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Does metformin therapy influence the effects of intensive lifestyle intervention? Exploring the interaction between first line therapies in the Look AHEAD trial

Tasuku Terada [a], Normand G. Boulé [b,*]

[a] Division of Cardiac Prevention and Rehabilitation, Exercise Physiology and Cardiovascular Health Lab, University of Ottawa Heart Institute, Ottawa, ON K1C 4W7, Canada
[b] Faculty of Kinesiology, Sport, and Recreation, and Alberta Diabetes Institute, University of Alberta, 1-052 Li Ka Shing Centre for Health Research Innovation, Edmonton, AB T6G 2E1, Canada

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ABSTRACT

Aims: Metformin and lifestyle intervention are frequently prescribed together as first-line treatments for type 2 diabetes. However, little is known about their interplay. We investigated if the effects of a lifestyle intervention on glycemia, body mass and cardiorespiratory fitness (CRF) were influenced by metformin therapy.
Methods: Participants randomized to intensive lifestyle intervention (ILI) or diabetes support and education (DSE) from the Look AHEAD trial were categorized into metformin therapy vs. no metformin. A two-by-two ANCOVA (i.e., metformin therapy vs. no metformin by ILI vs. DSE) was used to examine the changes in glycated hemoglobin A1C, fasting plasma glucose (FPG), body mass, and CRF over the first year post-randomization, with a primary interest in the metformin-by-lifestyle interaction effect.
Results: Data from 1982 participants were analyzed. There was a significant metformin-by-lifestyle interaction effect on A1C ($p = 0.031$) and FPG ($p = 0.043$), resulting from larger reductions associated with metformin therapy compared to no metformin following DSE, but slightly smaller reduction associated with metformin therapy compared to no metformin following ILI. Metformin therapy was associated with smaller weight loss (-4.7 ± 6.2 vs. -5.7 ± 6.3 kg; main effect: $p = 0.001$) but not with differential CRF changes when compared to no metformin.
Conclusions: The interaction between metformin therapy and lifestyle intervention on glycemia highlights the complicated nature of combining therapies. While the small influence of background metformin therapy on intensive lifestyle intervention should not discourage the concomitant use of these therapies, our results showed that, for individuals undergoing intensive lifestyle therapy, background metformin therapy conferred little additional benefits.

1. Introduction

In 2015, an estimated 30.2 million US adults were living with diabetes [1]. Hyperglycemia defines diabetes and glycemic control is fundamental to diabetes care [2]. The established independent, anti-hyperglycemic effects of pharmacotherapies [3] and lifestyle intervention [4] have led to their simultaneous prescriptions to manage or treat type 2 diabetes. Among several medications, metformin has been the most widely prescribed oral anti-hyperglycemic medication. Since 2010, metformin has been prescribed to 91.0% of patients newly diagnosed with type 2 diabetes in UK [5] and to 89.6% of patients in Denmark [6]. Between 2005 and 2010 in the US, 84.6% of patients with type 2 diabetes starting anti-hyperglycemic medication were prescribed metformin [7].

Metformin suppresses hepatic glucose output [8,9] and lowers glycated hemoglobin A1C (A1C) [8,10] with minimal safety and tolerability issues [8]. Its established effectiveness on glycemia, relatively minor side effects, and weight-neutral or weight-lowering nature [8,10,11] made metformin a preferred medication for people with type 2 diabetes. In addition to metformin, lifestyle intervention including physical activity and dietary restriction is another cornerstone therapy for people with type 2 diabetes [12]. Intensive lifestyle intervention is a key strategy to lower blood glucose concentration and body mass, and to increase cardiorespiratory fitness (CRF) [13]. Several guidelines endorse metformin therapy and lifestyle intervention for the management of type 2 diabetes [2,14,15].

Given the frequency in which metformin and lifestyle intervention are concurrently prescribed as a first-line treatment for type 2 diabetes [16], surprisingly few studies have examined their interplay. Studies investigating the combined effects of metformin and exercise have shown conflicting findings. While some studies have shown additive effects of

Abbreviations: CRF, cardiorespiratory fitness; DSE, diabetes support and education; FPG, fasting plasma glucose; ILI, intensive lifestyle intervention; MET, metabolic equivalent.

* Corresponding author at: University of Alberta, Faculty of Kinesiology, Sport, and Recreation, and Alberta Diabetes Institute, 1-052 Li Ka Shing Centre for Health Research Innovation, Edmonton, AB T6G 2E1, Canada.
E-mail address: nboule@ualberta.ca (N.G. Boulé).

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metformin and exercise on acute glucose uptake in participants with [17] and without type 2 diabetes [18], several small, well-controlled, short-term studies have identified potential negative interactions between metformin therapy and exercise. Studies have shown that combining metformin therapy and exercise can acutely blunt insulin-sensitizing effects of exercise in individuals with prediabetes [19] and insulin resistance [20], or hinder hypoglycemic effects of metformin in type 2 diabetes [21]. The meaningfulness of these effects in the context of longer-term, less controlled trials remains unclear.

To our knowledge, only one study has examined the long-term influence of metformin therapy on the established effects of exercise training on glycemia in type 2 diabetes [22]. Although the study found no influence of metformin on the glucose-lowering effect of exercise training, the study did not include dietary intervention for weight loss and may have been underpowered to detect the interplay between metformin therapy and exercise training. There is no study investigating the influence of metformin therapy on improvements in glycemia, body mass, and CRF typically induced by long-term intensive lifestyle intervention including both exercise and dietary restriction.

