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Short communication

Cardiac telerehabilitation with long-term follow-up reduces GlycA and improves lipoprotein particle profile: A randomised controlled trial☆

Ernesto Dalli-Peydró [a,*], Rafael Gisbert-Criado [b], Nuria Amigó [c], Nuria Sanz-Sevilla [d], Juan Cosín-Sales [a]

[a] Department of Cardiology, Hospital Arnau de Vilanova, Calle San Clemente 12, 46015 Valencia, Spain
[b] Department of Clinical Laboratory, Hospital Arnau de Vilanova, Valencia, Spain
[c] Biosfer Teslab, IISPV, CIBERDEM, University Rovira i Virgili. Plaça de Prim, 10, 2° 5ª, 43201 Reus, Tarragona, Spain
[d] Department of Physical Medicine and Rehabilitation, University Hospital Doctor Peset, Avda. Gaspar Aguilar 90, 46017 Valencia, Spain

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ABSTRACT

Background: A 10-month strategy of cardiac telerehabilitation (CTR) improved outcomes over a standard centre-based cardiac rehabilitation (CBCR), as recently published. We hypothesised that prolonged telerehabilitation could also improve proinflammatory status and lipoprotein particle composition.
Methods: A randomised controlled trial compared a prolonged CTR program with CBCR in post-ACS patients. Patient's age was 18–72 years with low-risk criteria. Blood samples were drawn at baseline, at 4- and 10-months follow-up. Advanced lipoprotein characterization was performed using the NMR-based Liposcale test. Signals from glycoproteins (GlycA and GlycB) were also assessed.
Results: The final analysis included 31 patients in the CTR group and 25 patients in the CBCR group. GlycA decreased in the CTR group ($p = 0{,}007$). LDL particle number (LDL-P) increase in both groups, but it was at the expense of small-sized LDL in the CBCR group ($p = 0.012$). Triglycerides in intermediate-density lipoprotein (IDL-TG) increased only in the CBCR group ($p = 0.043$). The triglyceride-to-HDL (TG/HDL) ratio decreased only in the CTR group ($p = 0.006$). The TG/HDL ratio was correlated with GlycA (Spearman's correlation coefficient: 0.558, $p < 0.001$) but not with CRP ($p = 0.101$).
Conclusions: Our results showed that a 10-month CTR program reduced GlycA levels, the TG/HDL ratio and avoided unfavourable long-term changes in lipoprotein particle composition.
Registration at http://ClinicalTrials.gov. NCT number: 04942977

1. Introduction

We recently demonstrated that a 10-month extended follow-up strategy of cardiac telerehabilitation (CTR) achieved better outcomes than a standard, centre-based cardiac rehabilitation (CBCR) programme; particularly, improvements in the apoB/apoA-1 ratio and non-high-density lipoprotein (HDL) cholesterol levels were observed [1]. Low-density lipoprotein (LDL) cholesterol is conventionally regarded as the most relevant biomarker for coronary heart disease (CHD); however, increased remnant cholesterol and qualitative alterations in lipoprotein particles are associated with residual risk and low-grade inflammation [2]. GlycA, a novel inflammatory biomarker, has gained interest for cardiovascular disease (CVD) risk assessment [3].

Cardiac rehabilitation is recommended for patients with acute coronary syndrome (ACS) (class I, level of evidence A). CTR has proven to be as safe [4], beneficial and cost-effective as CBCR over the same duration [5], and while cardiac rehabilitation reduces major cardiovascular events, the benefit appears to be linear, with greater risk reduction at higher doses and without an upper threshold, as it favours the maintenance of cardiorespiratory fitness and healthy lifestyle changes over time [6]. We designed a new telerehabilitation system called Cardioplan and hypothesised that a prolonged monitoring strategy would also improve proinflammatory status and lipoprotein particle composition.

☆ The study was approved by the ethics committee of the Hospital Arnau de Vilanova and the Spanish Agency of Medicines and Medical Devices (484/14/EC).

* Corresponding author at: Department of Cardiology, Hospital Arnau de Vilanova, C/ San Clemente 12, 46015 Valencia, Spain.
E-mail address: ernestodallip@gmail.com (E. Dalli-Peydró).

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2. Material and methods

A randomised controlled trial was designed to compare a prolonged CTR programme with CBCR among post-ACS patients (http://ClinicalTrial.gov No. NCT04942977). The study followed the CONSORT-EHEALTH guidelines, and each participant signed an informed consent form before participation. The trial was conducted in accordance with the ethical principles of the Declaration of Helsinki and approved by the local ethics committee.

