REVIEW

The role of metabolic syndrome in sudden cardiac death risk: Recent evidence and future directions

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Abstract

Metabolic syndrome (MetS) is a frequent condition whose deleterious effects on the cardiovascular system are often underestimated. MetS is nowadays considered a real pandemic with an estimated prevalence of 25% in general population. Individuals with MetS are at high risk of sudden cardiac death (SCD) as this condition accounts for 50% of all cardiac deaths in such a population. Of interest, recent studies demonstrated that individuals with MetS show 70% increased risk of SCD even without previous history of coronary heart disease (CHD). However, little is known about the interplay between the two conditions. MetS is a complex disease determined by genetic predisposition, unhealthy lifestyle and ageing with deleterious effects on different organs. MetS components trigger a systemic chronic low-grade pro-inflammatory state, associated with excess of sympathetic activity, cardiac hypertrophy, arrhythmias and atherosclerosis. Thus, MetS has an important burden on the cardiovascular system as demonstrated by both preclinical and clinical evidence. The aim of this review is to summarize recent evidence concerning the association between MetS and SCD, showing possible common aetiological processes, and to indicate prospective for future studies and therapeutic targets.

KEYWORDS

dyslipidemia, hypertension, metabolic syndrome, sudden cardiac death

1 | INTRODUCTION

Metabolic syndrome (MetS) accounts for different metabolic disorders including impaired fasting glucose (IFG), high blood pressure (BP), abdominal obesity, high triglycerides (TGs) and low high-density lipoprotein cholesterol (HDL-C).[1] From being a condition typically associated with Western lifestyle and habits, the incidence

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Abbreviations: BP, blood pressure; CAD, coronary artery disease; CHD, coronary heart disease; CMs, cardiomyocytes; CV, cardiovascular; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; HG, hyperglycaemia; HTN, hypertension; IFG, impaired fasting glucose; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; MetS, metabolic syndrome; QTd, QT dispersion; SCD, sudden cardiac death; TGs, triglycerides; VAT, visceral adipose tissue; WC, waist circumference.

of MetS is now rising in developing countries with the result of becoming a real pandemic, urging rapid and worldwide counteractions. Indeed, to date, MetS is estimated to affect around one person every four with slightly increased prevalence in women.[2,3] Lifelong exposure to MetS components has been shown to exert deleterious effects in most systems and organs. Specifically, MetS deeply impacts on the cardiovascular (CV) system increasing CV risk by more than 2-fold.[4]

Sudden cardiac death (SCD) is defined as a sudden unexpected arrest of CV system that occurs in a short time period (within 1 h of symptom onset) in subjects with or without previously recognized congenital or acquired cardiac alterations.[5,6] More than 50% of total cardiac death are defined as SCD.[7,8] In the United States, its incidence rates up to 60 per 100,000 persons every year, with men more likely of being victims of SCD as compared with women (rates: 76 and 45 per 100,000 persons, respectively).[9]

Though MetS is not included among risk factors for SCD, the relationship between its components and CV risk is well known.[4,10,11] Recent studies evidenced a noteworthy increased risk—up to 70%[12]—of SCD among patients with MetS without history of coronary heart disease (CHD).[12–14] In this review, we report on recent evidence associating MetS components with increased risk of SCD. Preclinical and clinical evidence will be dissected to summarize recent pathophysiological and clinical knowledge and highlight potential therapeutic target to reduce its burden.

