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Effects of the combination of metformin and exercise on glycated hemoglobin, functional capacity, lipid profile, quality of life, and body weight

Sherif Eltonsy[1], Monique Dufour Doiron[2], Patrice Simard[3], Caroline Jose[1,4], Martin Sénéchal[5], Danielle R. Bouchard[5], Rémi LeBlanc[4] and Mathieu Bélanger[1,4]

Abstract

Objective: To evaluate the impact of the combination of metformin and exercise on changes in glycated hemoglobin (HbA_{1c}), functional capacity, the lipid profile, quality of life, and weight.

Methods: Data from a 12-week cardiovascular rehabilitation program (2014–2016) were retrospectively evaluated. Metformin exposure was determined through recorded prescriptions, and average minutes of exercise per week were computed from exercise logs. The primary outcomes were changes in HbA_{1c} and functional capacity (6-minute walk test [6MWT]) over 12 weeks. The secondary outcomes were changes in the lipid profile, quality of life, and weight. Directed acyclic graphs were used to identify potential confounders, accounted for with multiple linear regression.

Results: The cohort comprised 403 patients (85 metformin users, 318 non-users). The average amount of exercise was 102.7±48.7 minutes/week among metformin users and 107.7±58.1 minutes/week among non-users. Although changes in HbA_{1c} were similar for both groups, the coefficient for the metformin–exercise interaction indicated significantly greater improvements in

[1]Centre de formation médicale du Nouveau-Brunswick, Canada, Université de Moncton, Canada
[2]Vitalité Health Network
[3]Université de Montreal, Canada
[4]Department of Family Medicine, Université de Sherbrooke, Canada
[5]Cardio-metabolic Exercise & Lifestyle Laboratory, Faculty of Kinesiology, University of New Brunswick, Canada

Corresponding author:
Sherif Eltonsy, Centre de Formation Médicale du Nouveau-Brunswick, Pavillon J.-Raymond-Frenette, 100 rue des Aboiteaux, Moncton, New Brunswick E1A 3E9, Canada.
Email: sherif.eltonsy@umoncton.ca

the 6MWT among metformin users. There were no between-group differences in any secondary outcomes.

Conclusions: The combination of metformin and exercise led to greater gains in functional capacity than exercise alone. This combination did not appear to influence the effects of either treatment on other outcomes.

Keywords

Metformin, exercise, diabetes, interaction, glycated hemoglobin, cohort

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Introduction

Type 2 diabetes affects at least 285 million people worldwide and directly causes an estimated 1.5 million deaths per year.[1] Several clinically effective therapeutic options exist to manage diabetes and reduce its associated risk of morbidity and mortality. Lifestyle modification, including physical activity, is a first-line therapy for patients with type 2 diabetes.[2,3] Physical activity provides several health benefits for patients with type 2 diabetes, including improvements in glycemic control, insulin sensitivity, blood pressure, the lipid profile, muscular strength, and bone mineral density.[2,3] Moreover, physical activity can reduce body weight, the risk of coronary artery disease, and depression while improving patients' quality of life.[2,3] From a pharmaceutical viewpoint, metformin represents the first-line medication for diabetes management.[2,3] Metformin is recognized as the best drug for monotherapy of type 2 diabetes because it possesses the largest evidence base for efficacy and safety, including evidence of reducing the risk of cardiovascular events and death.[2–4]

Given the individual beneficial effects of each therapy, it has been hypothesized that the combination of exercise and metformin use will lead to additive health effects.[2,3] The cumulative effects of exercise and metformin on glucose levels and functional capacity were demonstrated in a laboratory-based study assessing a single exercise session[5] and in a 12-week experimental study.[6] Nevertheless, other studies have suggested that the benefits of metformin and exercise might not be additive. [7–12] One study showed that the combination of exercise and metformin led to a greater reduction in the postprandial glucose level than would have been expected by adding the individual effects of each therapy.[13] However, other studies have suggested the presence of deleterious effects associated with the combination of exercise and metformin use. For example, one study showed that adding metformin blunted the effects of exercise on insulin sensitivity by 25% to 30%.[8] Another study showed a significant reduction in maximal cardiorespiratory capacity with metformin use after one exercise session,[9] and a significant negative interaction was found in another study examining postprandial blood glucose.[11] Moreover, when looking at outcomes such as insulin sensitivity, adenosine monophosphate-activated protein kinase, oxygen uptake, the lipid profile, and quality of life, four studies of individuals with diabetes or impaired glucose tolerance showed

that adding metformin conferred no additional benefit over exercise alone.[7,10,12,14]

Because these preliminary results stem from experimental studies that did not account for potential confounding and that often included only a small number of participants, further studies of patients in real-world settings are needed. More research is needed to help develop a clearer understanding of the potential interactions between metformin and exercise and to clarify whether combining these two forms of treatment is advisable. Therefore, the primary objective of the current study was to examine the impact of the interaction between metformin use and exercise on the glycated hemoglobin (HbA_{1c}) level and functional capacity and, as secondary outcomes, the lipid profile, quality of life, and body weight.