Patients were recruited at discharge after an ACS, between May 28, 2019 and March 10, 2020, when recruitment was stopped due to the COVID-19 pandemic. Patient age was limited to 18–72 years old. All patients had to meet low-risk criteria with left ventricular ejection fraction ≥50%, no ischaemia on effort, and have minimal smartphone usage skills.

The main exclusion criteria were reduced mobility, pulmonary diseases, neoplasms, and cognitive impairment. The CTR programme comprised four hospital supervised sessions of exercise performed over 2 weeks: the smartphone application subsequently guided participants through a schedule of exercise sessions, as well as data entry of their subjective general condition, vital signs, medication adherence, and food intake for 10 months. The exercise module recorded every exercise session and provided access to resistance training, warm-up and stretching videos, a virtual educational classroom, and suggested websites. The healthcare team monitored seven variables based on a traffic light color code, and if necessary, communicated with patients to reinforce scheduled data entry and adherence to recommendations via text messages. Technical assistance in the case of sensor/system failure was provided through a call center. Access was password-protected to ensure confidentiality. The CBCR programme comprised 16 sessions of supervised exercise performed over 2 months of treatment; patients were then followed-up by the corresponding specialist and primary care provider. Both groups were provided the same education programme, including the advice to engage in moderate physical activity (150 min/week), strength exercises twice a week and follow a Mediterranean diet. Blood samples were drawn at baseline and at the 4- and 10-month follow-up, and medications could be modified during the study period (excluding lipid-lowering therapies). If the LDL level exceeded 100 mg/dL at 4 months, the treatment was modified, and the patient was excluded from the lipid sub-study. The details and results of this trial were recently published [1].

Each sample was labelled with a number for shipment to the laboratory with no possibility to identify the allocation group. Proton nuclear magnetic resonance (^{1}H NMR) based on lipoprotein and glycoprotein profiles was performed using 300-μL plasma samples (Biosfer Teslab, Reus, Spain). The Liposcale® test (*CE* Mark) was used to determine the lipid composition, mean size, and number of particles for the subtypes (large, medium, and small) of the three main lipoprotein types (very low-density lipoprotein [VLDL], low-density lipoprotein [LDL], and high-density lipoprotein [HDL]) from the NMR spectra (nine in total) [7]. We determined the concentration of the circulating glycoproteins by deconvoluting the specific region where glycoproteins—quantifying the concentration of the acetyl groups of *N*-acetylglucosamine and *N*-acetyl galactosamine (GlycA) and *N*-acetylneuraminic acid (GlycB)—bonded to plasmatic proteins, thereby generating the respective NMR signals as previously reported [8].

The baseline and final levels were compared between groups using Student's *t*-test for paired samples (or the Wilcoxon signed-rank test when parametric assumptions could not be made). The effects of treatment (change between final and baseline values) were compared using an independent-samples *t*-test (or the Mann–Whitney *U* test when parametric assumptions could not be made), and the relationship between two variables was assessed using Pearson's correlation coefficient (or Spearman's rank correlation coefficient when parametric assumptions could not be made). Exact two-sided *p*-values were calculated whenever possible, and $p \leq 0.05$ indicated statistical significance. Data were analysed using R. 4.1.2 software for Microsoft Windows [9].

3. Results

Although 67 patients were enrolled in the study, only 59 were included in the intention-to-treat analysis; 31 and 28 patients were randomised to the CTR and CBCR groups, respectively. Among them, 56 had full blood test results (31 patients in the CTR group and 25 patients in the CBCR group); no differences were observed at baseline between groups [1]. At ten months, GlycA only significantly decreased in the CTR group ($p = 0.007$), with borderline significant differences observed when compared with the CBCR group ($p = 0.074$) (Fig. 1). While the LDL particle number increased in both groups, this occurred at the expense of medium-sized LDL in the CTR group ($p = 0.013$) and small-sized LDL in the CBCR group ($p = 0.012$). Triglycerides in intermediate-density lipoproteins (IDL-TGs) only increased in the CBCR group ($p = 0.043$), and HDL diameter decreased in the CBCR group when compared with that at baseline ($p = 0.001$) and in the CTR group (-0.047 ± 0.06 vs. -0.015 ± 0.09 nm; $p = 0.019$).

