS in both Western and developing countries [3]. Yet, the exact pathogenesis of the MetS remains debatable, as well as the crucial factors (mediators) linked to the elevated CV risk [4]; indeed, CV diseases (CVD) still represents the leading cause of death worldwide [5]. Although guidelines emphasize the need of tight control of CV risk, current approaches for the prevention and treatment of CVD are not completely effective ('residual risk') in terms of risk reduction, even when using a number of combined strategies [6]. Therefore, there is a need for the identification of novel biomarkers of CV risk, as well their effective management in subjects with the MetS [7].

The present issue of the journal focuses on novel therapeutic targets for the MetS. We discuss the reviews included in this issue as well as additional topics.

2. The Reviews Included in this Issue

Katsiki *et al*. [8] have discussed the role of the MetS in non-cardiac vascular diseases. They provide a comprehensive an up to-date review on this topic, highlighting the importance of treating these high-risk individuals, early and "to target". In this context, multifactorial treatment, including a statin, has been proven beneficial.

Rizzo *et al*. [9] have discussed the link between incretin-based therapies, glucometabolic health and endovascular inflammation in subjects with type-2 diabetes and the MetS. Incretin peptides are a group of gastrointestinal hormones that play a prominent role in the regulation of glucose metabolism; incretin-based therapies represent an important treatment option for patients with type-2 diabetes, with and without the MetS. Yet, these pharmaceutical agents are particularly beneficial in patients who are overweight or obese, and in whom traditional first-line oral agents have failed to maintain adequate glycemic control. Further, increasing evidence suggests that incretin-based therapies may also impact the CV system, including beneficial effects on lipids, blood pressure, systemic inflammation and endothelial dysfunction.

Abate *et al*. [10] have highlighted the role of the inflammatory cytokine resistin in CVD, diabetes and the MetS. Resistin is an adipocyte- and monocyte-derived cytokine, which has been implicated in the modulation of insulin action, energy, glucose and lipid homeostasis. Resistin has been associated with insulin resistance and many of its known complications. Resistin seems to play a significant role in the heightened inflammatory state induced by metabolic stress linked to excessive caloric intake, thus contributing to the risk for MetS, type 2 diabetes and CVD.

Barbagallo *et al*. [11] have reviewed the role of the heme oxygenase system in the MetS and further discussed the role of heme oxygenase-1 (HO-1) and how to exploit its beneficial effects as a therapeutic strategy to prevent complications and improve insulin sensitivity. Molecular chaperones and the heat shock response play a major role in the maintenance of cellular homeostasis under various pathological conditions. In particular, their role is to regulate protein conformation, protect proteins from misfolding and aggregation, and maintain signalling and organellar networks. Among various heat shock proteins, HO-1 seems to play an important role in the MetS; indeed, the HO system seems to regulate the complex pathophysiological cascade involved in insulin resistance mechanisms and adipocyte function, as measured by the release of important adipokines.

Li Vecchi *et al*. [12] have reviewed the link between the MetS and immunodeficiency virus (HIV)-infection. Considerable differences in the prevalence of the syndrome in human HIV-infected subjects have been reported, as a consequence of several limitations regarding the MetS diagnostic criteria. New evidence suggests that the use of optimal waist cut-off points specific for the various ethnic populations could represent a step forward in overcoming these limitations. Although metabolic disorders have been associated indirectly with highly active antiretroviral therapy, current circumstances could change the framework of MetS in the HIV setting; for example, the aging HIV population and newer, less metabolically toxic antiretroviral drugs. Lipotoxicity and adipokines have been focused as key issues for explaining MetS in HIV patients, and several studies have investigated the pathophysiology of MetS and CV complications in HIV infection. Evidence shows that both HIV infection *per se* and HIV-related chronic immune activation, despite antiretroviral therapy, are critical factors linking MetS and CV complications.

Cerne and Lukac Bajalo *et al*. [13] have reviewed the available evidence on the role of cell-free nucleic acids as a non-invasive route for investigating atherosclerosis. Cell-free nucleic acids (cf-NA) are nucleic acids (DNA, mRNA, miRNA, mitochondrial DNA) found in plasma and cell-free fractions of various other biological fluids. They have all the characteristics of the nucleic acids in the cells of their origin, thus constituting an emerging field for non-invasive assessment. Novel applications for the quantitative and qualitative analysis of cf-NA are emerging. This analysis is currently investigated as a novel research tool for the diagnosis and prognostic evaluation of acute coronary syndrome, for prediction of CVD, for non-invasive early detection of atherosclerosis and understanding its pathological mechanism *in vivo*, for assessing various issues of treatment for atherosclerosis *in vivo*, as well as for the unique simultaneous measurement of mRNA levels and protein concentrations in a single sample of plasma. Since this is a novel field, the authors have carefully reviewed published data as well as the most important analytical considerations.