The Look AHEAD (Action for Health in Diabetes) trial is the largest multicenter clinical trial (ClinicalTrial.gov, number NCT00017953) designed to compare the effects of intensive lifestyle intervention (ILI) and diabetes support and education (DSE) on the prevention of cardiovascular disease in type 2 diabetes [13]. Using data available from the Look AHEAD trial, the primary purpose of the study was to examine if metformin therapy prior to and during intensive lifestyle intervention would interfere with the established hypoglycemic effects of lifestyle intervention in type 2 diabetes. The secondary outcomes of interest were body mass and CRF. It was hypothesized that background metformin therapy would be associated with greater improvement in indicators of glycemia, body mass, and CRF following DSE but not following ILI.

2. Materials and Methods

2.1. Participants

For the purpose of this secondary analysis, data were obtained from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Central Repository. From August 2001 to April 2004, adults with type 2 diabetes living with overweight and obesity (BMI ≥ 25 kg/m^2), aged 45–76 years were recruited at 16 clinical sites in the US and underwent ILI or DSE [13]. Details of ILI have been described elsewhere [13]. Briefly, ILI aimed at achieving and maintaining weight loss of ≥7% through at least 175 min/week of moderate intensity physical activity and reduced caloric intake. ILI participants met with intervention teams that included registered dieticians, behaviour psychologists, and exercise specialists weekly for the first 6 months and 3 times per month for the next 6 months. Participants in DSE were invited to 3 group sessions each year and received general information related to healthy eating and physical activity but did not receive the comprehensive components of the intervention nor specific strategies for weight loss [23].

Medical or pharmacological care to control hyperglycemia was provided by the participants' physicians independent of the Look AHEAD protocol. Participants brought all prescription medications to the baseline and one-year visits to insure recording accuracy. Participants in ILI and DSE were divided into metformin therapy or no metformin according to metformin prescription at baseline. Data from the first year (Phase I) was analyzed because lifestyle intervention was most strictly implemented and alterations in medical prescriptions were least frequent [23]. The ethics approval of this secondary analysis was obtained from University of Alberta Health Research Ethics Board (Pro00074654).

2.2. Outcome Measures

The primary outcomes were A1C and fasting plasma glucose (FPG). A1C was measured by a dedicated ion-exchange high-performance liquid chromatography instrument (Biorad Variant II). FPG was measured by the glucokinase method on the Hitachi 917 chemistry autoanalyzer. The secondary outcomes were body mass and CRF. Body mass were measured in duplicate using a digital scale and stadiometer. Details of a graded exercise test for CRF assessment are described elsewhere [23]. In brief, the test consisted of a participant walking on a motorized treadmill at a constant self-selected walking speed, with the elevation of the treadmill increased by 1.0% every minute starting from 0%. CRF was defined as the estimated metabolic equivalent (MET) based on walking speed and grade in which 80% of the maximal heart rate was attained among participants not taking beta-blockers or achieving a rating of 16 out of 20 on the rating of perceived exertion scale among participants taking beta-blockers. Because data on changes in CRF were available in a form of percent changes, absolute changes were calculated as baseline MET times percent changes. All measures were taken at baseline and at one year following randomization.

2.3. Statistical Analysis

Categorical variables are presented as frequencies and percentages, and continuous variables as mean ± SD unless otherwise stated. Baseline characteristics according to metformin therapy and lifestyle intervention were compared with χ^2 statistics for categorical variables and 2 × 2 ANOVA (metformin therapy vs. no metformin by ILI vs. DSE) for continuous variables.

To assess the interplay between metformin therapy and lifestyle intervention, we used 2 × 2 ANCOVA (metformin therapy vs. no metformin by ILI vs. DSE) on changes in A1C, FPG, body mass and CRF, with a primary focus on the interaction effects. The analyses were adjusted for age, sex, race/ethnicity, duration of diabetes, baseline anti-hyperglycemic medication prescription, orlistat and statin prescription, source of care (i.e., community health center, hospitals, private doctor's office or no usual care), changes in any anti-hyperglycemic medication prescriptions (i.e., consistent, increased/initiated, decreased/discontinued, mixed [e.g., an increase in certain anti-hyperglycemic medications while decrease in another]), changes in caloric and macronutrient intake. When significant interaction was found, we preformed post-hoc analyses comparing metformin vs. no metformin separately for ILI and DSE while adjusting for the same covariates. For sensitivity analysis, we performed the same analyses while excluding participants who altered any anti-hyperglycemic medications. Data were analyzed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA). $p < 0.05$ was considered significant.

3. Results

3.1. Baseline Characteristics

Of 5145 participants randomized (1:1) to either ILI or DSE [13], we accessed the data from 4906 participants as data on 239 participants from American Indian clinical sites were not archived in the NIDDK repository [24]. After excluding participants with missing variables (e.g., metformin prescription: $n = 372$; A1C: $n = 254$; and, dietary data: $n = 2802$), data of 1982 participants with complete data were analyzed. At baseline, participants included in the analyses were significantly younger (57.4 ± 7.2 vs. 59.9 ± 6.2 years, $p < 0.001$) and had higher A1C (7.4 ± 1.2 vs. 7.2 ± 1.1% [57.1 ± 13.4 vs. 55.1 ± 12.1 mmol/mol], $p < 0.001$), body mass (101.7 ± 19.8 vs. 100.6 ± 18.8 kg, $p = 0.046$), and CRF (7.3 ± 2.0 vs. 7.1 ± 2.0 METs, $p < 0.001$) when compared to those excluded. A smaller proportion of participants included in the analyses were on metformin therapy (60.2 vs. 63.8%, $p = 0.012$) and randomized to DSE (48.0 vs. 51.4%, $p = 0.021$) when compared to those who were excluded.

