Clinical update

The role of metabolic syndrome in heart failure

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Metabolic syndrome (MS) is a highly prevalent condition in patients affected by heart failure (HF); however, it is still unclear whether, in the setting of cardiac dysfunction, it represents an adverse risk factor for the occurrence of cardiac events. The epidemiologic implications of MS in HF have been studied intensely, as many of its components contribute to the incidence and severity of HF. In particular, insulin resistance, diabetes mellitus, and lipid abnormalities represent the main components that negatively influence disease progression and evolution. Yet, other components of the MS, i.e. overweight/obesity and high blood pressure, are favourably associated with outcome in HF patients. The aim of this review was to report epidemiology and prognostic role of MS in HF and to investigate current clinical implications and future research needs.

Introduction

Metabolic syndrome (MS) and heart failure (HF) are steadily increasing conditions, with a prevalence of 34% and of 1–2% in the general population, respectively. It is estimated that the prevalence of HF exceeds 8% in subjects over the age of 75 years, and HF has become the principal cause of mortality, hospitalization, and healthcare expenditures in individuals over the age of 65 years.

Metabolic syndrome represents a cluster of cardiovascular (CV) risk factors, including high blood pressure, insulin resistance (IR), lipid abnormalities, and obesity that are associated with increased risk of HF (Table 1, Figure 1). It is then intuitive that MS fosters an increased risk of HF. It is debated whether MS independently predicts CV prognosis or merely reflects the impact of individual risk factors included in its definition. Yet, it needs to be pointed out that MS is diagnosed in a dichotomous manner (i.e. present or absent) and incorporates continuous variables that are also used in a dichotomous way, thus limiting its value in predictive mathematical models with potential risk of overadjustment.

In patients with HF, some CV risk factors that are components of MS have been reported to play a counterintuitive protective prognostic impact. In fact, obesity and high blood pressure are associated with improved survival in HF patients. Thus, the prognostic impact of MS in HF patients is not obvious and may differ from that observed in the general population.

The scope of this review is to report the prevalence and incidence of MS in HF patients, exploring prognostic association, mechanistic relationships, current clinical implications, and future research needs.

Impact of metabolic syndrome components on heart failure incidence and prognosis

Insulin resistance, hyperglycaemia, and diabetes mellitus

Several studies indicate that diabetes mellitus (DM) and IR are not only causative factors of HF, but patients with HF and DM or IR also have a more aggressive form of left ventricular (LV) dysfunction with higher mortality rates than those without HF and DM or IR. Insulin resistance is highly prevalent (up to 60%) in patients affected by HF, and a complex pathophysiological interaction exists between these two conditions, since IR may represent, at the same time, cause and consequence of HF. Similarly, DM is common in HF patients with a prevalence that ranges from 10 to 30% up to 40% in hospitalized patients.

Insulin resistance and DM are responsible for several functional, metabolic, and structural alterations that ultimately generate...
myocardial damage and HF progression. In particular, abnormalities in contractile proteins and impaired relaxation, change in substrate utilization, cellular injury, microvascular dysfunction, and neurohormonal and sympathetic nervous systems activation are main mechanisms that accompany IR and DM in HF patients. Hyperglycaemia is responsible for several cellular pathway abnormalities, including increased polyol and hexosamine pathway flux and modification of proteins, formation of advanced glycation endproducts (AGEs), and increased protein kinase C expression, conditions leading to overproduction of superoxide and oxidative stress. In particular, hyperglycaemia, and the associated increase in AGEs, results in increased arterial stiffness and increased amounts of oxidative species, which contribute to cellular dysfunction and apoptosis.

Glucose transport is impaired in the diabetic heart, in part due to a decrease in the myocardial concentration of glucose transporters GLUT 1 and GLUT 4 proteins and mRNA levels. The consequent increase of free fatty acid (FFA) myocardial uptake occurring in conditions like diabetes and obesity leads to disproportionately high rates of long-chain FFA oxidation with reduced phosphate/oxygen ratio compared with glucose oxidation and to a disproportionate oxidative request to mitochondria with uncoupling of mitochondrial oxidative phosphorylation. In addition, the impaired expression of contractile proteins, as myosin isoforms and fetal beta myosin heavy chain, is responsible for depressed myofibrillar ATP activities and abnormalities of the sarcoplasmic reticular and sarcolemmal calcium transport processes with consequent calcium overload and impaired diastolic performance.

