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Obesity Cardiomyopathy and Sudden Cardiac Death

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Introduction

Obesity, defined as an elevated body mass index (BMI) > 30kg/m^2, has reached epidemic proportions worldwide. As of 2022, 1 in 8 people are living with the condition, with the number of adults affected having doubled since 1990. (1) Obesity Cardiomyopathy (OCM) describes cardiomegaly and/or myocardial dysfunction in the presence of an elevated BMI >30kg/m^2. (2) Whilst cardiomegaly on autopsy is common in obese individuals, OCM is only presumed in the absence of common offending conditions such as hypertension, diabetes and coronary artery disease (CAD). (3) OCM can be associated with sudden cardiac death (SCD) and hence may be a trigger for genetic testing. Although NHS England has delineated clear testing criteria for sudden unexplained death, the role of genetic testing in those with OCM who do not meet the traditional SCD criteria is not clear. (4)

Take Home Messages

- Obesity Cardiomyopathy (OCM) describes structural and functional changes to the myocardium in the context of elevated BMI (BMI>30kg/m^2), and in the absence of the traditional risk factors for heart failure.
- Obesity has been observed to be an independent risk factor for Sudden Cardiac Death (SCD).
- There is no genetic testing pathway for SCD in OCM outside the context of the current National Genomic Testing Directory guidelines.
- No monogenic basis for OCM has been identified. Further exploration of the obese SCD population is needed to help mould genomic testing guidelines.

Obesity and the heart.

It is recognised that obese individuals are more prone to myocardial abnormalities, independent of traditional heart failure risk factors, such as CAD, hypertension, diabetes and obstructive sleep apnoea. (5) In a study looking at the SCD population in which patients with CAD, Hypertrophic Cardiomyopathy, Hypertension and Valvular Heart Disease were excluded, the odds ratio for cardiomegaly in obese patients was 5.3 (95% CI: 2.9-9.6; p<0.001). (6) Postmortem and epidemiological data links obesity to heart failure (**see Table 1**). Left ventricular remodelling has been seen in obese individuals, with increased myocardial mass, wall thickness and cavity dilatation. (7) Cardiomegaly has been observed to be more common in obese compared to normal weight individuals. (8) Both eccentric and concentric LVH have also been described.(5) At post mortem, myocyte hypertrophy and fibrosis have been reported both in animal models and clinical studies of obese patients.(9) The cumulative effect of such findings have established OCM as a diagnosis in its own right. Several mechanisms for OCM have been proposed, highlighting its multifactorial nature. These include inflammation, oxidative stress, adrenergic and renin-angiotensin aldosterone pathways. (10)

Table 1: Epidemiological and Postmortem data for obesity as a risk factor for heart failure. (Adapted from Wong and Marwick(5))

POSTMORTEM DATA		
Study	Study population	Main findings
Amad et al (1965)(9)	Severely obese individuals with an average weight of 143kg, mean age 51 years (n=12).	Increase heart weight and left ventricular wall thickness.
Kasper et al (1992)(11)	43 obese individuals (average weight 130kg, mean age 42 years) compared to 409 similarly aged lean individuals.	Obese individuals were more likely to have a diagnosis of Dilated Cardiomyopathy (DCM). then lean individuals (77% versus <35%, p<0.001).

Warnes and Roberts (1984)(12)	12 severely obese individuals (average weight 173kg; mean age 37 years).	Increased heart weight, microscopic left and right ventricular hypertrophy.
EPIDEMIOLOGICAL DATA		
Dwyer et al (2000)(13)	233 individuals (mean age 58 years), normal coronary arteries and no other structural cardiac disorders or causes of myocardial disease.	Obesity is an important risk factor for left ventricular dysfunction in those with angiographically normal coronary arteries.
Murphy et al (2006) (14)	15,402 individuals, age range 45–64 years.	After an average follow-up of 20 years, the obesity associated adjusted risk of heart failure was 2.09
He et al (2001)(15)	13,643 individuals (25–74 years), no history of heart failure at baseline	Incidence of heart failure was associated with being overweight (RR 1.30), independent of the presence or absence of coronary heart disease, diabetes or hypertension (average follow up of 19 years)

Obesity and SCD

Although obesity is an established risk factor for cardiovascular disease, the relationship between obesity and SCD is less clear. (16) There is evidence to suggest that obesity alone is an independent risk factor for sudden cardiac death. One study looking at over 10,000 middle aged individuals in the general population found that obese subjects were at increased risk of SCD (HR 1.79 [1.44-2.23]; $p<0.001$) compared to lean individuals. (17) However, the aetiology of these deaths has not been clearly established. In a cohort of 212 obese patients, 50% had a normal heart on postmortem (Sudden Arrhythmic Death Syndrome), 12% had critical CAD and 12% had unexplained LVH; the latter cohort possibly representative of the OCM group. (16) Another study of 1202 cases of SCD, 53 cases of OCM were identified.(8) In the vast majority of this group, death occurred during sleep (91%; n=48), with only 6% occurring during exertion. The association between obesity, QT prolongation and resultant electrical instability has previously been explored and potentially provides a substrate for this high proportion of sleep related deaths. (18)

Genetics in SCD and OCM – to test or not to test?