At the 10-month follow-up, GlycA correlated with high-sensitivity C-reactive protein (CRP) (Spearman's correlation coefficient: 0.428; $p = 0.001$), and the triglyceride-to-HDL (TG/HDL) ratio only decreased in the CTR group ($p = 0.006$). Comparisons between the groups showed no significant difference ($p = 0.108$) (Table 1). At the 10-month follow-up, the TG/HDL ratio correlated with GlycA (Spearman's correlation coefficient: 0.558, $p < 0.001$) but not with CRP ($p = 0.101$).

4. Discussion

Our results demonstrated that a 10-month CTR programme reduced GlycA levels and the TG/HDL ratio and avoided unfavourable long-term changes in lipoprotein particle composition when compared with the CBCR programme. These findings were mainly related to physical activity maintenance during the 10-month follow-up, with improved oxygen consumption, and higher adherence to the Mediterranean diet. Other benefits already published were less psychological distress, better quality of life, and early return to work [1].^{1}H NMR based on GlycA shows lower inter-individual variability, and lower punctual fluctuations associated with acute inflammatory processes not necessarily related to subclinical atherosclerosis [8]. Therefore, GlycA can improve the predictive outcomes of CRP in patients with CHD [10].

Thus far, only exercise-based lifestyle interventions have reduced GlycA levels; this was achieved through mechanisms related to visceral adiposity composition [11]. Postprandial hypertriglyceridemia is known to be associated with increased postprandial GlycA levels [12]. GlycA, not CRP, inversely correlated with gut microbiome diversity; additionally, it reflected metabolic status in overweight women better than CRP [13]. Although statins decrease the levels of some inflammatory markers—such as CRP—they do not appear to affect GlycA levels, as demonstrated with rosuvastatin in the JUPITER study [14]. Owing to the significant association between GlycA levels and the risk of both new coronary events and mortality [10,15], the favourable effect of prolonged CTR on GlycA levels—which has not been previously described— in addition to statin therapy for managing CVD risk, must be regarded as a positive finding.

Regarding advanced lipoprotein parameters determined using ^{1}H NMR, our results revealed that a prolonged CTR programme was associated with multiple lipoprotein measures that were typically consistent with cardiovascular disease prevention [16,17]. Worsening of the TG/HDL ratio has been shown to predict CHD and CVD mortality, as well as predisposition to diabetes mellitus [18]. By applying our novel strategy of prolonged monitoring, the system we designed prevented worsening of the TG/HDL ratio, at least during the first year. It is well known that increase in small LDL, HDL, and VLDL particles, as well as the increase in IDL-TGs, as observed in the CBCR group, are all related to atherosclerosis progression [19].

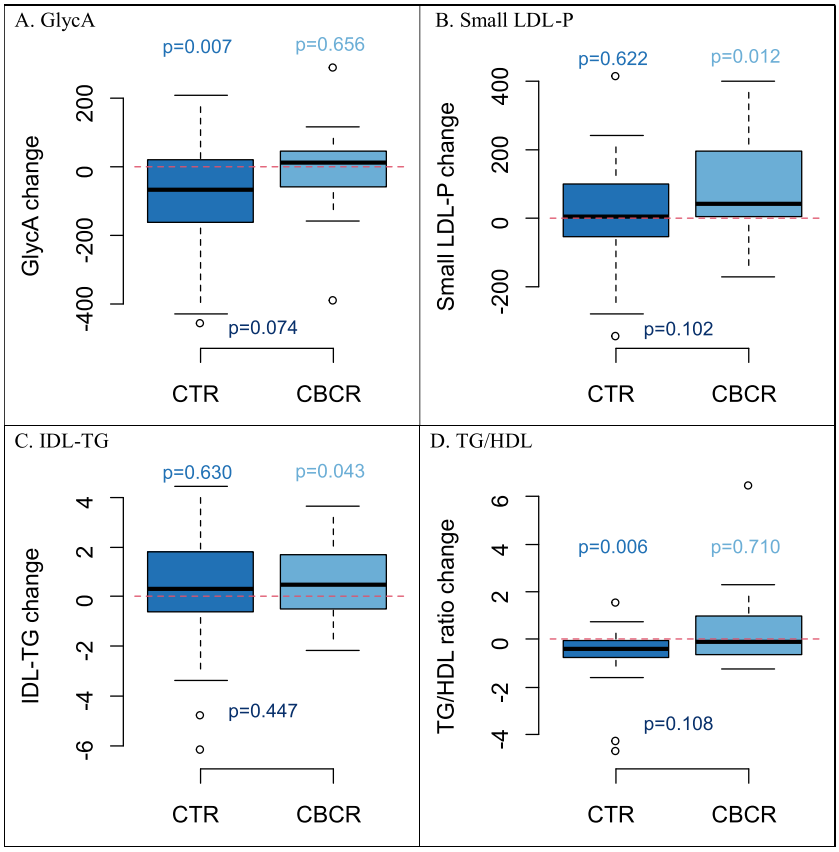

Fig. 1. Effect of extended cardiac telerehabilitation (CTR) and standard centre-based cardiac rehabilitation (CBCR).
Legend: GlycA; (B) small low-density lipoprotein (small LDL-P); (C) IDL-triglycerides (IDL-TG); and (D) triglyceride-to-HDL ratio (TG/HDL).