2 | METABOLIC SYNDROME: CLINICAL CRITERIA, RISK FACTORS AND PATHOPHYSIOLOGY

MetS definition has slightly changed during the years.[1] The clinical criteria of MetS according to the *International Diabetes Federation—American Heart Association/National Heart, Lung, and Blood Institute Joint Interim Statement* are summarized in Figure 1.[15] The complex interplay among the different alterations characterizing MetS accounts for its high number of modifiable and nonmodifiable risk factors. Among the latter, genetic predisposition, male sex and ageing[3,16,17] have been widely investigated with recent acquisitions highlighting the important role for genes related to lipid and glucose balance in MetS predisposition.[18,19] Among modifiable risk factors, unhealthy lifestyles—especially the association of overeating with reduced physical activity—favourite energy overflow, leading to adipose tissue hypertrophy. Adipose tissue not only has storage activity but can produce and release several molecules (i.e., adipokines) signalling at local and systemic levels. Adipokines are pivotal mediators of metabolic and CV pathophysiology and include pro-inflammatory (i.e., tumour necrosis factor-α, interleukin-6, Leptin, Resistin, Lipocalin) and anti-inflammatory (i.e., Adiponectin, secreted frizzled-related protein 5) molecules.[20–23] The dysfunctional adipose tissue increases the synthesis and release of pro-inflammatory adipocytokines, a condition known as metaflammation which is increasingly recognized as the common pathway of the
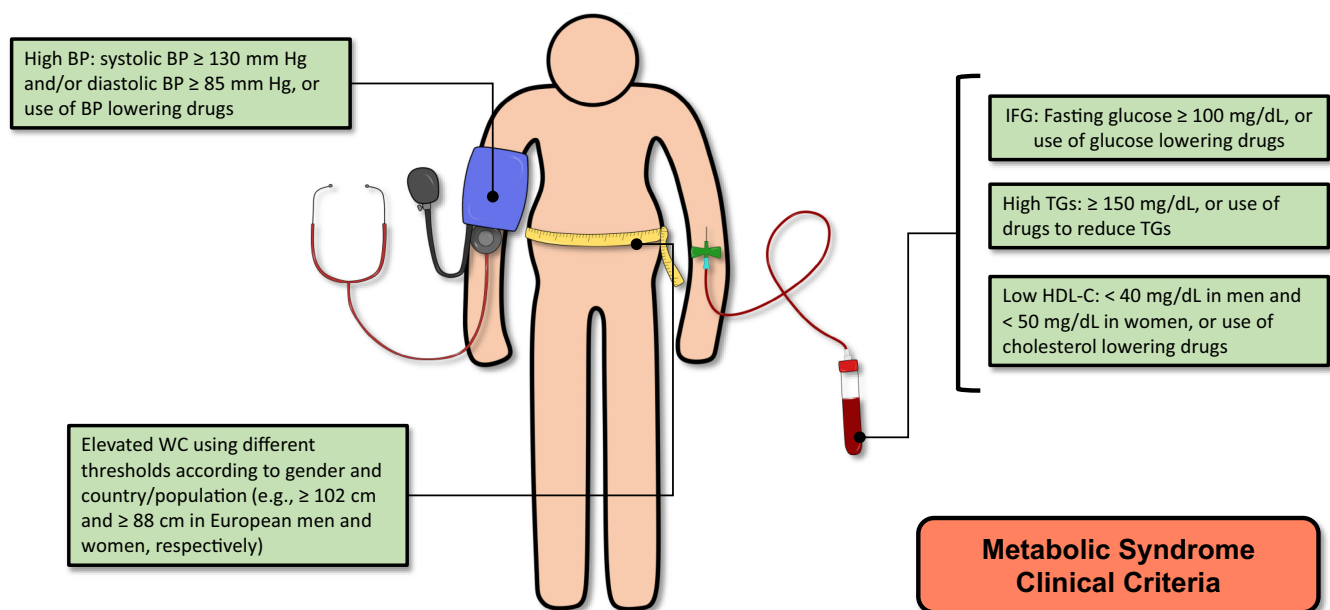
FIGURE 1 Metabolic syndrome diagnostic criteria. As reported by the International Diabetes Federation—American Heart Association/National Heart, Lung, and Blood Institute Joint Interim Statement definition.[15] BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; IFG, impaired fasting glucose; TGs, triglycerides; WC, waist circumference

different features of MetS.[24] More specifically, MetS patients tend to have a lower adiponectin/leptin ratio that is considerable as an indicator of dysfunctional adipose tissue.[25] Of interest, ageing—another MetS risk factor—contributes to the setting up of inflammatory and metabolic alterations in vulnerable individuals. Specifically, elderly people show chronically increased level of pro-inflammatory mediators even in the absence of appropriate immunogenic stimuli (i.e., inflamm-ageing) thought to facilitate different degenerative diseases including atherosclerosis and its ischaemic complications (ischaemic stroke and myocardial infarction). Metaflammation and inflamm-ageing share different features and mechanisms that have been previously reviewed.[26,27]

Obesity is classically associated with MetS[28] beside not being essential for its diagnosis.[15,29] Indeed, recent evidence supports the fact that patients might be 'metabolically obese' even when showing normal weight and WC.[30] In those patients, VAT within the intraperitoneal and retroperitoneal spaces is dysfunctional and associates with higher cardiometabolic risk.[31,32] VAT has an elevated lipolytic activity and can cause hyperinsulinaemia and insulin resistance.[33] Furthermore, compared with subcutaneous adipose tissue, VAT shows increased inflammatory cell infiltration as well as metabolically active adipocytes.[34] Consequently, the amount and functional status of VAT has been recognized as an important contributing factor to MetS.[35–38]