Patients and methods

Study design and source of data

A population-based retrospective cohort was constructed using data from the electronic records of participants in the Cardiac Wellness Program, a cardiac rehabilitation program established in Moncton, New Brunswick, Canada. The Cardiac Wellness Program provides services to patients with cardiac disease and patients at risk of cardiovascular disease in the greater Moncton area and receives 200 to 400 new referrals annually. The Cardiac Wellness Program is affiliated with the Canadian Association of Cardiovascular Prevention and Rehabilitation.[15] Once a patient is admitted into the program, an electronic record is created based on the patient's hospital services information. Additional information is obtained through individual interviews with the program's staff, laboratory tests results, and program utilization (e.g., details of physical exercise performed) throughout the 12 weeks of cardiovascular rehabilitation. The study protocol was first developed and registered in The European Union electronic Register of Post-Authorisation Studies (reference number: EUPAS13582, http://www.encepp.eu/encepp/studiesDatabase.jsp).

Patient selection

Patients with and without diabetes mellitus were included in the primary cohort. The cohort inclusion criteria were an age of $\geq$25 years at admission, attendance in at least one exercise session of the program with recorded admission dates from January 2014 to June 2016, and completion of the discharge reassessment at the end of the program. We excluded patients with missing data on any of the primary exposures of interest (i.e., medication use and exercises performed during the program) or the primary outcomes. A subcohort from this population was also constructed using only patients with an HbA_{1c} level at admission of $\geq$5.7% ($\geq$39 mmol/mol). This subcohort resembles a population of patients with prediabetes (HbA_{1c} level of 5.7%–6.4%) and diabetes (HbA_{1c} level of $\geq$6.5%) according to the most recent guidelines from the American Diabetes Association.[3] This subcohort was essentially formed to mitigate potential confounding from diabetes among metformin users versus non-users.

Exposure assessment

The 12-week cardiac rehabilitation program was based on recommendations of the Canadian Association of Cardiovascular Prevention and Rehabilitation.[16] The program included an individualized exercise plan based on the patients' conditions and needs. Individual sessions generally consisted of a brief warm-up: 30 to 45 minutes of exercise using a variety of aerobic modalities including treadmills, stationary cycles,

arm ergocycles, elliptical trainers, and rowers; and a brief cool down and stretching session. Exercise intensity was prescribed following the Karvonen method, with the heart rate typically ranging from 45% to 85% of the heart rate reserve, based on the referral diagnosis and patient's exercise capacity.[17] We quantified the amount of exercise as the average number of minutes of exercise performed per week during the 12-week cardiac rehabilitation program.

Exposure to metformin (in either brand or generic form) was determined through a search among all recorded medications used at admission to the Cardiac Wellness Program. In a sensitivity analysis, the doses of metformin were categorized as >0 to 500 mg, >500 to <1000 mg, and ≥ 1000 mg.

Outcome definitions

The primary outcomes were the changes in HbA_{1c} and functional capacity from admission to discharge. The HbA_{1c} level was measured at the hospital laboratory in a fasting state. Functional capacity was measured as the distance walked during a 6-minute period using the standard 6-minute walk test (6MWT).[18] The 6MWT was carried out in a 30-m hallway. One well-trained kinesiologist supervised the test. The patients were instructed to walk the length of the hallway as many times as possible in the allotted period of 6 minutes. The patients were allowed to stop and rest during the test but were instructed to resume walking as soon as they felt able to do so.

The secondary outcomes were changes in the lipid profile (total cholesterol, triglycerides, low-density lipoprotein, and high-density lipoprotein), quality of life as measured using the 36-Item Short-Form Health Survey (SF-36),[19] and body weight. The lipid profile was measured at the hospital laboratory in a fasting state, while the SF-36 score and body weight were determined by trained staff at the cardiac rehabilitation center.

