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Subclinical systolic dysfunction in genotype-positive phenotype-negative relatives of dilated cardiomyopathy patients: A systematic review and meta-analysis

The absence of left ventricular (LV) dilatation and systolic dysfunction, as assessed by LV ejection fraction (LVEF), in family members of genetically confirmed dilated cardiomyopathy (DCM) patients, carrying pathogenic (P) or likely pathogenic (LP) familial gene variants categorizes them as a subgroup called genotype-positive phenotype-negative (GEN+ PHEN−). Identifying GEN+ PHEN− who are at the highest risk of developing the disease throughout their lifetime is crucial. Speckle-tracking echocardiography provides a measure of myocardial deformation through LV global longitudinal strain (GLS), recognized as an earlier marker of subclinical LV systolic dysfunction compared to LVEF.[1]

Recent studies suggested the presence of early subclinical LV systolic dysfunction in GEN+ PHEN− relatives of DCM patients, identified by reduced GLS values. Therefore, we investigated this issue through a meta-analysis of echocardiographic studies reporting GLS data in GEN+ PHEN− relatives of DCM patients versus controls.

The present research was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, with PROSPERO identifier CRD42023484609. The PubMed, OVID-MEDLINE and Cochrane library databases were analysed to search English-language review papers published from the inception up to 30 October 2023. Main inclusion criteria were: (i) English review papers or abstract; (ii) comparative studies providing echocardiography data on LV GLS in GEN+ PHEN− relatives of DCM patients and controls; and (iii) minimum set of clinical/demographic data. Literature search and data extraction were performed by two reviewers and independently checked by another reviewer. The outcome of the meta-analysis was to compare two-dimensional LV GLS, in GEN+ PHEN− and GEN− PHEN− or healthy controls. Specifically, only if data on GEN− PHEN− relatives were not available, healthy controls were used. To this purpose, a pooled analysis was performed using fixed or random effects models (the latter when *I*-square heterogeneity was >75%) by Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ, USA). Standard mean difference (SMD) with 95% confidence interval (CI) was calculated to evaluate the statistical difference of variables. The limit of statistical significance was set at $p < 0.05$. Publication bias was assessed by using the funnel plot method according to the trim and fill test.

After removing duplicates, the initial literature search identified 293 papers. At the end of the selection process on the whole, 570 subjects were included in seven studies: 357 GEN+ PHEN− relatives of DCM patients and 213 controls.[2–8] *Table 1* summarizes the main findings of selected studies. In all studies, every GEN+ PHEN− exhibited the confirmed existence of the familial variant responsible for DCM in the proband, either a P variant or a LP variant (the variants of uncertain significance were not considered causative by the authors). All the studies

Table 1 Summary of study characteristics and echocardiographic variables of subjects included in the systematic review and meta-analysis

Author, year	Implicated genes (%)	Sample size (*n*)		Male (%)		Age (years)		GLS (%)		LVEF (%)	
		GEN+ PHEN−	Controls	GEN+ PHEN−	Controls	GEN+ PHEN−	Controls	GEN+ PHEN−	Controls	GEN+ PHEN−	Controls
Lakdawala, 2012[2]	MYH7 (75%), TPM1 (25%)	12	29	8	38	25 ± 19	22 ± 16	17.2 ± 0.6	20.3 ± 0.6	59 ± 3	62 ± 5
Van der Bijl, 2019[3]	TTN (48%), LMNA (20%), Sarcomeric (10%), other (22%)	50	28	44	43	50 ± 15	52 ± 14	19.7 ± 3.5	21.7 ± 1.5	64.3 ± 6.7	66.8 ± 5.7
Triantafyllou, 2020[4]	TTN, BAG3, DSP, FLNC, LMNA, DMD, RBM20, TPM1 (frequencies N/A)	45	29	N/A	N/A	N/A	N/A	18.2 ± 1.5	18.6 ± 2.9	57.3 ± 5	59.1 ± 4
Verdonschot, 2020[5]	TTN (33%), LMNA (15%), TPM1 (15%), SCN5A (12%), other (25%)	31	12	N/A	N/A	N/A	N/A	20.38 ± 3.8	21.9 ± 3.4	N/A	N/A
Paldino, 2021[6]	TTN (44%), FLNC (17%), LMNA (7%), sarcomeric (20%), DSP (2%), other (10%)	41	17	49	41	37 ± 14	31 ± 15	18.8 ± 2.7	22 ± 2.1	60.5 ± 8	N/A
Taha, 2021[7]	PLN (100%)	139	70	42	37	32 ± 16	34 ± 14	19.9 ± 1.9	21.5 ± 1.8	58.3 ± 4.2	59.8 ± 4.4
Wilcox, 2023[8]	N/A	39	28	31	36	42 ± 24	46 ± 20	19.6 ± 2.6	21.5 ± 2.5	59.5 ± 3.5	61.8 ± 3.9