Baseline characteristics of included participants are summarized in Table 1. At baseline, participants on metformin therapy were significantly younger (56 ± 7 vs. 58 ± 7 years, $p < 0.001$), had higher A1C

Table 1
Participant characteristics at baseline.

Participants characteristics	DSE		ILI		Metformin vs. No metformin	ILI vs. DSE	Interaction Effect
	Metformin	No metformin	Metformin	No metformin			
Number of participants (*n*)	570	382	624	406			
Sex, *n* (%) female	324 (56.8)	219 (57.3)	374 (59.9)	237 (58.4)	0.794	0.303	
Age (year)	57 (6)	58 (7)	56 (6)	57 (7)	<0.001	0.065	0.761
Race					0.989	0.970	
African American	87 (15.3)	52 (13.6)	91 (14.6)	61 (15.0)			
Hispanic	75 (13.2)	62 (16.2)	92 (14.7)	49 (12.1)			
White	388 (68.1)	253 (66.2)	416 (66.7)	281 (69.2)			
Others	20 (3.5)	15 (3.9)	25 (4.0)	15 (3.7)			
Anthropometrics							
Body mass (kg)	102.1 (19.2)	101.3 (19.8)	101.9 (20.4)	101.2 (19.6)	0.408	0.858	0.959
Body mass index (kg/m^2)	36.1 (5.7)	36.3 (6.2)	36.2 (6.2)	36.1 (6.2)	0.935	0.826	0.678
Waist circumference (cm)	114.6 (14.5)	114.4 (14.3)	114.3 (14.7)	114.0 (14.9)	0.702	0.592	0.922
Blood glucose							
A1C (%)	7.5 (1.2)	7.2 (1.3)	7.4 (1.2)	7.3 (1.2)	0.002	0.627	0.228
A1C (mmol/mol)	58.4 (13.5)	55.7 (13.9)	57.3 (12.9)	56.1 (13.4)	0.002	0.627	0.228
Fasting plasma glucose (mg/dL)	159.8 (50.1)	152.3 (43.3)	156.9 (45.8)	152.8 (46.2)	0.007	0.582	0.417
Cardiorespiratory fitness (MET)	7.3 (1.9)	7.3 (2.0)	7.4 (1.9)	7.3 (2.1)	0.987	0.934	0.736
Anti-hyperglycemic medication, *n* (%)							
Alpha-glucosidase inhibitor	8 (1.4)	1 (0.3)	4 (0.6)	3 (0.7)	0.509	0.226	
Thiazolidinedione (TZD)	168 (29.5)	85 (22.3)	164 (26.3)	103 (25.3)	0.147	0.778	
DPP-4 inhibitor	0 (0)	0 (0)	0 (0)	0 (0)			
Meglitinide	22 (3.9)	6 (1.6)	23 (3.7)	12 (3.0)	0.065	0.562	
Sulfonylurea	275 (48.2)	158 (41.4)	321 (51.4)	159 (39.2)	<0.001	0.875	
Incretin mimetics	0 (0)	0 (0)	0 (0)	0 (0)			
Insulin	81 (14.3)	67 (17.6)	93 (14.8)	65 (16.1)	0.189	0.899	
Pramlintide	0 (0)	0 (0)	0 (0)	0 (0)			
Other medication, *n* (%)							
Orlistat	0 (0.0)	3 (0.8)	0 (0.0)	3 (0.7)			
Statin	243 (42.7)	122 (32.0)	290 (46.5)	138 (34.0)	<0.001	0.145	

Data are *n* (%) for categorical variables or mean (SD) for continuous variables.
A1C: glycated hemoglobin A1C; DSE: diabetes support and education; ILI: intensive lifestyle intervention; MET: metabolic equivalent.

(7.4 ± 1.3 vs. 7.3 ± 1.3% [57.8 ± 13.2 vs. 55.9 ± 13.7 mmol/mol], $p = 0.002$) and FPG (158.3 ± 46.0 vs. 152.6 ± 47.6 mg/dL, $p = 0.007$) when compared to no metformin. At baseline, statin and sulfonylurea were more frequently prescribed to participants who were on metformin therapy when compared to no metformin (both $p < 0.001$).

3.2. Anti-hyperglycemic Medications

Changes in prescribed anti-hyperglycemic medications are summarized in Table 2. Overall, 221 (11.2%) participants increased/initiated at least one anti-hyperglycemic medication; 470 (23.7%) participants decreased/discontinued at least one anti-hyperglycemic medication; and, 120 (6.1%) participants had mixed changed. At one-year follow-up, in the DSE group, participants who had not been prescribed metformin therapy at baseline were more likely to initiate metformin therapy (22.8 vs. 0.0%, $p < 0.001$) and more likely to decrease/discontinue insulin prescription (8.9 vs. 3.3%, $p < 0.001$) when compared to those who had been on metformin therapy at baseline. In the ILI group, at one-year follow-up those who had been on metformin therapy at baseline were more likely to decrease/discontinue metformin therapy (14.6 vs. 0.0%, $p < 0.001$) and increase/initiate thiazolidinedione (TZD) therapy (3.8 vs. 1.0%, $p = 0.010$) when compared to those who had not been on metformin therapy at baseline.

