



Genetics-diet crossroads: Unveiling new insights into hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) stands as the most common congenital heart disease, marked by hypertrophic, non-dilated left ventricle without any secondary cause [1,2]. Being a genetically heterogeneous disease of the cardiac sarcomere, mutations in the MYH7 (β -myosin heavy chain) and MYBPC3 (myosin-binding protein C) genes together account for about 70 % of cases [3]. While commonly inherited in an autosomal dominant manner, penetrance of the phenotype is often incomplete [3]. Given the limited correlation between HCM genotype and phenotypic expression, even among family members carrying the same mutation [3], it becomes imperative to consider environmental factors in HCM manifestation. Yet, non-genetic determinants of phenotype variability are still poorly understood.

Symptoms of HCM can range from complete absence, to manifestations such as fatigue, shortness of breath, chest pain, palpitations, syncope, and, in severe instances, cardiac arrhythmias, heart failure, or even sudden cardiac death [4]. While modern management of patients has reduced HCM-related mortality, which stands at approximately 0.5 % per year, it still remains fairly uniform across age groups and accumulates over extended timeframes [5,6]. Prevalence of symptomatic HCM ranges from 0.031 % to 0.076 % globally, with an estimated prevalence of 0.2 % to 0.5 %, taking into account the clinically silent population [7–9].

Recent research suggests that HCM may be intertwined with conventional cardiovascular risk factors. Specifically, poor metabolic control, characterized by obesity, reduced glucose tolerance, and dyslipidemia, appears to correlate with clinical disease expression and adverse outcomes [10,11]. Thus, comprehending disease penetrance and risk stratification is crucial for minimizing the impact of HCM on patients' lives.

To explore this uncharted territory connecting unfavorable metabolic health and HCM disease penetrance, a recent study by Nollet et al. presented a novel preclinical mouse model of HCM in which genetic predisposition is integrated with systemic metabolic stress [12]. The study revealed that a Western diet (WD) feeding regime high in energy density, saturated fats, and simple carbohydrates triggered cardiac dysfunction in mice carrying a heterozygous *Mybpc3*^{c.772G>A} mutation (HET), which otherwise do not exhibit cardiac impairment [13]. Importantly, the study demonstrated that cardiac hypertrophy and dysfunction is limited to HET mice on WD and not observed in mice with the mutation alone or those subjected to WD alone. Thus, the authors concluded that HET mice on WD closely mimic HCM patients at risk carrying pathogenic gene variants in heterozygosity.

Moving forward, Nollet et al. presented compelling evidence of how WD feeding negatively impacts systemic and cardiac metabolic health in mice, regardless of genetic background. Within 8 weeks of dietary

intervention, the authors observed an increase in serum biomarkers associated with systemic metabolic maladaptation, such as saturated free fatty acids, acylcarnitines, ketones, sugar derivatives, uric acid, and prostanoid species. On a tissue-specific level, the study revealed impaired mitochondrial respiration, increase in metabolites indicative of elevated glutathione turnover and altered lipid pools in murine hearts. Interestingly, in wildtype hearts, WD was only associated with mild changes in cardiac function, suggesting that hearts without HCM genetic predisposition can better withstand metabolic stress, at least within the observed timeframe. In contrast, HET mice developed severe cardiac dysfunction and hypertrophy, that could not be attributed to a diet-induced worsening of MYBPC3 haploinsufficiency or hypophosphorylation.

Data presented by Nollet et al. raise the question of whether HCM-associated gene variants like *Mybpc3*^{c.772G>A} might limit the heart's metabolic adaptability. The adult heart predominantly relies on fatty acid metabolism to meet its high energetic demands but, mainly depending on substrate availability, can flexibly switch between substrates as needed [14,15]. In response to WD, mice showed an increase in cardiac abundance of proteins associated with lipid metabolism concomitant with a decline in proteins related to glycolytic pathways, irrespective of their genotype. Interestingly, the study highlighted a significant difference in the abundance of proteins responsible for peroxisomal and mitochondrial fatty acid metabolism in HET hearts compared to their wildtype counterparts on WD. This was associated with accumulation of acylcarnitines and changes in cardiolipin composition. These findings provided a glimpse into potential links between sarcomere gene variants and cardiac metabolic capacity.

Nollet et al.'s work presents an exciting model that offers novel insights into the complex interplay between systemic health, genetic predisposition, and HCM. As with any groundbreaking research, new questions arise, and new hypotheses emerge.

Surprisingly, the study did not find an increase in body weight among mice on WD, challenging the assumption that obesity is a primary factor in HCM disease manifestation. Considering the higher energy-density of WD compared to the dietary control, one could argue, that mice on WD must have presented with either reduced food intake or increased energy expenditure. If cardiac phenotype in HET mice is indeed unrelated to the overall energy surplus of their diet, it would be most interesting to further delineate its nutritional content. Investigations into individual factors like fatty acid composition and their impact on cardiac dysfunction are warranted.

Expression of HCM phenotype in HET mice under WD feeding was rather mild. The study's relatively short 8-week duration may not have captured all genotype-dependent effects and longer-term investigations

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may yield additional insights. Others reported pronounced cardiac dysfunction in wildtype mice fed with a WD from 16 weeks onward and showed a disruption of cardiac energy metabolism, with increased lipid accumulation and reduced glucose utilization only after 20–24 weeks on the diet [16]. By increasing the time period of WD feeding in the presented model, a stronger association between metabolic stress and HCM phenotype could potentially be uncovered.