BAG3, Bcl-2–associated athanogene 3; DMD, dystrophin; DSP, desmoplakin; FLNC, filamin C; GEN+ PHEN−, genotype-positive phenotype-negative; GEN− PHEN−, genotype-negative phenotype-negative; GLS, global longitudinal strain; LMNA, lamin A/C; LVEF, left ventricular ejection fraction; MYH7, beta-myosin heavy chain 7; N/A, not available; PLN, phospholamban; TPM1, alpha-tropomyosin 1; TTN, titin; RBM20, RNA binding motif protein 20; SCN5A, sodium voltage-gated channel alpha subunit 5.

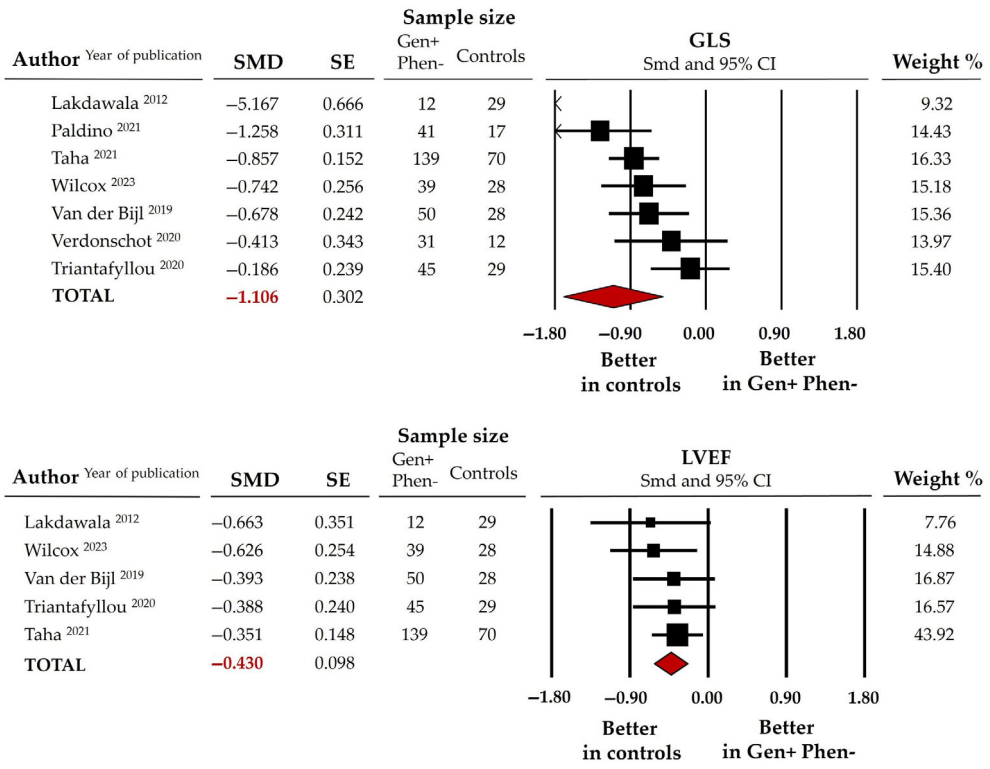

Figure 1 Forest plots for standard mean difference (SMD) of global longitudinal strain (GLS) and left ventricular ejection fraction (LVEF) in genotype-positive phenotype (GEN+ PHEN−) relatives of dilated cardiomyopathy patients and controls. Relative weight of each study is reported on the right side. CI, confidence interval; SE, standard error.