Even though the precise mechanisms underlying MetS pathophysiology are not completely understood, insulin resistance and chronic inflammation are considered as the mainstays of MetS.[39] Insulin resistance boosts adipose tissue lipolysis, blunts glucose uptake by muscles and causes an excess of hepatic production of glucose and TGs prompting higher circulating levels of free fatty acids and glucose.[39] In people affected by MetS, hypertension (HTN) is probably related to renin-angiotensin system activation and to the loss of insulin vasodilator effect on vessels.[40,41] Further, MetS patients seem to have increased levels of sympathetic nerve activity,[42–44] causing reduced pancreatic insulin release, increased glucose production in the liver, augmented lipolysis in the adipose tissue and arterioles vasoconstriction.[42] Moreover, since renin-angiotensin system activity also depends on sympathetic nervous system, the higher sympathetic activity found in these patients could probably determine an angiotensin-mediated increase in blood pressure values.[45]

3 | SUDDEN CARDIAC DEATH AND METABOLIC SYNDROME

Many diseases are associated with SCD such as diabetes,[46] HTN,[47] left ventricular hypertrophy (LVH),[48] CHD[49] and heart failure (HF),[49] but the strength of these associations vary among different populations, age and sex groups. Coronary artery disease (CAD) is listed as the most important cause of SCD,[50,51] being causative for almost 75% of total SCD burden in Western countries.[52] Also, genetic cardiac abnormalities are important causes of SCD especially in subjects aged less than 35 years, whereas CAD represents the leading underlying cause in victims aged more than 35 years.[52]

The pathogenesis of SCD highly depends on its causative factor, although common final pathways are thought to sustain the final events. Specifically, the most accepted mechanism is the onset of a ventricular arrhythmia, caused by different possible triggers, such as acute ischaemia, ion disorders or structural alterations.[52] Ventricular tachyarrhythmias are frequent and often lethal, estimated to sustain up to 80% of total SCD.[7] They show circadian and infradian variations (i.e., higher prevalence of SCD during winter and in the morning) and can be triggered by vigorous physical activity and psychological stressors such as anxiety and depression).[52] As previously mentioned, in most cases, an acquired or genetic cardiac disorder constitute the background for such fatal arrhythmias.[53]

As for MetS, the sympathetic nervous system could play an important role in determining SCD as well.[54] In younger subjects, ventricular arrhythmias seem to be associated with an excess of heart sympathetic stimulation, particularly when the arrhythmic risk is genetically determined.[55] Specifically, sympathetic activation plays an important role in subjects with long QT and catecholaminergic polymorphic ventricular tachycardia.[55,56] On the other hand, the sympathetic system may exert a protective effect in patients with Brugada or J-wave syndromes.[57] Less is known on its role in older subjects including those with MetS. However, a higher sympathetic activity has been involved in the formation of atherosclerotic plaque and can cause coronary vasoconstriction,[58,59] therefore favouring cardiac ischaemia. Furthermore, some evidence also supports a role for sympathetic triggering of arrhythmia in elderly patients with CHD.[57] However, the extent of such an association remains to be fully disclosed.

4 | HYPERGLYCAEMIA

According to the American Diabetes Association, IFG is defined as the presence of fasting plasma glucose concentrations between 100 and 125 mg/dl (5.6 to 6.9 mmol/L) and impaired glucose tolerance as plasma glucose concentrations between 140 and 199 mg/dl (7.8 to 11.0 mmol/L) at the second hour of the oral glucose tolerance test.[60] Patients with IFG, impaired glucose tolerance or haemoglobin A_{1c} between 5.7 and 6.4% are

at high risk of developing overt diabetes,[60] such conditions are often defined as prediabetes.[61] IFG, impaired glucose tolerance and diabetes alongside their interplay with the other components of MetS have direct and indirect deleterious effect on cardiac function and predispose to SCD as demonstrated by several basic science as well as clinical evidence.

4.1 | Basic science research

Hyperglycaemia (HG) has been shown to have different damaging effects on cardiomyocyte (CM) function and survival. Exposure to high glucose environment induces CM death both in vitro and in vivo in different animal models of disease including ischaemic[62–65] and non-ischaemic ones.[66–69] Lower levels of adenosine triphosphate (ATP), adenosine monophosphate (AMP), fumarate, succinate, aspartate and creatinine, alongside increased branched-chain amino acids content in CM exposed to HG favour their apoptosis.[69] Similarly, also oxidative stress through its activating effect on cytochrome c-activated caspase-3 pathway can explain the higher rate of apoptosis in CMs exposed to HG conditions.[66]

Moreover, HG was shown to affect the contractile function of CMs by impairing intracellular calcium balance and causing ventricular dilatation and systolic disfunction.[70] Also, HG can prolong action potentials of CMs by inducing calcium mismatch.[71] In rat models of prediabetes fed with a high-sucrose diet, HG was shown to induce LVH, independently from obesity and HTN.[72] Furthermore, in streptozotocin-induced diabetic rats, HG causes QT interval elongation, with cardiac repolarization being reversed only after 4 days of insulin infusion.[73]