Confounding variables

Directed acyclic graphs were used to identify potential confounders and specify variables to be included in the models to minimize bias.[20–22] For important variables that were inconsistently recorded in the database (e.g., common comorbidities in patients with diabetes), we adjusted for variables acting as their proxies. Three classes of potential confounders were included in the analysis: sociodemographic and clinical variables measured at admission, including age (years), sex, tobacco smoking (non-smoker, previous smoker, or current smoker), body weight at admission (kg), and systolic and diastolic blood pressure (mmHg); medications used at admission, including cholesterol-lowering medications (yes/no), anticoagulants (yes/no), antiplatelets (yes/no), cardiovascular medications such as antihypertensive and angina medications (yes/no), other oral antidiabetics (yes/no), and insulin (yes/no); and exercise-related variables, including adherence to an exercise schedule (percentage of weekly sessions performed/prescribed) and the 6MWT result measured at admission (m).

Statistical analysis

All analyses were conducted among the full cohort of participants and among patients with an HbA_{1c} level at admission of $\geq 5.7\%$ (≥ 39 mmol/mol). Descriptive statistics for the patients' characteristics were calculated and compared between the metformin users and non-users. Figure plots representing the crude change in primary outcomes as a function of the average amount of exercise in minutes/week and metformin use were

depicted. The primary and secondary outcomes were analyzed in crude models using multiple linear regression, with metformin use, average exercise in minutes/week, and their interaction product terms serving as independent variables.[23–25] Adjusted models were then developed by adding potentially confounding variables. In the sensitivity analysis, additional regression models for metformin doses were used to explore the potential presence of dose–response relationships. Given the proportion of missing data among the primary and secondary outcomes, we performed an additional sensitivity analysis accounting for missing data. We used the full information maximum likelihood method, which treats complete and incomplete observations in an integrated manner by maximizing the likelihood function of the incomplete data.[26–28]

In the pre-hoc sample size calculation using a type I error of 0.05 and 80% power, a total sample size of 396 patients (in 1:1 groups) was estimated to be sufficient to detect a Cohen's f^2 effect size of 0.02. The actual study power was lower than this because of unbalanced sampling caused by the lower number of metformin users than non-users. Statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA) and DAGitty for causal diagrams.[29]

Ethics

This study was approved by the Research Ethics Committee of the Vitalité Health Network. The study protocol was first developed and registered in The European Union electronic Register of Post-Authorisation Studies (Reference number: EUPAS13582, http://www.encepp.eu/encepp/studiesDatabase.jsp). Permission to access the anonymized data records of participants in the Cardiac Wellness Program was granted by the program manager (MDD) after approval from the Research Ethics Committee. Participants' records were anonymized and identifiers were omitted; therefore, the need for consent to participate was waived by the Research Ethics Committee. Written consent to participate was obtained from the program staff.

Results

In total, 837 admissions of 807 patients to the cardiac rehabilitation program were recorded from January 2014 to June 2016. Of these, we excluded 427 admissions that had missing data on the primary outcomes, medications used, or minutes of exercise performed during the program. For sample selection, we included only one admission per patient (the first admission). The final sample analyzed for the primary cohort comprised 403 patients for whom we had the necessary information on their exposures and at least one of the primary outcomes; these patients were categorized into 85 metformin users and 318 metformin non-users. Among these patients, 198 (58 metformin users and 140 metformin non-users) had an HbA_{1c} level at admission of $\geq$5.7% ($\geq$39 mmol/mol) and were retained for the subcohort analyses. Analyses based on this subcohort resulted in similar effect estimates as those conducted among the primary cohort, but the confidence intervals were wider. Therefore, in the interest of parsimony and study power considerations, we present the results obtained from the primary cohort in the following sections and those from patients with an HbA_{1c} level of $\geq$5.7% in the appendix.

Among the metformin users, 29 (34.1%) were low-dose users (>0 to 500 mg), 17 (20.0%) were medium-dose users (>500 to <1000 mg), and 39 (45.9%) were high-dose users ($\geq$1000 mg) (Table 1). The overall mean age was similar in both groups, with comparable baseline blood pressure levels and SF-36 scores. However, metformin

Table 1. Characteristics of patients included in the analyses according to metformin use