Rosselli *et al*. [14] have performed a comprehensive review of the link between chronic liver disease and the MetS. The authors have highlighted that the MetS impacts on the liver in different ways. Non-alcoholic fatty liver disease (NAFLD) is considered the hepatic manifestation of the MetS, and is characterized by triglyceride accumulation and a variable degree of hepatic injury, inflammation and repair. The appearance of NAFLD is mainly dependent on increased flow of fatty acids derived from an excess of lipolysis from insulin-resistant adipose tissue. Yet, in the presence of significant hepatocellular injury and inflammation, the picture is defined 'steatohepatitis' (NASH) that has the potential to progress to advanced fibrosis and cirrhosis. The presence of NASH is associated with lower life expectancy, both due to liver-related death and an increase in CV events. Development of NASH is based on lipotoxicity and is influenced by signals derived from outside the liver, as well as from intrahepatic activation of inflammatory and fibrogenic pathways. The presence of the MetS is also associated with worse outcomes in patients with cirrhosis due to any cause, and has complex interactions with hepatitis C virus infection. Moreover, the MetS

poses a higher risk of development of hepatocellular carcinoma. Therefore, the authors concluded that the presence of metabolic alterations has a severe and multifaceted impact on the liver, and is responsible for a higher risk of liver-dependent and -independent mortality.

Gouni-Berthold *et al*. [15] have discussed the role of pharmacologic therapy for CV risk reduction in patients with the MetS. The authors have highlighted that the cornerstone of MetS treatment is lifestyle modification, encompassing weight reduction and physical exercise. However, pharmacotherapy is usually also required to achieve the recommended target values for the various components of the MetS, such as hypertension, dysglycemia and dyslipidemia. Regarding lipid treatment, statins are the main therapeutic agents while for blood pressure control a significant amount of pathophysiological and clinical evidence would suggest the use, as first line agents, of angiotensin-converting-enzyme inhibitor inhibitors or angiotensin receptor blockers. Metformin seems to be the drug of choice for dysglycemia, especially since recent evidence questions the safety of thiazolidinediones. In general, a multifactorial approach is recommended to decrease CV risk in patients with the MetS.

Grosso *et al* [16] have reviewed the beneficial effects of Mediterranean diet on the MetS. The role of food and nutrients in the aetiology of chronic diseases has become clearer over the last 15 years. In their article the authors collected evidence on the beneficial impact of Mediterranean diet on MetS by analyzing epidemiological reports, documenting its prevalence in subjects adopting this dietary pattern. The authors also explored the role of the single components of the diet and the specific aspects characterizing the MetS (i.e. metabolic indices, body weight and blood pressure). Subjects adherent with the Mediterranean diet have lower prevalence and incidence rates of MetS; moreover, specific components of this dietary pattern may play a significant role in the prevention of several morbid conditions related to the MetS.

3. Brief Comment on Selected Biomarkers of CVD Risk not Considered in this Issue

Several studies have suggested that measuring low-density lipoproteins (LDL) particle size, small dense (sd) LDL cholesterol content and LDL particle number provides additional assessment of CVD risk, and available evidence has been reviewed in 2011 with a consensus statement on the pathophysiology, atherogenicity and clinical significance of LDL subclasses [17,18]. Several mechanisms are involved in the enhanced atherogenicity of sdLDL, including enhanced oxidative susceptibility, increased filtration through the endothelium, reduced LDL receptor affinity, prolonged circulation time and higher proteoglycan binding [19-21]. In addition, several studies have reported an association between CVD risk and sdLDL (reviewed in [22,23]), including prospective epidemiologic studies, as well as clinical intervention trials.

In 2000. Hulthe *et al*. [24] assessed the prevalence of MetS in a population-based sample of clinically 58 years old healthy men. The authors found that LDL size was significantly smaller in subjects with the MetS, in relation to those without it. This finding was consistent with previous observations. Haffner *et al*. had already shown in 1995 that LDL size was decreased in subjects with multiple metabolic disorders [25]. Further, they found that the association between LDL size and the number of metabolic disorders remained statistically significant even after adjustment for obesity, body fat distribution, gender, ethnicity, proinsulin and insulin concentrations [25]. More recently, several studies have highlighted that sdLDL may represent a valuable marker for the diagnosis and the severity of the MetS [26-28]. Using the Lipoprint system, Gazi *et al*. [26] have shown that subjects with the MetS exhibit significantly higher concentrations of sdLDL than individuals who do not fulfil the criteria for this syndrome. In another study [29], we have performed a 2-year follow-up study in subjects with the MetS: at the end of the follow-up period, we found an independent predictive role of elevated sdLDL for future cardio- and cerebro-vascular events, which was the same or even superior to that found for traditional CVD risk factors.

Another European panel of experts recently produced a statement on the role of postprandial hypertriglyceridaemia [30,31]. There is evidence that this type of dyslipidaemia represents another risk marker.

There is also a need to consider that there is evidence that MetS is associated with other non-vascular pathologies such as impaired kidney function (including calculi) and an increased risk of cancer [32-33].

4. Conclusion

CVD still represent a leading cause of death worldwide and is strongly associated with the MetS. Although guidelines recommend aggressive treatment, a large residual risk remains. Therefore, there is a need for new treatments and identification of novel biomarkers of CVD risk in subjects with the MetS. Atherogenic lipoproteins, including sdLDL, may represent a valuable marker, but further studies are needed in order to fully assess their role in clinical practice.

Declaration of Interest

This editorial was written independently; no company or institution supported the authors financially or by providing a professional writer. Some of the authors have given talks, attended conferences and participated in trials and advisory boards sponsored by various pharmaceutical companies.

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