Impairment of microvascular circulation and of cardiac sympathetic innervation is commonly observed in HF patients affected by DM and/or IR. In fact, DM is associated with impaired peripheral and endothelial-mediated coronary flow reserve that can contribute to HF progression through repetitive ischaemic insults. HF patients with DM or without DM but with IR show more impaired cardiac sympathetic innervation, compared with non-diabetic and non-IR patients, indicating chronic adrenergic hyperactivity, that correlates with HbA1c levels and IR indices. We recently reported that levels of GRK2, a protein kinase involved in the desensitization of cardiac beta-receptors, are significantly more elevated in HF patients with DM compared with non-diabetic HF patients. Since elevated GRK2 levels also impair insulin and adiponectin signalling in experimental models, a working hypothesis can be postulated whereby a vicious circle between HF and IR might contribute to worse prognosis in HF.

**Table 1** Metabolic syndrome definitions

<table>
<thead>
<tr>
<th>NCEP ATP III</th>
<th>IDF</th>
<th>WHO</th>
<th>EGIR</th>
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<tr>
<td>Three or more of the following five criteria:</td>
<td>Central obesity (defined as waist circumference ≥ 94 cm for Europid men and ≥ 80 cm for Europid women, with ethnicity specific values for other groups) plus any two of the following four factors:</td>
<td>Insulin resistance* or diabetes plus two of the following five criteria:</td>
<td>Hyperinsulinaemia plus two of the following four criteria:</td>
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<td>Fasting blood sugar over 100 mg/dL</td>
<td>Fasting plasma glucose ≥ 100 mg/dL, or previously diagnosed type 2 diabetes. If above 100 mg/dL, OGTT is strongly recommended but is not necessary to define the presence of the syndrome</td>
<td>Blood pressure ≥ 140/90 mmHg or hypertension-specific treatment</td>
<td>—</td>
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<tr>
<td>Blood Pressure over 130/85 mmHg</td>
<td>Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or treatment of previously diagnosed hypertension</td>
<td>Fasting triglyceride level over 150 mg/dL</td>
<td>Blood pressure ≥ 140/90 mmHg or hypertension-specific treatment</td>
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<tr>
<td>Fasting triglyceride level over 150 mg/dL</td>
<td>Triglyceride level ≥ 150 mg/dL or specific treatment for this lipid abnormality</td>
<td>Fasting triglyceride level over 150 mg/dL or specific treatment for this lipid abnormality</td>
<td>Fasting triglyceride level ≥ 177 mg/dL or ≥ 150 mg/dL in males and ≥ 130 mg/dL in females, or specific treatment for this lipid abnormality</td>
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<tr>
<td>Fasting HDL cholesterol level &lt; 40 mg/dL (men) or 50 mg/dL (women)</td>
<td>HDL cholesterol &lt; 40 mg/dL in males and &lt; 50 mg/dL in females, or specific treatment for this lipid abnormality</td>
<td>Fasting HDL cholesterol level &lt; 35 mg/dL (men) or 39 mg/dL (women)</td>
<td>Fasting HDL cholesterol level &lt; 39 mg/dL</td>
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<tr>
<td>Waist circumference over 40 in. (men) or 35 in. (women)</td>
<td>—</td>
<td>Waist/hip ratio &gt; 0.90 (men) or &gt; 0.85 (women); or BMI &gt; 30 kg/m²</td>
<td>Waist circumference ≥ 94 cm for men and ≥ 80 cm for women</td>
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HDL, high-density lipoprotein.

*Insulin resistance defined as: impaired fasting glucose (IFG), defined as a fasting glucose level above a predetermined cut-off, [commonly 100 mg per decilitre (mg/dL)] or impaired glucose tolerance (IGT), defined as a glucose level above a predetermined cut-off, commonly 140 mg/dL, for 120 min after ingestion of 75 g of glucose load during an oral glucose tolerance test or insulin resistance at euglycaemic clamp studies.