HG favours the atherosclerotic process in different ways.[74,75] An interesting explanation of this complex process concerns the formation of toxic products after the interaction between glucose and other molecules. More specifically, advanced glycosylation end products are formed because of the interaction between proteins, lipid or nucleic acids and glucose via chemical processes of non-enzymatic glycation and oxidation.[76] In general, the more blood glucose is present, the more advanced glycosylation end products are likely to be created.[77] Advanced glycosylation end products have been shown to play important role in regulation of inflammation, extracellular matrix modifications, lipoprotein modification and cellular proliferation, all processes deeply involved in the pathophysiology of atherosclerosis.[74,78]

4.2 | Clinical research

Preclinical evidence found confirmation in clinical cohorts as diabetes and prediabetes individuals show increased all-cause and CV mortality.[79] As reported by a recent meta-analysis, those individuals have a 2-fold higher risk and a 23% of increased risk, respectively, of SCD compared with people without glucose alterations.[80] In a prospective study assessing middle-aged men, non-diabetic subjects with IFG showed a 1.5-fold risk of SCD compared with patients showing normal fasting plasma glucose even after adjustments for other CVDs risk factors.[81] Remarkably, the authors showed that every 1 mmol/L augmentation of fasting plasma glucose was associated with a 10% increase of SCD risk.[81] Moreover, haemoglobin A_{1c} is associated with SCD risk, even among patients without previously known CVDs.[82] Yet, the association between diabetes and SCD is far from being non-controversial, with a recent report based on competing risk analysis highlighting that in primary prevention implantable cardiac defibrillator (ICD) patients, diabetes is associated with the risk of death without, but not with, sustained ventricular arrhythmias and appropriate ICD therapies.[83] Of importance, diabetes mellitus is associated with several causes of sudden cardiac arrest including CHD, HF with preserved or reduced ejection fraction, and arrhythmias particularly due to QT prolongation.[84] Thus, a prospective population-based cohort study evidenced that IFG predispose to QT elongation and reduction of RR interval.[85] Also, the authors demonstrated a higher risk of SCD among these patients and proposed sympathetic activity as the main cause of RR shortening.[85]

As long-time recognized, diabetes and prediabetic conditions are among the more prevalent causes of CHD. Several studies showed a higher risk of CAD in patients with or without diabetes in correlation with their glycaemic profile.[86–90] However, CAD prevalence is higher among diabetic subjects rather than non-diabetic ones.[89] Also, a diet with elevated glycaemic load is related to CAD.[91,92] Elevated fasting plasma glucose is independently predictive of LVH in patients without diabetes even without prior history of CVDs.[93,94] Prediabetes and diabetes associate with higher risk of HF[95–99] by increasing the risk of CAD, heart microvascular function and LVH.[95] Furthermore, insulin resistance is associated with a higher risk of diastolic dysfunction in both prediabetes[100] and diabetic[101,102] patients. Such an association is probably due to the reduced glucose uptake found in cardiomyocytes in cases of insulin resistance, leading to metabolic alterations that pave the way towards chronic HF.[103]

5 | HYPERTENSION

According to the 2018 ESC/ESH Guidelines,[104] HTN is defined as the presence of elevated systolic and/or diastolic BP (≥140 and ≥90 mm Hg, respectively). With respect to MetS diagnosis, the Joint Interim Statement includes individuals with high normal BP (≥130 systolic and/or diastolic ≥85 mm Hg) or those taking anti-HTN medications. HTN accounts for an important part of the total burden of diseases[15]; as an example, a recent study in Italy quantified a prevalence of hypertension up to 26% in MetS individuals.[105]

5.1 | Basic science research

Increased blood pressure values exert several detrimental effects on the heart. Mechanical straining, oxidative stress, neurohormonal activation (i.e., renin-angiotensin and sympathetic system activation) and upregulation of pro-inflammatory cytokines account for the increased CM apoptosis observed in basic research studies with hypertensive models.[106] Increased levels of norepinephrine cause CM apoptosis in neonatal rats in a time- and dose-dependent manner,[107] while increased CM apoptosis favourites the transition from LVH to overt ventricular dysfunction in different animal models of HTN.[108,109]

Hypertensive animal models have a higher risk of developing cardiac hypertrophy.[108,110–113] Rat hearts working against pressure overload show a higher risk of metabolic impairments, such as an augmented glucose uptake in CMs and LVH.[114] Such metabolic alterations precede the onset of overt cardiac hypertrophy or ventricular dysfunction[114] and may partially account for the episodes of SCD reported in hypertensive male rats.[115] Accordingly, LVH associates with SCD in patients.[116–118]