3.3. Dietary Intake

Caloric and macronutrient intake at baseline and one-year follow-up are summarized in Table 3. At baseline, participants with metformin therapy had greater daily total caloric (2027 vs. 1938 kcal/day, $p = 0.027$), protein (86 vs. 82 g/day, $p = 0.027$), and fat intake (221 vs. 210 g/day, $p = 0.011$) when compared to no metformin. There were no differences between ILI and DSE at baseline.

Significantly greater reduction in fat intake was observed in ILI when compared to DSE (−25.9 vs. −14.8 g, $p < 0.001$), whereas the reduction in carbohydrate intake was significantly greater in DSE when compared to ILI (−33.3 vs. −7.4 g, $p < 0.001$). Changes in total caloric intake and protein intake were not different between ILI vs. DSE. Changes in caloric or macronutrient intake did not differ between metformin therapy vs. no metformin.

3.4. Changes in Glycemia

There was a significant metformin therapy by lifestyle intervention interaction effect on A1C ($p = 0.031$, Fig. 1A). Following ILI, reduction in A1C associated with metformin therapy and no metformin were −0.72 ± 1.02% (−7.9 ± 11.1 mmol/mol) vs. −0.83 ± 0.98% (−9.1 ± 10.7 mmol/mol), respectively ($p = 0.146$). Following DSE, reduction in A1C associated with metformin therapy and no metformin were −0.24 ± 0.96% (−2.6 ± 10.5 mmol/mol) vs. −0.15 ± 1.01% (−1.7 ± 11.0 mmol/mol), respectively ($p = 0.051$). Our sensitivity analysis excluding those who altered anti-hyperglycemic medications ($n = 1169$) showed no interaction effect ($p = 0.654$; Fig. 1B). In our sensitivity analysis, changes in A1C associated with metformin and no metformin therapy were −0.72 ± 1.43 vs. −0.75 ± 1.32% ($p = 0.506$) following ILI and −0.18 ± 1.18 vs. −0.16 ± 1.62% ($p = 0.959$) following DSE.

We found a significant metformin therapy by lifestyle intervention interaction effect on FPG ($p = 0.043$, Fig. 2A). Following ILI, mean changes in FPG associated with metformin therapy and no metformin were −24.4 ± 46.2 mg/dL vs. −25.0 ± 39.8 mg/dL, respectively ($p = 0.817$). Following DSE, mean changes in FPG associated with metformin therapy and no metformin were −9.5 ± 45.8 mg/dL vs. −1.8 ± 41.4 mg/dL, respectively ($p = 0.033$). The interaction effect remained significant after excluding participants who altered any anti-hyperglycemic medication during the assessment period ($p = 0.040$, Fig. 2B). Our sensitivity analysis showed that changes in FPG associated with metformin and no

Table 2
Changes in prescribed medication.

Medication, *n* (%)	DSE		ILI	
	Metformin	No metformin	Metformin	No metformin
Overall hypoglycemic medication prescription				
Increased/initiated	60 (10.5)	102 (26.7)‡	24 (3.8)	35 (8.6)†
Decreased/discontinued	87 (15.3)‡	45 (11.8)	249 (39.9)‡	89 (21.9)
Mixed	17 (3.0)	37 (9.7)‡	24 (3.8)	42 (10.3)‡
Metformin				
Increased/initiated	0 (0)	87 (22.8)‡	0 (0)	59 (14.5)‡
Decreased/discontinued	43 (7.5)‡	0 (0)	91 (14.6)‡	0 (0)
Alpha-glucosidase inhibitor				
Increased/initiated	3 (0.5)	0 (0)	2 (0.3)	2 (0.5)
Decreased/discontinued	6 (1.1)	1 (0.3)	3 (0.5)	1 (0.2)
Thiazolidinedione (TZD)				
Increased/initiated	41 (7.2)	30 (7.9)	24 (3.8)*	4 (1.0)
Decreased/discontinued	23 (4.0)	19 (5.0)	43 (6.9)	21 (5.2)
DPP-4 inhibitor				
Increased/initiated	0 (0)	0 (0)	0 (0)	0 (0)
Decreased/discontinued	0 (0)	0 (0)	0 (0)	0 (0)
Meglitinide				
Increased/initiated	10 (1.8)	5 (1.3)	3 (0.5)	1 (0.2)
Decreased/discontinued	0 (0)	0 (0)	0 (0)	0 (0)
Sulfonylurea				
Increased/initiated	27 (4.7)	25 (6.5)	15 (2.4)	7 (1.7)
Decreased/discontinued	36 (6.3)	20 (5.2)	137 (22.0)	68 (16.7)
Incretin mimetics				
Increased/initiated	0 (0)	0 (0)	0 (0)	0 (0)
Decreased/discontinued	0 (0)	0 (0)	0 (0)	0 (0)
Insulin				
Increased/initiated	0 (0)	0 (0)	0 (0)	0 (0)
Decreased/discontinued	19 (3.3)	34 (8.9)‡	55 (8.8)	35 (8.6)

DSE: diabetes support and education; ILI: intensive lifestyle intervention.
Significantly more frequent between metformin therapy vs. no metformin within the intervention group:
* $p < 0.05$.
† $p < 0.01$.
‡ $p < 0.001$.

metformin therapy were -21.5 ± 42.7 vs. 24.2 ± 35.8 mg/dL ($p = 0.509$) following ILI and -11.0 ± 44.8 vs. -3.4 ± 36.7 mg/dL ($p = 0.062$) following DSE.