**Obesity**

It is estimated that obesity (BMI > 30 kg/m²) doubles the risk of developing HF after adjustment for associated co-morbidities. In particular, obesity increases HF risk through several biochemical, structural, and functional mechanisms. In moderate and severely obese patients (BMI > 35 kg/m²), several central haemodynamic abnormalities have been reported. In particular, excessive adipose accumulation is associated with an increase in central volemia and cardiac output. Right heart haemodynamics, including pulmonary artery, pulmonary vascular resistances, right atrial pressure, and
pulmonary capillary wedge pressure are usually elevated in severe obesity.23 The frequent coexistence of hypoxaemia related to sleep apnoea contributes to abnormalities of right heart parameters.21,24 Cardiac morphology appears also affected by obesity. Increased LV mass, usually associated to enlarged end-diastolic volume (eccentric hypertrophy), has been reported in obese normotensive subjects.21,25 Left ventricular diastolic function is commonly impaired in obese patients, and the degree of impairment of LV diastolic filling correlates with the severity of obesity.25 Yet, LV systolic function is typically preserved or only mildly impaired in obesity.21,24 Apart from visceral obesity, ectopic accumulation of fat in non-adipose tissue, including liver, muscle, and heart (where epicardial and pericardial fat can be measured) has been correlated to increased cardiometabolic risk and cardiac structure abnormalities.26 Recently, Pucci et al.27 showed that pericardial fat accumulation was independently correlated with LV mass and inversely correlated with LV mid-wall stress abnormalities in morbid obese patients, whereas cardiac steatosis has been observed in patients with dilated cardiomyopathy.28 Obesity and ectopic fat accumulation have been associated with neurohormonal and metabolic abnormalities, including cytokines production defects, renin–angiotensin–aldosterone system and sympathetic nervous system overactivity.29

In fact, the adipose tissue can be considered as an endocrine organ that produces several biologically active adipokines. Adiponectin is the most abundant adipokine produced by fat tissue that has been demonstrated to exert anti-inflammatory and insulin-sensitizing actions, the latter through stimulation and activation of AMP-mediated protein kinase phosphorylation.30 As nicely summarized by Kadowaki et al., obesity and DM are associated with reduced levels of adiponectin and type 1 and 2 adiponectin receptors, responsible for impaired insulin sensitivity and oxidative metabolism in patients with MS. Adipokine levels correlated with several anthropometric parameters, including BMI, waist circumference, and visceral fat deposition.31 In particular, a positive correlation was found between visceral fat accumulation and leptin, resistin, and visfatin levels, whereas an inverse correlation was found with myocardial protective adipokines, adiponectin, and ghrelin.31 This latter peptide, produced in the gut, exerts a protective CV action through several mechanisms among which are amelioration of oxidative metabolism, reduction of cardiac adrenergic activity, and anti-angiotensin 2-induced cardiac apoptosis.32 In contrast, leptin promotes inflammation and ROS production, whereas resistin impairs insulin sensitivity in obese patients.33 Interestingly, plasma resistin levels were independently associated with increased risk of developing HF in the Framingham cohort, after adjustment for other risk factors and incident coronary artery disease, whereas adiponectin levels were not.34 Leptin levels were inconsistently associated with increased HF levels, but the association was no longer significant after adjustment for BMI.35 Yet, Bobbert et al.36 reported that both resistin and leptin levels adversely influenced prognosis in patients with systolic HF.

Activation of the renin–angiotensin system plays a central role in MS, as it is both contributor to and target of many components of the MS.37 Increased activation of precursors of angiotensin 2 and increased angiotensin 2 activity and angiotensin receptor 1 expression have been described as consequence of hyperglycaemia, IR, and
obesity in different cell types. In turn, elevated angiotensin 2 levels impair insulin signalling through several mechanisms, including tyrosine phosphorylation of the insulin receptor and inhibition of phosphatidylinositol 3-kinase recruitment of glucose transport due to increased oxidative stress. At the cardiac level, increased angiotensin 2 activity promotes oxidative stress, mainly through activation of NADPH oxidase enzyme activity, fibrosis, and apoptosis, leading to myocardial damage. At the vascular level, angiotensin 2 overproduction from hypertrophic adipocytes in obesity has been reported to substantially contribute to hypertensive stress, through increased vasoconstriction, adrenergic activity stimulation, and increased mineralocorticoid hormone production.

Abnormal activation of the endocannabinoids system was more recently described in obese and diabetic patients, in whom levels of anandamide and 2-arachidonoglycerol, the most common endocannabinoids, have been reported to be elevated compared with controls. In an experimental mouse model, DM-induced cardiomyopathy was associated with increased endocannabinoid concentration and receptor expression, leading to increased oxidative stress, inflammation, fibrosis, and apoptosis. Interestingly, most diabetic-induced changes were reverted by endocannabinoid receptor 1 antagonists or by genetic deletion of cannabinoid receptor 1. In addition, in the same experimental model, endocannabinoids' activation promoted activation of the renin–angiotensin system, and in a different experimental model, the formation of a heteromer between angiotensin receptor 1 and endocannabinoid receptor 1 resulted in amplification of the angiotensin 2 effects.