	Metformin users (85 patients)	Metformin non-users (318 patients)
Sociodemographic and clinical variables measured at admission		
Age, years	64.3 ± 8.7	65.1 ± 11.3
Sex, male	60 (70.6)	196 (61.6)
Tobacco smoking		
Nonsmoker	39 (46.4)	171 (54.3)
Previous smoker	38 (45.2)	122 (38.7)
Current smoker	7 (8.3)	22 (7.0)
Body weight, kg	103.0 ± 23.3	88.5 ± 20.0
Blood pressure, mmHg		
Systolic	121.2 ± 16.0	120.9 ± 15.7
Diastolic	69.4 ± 9.2	70.3 ± 10.1
HbA_{1c}, %	7.1 ± 1.3	5.8 ± 0.6
HbA_{1c}, mmol/mol	54 ± 14.2	40 ± 6.6
Lipids, mmol/L		
Total cholesterol	3.5 ± 0.8	4.1 ± 1.1
Triglycerides	1.7 ± 1.0	1.5 ± 0.7
LDL	1.7 ± 0.6	2.2 ± 0.9
HDL	1.0 ± 0.3	1.2 ± 0.3
6-minute walk test, m	417.4 ± 123.2	456.1 ± 109.4
SF-36 score	76.6 ± 24.8	74.4 ± 25.2
Medications used		
Other oral antidiabetics	37 (43.5)	7 (2.2)
Insulin	17 (20.0)	11 (3.5)
Cardiovascular medications	79 (92.9)	281 (88.4)
Cholesterol-lowering medications	74 (87.1)	230 (72.3)
Anticoagulants	11 (12.9)	65 (20.4)
Antiplatelets	62 (72.9)	216 (67.9)
Metformin doses		
>0 to 500 mg	29 (34.1)	NA
>500 to <1000 mg	17 (20.0)	NA
≥1000 mg	39 (45.9)	NA
Exercise performed during 12-week cardiac rehabilitation program		
Total minutes of exercise	1050.4 ± 669.2	1036.5 ± 729.7
Adherence to exercise schedule (weekly sessions performed/prescribed), %	80.1 ± 28.4	75.6 ± 29.3
Average of weekly exercise, minutes	102.7 ± 48.7	107.7 ± 58.1

Data are presented as n (%) or mean ± standard deviation.
HbA_{1c}, glycated hemoglobin; SF-36, 36-Item Short-Form Health Survey; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NA, not available

users comprised more previous and current smokers, comprised more male patients, and weighed an average of 14.5 kg more than metformin non-users. As expected, the use of insulin and other oral antidiabetics was more frequent among metformin users. Cholesterol-lowering medication use was also more frequent among this group, but the use of anticoagulants was more prevalent among metformin non-users.

At admission, metformin non-users performed better on their 6MWT (38.7 additional meters). Metformin non-users also performed more minutes of exercise per week during the 12-week rehabilitation program than metformin users (5.0 additional minutes/week). However, metformin users were more adherent to their prescribed exercise program than were non-users (80.1% vs. 75.6%, respectively).

Primary outcomes

From admission in the 12-week rehabilitation program to discharge, no clinically meaningful changes in HbA_{1c} were observed among metformin users (HbA_{1c} change from 7.10% [54 mmol/mol] to 7.00% [53 mmol/mol]) or non-users (from 5.81% [40 mmol/mol] to 5.82% [40 mmol/mol]). Improvements in the 6MWT distance were not statistically significant among metformin users (increase of 27.5 m) but were statistically significant among metformin non-users (increase of 42.7 m, $P < 0.001$).

In the crude models, the rate of change in HbA_{1c} (interaction between metformin use and average exercise in minutes/week: $\beta = -0.007$, 95% confidence interval [CI] $= -0.019$ to -0.003) as a function of the amount of exercise accumulated during the 12-week period was more favorable among the metformin users than non-users (Figure 1, panel A). However, the between-group difference in the effect of exercise on HbA_{1c} was no longer statistically significant after adjusting for potential confounders (Table 2; results of the full model in Additional Table 1). For the outcome of the change in the 6MWT distance, the interaction between metformin use and average exercise in minutes per week was not statistically significant in the unadjusted models ($\beta = 0.335$, 95% CI $= -0.026$ to 0.696) (Figure 1, panel B). However, the interaction became statistically significant following adjustments, suggesting that the beneficial effect of exercise was amplified when treatment included metformin (Table 2).

In the sensitivity analyses, we found no indication of significant interactions between the metformin dose and average exercise in minutes per week for any of the primary outcomes (results available upon request). However, in a second set of sensitivity analyses accounting for missing data, we found that the combination of metformin and exercise led to greater benefits than could be expected by adding the individual impact of each single therapy. Specifically, we observed a significant interaction between metformin use and average exercise in minutes per week for the outcome of the change in HbA_{1c} in both the crude model ($\beta = -0.007$, 95% CI $= -0.012$ to -0.003) and adjusted model ($\beta = -0.006$, 95% CI $= -0.010$ to -0.002). Similarly, a positive interaction between metformin use and exercise was noted for the outcome of the change in the 6MWT distance (crude: $\beta = 0.335$, 95% CI $= -0.019$ to 0.689; adjusted: $\beta = 0.402$, 95% CI $= 0.065$ to 0.739).