3.5. Changes in Body Mass

There was no interaction effect on the change in body mass ($p = 0.130$, Fig. 3A). Metformin therapy was associated with smaller reduction in body mass in comparison to no metformin (-4.7 ± 6.2 vs. -5.7 ± 6.3 kg, $p = 0.001$). Consistent to the previous report [13], ILI was associated with significantly greater reduction in body mass (-8.8 ± 6.6 vs. -1.5 ± 6.7 kg; $p < 0.001$) when compared to DSE. Our sensitivity analysis excluding those who altered any anti-hyperglycemic medications showed a significant metformin therapy-by-lifestyle intervention interaction effect on body mass ($p = 0.005$, Fig. 3B). Following ILI, changes in body mass associated with metformin therapy and no metformin were -7.2 ± 6.5 and -9.1 ± 7.5 kg, respectively ($p = 0.083$). Following DSE, changes in body mass associated with metformin therapy and no metformin were -0.9 ± 4.2 and -1.0 ± 4.7 kg, respectively ($p = 0.534$).

3.6. Changes in Cardiorespiratory Fitness

There was no interaction effect on changes in CRF ($p = 0.583$, Fig. 4). ILI was associated with significantly greater increase in CRF when compared to DSE (1.6 vs. 0.8 METs, $p < 0.001$). There was no difference

Table 3
Caloric intake and macronutrient consumption.

Participants characteristics	DSE		ILI		Metformin vs. No metformin	ILI vs. DSE	Interaction effect
	Metformin	No metformin	Metformin	No metformin			
Caloric intake (Kcal)							
Baseline	2013 (892)	1958 (958)	2040 (866)	1918 (757)	0.027	0.859	0.401
Change in caloric intake	−306 (654)	−312 (807)	−376 (773)	−295 (665)	0.263	0.432	0.197
Protein intake (g)							
Baseline	86.0 (40.2)	82.8 (39.8)	86.2 (37.8)	81.8 (33.5)	0.027	0.827	0.724
Change in protein intake	−10.1 (30.7)	−11.0 (35.5)	−11.3 (33.7)	−8.7 (31.6)	0.560	0.727	0.260
Fat intake (g)							
Baseline	89.0 (46.1)	87.3 (50.3)	90.4 (44.0)	84.8 (38.7)	0.080	0.779	0.338
Change in fat intake	−14.3 (34.0)	−15.2 (42.3)	−27.3 (39.8)	−24.6 (33.6)	0.602	<0.001	0.305
Carbohydrate intake (g)							
Baseline	219.0 (94.4)	210.9 (101.4)	222.3 (95.4)	208.3 (87.6)	0.011	0.922	0.500
Change in carbohydrate intake	−33.9 (75.0)	−32.8 (86.5)	−13.3 (89.0)	−1.5 (82.7)	0.094	<0.001	0.161

Data are mean (SD).
There were no interaction effects between metformin therapy and lifestyle intervention.
DSE: diabetes support and education; ILI: intensive lifestyle intervention.

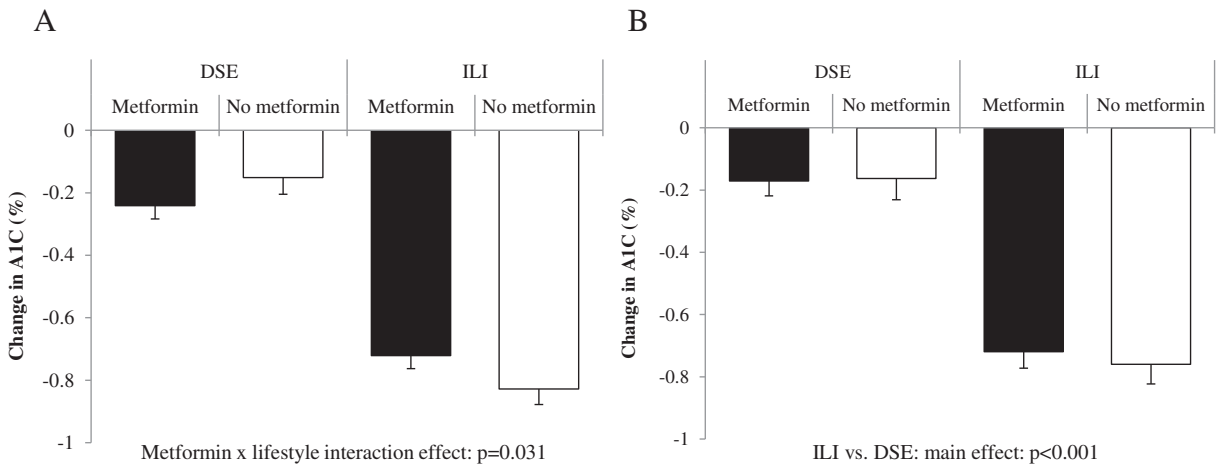

Fig. 1. Changes in glycated hemoglobin A1C according to baseline metformin therapy and lifestyle intervention: (A) All participants; and (B) participants who did not alter anti-hyperglycemic medication. Data are reported as adjusted mean square ± standard error of the mean. DSE: diabetes support and education; ILI: intensive lifestyle intervention.

between metformin therapy and no metformin. Our sensitivity analysis showed consistent outcomes.