Nevertheless, hypertension and LVH are underlined by complex intracellular alterations that may account themselves for the risk of SCD. For instance, mice over-expressing angiotensin-converting enzyme show a higher risk of arrhythmias and SCD even when having normal blood pressure and no ventricular hypertrophy.[119] On the other hand, hearts of normotensive mice exposed to high levels of angiotensin II are more prone to develop cardiac hypertrophy[120] and ventricular dysfunction,[121] while blocking angiotensin receptors may reduce arrhythmias in LVH mice.[122] High levels of oxidative stress, together with increased inflammation, ion transport alterations and morphological changes have been identified as possible underlying mechanisms of the association between hypertension, LVH, arrhythmias and SCD.[123–126]

5.2 | Clinical research

Hypertension is a known risk factor for most causes of SCD. Accordingly, men with basal systolic BP >145 mm Hg as compared with normotensive patients have a 2-fold increased risk of SCD[127] and every 20/10 mm Hg increase of systolic/diastolic BP associates with up to 20% higher risk of SCD.[128] HTN causes LVH and cardiac hypertrophy is associated with a higher risk of SCD,[117,118,129] especially in black people.[52,130] Even though the pathogenesis of this association is not fully understood, LVH not only alters the cardiac muscular structure but also its electric activity and hypertrophic hearts have a higher risk of arrhythmia onset.[118,131,132] Indeed, LVH favours cardiac fibrosis in hypertensive subjects,[133] and cardiac fibrosis impairs heart conduction, eventually favouring arrhythmias.[134–136]

Cardiac hypertrophy initially compensates the hypertensive state, but this adaptation becomes pathological when the hypertensive stimulus reiterates during the time. LVH is common among subjects affected by HTN, but even people with high normal blood pressure have a higher risk of developing LVH compared with normotensive subjects.[137] Recently, genetic factors have shown an important role in developing LVH as a response to BP increase.[138] In this study, every 10 mm Hg augmentation of genetically predicted systolic BP was associated with almost 5 g of left ventricular mass increment.[138]

However, some studies reported that the ventricular dysrhythmias found in hypertensive subjects with LVH may have weak associations with SCD.[139,140] Nonetheless, the presence of cardiac or non-cardiac comorbidities increases the risk of SCD in patients with LVH. Among them, the presence of cardiac ischaemia or fibrosis,[48] but also renal failure requiring haemodialysis which was reported to increase the sympathetic activity and the risk of SCD in patients with LVH.[141]

6 | WAIST CIRCUMFERENCE, TRIGLYCERIDES AND HIGH-DENSITY LIPOPROTEINS

WC is used to assess abdominal fat. Even though imaging techniques are needed to precisely estimate the amount of VAT, WC correlates with VAT irrespective of ethnicity and gender differences.[142,143]

High TGs and low HDL-C blood levels takes part to MetS diagnostic criteria.[15] HDL particles transport cholesterol from the periphery to the liver,[144] whereas TGs are energetic molecules used by cells via β-oxidation or stored in adipocytes as stocks.[145] Lack of HDL-C and excess in TGs are related to a higher risk of CHD, especially in

women.[146] In MetS subjects, the excess of free fatty acids in the blood enhances gluconeogenesis, lipogenesis, reducing glucose sensitivity and favouring the onset of further metabolic disturbances.[39]

6.1 | Basic science research

Up to 70% of cardiac adenosine triphosphate derives from fatty acid β-oxidation,[147] and obesity is associated with an increased cardiac fatty acid β-oxidation.[148] Accordingly, mouse models of obesity show increased TGs uptake in CMs.[148,149] However, TGs—when in excess—may cause detrimental effects on the heart. This condition is known under the name of cardiac 'lipotoxicity' and includes reactive oxygen species production, release of mitochondrial cytochrome c and apoptosis, as the main mechanisms of damage.[150,151] Accordingly, a study assessing mice with carnitine palmitoyltransferase-1b deficiency—a protein involved in β-oxidation—showed that these mice have a higher TGs accumulation in the myocardium, leading to cardiac hypertrophy, impaired cardiac contractions, congestive HF and premature death after cardiac pressure overload when compared with control mice.[152] Similarly, mice with deficiency of very-long-chain acyl-coenzyme A dehydrogenase, another crucial enzyme of β-oxidation, that are fed with a diet rich of TGs show a noteworthy increment of VAT, resulting in the development of MetS-like phenotype.[153]

As for arrhythmias, evidence suggests that high-fat diet can trigger ventricular arrhythmias in mice through the release of Ca^{++} from sarcoplasmic reticulum and ion channel activation.[154] Similarly, another study demonstrated the presence of QT intervals elongation, QT dispersion (QTd) augmentation, increased sympathetic innervation, an augmented Ca^{++} current density and a higher risk of ventricular fibrillation in the heart of rabbits fed with a high cholesterol diet.[155] Of interest, administration of simvastatin reduced the risk of ventricular fibrillation in similarly fed rabbits.[156]

