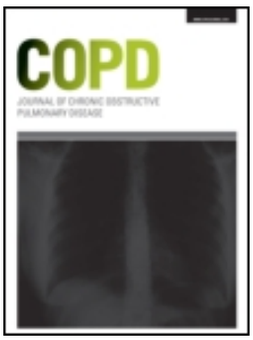

COPD: Journal of Chronic Obstructive Pulmonary Disease

ISSN: 1541-2555 (Print) 1541-2563 (Online) Journal homepage: https://www.tandfonline.com/loi/icop20

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To cite this article: Paul Sexton, Patricia Metcalf & John Kolbe (2014) Respiratory Effects of Insulin Sensitisation with Metformin: A Prospective Observational Study, COPD: Journal of Chronic Obstructive Pulmonary Disease, 11:2, 133-142, DOI: 10.3109/15412555.2013.808614

To link to this article: https://doi.org/10.3109/15412555.2013.808614

COPD JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

informa healthcare

COPD, 11:133–142, 2014
ISSN: 1541-2555 print / 1541-2563 online

DOI: 10.3109/15412555.2013.808614

ORIGINAL RESEARCH

Respiratory Effects of Insulin Sensitisation with Metformin: A Prospective Observational Study

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Abstract

The mechanism for the association between diabetes mellitus and lung function impairment is unknown, as are any respiratory effects of antidiabetic agents. We aimed to assess whether treatment with metformin, an oral insulin-sensitising agent, improved lung function or symptoms in individuals with COPD and glucose intolerance. A prospective open-label observational study was conducted. Participants with moderate or severe COPD, BMI > 25 kg/m^2, and type 2 diabetes mellitus or impaired glucose tolerance took metformin twice daily for 6 months. Clinical outcomes included St George's Respiratory Questionnaire (SGRQ), transition dyspnoea index, and incremental shuttle walk test. Physiological outcomes including pulmonary function tests, exhaled nitric oxide, respiratory mouth pressures and handgrip strength. In total, 17 participants completed the study. SGRQ score improved by a median of 5 points, and TDI scores improved by 2 points. Inspiratory mouth pressures increased by 7.5 cmH_2O. There were trends to improvements in hyperinflation, gas trapping and shuttle walk distance. Spirometry and exhaled nitric oxide were unchanged. In this proof-of-concept study, metformin was associated with improved dyspnoea and health status in COPD, possibly related to increased inspiratory muscle strength. These and other endpoints should be examined in a definitive study.

Introduction

Perhaps the most important consequence of the epidemic of diabetes mellitus (DM) is the burden of disease and disability caused by end-organ damage. Chronic hyperglycaemia damages blood vessels and connective tissue, leading to well-known complications of coronary artery disease, stroke, peripheral vascular disease, retinopathy, nephropathy, peripheral neuropathy, and joint contractures (1). DM also adversely affects respiratory function (2), although the mechanism remains unclear. Confounding by obesity is unlikely, since respiratory impairment is seen in type 1 DM, which is characterised by a slim body habitus (3). Chronic glycosylation of pulmonary connective and vascular tissue is supported by some histopathological evidence (4, 5), but there is also extensive evidence of respiratory dysfunction in prediabetic individuals (6), and lung function abnormality is unrelated to diabetes duration or control (2). The spirometric pattern is characteristically restrictive rather than obstructive (7), arguing against airways disease as the cause. Insulin resistance is associated with skeletal muscle dysfunction (8), but its effects on respiratory muscle are mostly unknown.

The lung function impairment that accompanies DM is typically mild, but could become clinically significant when patients also suffer from chronic

Keywords: Chronic obstructive pulmonary disease, Diabetes mellitus, insulin resistance, Metformin, respiratory muscle strength

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cardiorespiratory conditions. In particular, DM is a common co-morbidity in COPD (9) and baseline COPD is associated with increased risk of incident DM (10).

Despite the evidence linking DM with respiratory impairment, there is almost no literature examining the respiratory effects of insulin (11, 12) or other antidiabetic medications (13, 14). Metformin is a widely available oral antidiabetic medication which acts to both control hyperglycaemia and directly increase end-organ insulin sensitivity. Metformin is well-tolerated by non-diabetic individuals. The effects of metformin and thiazolidinediones on respiratory function among patients with COPD and T2DM were recently examined in a retrospective study (13); mean FVC was 132 mL higher among patients taking metformin or thiazolidinediones than among controls. Though allocation bias is a concern in the study design, the observed effect on FVC was impressive.