4. Discussion

This study assessed how metformin therapy prior to and during lifestyle intervention influenced the established effects of intensive lifestyle intervention in people with type 2 diabetes. The main finding of the current study is the metformin therapy-by-lifestyle intervention interaction effect on glycemia, highlighting that background metformin therapy was associated with different changes in glycemia following ILI and DSE. While the influence of metformin therapy may be considered small, this finding underscores the complexity of combining first-line anti-hyperglycemic treatments: pharmacotherapy and lifestyle intervention.

Our results showed that the degree of reduction in FPG associated with metformin therapy compared to no metformin differed between ILI vs. DSE. Following DSE, a greater reduction in FPG associated with metformin therapy confirmed the established independent anti-hyperglycemic effect of metformin [8,10]. Interestingly, following ILI, we observed very similar or slightly smaller reduction in FPG associated with metformin therapy when compared to no metformin. This was unlikely due to changes in anti-hyperglycemic medication prescription as our sensitivity analysis excluding those who altered any anti-hyperglycemic medications showed consistent results. While the difference between metformin therapy and no metformin within the ILI group was small and not clinically meaningful, our finding showed that metformin therapy by itself was associated with continued improvement in FPG but combining metformin therapy and lifestyle intervention conferred little additional benefit on FPG compared to ILI without metformin therapy.

In addition to FPG, we found a significant metformin therapy by lifestyle intervention interaction effect on A1C, although our sensitivity analysis did not confirm the interaction effect. In the DSE group, a proportion of participants who increased or initiated anti-hyperglycemic medications were larger in participants not prescribed metformin when compared to those prescribed metformin therapy, and a proportion of participants who decreased or discontinued anti-hyperglycemic medications were larger in metformin therapy than no metformin. A reduction in anti-hyperglycemic medication probably happened in those who had relatively large improvements in glycemia, whereas an increase in anti-hyperglycemic medication probably happened in those who had worsened or showed little improvements in glycemia. Removing these participants who showed relatively large changes in our sensitivity analysis may have diminished the difference in A1C associated with metformin therapy vs. no metformin following DSE. For a similar reason, we suspect that exclusion of those who altered anti-hyperglycemic medication resulted in a smaller difference between metformin and no metformin following ILI. Smaller differences associated with metformin therapy and no metformin within ILI and DSE may explain lack of interaction effect in our sensitivity analysis on A1C.

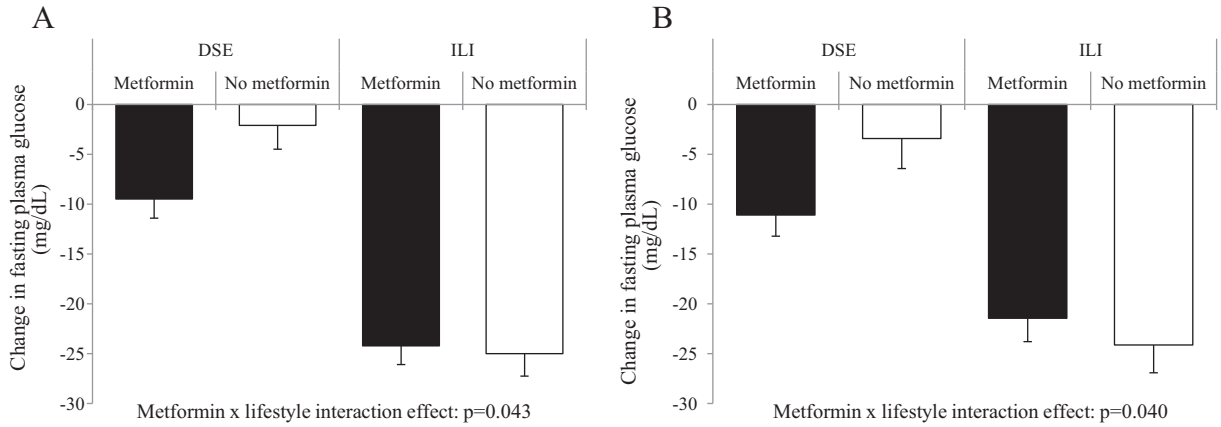

Fig. 2. Changes in fasting plasma glucose according to baseline metformin therapy and lifestyle intervention: (A) All participants; and (B) participants who did not alter anti-hyperglycemic medication. Data are reported as adjusted mean square ± standard error of the mean. DSE: diabetes support and education; ILI: intensive lifestyle intervention.