6.2 | Clinical research

Victims of SCD are likely to have a wider WC,[13] though the correlation between abnormal WC and SCD is not completely demonstrated now. In fact, a recent meta-analysis showed that both the augmentation of waist-to-hip ratio and BMI were predictive of SCD risk, whereas no dose-response conclusions about WC were possible because of too few studies including this parameter.[157]

Nonetheless, WC is associated with electrocardiographic alterations that may predispose the onset of arrhythmias. For instance, a higher WC correlates with prolonged QTc interval in obese young men.[158] Also, the QRS|T angle is frequently abnormally deviated in MetS individuals, particularly among MetS women elevated abdominal obesity.[159] Of interest, the QRS|T angle represents the difference between cardiac depolarization and repolarization, and its alteration has been related to ventricular arrhythmias and therefore prediction of SCD.[160]

Dyslipidaemia can concur in causing SCD through the development of coronary atherosclerosis and acute ischaemic CV events.[161] HDL-C protects against atherosclerotic plaques by favouring reverse cholesterol transport and through its anti-oxidant and anti-inflammatory properties.[162,163] Indeed, TGs/HDL-C[164] and low-density lipoprotein cholesterol (LDL-C)/HDL-C ratios[165] are directly related with SCD risk. Notably, low HDL-C levels are also an independent predictor of left ventricular mass in both treated and untreated hypertensive patients,[166,167] whereas TGs showed a weak association.[166,167] Similarly, elevated plasma TGs play a role in the development of atherosclerosis.[168–170] Accordingly, patients with 'hypertriglyceridemic waist', which consists of both abnormal TGs levels and elevated WC, have a higher risk of CAD (20643837) and higher amount of visceral adipose tissue.[171]

7 | METABOLIC SYNDROME AND SUDDEN CARDIAC DEATH INTERRELATIONS AND FUTURE DIRECTIONS

MetS is composed of different CV risk factors that mingle together, reinforce each other and cause detrimental effects on several organs, including the heart (Figure 2). As many patients are unaware of having MetS,[172] also many SCD victims were unaware of having CVDs when SCD occurred.[173] Even though SCD may happen even in apparently healthy subjects without evident cardiac abnormalities,[174,175] specific cardiac alterations are often found during post-mortem investigations.[176] CAD is considered as the main cause of SCD in subjects over 35 with MetS being one of its major risk factors.[52] Accordingly, all MetS components are reported to concur to the atherosclerotic process. Of interest, some of them show high rates of association and may need combined treatment strategies as recently discussed for diabetes and obesity.[177]

Recent studies evaluated the risk of SCD in individuals with MetS and no previous history of CHD suggesting an increased risk of SCD (Table 1).[12–14] Nonetheless, those studies were limited, heterogeneous and far from
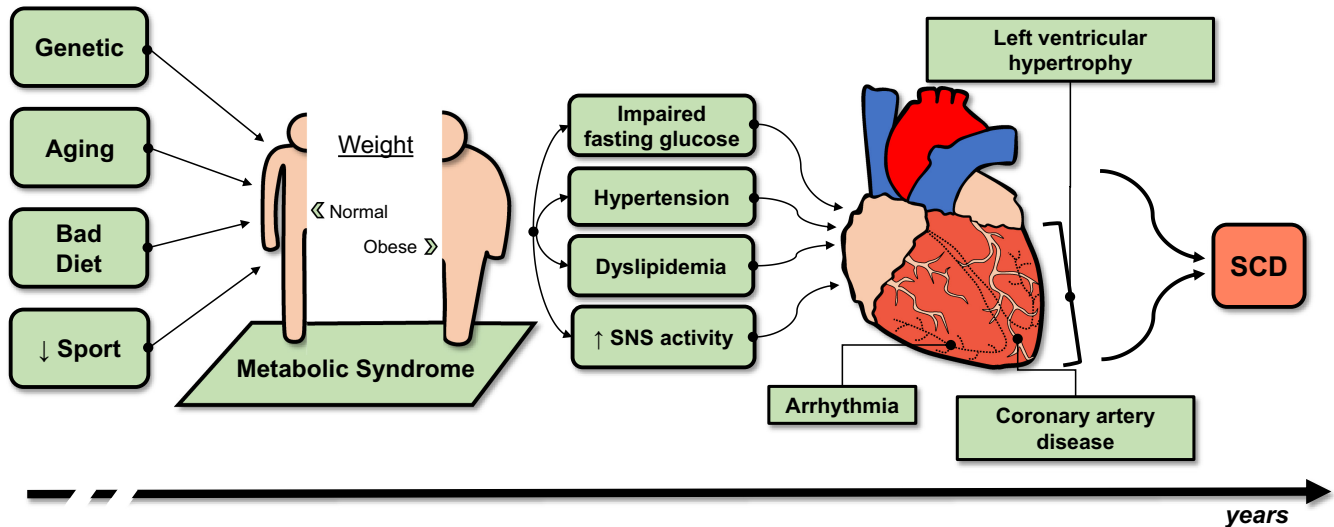
FIGURE 2 The detrimental effects of metabolic syndrome on the heart. Genetic determinants, but also ageing, diet and reduced physical activity concur in the development of MetS. Such individuals might appear lean even when 'metabolically obese'. Singularly and taken together, IFG, HTN, DysL and increased sympathetic activity are key elements in MetS pathophysiology with damaging effects on the heart favouring the development of CHD, LVH and AR, eventually causing SCD. However, such associations remain under-investigated, and the main underlying mechanisms are still poorly understood. SCD, sudden cardiac death; SNS, sympathetic nervous system