Secondary outcomes

As presented in Table 3 (full model results in Additional Table 2), the results from the adjusted models suggested no interaction between metformin use and average exercise in minutes per week for any of the secondary outcomes (i.e., lipid profile, SF-36 score, and body weight at discharge). Similar results were observed in the sensitivity analyses for these outcomes (data not shown).

Discussion

In this study of real-world patients enrolled in a 12-week cardiac rehabilitation program, we observed no deleterious effects of metformin on the benefits of exercise.

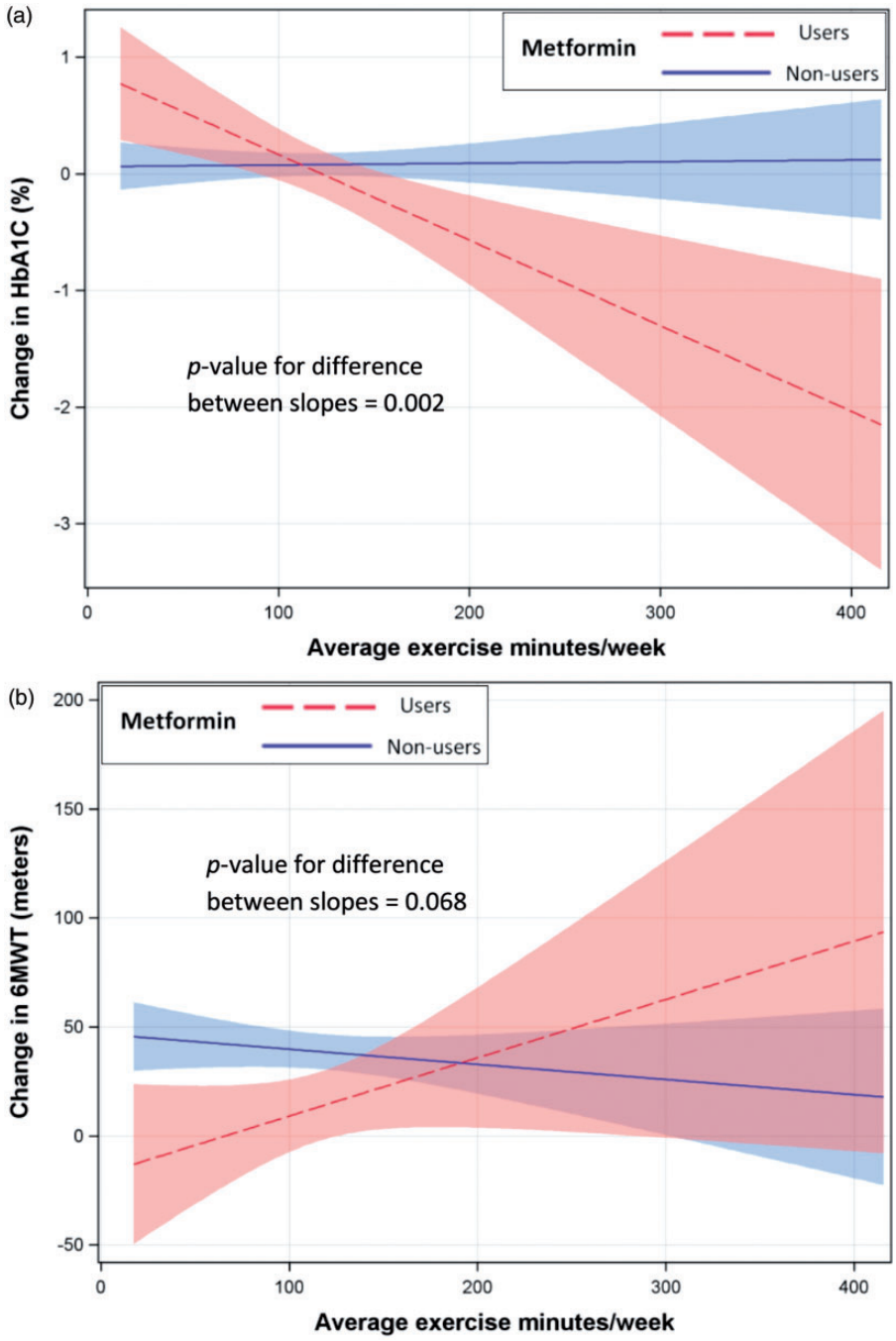

Figure 1. Crude model estimates and 95% confidence interval of change in (a) HbA_{1c} (%) and (b) 6MWT from baseline to end of 12-week cardiac rehabilitation program by average exercise in minutes per week and metformin use. HbA_{1c}, glycated hemoglobin; 6MWT, 6-minute walk test