Arterial hypertension
A total of 6–10% of HF patients have hypertensive aetiology. According to the model proposed by Vasan and Levy, in early stages, hypertension does not affect LV function until mechanical stress due to increased pressure load together with high levels of neurohormones, cytokines, and growth factors induce development of concentric LV hypertrophy that can progress to symptomatic HF with either preserved or abnormal LV function. The progression from concentric LV hypertrophy to HF with normal LV ejection fraction is characterized by changes in the extracellular matrix, worsening of diastolic function, and activation of several pathways that compromise the anti-apoptotic/pro-survival balance by an increase of apoptosis and fibrosis ultimately leading to remodelling, dilatation, and LV failure. As recently reviewed by Hall et al., impaired kidney function due to fat compression, with consequent reduced natriuresis, together with hyperactivity of the renin–angiotensin and sympathetic nervous systems characterize obesity-associated hypertension. Association of obesity and hypertension results in a shift towards more concentric LV hypertrophy, compared with obese normotensive patients. Yet, time and pathways of HF development in obese hypertensive patients are still not completely clear, since some patients rapidly progress to dilation and overt systolic HF, whereas in others cardiac hypertrophy and diastolic dysfunction remain the main structural and functional features. Yet, once the diagnosis of HF has been made, high blood pressure is associated with improved survival, condition likely reflecting greater cardiac reserve and possibility to tolerate more intense HF therapy.

Lipid abnormalities
Reduced high-density lipoprotein (HDL) and high triglyceride plasma levels are the lipid abnormalities included in the definition of MS. In a population study from the Framingham cohort, Velagali et al. reported that low HDL plasma levels were associated with a 40% increased risk of developing HF over a 26 years follow-up. Interestingly, the association was confirmed after adjustment for interim myocardial infarction, suggesting that it was not entirely explained by the increased risk of coronary artery disease associated with low HDL. Several effects of HDL have been described that may account for a protective role against development of HF, including improvement of endothelial dysfunction, anti-inflammatory, and anti-oxidant activity. High triglyceride plasma levels have been also independently associated with increased risk of developing HF in diabetic patients in the Multiethnic Study of Atherosclerosis, albeit the association was weakened after adjustment for incident myocardial infarction and HDL. Although increased plasma triglycerides reflect increased triglyceride myocardial content, intramyocardial triglyceride accumulation does not seem to exert a direct toxic effect but more likely represents an energy store for the myocardium. Yet, excess FFA that characterizes obesity and DM leads to increased cardiac triglyceride cell storage that may become a source of toxic lipid bioproducts when myocardial triglyceride storage capacity is exceeded and/or beta oxidation is impaired. Chokshi et al., in a population of patients with severe LV dysfunction, reported an abnormal increase of intramyocardial diacylglycerols and ceramide content that are toxic lipid bioproducts, associated with IR and impaired oxidative capacity, but not of triglycerides. Interestingly, IR and lipid abnormalities, as well as impairment of the phosphatidyl-inositole kinase pathway were reversible upon mechanical unloading of the LV. Thus, lipid accumulation in the heart, through production of toxic intermediate products and derangement of insulin and oxidative pathways, determines conditions known as lipotoxicity and lipoapoptosis that impair cardiac function and promote HF. Taken together, these findings point to a pathogenetic chain whereby obesity, through an imbalance between cardioprotective and cardiotoxic effects of adipokines, IR, lipid, and oxidative metabolism perturbations, as well as neurohormonal activation, promotes HF.

The obesity ‘paradox’ in heart failure: true protective effect or collider bias?
Although obesity is a well-recognized risk factor for HF, increasing evidences suggest an opposite prognostic impact of obesity on patients with HF. In fact, several investigations reported that an ‘obesity paradox’ exists among patients with HF, wherein those with higher BMI have more favourable survival than those with lower BMI, despite higher rates of hypertension and DM. Oreopoulos et al. in a meta-analysis including 28 209 patients with HF reported that mortality of overweight and obese patients was, respectively, 16 and 33% lower compared with patients with normal weight. Cardiovascular mortality was also 19 and 40% lower in overweight and obese patients compared with that in lean patients. This
counterintuitive association between obesity and HF has been consistently observed regardless of age, gender, systolic or diastolic HF, central or peripheral obesity, and chronic or acutely decompensated HF.55,56