providing firm conclusions. Specifically, HTN or prescription of anti-HTN drugs were more frequently reported in victims of SCD in two studies[12,13] but not in another one.[14] As stated in the study by Kurl et.al.,[13] HTN and insulin resistance are probably the key elements to be investigated in order to understand how and why MetS subjects are more likely to be victim of SCD. Meanwhile, WC and low HDL-C levels might be regarded as predictors for the development of CHD thus predisposing to SCD when underdiagnosed. Furthermore, patients can be lean but be 'metabolically obese'.[14] To overcome the limitations of WC, Empana et al.[14] suggested utilizing sagittal abdominal diameter and they found a higher prevalence of elevated abdominal adiposity in SCD patients. However, few data are available now and further studies are awaited to clarify the correlation between WC and SCD (Figure 3).

Concerning other aetiologies, LVH may be of some interest as we reported in the HTN section of this review. MetS subjects have higher incidence of LVH even if not affected by HTN.[178] Interestingly, a recent study evaluating almost 900 middle-aged men with 20-year follow-up showed that indexed left ventricular mass by body surface area was independently associated with a higher risk of SCD.[179] On the other hand, evidence on the association between HTN, LVH and SCD is often inconsistent requiring further investigation.[139,140]

The sympathetic nervous system seems to play an important role in the pathogenesis of MetS.[42–44] Worthy of interest, one of the possible triggers for ventricular arrhythmias is the excess of sympathetic hyperstimulation, particularly if cardiac ischaemia is present.[57] Accordingly,

some authors suggested that a higher parasympathetic tone could prevent SCD.[180–182] Thus, physically trained people might have some benefit in terms of SCD prevention, since physical activity could augment the cardiac parasympathetic nerve tone, particularly in the recovery period.[183] On the other hand, physical activity is related to an augmentation of sympathetic tone during the exercise,[184] and cases of cardiac arrest during excessive exercise are reported, especially in non-trained subjects.[185] In addition, daily low-intermediate physical activity could play a role in both the prevention and treatment of MetS.[186,187] Hence, the benefits of a higher parasympathetic tone and physical activity as prevention of both MetS and SCD may be of interest for future analyses.

8 | CONCLUSIONS

MetS is a common condition predisposing for both higher CV and metabolic risks. Of note, recent evidence shows a possible relationship between MetS and SCD. MetS characteristics such as HG, HTN, high TGs, low HDL-C, pro-inflammatory state and excess of sympathetic activity are concurring causes in heart damaging, paving the way towards cardiac alterations that could favour SCD. MetS subjects may have up to 70% of increased risk of SCD. Yet, such an association remains under-investigated, and the main underlying mechanisms are still poorly understood. The resulting lack of knowledge reflects in the absence of specific targets to reduce SCD risk in this population.

TABLE 1 Comparison of three studies about sudden cardiac death in patients with metabolic syndrome