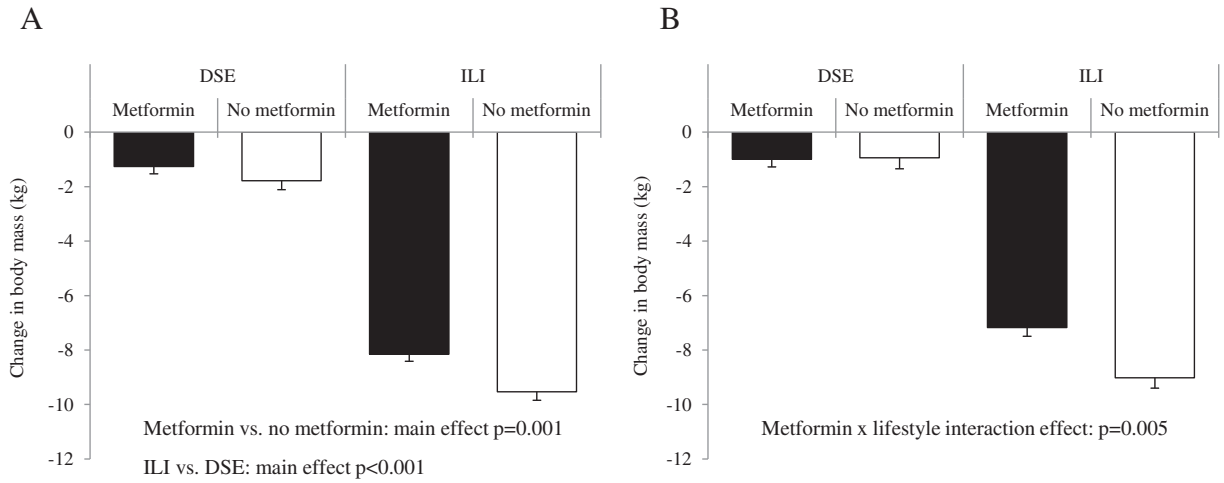

Fig. 3. Change in body mass according to metformin therapy and lifestyle intervention: (A) All participants; and (B) participants who did not alter anti-hyperglycemic medication. Data are reported as adjusted mean square ± standard error of the mean. DSE: diabetes support and education; ILI: intensive lifestyle intervention.

We do not have clear explanation on why metformin therapy and lifestyle intervention consistently showed a significant interaction effect on FPG but not on A1C. Metformin therapy primarily targets fasting glucose [25] by suppressing hepatic glucose output [8,9] but A1C is an aggregated measure of fasting and postprandial glucose. Notably, the contribution of fasting glucose and postprandial glucose to A1C depends on overall glycemic control. The relative contribution of postprandial glucose to A1C is especially high in individuals with fairly well controlled A1C (≤8.4%), whereas the relative contribution of fasting glucose to A1C increases gradually with the worsening glucose control [26]. Given the overall glucose control in our sample population (mean A1C = 7.4%), the effect of metformin on fasting glucose may not have been prominently reflected on A1C due to a relatively high contribution of postprandial glucose. This speculation is support by the Diabetes Prevention Program Research Group showing that, in individuals without diabetes (mean A1C: 5.9 ± 0.5), metformin has more pronounced effects on fasting glucose but less on postprandial glucose [27]. Alternatively, with reduced sample size in our sensitivity analyses, a smaller effect size in A1C compared to FPG may explain lack of interaction on A1C.

It is not clear why metformin therapy did not accentuate the hypoglycemic effect of ILI. Hepatic glucose output is a primary regulator of fasting glucose [28], and increased hepatic insulin resistance predominantly characterizes impaired fasting glucose [29]. Metformin therapy alone reduces fasting glucose by suppressing hepatic glucose output [30]. However, because both metformin and lifestyle intervention have an overlapping action on AMP-activated protein kinase (AMPK) [30–32] in the liver, metformin therapy may have influenced the effects of ILI on hepatic insulin sensitivity. A study on rats with obesity and type 2 diabetes have shown that combining metformin therapy with exercise [33] or combining metformin therapy with caloric restriction [34] have little additional benefits on fasting glucose, and suggested that metformin therapy can potentially impair exercise-induced hepatic mitochondrial adaptation [33]. A human study has also demonstrated that metformin therapy combined with exercise results in a greater hepatic glucose output compared to exercise alone in people with insulin resistance [20]. It is possible that metformin therapy, when used simultaneously with intensive lifestyle intervention, attenuates hepatic insulin sensitivity and increases hepatic glucose output.

Contrary to previously demonstrated weight-neutral and weight-lowering effects of metformin [8,10,11], our primary analysis showed a significantly smaller reduction in body mass associated with metformin therapy. When we conducted sensitivity analysis including only those who did not alter anti-hyperglycemic medications, we found a significant metformin therapy-by-lifestyle intervention interaction effect, which was primarily due to similar body mass reduction associated with metformin therapy and no metformin following DSE but slightly smaller reduction in body mass associated with metformin therapy compared to no

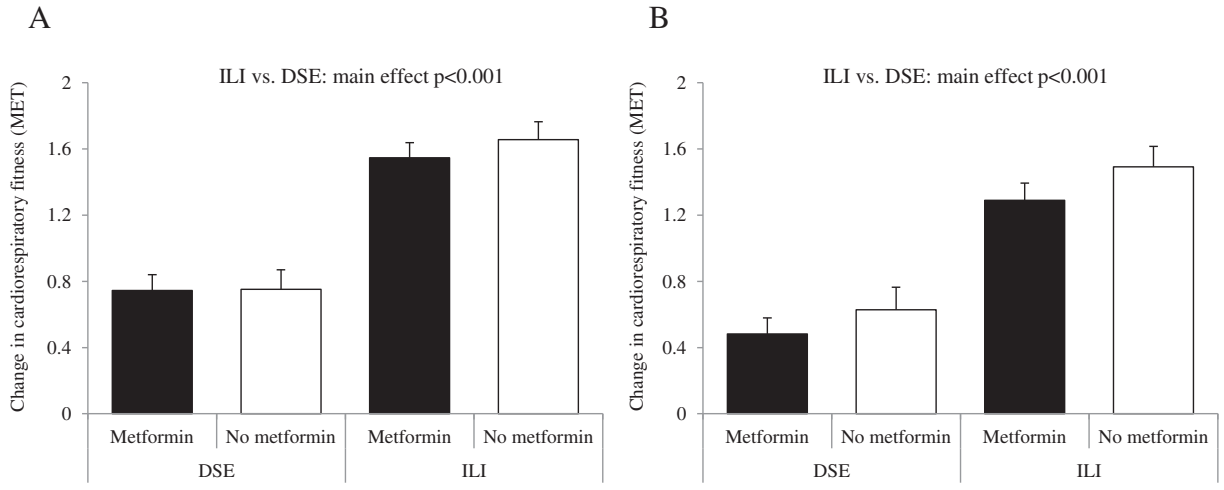

Fig. 4. Change in cardiorespiratory fitness according to metformin therapy and lifestyle intervention: (A) All participants; and (B) participants who did not alter anti-hyperglycemic medication. Data are reported as adjusted mean square ± standard error of the mean. DSE: diabetes support and education; ILI: intensive lifestyle intervention; MET: metabolic equivalent.