The favourable association of obesity and HF is not simply the result of poorer outcomes in patients with severe HF and cardia cachexia, as patients with high BMI, whether overweight (BMI 26–30 kg/m²) or obese (BMI > 30 kg/m²), show lower mortality rates than patients with normal BMI and those who are underweight.57 Notably, patients who are overweight or obese before development of HF have lower mortality after the onset of HF compared with patients with normal BMI.57

We also recently reported that MS, defined by ADF criteria that mandatorily include obesity, is associated with improved survival in HF patients58 (Figure 2). Interestingly, HF patients with MS but without DM showed the best survival compared with HF patients without DM and MS and with HF patients with DM but without MS, which showed the worst survival. These observations suggest that IR but not overweight unfavourably affects prognosis in HF patients and are consistent with previous observations reporting that normal weight individuals with MS carry increased risk of developing HF compared with obese individuals without MS.59

The favourable prognostic association between obesity, MS, and HF is not completely understood, and it remains to be definitively assessed whether it reflects a true protective effect, since this distinction would be relevant in terms of therapeutic management. Mechanistic hypotheses explaining improved survival in overweight and obese patients with HF mainly rely on the balance between the anabolic and catabolic burden. The cardiac cachexia observed in end-stage HF is associated with an abnormal cytokine and neurohormone profile with increased risk of mortality.60 In fact, in advanced stages of HF, a condition known as malnutrition-inflammation complex syndrome (MICS) is commonly observed and represents the link among cardiac cachexia, weight loss, and cytokine activation have been demonstrated with consequent endotoxin absorption or reduced clearance, so that malnourished HF patients are more predisposed to infections, inflammatory activation, and poor outcome.60 Hence, the presence of a condition that counterbalances the effects of inflammation and protein malnutrition, as overweight or moderate obesity, may be beneficial in patients affected by HF.

However, it is less clear whether intentional changes of BMI in patients with HF, either weight gain or weight loss, are associated with CV risk modification. In fact, several observations indicate that unintended weight loss (at least 5% of baseline weight) is associated with poorer prognosis in HF patients, likely reflecting wasting conditions.61 In contrast, no conclusive data are available that adequately investigated the prognostic impact of programmed weight reduction in obese HF patients. Similarly, unwanted weight gain, reflecting deteriorating haemodynamic status, is associated with worse prognosis in HF patients,62 whereas no studies have assessed the prognostic implication of adipose tissue increase in underweight or normal weight HF patients. Thus, future research is obviously needed in this context.

However, the possibility should not be overlooked that the inverse association between obesity or MS and prognosis in HF patients may merely reflect a collider stratification bias whereby patients with HF and obesity and/or MS represent a selected subset of HF patients in whom other confounder risk factors that are associated with worse survival in HF are less represented, resulting in a biased favourable association of obesity and MS with HF in analysis not adequately adjusted for confounder risk factors. In addition, earlier symptoms and signs (dyspnoea, oedema) fostered by obesity may result in precarious identification of LV dysfunction with resulting more aggressive treatment and better prognosis.

Clinical implications and future perspectives

Metabolic syndrome is highly prevalent in patients with HF and is associated with multiple molecular, cellular, and neurohormonal responses that may affect prognosis. Insulin resistance and lipid abnormalities represent components of MS associated with several pathogenetic abnormalities that unfavourably influence disease progression. Yet, other components of MS, including overweight/obesity and high blood pressure, are favourably associated with outcome in HF patients. These observations caution against extrapolation of benefits of treatment of CV risk factors in the general population to patients with HF, as reflected by the fact that HF guidelines do not recommend weight reduction in HF patients with BMI < 30 kg/m².64,65 Further studies are needed in this field to identify the mechanistic basis underlying the ‘obesity paradox’ phenomenon and clarify the most appropriate body habitus and therapeutic strategies in HF patients with MS.

Conflict of interest: none declared.

References


Figure 2 All-cause death in heart failure patients with metabolic syndrome and diabetes mellitus (DM). Kaplan–Meier curves for all-cause death in heart failure patients divided in groups according to the presence/absence of metabolic syndrome and diabetes mellitus. Modified from Perrone Filardi et al. Intern J Cardial 2015.50

METS, metabolic syndrome.
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