Limitations and circumstances of the study include the small sample size, as this was a technology validation study. The onset of lockdown prevented the inclusion of the last 3 patients. One patient in the CBCR group was excluded after 4 months due to LDL cholesterol above 100 mg/dl. The main user complaints were Internet connection problems and handling difficulties in older patients.

We propose implementing this mobile health (mHealth) technology owing to the advantage of minimising the number of hospital rehabilitation sessions, which is essential during the current COVID-19 pandemic; additionally, it allows prolonged follow-up, thereby promoting self-care and a more effective adoption of healthy habits by patients. This mHealth strategy could achieve the hypothetical target of an 80% inclusion rate of eligible patients, enable an early return to daily life, and make efficient use of healthcare resources. Still, these positive results require further testing in multicentre studies; if confirmed, CTR may be a benchmark for cardiac rehabilitation, at least for low- to moderate-risk patients with ACS.

EDP, MD. "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation".

RGC, MD. "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation".

NA, PhD. "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation".

NSS, "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation".

JCS, MD, PhD, FESC "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation".

Previous presentations

Other results from this trial have been published in *Clinical Cardiology*. https://doi.org/10.1002/clc.23757

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Author's contributions

EDP made a substantial contribution to the concept, design of the work, acquisition, analysis, interpretation of data, drafted the article and approved the version to be published.

RGC contributed to the preparation and processing of laboratory samples for shipment to an external laboratory and approved the version to be published.

NA supervised the sample processing for the measurement of glycoproteins, lipid particles and the database elaboration. Revised critically the manuscript for important intellectual content and approved the version to be published.

NSS made a substantial contribution to acquisition of data and approved the version to be published.

JCS revised it critically for important intellectual content and approved the version to be published.

Table 1
Changes in Glycoscale® and Liposcale® test results at the 10-month follow-up.

	CTR group (n = 31)			CBCR group (n = 25)			
Glycoprotein Profile	Baseline	Final	p_1	Baseline	Final	p_2	p_{12}
GlycB (μmol/L), mean (SD)	406.5 (57.9)	369.9 (44.8)	0.002	408.4 (55.6)	386.0 (48.0)	0.032	0.351 t
GlycF (μmol/L), mean (SD)	242.8 (46.0)	231.2 (38.5)	0.272	244.4 (53.4)	249.9 (38.2)	0.231	0.098 u
GlycA (μmol/L), mean (SD)	840.7 (149.3)	758.2 (142.3)	0.007	819.6 (142.8)	808.3 (139.4)	0.656	0.074 t
H/W GlycB, mean (SD)	5.17 (0.75)	4.71 (0.58)	0.002	5.20 (0.71)	4.91 (0.62)	0.028	0.392 t
H/W GlycA, mean (SD)	20.9 (3.30)	18.8 (2.88)	0.003	20.7 (2.70)	19.8 (2.69)	0.086	0.162 t