The diminished oxidative response to a high-fat diet in HET mice raises a compelling need for a comprehensive examination of cardiac metabolism in HCM. Exploring the heightened serum levels of ketones and sugar metabolites piques curiosity about their potential role in compensating for the increased cardiac energy demand. Given the growing interest in metabolite signaling within the heart, it becomes imperative to consider auxiliary metabolic pathways and their contributions to the manifestation of HCM. This brings forth a series of pressing questions: Are there specific molecular regulators of energy metabolism that undergo alterations in the intricate interplay of genetic predisposition and dietary stressors in HCM? Could the dysfunction of the sarcomere unit be directly or indirectly connected to metabolic signaling? And, perhaps most importantly, can lifestyle modifications or pharmacological interventions offer a lifeline, rescuing cardiac metabolic flexibility in HCM and potentially improving cardiac function?

In conclusion, Nollet et al. have introduced an innovative model to explore cardiac health from a nutrigenomic perspective. Their work lays the foundation to identify patients at risk of clinical disease expression based on their genetic and dietary patterns, paving the way for more proactive, lifestyle-centered patient management in HCM. This “two-hit model” offers the potential to uncover molecular patterns of HCM disease modification that can be translated into clinical practice.

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Declaration of competing interest

None

References

- [1] Maron BJ, Maron MS. Hypertrophic cardiomyopathy. *Lancet* 2013;381:242–55.
- [2] Marian AJ, Braunwald E. Hypertrophic cardiomyopathy: genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. *Circ Res* 2017;121:749–70.
- [3] Sabater-Molina M, Perez-Sanchez I, Hernandez Del Rincon JP, Gimeno JR. Genetics of hypertrophic cardiomyopathy: a review of current state. *Clin Genet* 2018;93: 3–14.
- [4] Muresan ID, Agoston-Coldea L. Phenotypes of hypertrophic cardiomyopathy: genetics, clinics, and modular imaging. *Heart Fail Rev* 2021;26:1023–36.
- [5] Maron BJ, Rowin EJ, Casey SA, Link MS, Lesser JR, Chan RH, et al. Hypertrophic cardiomyopathy in adulthood associated with low cardiovascular mortality with contemporary management strategies. *J Am Coll Cardiol* 2015;65:1915–28.
- [6] Ho CY, Day SM, Ashley EA, Michels M, Pereira AC, Jacoby D, et al. Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the sarcomeric human cardiomyopathy registry (SHARe). *Circulation* 2018;138: 1387–98.
- [7] Maron MS, Hellawell JL, Lucove JC, Farzaneh-Far R, Olivetto I. Occurrence of clinically diagnosed hypertrophic cardiomyopathy in the United States. *Am J Cardiol* 2016;117:1651–4.
- [8] Bai Y, Zheng JP, Lu F, Zhang XL, Sun CP, Guo WH, et al. Prevalence, incidence and mortality of hypertrophic cardiomyopathy based on a population cohort of 21.9 million in China. *Sci Rep* 2022;12:18799.
- [9] Husser D, Ueberham L, Jacob J, Heuer D, Riedel-Heller S, Walker J, et al. Prevalence of clinically apparent hypertrophic cardiomyopathy in Germany—an analysis of over 5 million patients. *PLoS One* 2018;13:e0196612.
- [10] Lopes LR, Losi MA, Sheikh N, Laroche C, Charron P, Gimeno J, et al. Association between common cardiovascular risk factors and clinical phenotype in patients with hypertrophic cardiomyopathy from the European Society of Cardiology (ESC) EurObservational Research Programme (EORP) Cardiomyopathy/Myocarditis registry. *Eur Heart J Qual Care Clin Outcomes* 2023;9:42–53.
- [11] Park JB, Kim DH, Lee H, Hwang IC, Yoon YE, Park HE, et al. Obesity and metabolic health status are determinants for the clinical expression of hypertrophic cardiomyopathy. *Eur J Prev Cardiol* 2020;27:1849–57.
- [12] Nollet E, Algül S, Goebel M, Schlossarek S, van der Wel NN, Jans JJM, et al. Western diet triggers cardiac dysfunction in heterozygous Mybpc3-targeted knock-in mice: a two-hit model of hypertrophic cardiomyopathy. *J Mol Cell Cardiol Plus* 2023.
- [13] Vignier N, Schlossarek S, Fraysse B, Mearini G, Kramer E, Pointu H, et al. Nonsense-mediated mRNA decay and ubiquitin-proteasome system regulate cardiac myosin-binding protein C mutant levels in cardiomyopathic mice. *Circ Res* 2009;105: 239–48.
- [14] Karwi QG, Uddin GM, Ho KL, Lopaschuk GD. Loss of metabolic flexibility in the failing heart. *Front Cardiovasc Med* 2018;5:68.
- [15] Hue L, Taegtmeyer H. The Randle cycle revisited: a new head for an old hat. *Am J Physiol Endocrinol Metab* 2009;297:E578–91.
- [16] Maurya SK, Carley AN, Maurya CK, Lewandowski ED. Western diet causes heart failure with reduced ejection fraction and metabolic shifts after diastolic dysfunction and novel cardiac lipid derangements. *JACC Basic Transl Sci* 2023;8: 422–35.

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