Table 2. Adjusted coefficients, 95% confidence intervals, and P values for changes in HbA_{1c} and 6MWT

	Change in HbA_{1c} (n = 184)			Change in 6MWT (n = 169)		
Variable	β	95% CI	P value	β	95% CI	P value
Intercept	0.818	(−1.370 to 3.006)	0.460	112.286	(−1.339 to 225.679)	0.053
Metformin use	0.730	(−0.010 to 1.469)	0.053	**−58.677**	**(−107.402 to −9.952)**	**0.019**
Average exercise in minutes/week	0.000	(−0.002 to 0.002)	0.822	−0.108	(−0.252 to 0.0353)	0.138
Metformin use × average exercise interaction	−0.003	(−0.008 to 0.002)	0.246	**0.383**	**(0.005 to 0.762)**	**0.047**

HbA_{1c}, glycated hemoglobin; 6MWT, 6-minute walk test; CI, confidence interval. Bold values are statistically significant ($P<0.05$)

To the contrary, our results suggest that the combination of exercise and metformin use led to better glycemic control and greater gains in functional capacity than was expected from adding the individual effects of each treatment, and this was confirmed in the sensitivity analyses. These results are in agreement with other recent studies. For example, a crossover controlled trial of 10 patients with diabetes showed significant synergy between metformin and exercise ($P < 0.05$) in reducing the postprandial glucose level.[13] In another analysis, Viskochil et al.[30] reported a 24% statistically significant reduction in the level of proinsulin (i.e., the prohormone precursor to insulin) when exercise was combined with metformin, but not with exercise or metformin alone. Moreover, in a crossover trial involving 10 patients who had insulin resistance and were treated with metformin for at least 6 months, Ortega et al.[5] found that the combination of treatments led to a trend of greater, but not statistically significant, improvement in insulin sensitivity.

Notably, however, our results are in contrast to a number of studies involving small samples of healthy or prediabetic populations that suggested a non-additive or deleterious effect of the combination of metformin use and exercise.[7–10,14] For example, in samples of 10 to 32 participants, adding metformin to exercise reduced the effect of exercise on insulin sensitivity,[8] exercise capacity,[9] and postprandial blood glucose.[11] Other studies suggested no interaction between the two treatments. Specifically, studies involving 10 to 75 participants with insulin resistance showed no additional benefit when adding metformin to exercise alone on acute insulin sensitivity,[10] the blood glucose level,[10,12,31] or functional capacity.[14] Similarly, one larger study based on a secondary analysis of 225 patients with type 2 diabetes in a randomized controlled trial suggested that adding metformin to an exercise regimen led to no differences in HbA_{1c} or functional capacity improvements.[6] However, the results from that study may not be generalizable to the general population of patients using metformin because the participants completed 6 months of exercise training and the analyses did not include adjustments for potential confounders such as the concurrent use of other antidiabetics and other classes of medications. With respect to quality of life, Cadeddu et al.[14] reported no significant differences in the treatment effects of a combination of

Table 3. Adjusted coefficients, 95% confidence intervals, and P values for changes in SF-36 score, body weight, total cholesterol, LDL, HDL, and triglycerides

	Change in SF-36 score (n = 157)			Change in body weight (n = 282)			Change in total cholesterol (n = 221)		
Variable	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value
Intercept	−35.154	(−150.338 to 80.030)	0.545	0.207	(−5.809 to 6.223)	0.946	0.412	(−1.992 to 2.816)	0.735
Metformin use	6.875	(−29.016 to 42.765)	0.704	0.669	(−1.659 to 2.994)	0.571	0.066	(−0.681 to 0.814)	0.861
Average exercise in minutes/week	−0.015	(−0.124 to 0.093)	0.778	−0.002	(−0.010 to 0.005)	0.584	0.000	(−0.002 to 0.003)	0.916
Metformin use × average exercise interaction	0.037	(−0.226 to 0.300)	0.779	0.000	(−0.018 to 0.018)	0.967	−0.001	(−0.006 to 0.005)	0.832
	Change in LDL (n = 216)			Change in HDL (n = 221)			Change in triglycerides (n = 220)		
	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value
Intercept	−0.138	(−2.038 to 1.762)	0.886	0.326	(−0.265 to 0.917)	0.276	−0.291	(−1.708 to 1.127)	0.685
Metformin use	0.072	(−0.520 to 0.663)	0.811	0.051	(−0.133 to 0.235)	0.584	−0.205	(−0.646 to 0.236)	0.359
Average exercise in minutes/week	0.000	(−0.002 to 0.001)	0.648	0.001	(0.000 to 0.001)	0.014	0.000	(−0.002 to 0.001)	0.897
Metformin use × average exercise interaction	−0.001	(−0.005 to 0.004)	0.684	−0.001	(−0.002 to 0.001)	0.450	0.002	(−0.002 to 0.005)	0.342

SF-36, 36-Item Short-Form Health Survey; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CI, confidence interval

metformin and exercise versus exercise treatment alone. Likewise, in the current study, we observed no significant interactions between metformin and exercise for any of the secondary outcomes specified, including patient-reported quality of life. Future research should continue to investigate patient-centered outcomes to help determine whether an interaction exists between the two forms of treatment.