Lipoprotein Particle Profile	CTR group			CBCR group			p_{12}
	Baseline	Final	p_1	Baseline	Final	p_2	
VLDL-C, mean (SD)	16.5 (6.58)	14.3 (6.27)	0.232	14.9 (7.57)	15.1 (6.40)	0.861	0.570 u
IDL-C, mean (SD)	8.78 (3,03)	9.53 (3,55)	0.159	7.90 (1.67)	8.53 (2.95)	0.155	0.872 t
LDL-C, mean (SD)	97.8 (22.9)	102.5 (18.0)	0.021	93.5 (17.3)	100.4(20.3)	0.093	0.615u
HDL-C, mean (SD)	44.2 (12.8)	47.6 (11.4)	0.033	43.5 (7.7)	47.2 (9.0)	0.051	0.872 t
VLDL-TG, mean (SD)	73.3 (30.8)	66.3 (32.5)	0.234	70.0 (37.4)	72.0 (29.3)	0.773	0.317 t
IDL-TG, mean (SD)	10.81 (2.41)	11.03 (2.99)	0.630	9.90 (1.41)	10.54 (1.97)	0.043	0.447 t
LDL-TG, mean (SD)	11.54 (3.63)	11.89 (3.51)	0.626	10.82 (2.44)	11.12 (2.66)	0.575	0.951 t
HDL-TG, mean (SD)	15,69 (3,21)	15,32 (3.19)	0.574	15.34 (4.23)	15.03 (2.47)	0.744	0.959 t
VLDL-P (nmol/L), mean (SD)	53.4 (22.4)	47.9 (22.89)	0.190	49.2 (25.2)	52.1 (20.8)	0.542	0.183 t
Large VLDL-P (nmol/L), mean (SD)	1.64 (0.50)	1.46 (0.50)	0.051	1.51 (0.52)	1.56 (0.48)	0.641	0.096 t
Medium VLDL-P (nmol/L), mean (SD)	3.82 (1.43)	3.65 (1.50)	0.654	4.60 (2.73)	3.55 (1.69)	0.075	0.177 t
Small VLDL-P (nmol/L), mean (SD)	47.9 (21.3)	42.8 (21.4)	0.188	43.1 (22.5)	47.0 (19.3)	0.368	0.119 t
LDL-P (nmol/L), mean (SD)	1015 (239)	1055 (196)	0,042	963 (170)	1051 (228)	0.020	0.760 u
Large LDL-P (nmol/L), mean (SD)	132.8 (26.1)	138.6 (25.3)	0.245	128.6 (23.8)	128.8 (26.1)	0.970	0.462 t
Medium LDL-P (nmol/L), mean (SD)	208.1 (89.3)	229.7 (80.4)	0.013	197.0 (64.5)	208.5 (69.9)	0.412	0.123 u
Small LDL-P (nmol/L), mean (SD)	674.1 (160.8)	686.9 (141.4)	0.622	637.7 (121.1)	714.0 (176.0)	0.012	0.102 t
HDL-P (μmol/L), mean (SD)	26.05 (5.30)	27.15 (4.60)	0.119	25.56 (3.52)	27.35 (3.55)	0.034	0.510 t
Large HDL-P (μmol/L), mean (SD)	0.25 (0.03)	0.25 (0.02)	0.920	0.24 (0.02)	0.23 (0.02)	0.055	0.154 t
Medium HDL-P (μmol/L), mean (SD)	8.13 (1.18)	8.40 (1.42)	0.140	8.16 (0.95)	8.00 (1.26)	0.523	0.156 t
Small HDL-P (μmol/L), mean (SD)	17.67 (4.57)	18.50 (3.69)	0.188	17.17 (3.01)	19.13 (2.96)	0.006	0.216 t
VLDL-Z (nm), mean (SD)	42.09 (0.20)	42.11 (0.17)	0.706	42.20 (0.19)	42.03 (0.17)	0.001	0.003 t
LDL-Z (nm), mean (SD)	20.79 (0.28)	20.83 (0.28)	0.448	20.80 (0.26)	20.72 (0.29)	0.130	0.103 t
HDL-Z (nm), mean (SD)	8.24 (0.10)	8.22 (0.06)	0.875	8.24 (0.06)	8.19 (0.06)	0.001	0.019 u
TG/HDL ratio, mean (SD)	2.32 (1.43)	1.73 (0.90)	0.006	2.52 (1.64)	2.93 (2.43)	0.710	0.108 u
hsCRP (mg/L), mean (SD)	2.99 (3.34)	2.48 (3.73)	0.624	3.43 (3.16)	2.07 (2.33)	0.631)	0.132 u

CTR, cardiac telerehabilitation; CBCR, centre-based cardiac rehabilitation; p_1 (p_2), change in the CTR (CBCR) group; p_{12}, comparison of changes between the two groups; t, t-test for paired samples for p_1 and p_2 (independent samples for p_{12}); u, Wilcoxon test for p_1 and p_2 (Mann–Whitney U test for p_{12}); LDL, low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very low-density lipoprotein; P, particles; Z, size; C, cholesterol; TG, triglycerides; SD, standard deviation; hsCRP, high sensitive C-reactive protein.

Declaration of Competing Interest

Nuria Amigó has a patent ("Method for lipoprotein characterization") issued and is the stoke owner of Biosfer Teslab, the company that analyses the metabolites reported in the manuscript.

The other authors declare no conflicts of interest. The funders had no role in the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.08.017.

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