metformin following ILI. This interaction effect remained significant after removing participants who were prescribed orlistat at any point during the interested period (interaction effect: $p = 0.032$).

To disentangle the potential confounding by concurrent use of other anti-hyperglycemic medications, we conducted an additional analysis on a subset of participants who were exclusively on metformin therapy that did not alter medication prescription throughout the study period ($n = 463$: Supplementary Fig. S1). Such analysis showed no interaction effect on body mass change ($p = 0.058$) but consistently smaller reduction in body mass associated with metformin therapy when compared to no metformin (-4.4 ± 5.8 vs. -5.6 ± 6.0 kg, $p = 0.035$). Similar to our sensitivity analysis, there was a small difference in body mass reduction associated with metformin therapy and no metformin following DSE (-1.5 ± 4.3 vs. -1.4 ± 5.2 kg); the reduction in body mass associated with no metformin therapy was greater when compared with metformin therapy following ILI (-9.9 ± 7.0 vs. -8.2 ± 6.2 kg). These observations highlight the possibility that background metformin therapy could mitigate the weight-lowering effect of intensive lifestyle intervention. Further study is warranted to elucidate if metformin therapy attenuates the established effects of lifestyle intervention on weight loss.

Consistent with a previous study [22], our results showed that metformin was not associated with changes in CRF. Emerging evidence suggests that statin use can compromise an increase in CRF indirectly through inducing myalgia and directly through affecting mitochondrial function in skeletal muscle cells [35]. In addition to adjusting for statin use, further analyses were conducted separately on participants with and without statin prescription at baseline. As a result, we found that the metformin therapy by lifestyle intervention interaction effect on changes in CRF was significant in those who were prescribed statin at baseline ($n = 719$, $p = 0.043$) but not in those who were not prescribed statin ($p = 0.520$). Among those prescribed with statin at baseline, changes in METs between metformin therapy vs. no metformin were 1.6 ± 2.1 vs. 2.0 ± 2.3 METs in the ILI group and 0.7 ± 1.8 vs. 0.5 ± 1.5 METs in the DSE group. Statin by metformin therapy interaction is beyond the scope of this study. However, given that both statin and metformin are one of the most frequently prescribed medications, their interaction requires further exploration. When we repeated the analysis separately based on statin therapy on A1C and FPG, the pattern of changes remained the same as our primary analyses in both groups (i.e., statin therapy and no statin). However, the interaction effects on glycemia became no longer significant most likely due to reduced power.

The primary limitations of the present study were: the absence of randomization to metformin therapy; breaking ILI vs. DSE randomization by dividing participants according to metformin status; significant differences in baseline characteristics between participants included vs. excluded; and, potential confounding by concurrent anti-hyperglycemic medications. We attempted to minimize the impact of confounders by adjusting for various covariates in our analyses. However, residual confounding not included in our analyses may have existed. On a similar note, inclusion of several covariates dramatically reduced our sample size. Because dietary data were more frequently missing ($n = 2802$), we conducted analyses without adjusting for dietary intake and found consistent outcomes ($n = 4429$; Supplementary Fig. 2). In the primary analyses, we did not adjust for the baseline measure of the dependent variables because of minor imbalance at baseline. Repeating analyses while also adjusting for the baseline measure of the dependent variable showed consistent results to our main analyses for FPG, weight and CRF but not for A1C, where the interaction effect was not significant ($p = 0.121$, Supplementary Fig. 3). Given inconsistent interaction outcomes on A1C, the changes associated with therapies combining metformin and lifestyle intervention on A1C warrant further investigation. Second, while the differences are most likely attributable to the large sample size, significant differences at baseline between those included vs. excluded limits the generalizability of our results. Third, most participants taking metformin were simultaneously taking other anti-hyperglycemic medications. While we adjusted for these additional anti-hyperglycemic medications, it does not completely disentangle the potential impact of these medications. That being said, in a real life situation, metformin is often taken in combination with other anti-hyperglycemic agents. We consider that our analyses reflect glycemic responses in a real world setting. We attempted to perform analyses on those who were only on metformin, but sample size became small and the risk of type 2 error was high.

5. Conclusion

With established independent effects of pharmacotherapies and lifestyle intervention, combined therapies have widely been recommended with an expectation of further benefit. While the small magnitude of the observed interaction should not discourage the concomitant use of these therapies, the interaction between metformin therapy and lifestyle intervention on glycemia highlights the complicated nature of combining therapies.

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Author Contribution

NGB and TT were responsible for the conception and design of this substudy. NGB and TT analyzed and interpreted data. TT drafted the article and NGB critically revised the manuscript for important intellectual content. Both authors gave final approval for the submission of the manuscript.

Conflict of Interest

None.

Funding

None.

Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2019.01.004.

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