	Empana et al.[14]	Kurl et al.[13]	Hess et al.[12]
Type of study	Prospective cohort study	Prospective cohort study	Retrospective cohort study
Patients (n°)	6678	1466	13,168
Populations	European (France)	European (eastern Finland)	US (24.8% blacks)
Male prevalence	100%	100%	44%
Age range	Middle aged	Middle aged	Middle aged
Baseline CHD	no	no	no
Baseline diabetes	no	no	possible
Years of follow-up	21 (average)	21 (average)	23.6 (median)
MetS criteria	NCEP-ATP III and IDF	WHO, NCEP-ATP III, IDF and consensus definition	Consensus definition
MetS prevalence	Up to 16.7%[a]	Up to 38% (men died suddenly out of the hospital)[b]	33.7%
Increased risk for SCD in MetS patients (up to)	68%	160%	70%
Other information	HTN and elevated TGs were similarly reported in both sudden death and control groups. Conversely, larger abdomen adiposity and IFG were more prevalent in sudden death patients.	Men died suddenly out of the hospital or that died suddenly during the follow up had higher systolic and diastolic BP, a higher WC, but lower TGs compared with patients that survived during the follow-up	HTN or drug treatments for HTN, IFG or drug treatments with insulin or hypoglycaemic agents, and low HDL-C were independently related to SCD. The number of MetS components was proportionally associated with SCD risk.
Limitations and exceptions	No female and elderly enrolled; No HDL data; SAD substitutes WC	No female and elderly enrolled	No available data for non-sudden cardiac deaths

Abbreviations: BP, blood pressure; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; IFG, impaired fasting glucose; MetS, metabolic syndrome; SAD, sagittal abdominal diameter; SCD, sudden cardiac death; TG, triglyceride; WC, waist circumference.

[a]The prevalence of MetS was different depending on different MetS criteria: 14.4% and 16.7% for NCEP-ATP III and IDF, respectively.

[b]Using the consensus definition (PMID:IDF-AHA/NHLBI Joint Interim Statement) of MetS in patients that died suddenly out of hospital. Note that the authors subdivided the patients into three groups: men died suddenly out of the hospital, died suddenly during the follow-up and survived during the follow-up.
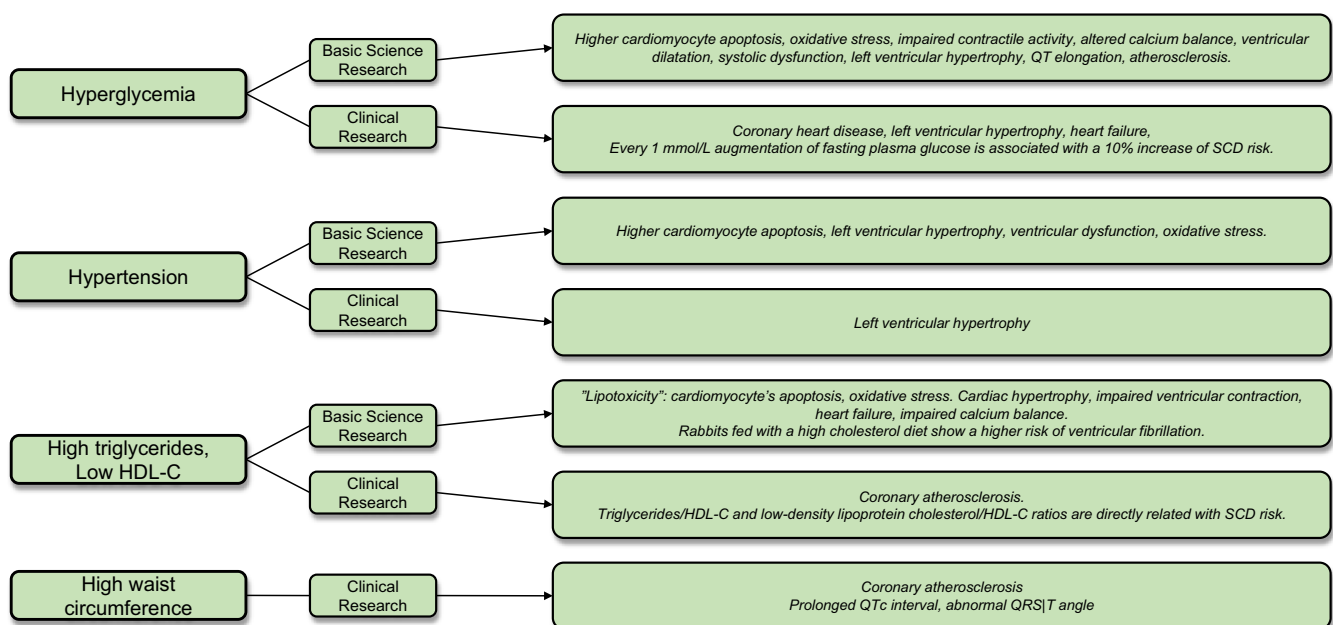

FIGURE 3 Take-home figure. HDL-C, high-density lipoprotein cholesterol; SCD, sudden cardiac death

CONFLICTS OF INTEREST

LL is coinventor on the International Patent (WO/2020/226993) filed in April 2020 and relating to the use of antibodies which specifically bind IL-1α to reduce various sequelae of ischaemia-reperfusion injury to the central nervous system. The other authors report no conflict of interest.

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