The discrepancies in the results of different studies may be attributable to the following factors. First, the meal tolerance test and euglycemic clamps mostly used in controlled studies reveal blood glucose levels within short timeframes; in contrast, HbA_{1c} reflects the average blood glucose concentration over a longer period of time.32 Second, only a minority of studies included $\geq$12 weeks of exercise;[6,8,14] the rest investigated the effects of single sessions of exercise. Interestingly, the results reported by Boulé et al.[6] and the results of the current study, which are the two largest studies to date and which included 3 and 6 months of exercise, did not suggest any departure from the expected additivity of the effects of exercise and metformin. This suggests that even if metformin may blunt acute exercise benefits, this effect is at most minor and is not sustained when an exercise regimen is maintained for several weeks. Third, the dose of metformin used in some short-term studies was higher (i.e., 2000 mg/day) than that typically used in practice.[7–11] Studies using lower doses (average dose of 1000–1600 mg/day) revealed no deleterious interactions.[5,6,14] Most of the metformin users in the current study were using low to medium doses (>0 to <1000 mg/day). Finally, the varying health status of the participants included in different studies might account for additional discrepancies.

A major strength of the current study is our examination of the interaction between metformin use and exercise in a cohort of real-world individuals enrolled in a cardiac rehabilitation program. Although the participants in this cardiac rehabilitation program are not representative of the general population, their health condition reflects that of the target population that would mostly benefit from both therapies. Moreover, this is one of the largest studies to date investigating this interaction. We also adjusted for numerous potentially confounding variables, including smoking and different classes of medications used for chronic diseases. In addition, we used a large set of statistical models and sensitivity analyses, including models with the full information maximum likelihood method, all of which provided confirmation of our observed estimates.

The results of this study should nevertheless be interpreted with consideration of the following limitations. We were unable to reduce bias caused by unmeasured confounding factors. However, because the objectives of this retrospective analysis had no influence on the collection of data, we suspect that the potential for measurement errors in the recording of data would be similar for metformin users and nonusers such that if bias occurred, it was most likely non-differential. We had no data on the patients' diabetes history or duration of metformin use prior to enrollment. We were unable to adjust for other comorbidities among patients with diabetes (e.g., hypertension) because of inconsistent data recording; however, we adjusted for variables that act as their proxies (e.g., medications used for treatment). Data on exercise and other physical activities performed outside of the rehabilitation program were not available. Metformin use was measured using the recorded prescription data and patient interviews; actual intake of the medication was unknown. Although we obtained similar results in analyses of a combination of patients with and without diabetes and of a subcohort of patients believed to have diabetes or prediabetes,

we cannot rule out the potential for residual confounding as a result of indication bias. Additionally, because the metformin users had a higher body weight, they might have had more potential to benefit from the combination therapy. Although the study was adequately powered for the primary analyses, it was underpowered for some of the secondary outcomes and dose analysis, in which a significant effect could have been missed due to the small sample sizes. Finally, the data were retrieved from one center, affecting the generalizability of our results.

Conclusions

In conclusion, evidence from the current study coupled with that from previously published studies on prolonged ($\geq$12 weeks) exposure to a combination of metformin and exercise indicates that both forms of therapies can be expected to provide their anticipated benefits when combined. In the current study, the combination of therapies was actually associated with greater gains in functional capacity, and possibly HbA_{1c} levels, than was expected from adding the individual effects of each treatment. These results add confidence in combining the two therapies for diabetes management. Consequently, because both exercise and metformin are considered cornerstones in the treatment and prevention of diabetes, we encourage healthcare practitioners to continue prescribing both therapies concomitantly.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SE, MDD, PS, CJ, MS, DRB, RL, and MB contributed to the concept and design of the study. SE and MB performed the data analysis and wrote the first draft. SE, MDD, PS, CJ, MS, DRB, RL, and MB interpreted the data. SE, MDD, PS, CJ, MS, DRB, RL, and MB contributed to drafting and revising of the full manuscript and approved the manuscript as submitted. SE, MDD, PS, CJ, MS, DRB, RL, and MB met the criteria for authorship and take public responsibility for the study contents.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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ORCID iD