defined PHEN− on the basis of a preserved LVEF. Notably, female gender was the most represented across all studies, with individuals' average age ranging from 22 to 52 years. The control group more frequently consisted of GEN− PHEN− relatives rather than healthy controls (5 vs. 2). The involved genes were heterogeneous, except for one study that exclusively included familial variants in phospholamban (PLN). Compared with controls, LV function was significantly worse in the pooled GEN+ PHEN− group. Precisely, as shown in *Figure 1*, both GLS (19.06 ± 0.53% vs. 21.04 ± 0.39%, data from seven studies) and LVEF (59.7 ± 0.8% vs. 61.8 ± 1.1%, data from five studies) were relevantly lower in the pooled GEN+ PHEN− group than in the control group (SMD: −1.11 ± 0.30 [95% CI −1.698 to −0.514] for GLS, $p < 0.001$; and SMD: −0.43 ± 0.09 [95% CI −0.621 to −0.238] for LVEF, $p < 0.001$). The presence of a single study effect was excluded at sensitivity analysis; a relevant publication bias was not present. Furthermore, even when compared to only GEN−PHEN− (excluding healthy controls), GLS of the GEN+ PHEN− group proved to be significantly worse (SMD: −0.62 ± 0.12, $p < 0.001$, data from five studies). Therefore, our meta-analysis shows the presence of subclinical systolic dysfunction in GEN+ PHEN− relatives of DCM patients, identified by worse GLS values compared to controls and confirmed by a subtle but consistent reduction in LVEF.

The identification of subclinical LV systolic dysfunction in GEN+ PHEN− relatives of DCM patients has several clinically relevant implications. Firstly, this finding emphasizes that carriers traditionally considered PHEN− actually exhibit a subclinical PHEN+ whose prognostic role is currently unclear. Specifically, it is uncertain whether individuals identified as GEN+ PHEN− with reduced GLS values, as opposed to those with normal GLS values, have a higher likelihood of developing the DCM phenotype over their lifetime, and therefore, merit closer clinical follow-up and earlier interventions. In this regard, Verdonschot *et al.*[5] found that abnormal baseline GLS was associated with a deterioration of LVEF and with more cardiac hospitalizations and deaths over 36–40 months. Similarly, Paldino *et al.*[6] found that 15% of GEN+ PHEN− with reduced LV GLS developed overt LV systolic dysfunction during a median follow-up of 27 months. Should future studies demonstrate that GEN + PHEN− relatives with altered GLS are more likely to develop the overt DCM phenotype, it may be worthwhile to routinely incorporate GLS in the phenotypic screening and follow-up of these individuals. Unfortunately, there are currently insufficient data available to establish specific genotype−phenotype subclinical associations through GLS in this setting. Taha *et al.*[7] discovered that GEN+ PHEN− relatives of probands carrying causative mutations on PLN more frequently exhibit regional post-systolic shortening in the LV apex. It would be interesting to characterize genotype-specific strain patterns in other variants, such as titin and lamin A/C, to enhance early detection in relatives with a particular pathogenic variant. Furthermore, considering that GLS values, despite being reduced compared to controls, fall within accepted normal ranges (with the limitation of heterogeneity in vendor-specific cut-off), it would be clinically necessary to identify a cut-off that can effectively distinguish the presence of subclinical PHEN+ among GEN+ PHEN− relatives.

In conclusion, the results of our meta-analysis show the presence of subclinical systolic dysfunction in GEN+ PHEN− relatives of DCM patients. These findings support the utility of conducting large prospective studies to assess the impact of altered GLS on the development of overt DCM and clinical outcomes in GEN+ PHEN− relatives, highlighting its potential clinical role in phenotypic screening.

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