SCD events that are deemed unexplained are often followed by genetic panel testing, as outlined by the National Genomic Test Directory (**see Table 2**). This encompasses a defined set of genes with well described genotype-phenotype associations (**see Figure 1**). In the context of SCD, a label of OCM does not trigger specific gene panel testing. This is largely explained by the fact that obesity has long been considered a complex, multifactorial condition with both polygenetic and environmental influences.(19) Studies exploring the genetic basis for this condition have not highlighted any monogenic aetiologies. The Fingesture study collected data from over 5000 autopsy-verified SCD patients and identified 151 patients with non-specific LVH and fibrosis in the context of hypertension and/or obesity. Variants of unknown significance were found in 32% of this group. (20) Likely pathogenic variants were identified in 10% of this cohort, however importantly, this difference was not statistically significant in comparison to the control group ($p=0.21$). Patients with likely pathogenic

variants were more likely to have a lower BMI and heart weight, hence contrasting with the OCM group. (20) This highlights the lack of clarity for obese SCD patients from a monogenic perspective.

Table 2: Testing criteria for sudden unexplained death or survivors of a cardiac event (R138)(21)	
1	Sudden death with normal post-mortem before the age of 40, OR
2	Sudden death with normal post-mortem below the age of 60, with a family history of unexplained SCD under the age of 40 in a 1st or 2nd degree relative (in whom no post-mortem was carried out) OR
3	Sudden death with normal postmortem below the age of 60, with a family history of unexplained SCD under the age of 60 in a 1st or 2nd degree relative (where the relative also had a normal post-mortem)
4	Survivors of proven cardiac arrest (idiopathic ventricular fibrillation) with no phenotype on comprehensive evaluation AND under the age of 45

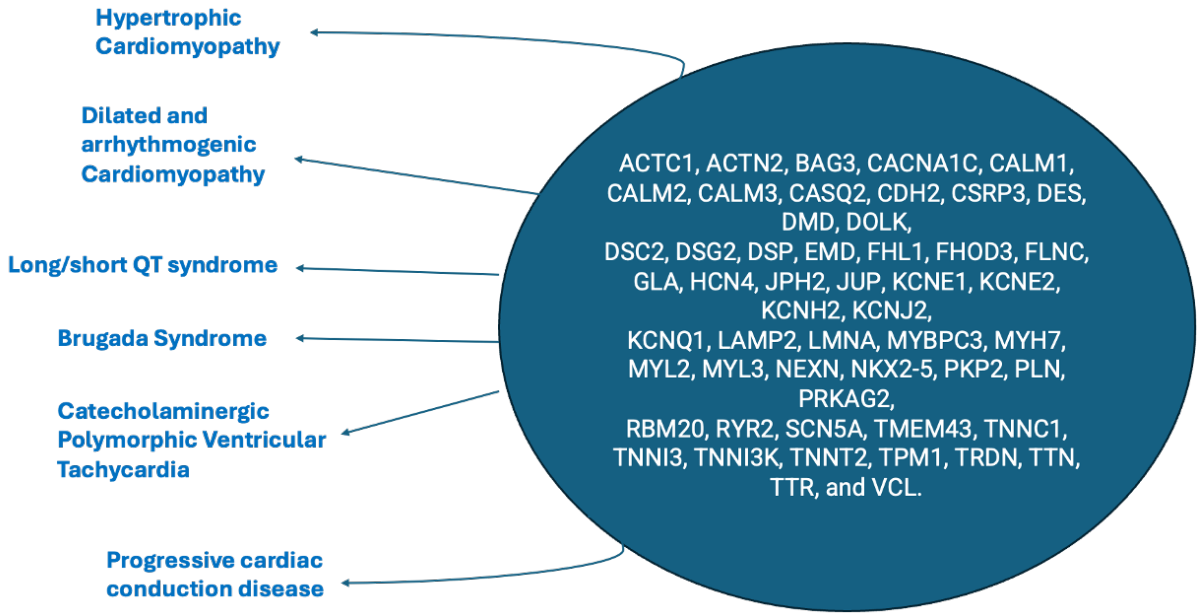

Figure 1: R138 Sudden Cardiac Death Genetic Panel. Image created by Yande Kasolo

Whilst Obesity Cardiomyopathy has cemented itself as diagnostic entity, the aetiology of this condition and obesity alone is multifaceted. To date, a monogenic cause has not been identified for OCM, hence generalised genetic panel testing in SCD survivors and their relatives may not be justified in clinical practice. In a research setting, exploring SCD cases in obese patients may provide more guidance from a genetics perspective in the future.

The limitations of body mass as a blanket weight discriminator must also be appreciated; there is some evidence to suggest that visceral fat as opposed to BMI is more strongly linked with sudden cardiac death. Exploring this avenue may provide more valuable genomic data to mould future guidelines. (20) Finally, it is important to consider the rapidly evolving role of glucagon-like peptide receptor agonists in obese individuals in weight loss and modulation of cardiovascular risk factors. Evaluation of the OCM population in this context is likely to be a future area of focus.

Disclosures

No relevant disclosures.

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