Sherif Eltonsy http://orcid.org/0000-0002-0520-5406

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Appendix

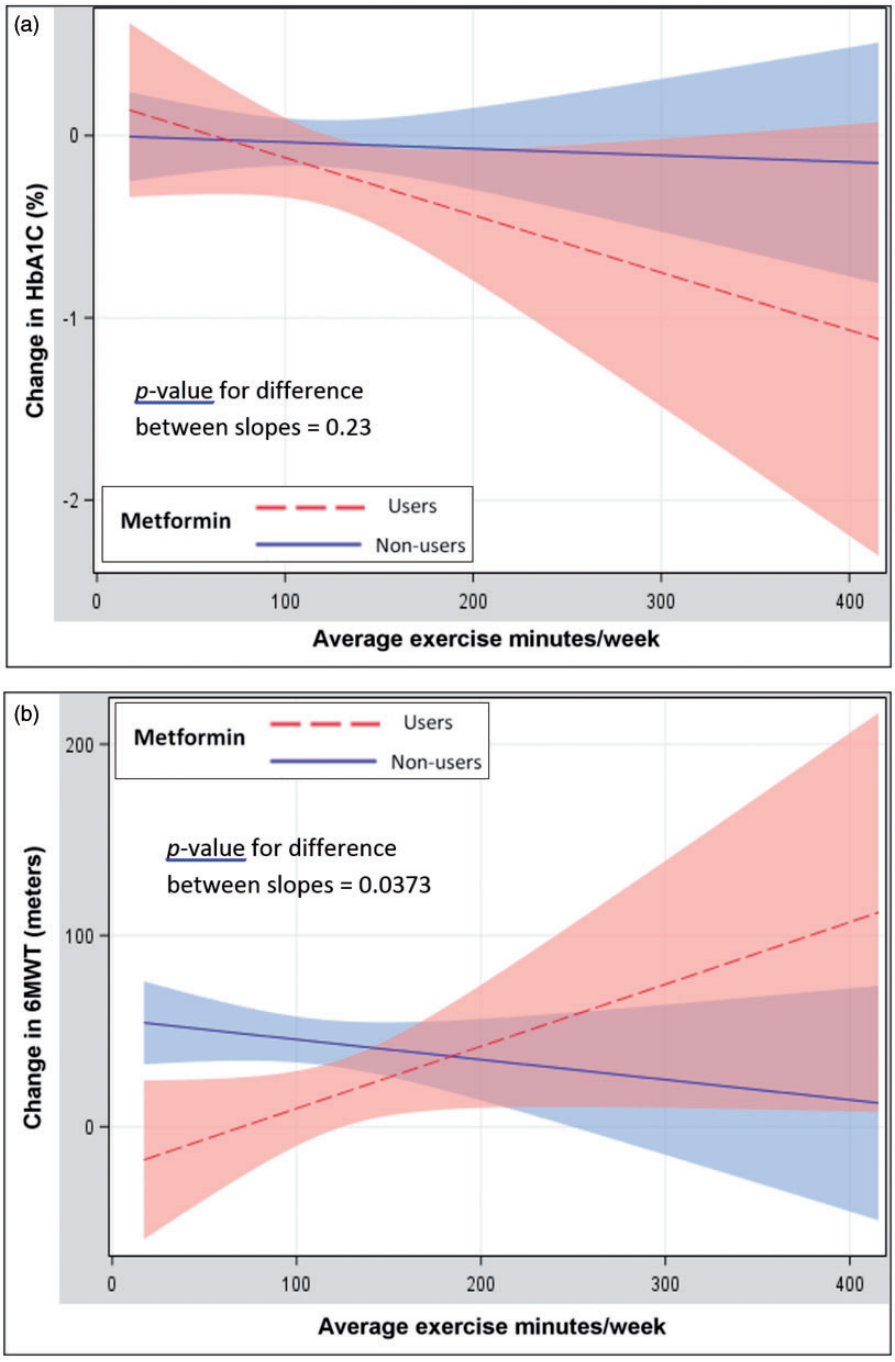

Figure A1. Crude model estimates and 95% confidence interval of change in (a) HbA_{1c} (%) and (b) 6MWT from baseline to end of 12-week cardiac rehabilitation program by average exercise in minutes per week and metformin use among patients with an HbA_{1c} level at admission of $\geq$5.7% ($\geq$39 mmol/mol). HbA_{1c}, glycated hemoglobin; 6MWT, 6-minute walk test