We conducted a prospective open-label observational study assessing the effects of metformin on respiratory symptoms, quality of life and lung function. We wished to assess first whether any effect was detectable; second, what the mechanism for such an effect might be; and third, the amount of time taken for the effect to appear. We therefore included endpoints that were both clinically relevant, and informative with regard to how glucose intolerance influences lung function.

Methods

Study design and participants

This was a prospective open-label observational study. Adults aged 18–75 who were overweight or obese (BMI > 25 kg/m^2) with symptomatic COPD (GOLD stage 2 or higher on post-bronchodilator spirometry) and either impaired glucose tolerance (IGT) or diet-controlled type 2 diabetes mellitus (T2DM) were invited to participate. Most participants were recruited from specialist respiratory outpatient clinics; some were recruited from primary care using advertisements. Participant recruitment and study design are depicted in Figure 1.

Participants were ineligible if they had a history of congestive heart failure, chronic respiratory failure, other active respiratory disease, hepatic cirrhosis, chronic liver failure, weekly alcohol intake above 21 units (males) or 14 units (females), or previous documented episode of lactic acidosis; if estimated GFR was < 45 mL/min; or if they were were taking metformin, other hypoglycaemic agents, or regular oral corticosteroids. All participants provided written consent. Ethical approval was obtained from the Auckland Ethics Committees.

Study procedures

Subjects attended an initial screening visit where written consent was obtained. Spirometry was measured according to ATS/ERS guidelines (15) using an electronic spirometer (Micro Plus CE 0120, CareFusion 232 Limited, Chatham Maritime, Kent, UK), 15 minutes after inhalation of 400 mcg of salbutamol via spacer. Blood was drawn to measure renal function, liver function and coagulation.

Eligible participants then attended a baseline visit where several procedures were performed. Exercise capacity was assessed using an incremental shuttle walk test. Health-related quality of life was measured using the St George's Respiratory Questionnaire (SGRQ) (16). Dyspnoea was assessed using the Baseline Dyspnoea Index (BDI) (17). Habitual physical activity was assessed using the CHAMPS questionnaire (18).

Dynamic and static lung volumes, gas transfer (DLCO), respiratory mouth pressures and exhaled nitric oxide were measured in a pulmonary function laboratory according to ATS/ERS guidelines (15). Handgrip strength was measured using a Jamar Plus digital dynamometer (Patterson Medical, Bolingbrook, Illinois, USA). Body fat content and distribution were measured using a Tanita BC-418 body composition analyser (Tanita Corporation, Arlington Heights, Illinois, USA).

Following this visit, all participants began taking metformin at an initial dose of 500 mg twice daily, increasing to 850 mg twice daily after 4 weeks. Subjects attended three interim followup visits, scheduled every 6 weeks. At these visits body weight, waist and hip circumference, handgrip strength, and spirometry were remeasured, venesection was repeated, and the transition dyspnoea index (TDI) questionnaire was administered.

Criteria for withdrawal included participant choice, unacceptable side effects, significant changes in regularly prescribed respiratory medications, or at the discretion of the responsible physician following hospitalisation with a severe illness associated with risk of lactic acidosis. Participants who experienced significant gastrointestinal side effects were offered a dose reduction (to 500 mg twice daily) as an alternative to withdrawal. After 6 months, subjects attended a final visit where the procedures of the initial visit were repeated.

Statistical analysis

Analysis was performed using the statistical software package R (http://www.r-project.org). Nonparametric methods were used for hypothesis testing. Paired Wilcoxon signed-rank tests were used to detect changes in continuous variables between the study beginning and end. Spearman's test was used to test for correlations between each outcome variable and potential confounders. The significance limit was set at 0.05. In all tables, median and range are given for measurements at baseline and final visits, and for the difference between these measurements.

Results

Baseline characteristics

A total of 17 participants completed the study. Participant baseline characteristics are shown in Table 1. Most subjects (76%) were of European ethnicity, and 59% were current or former smokers.

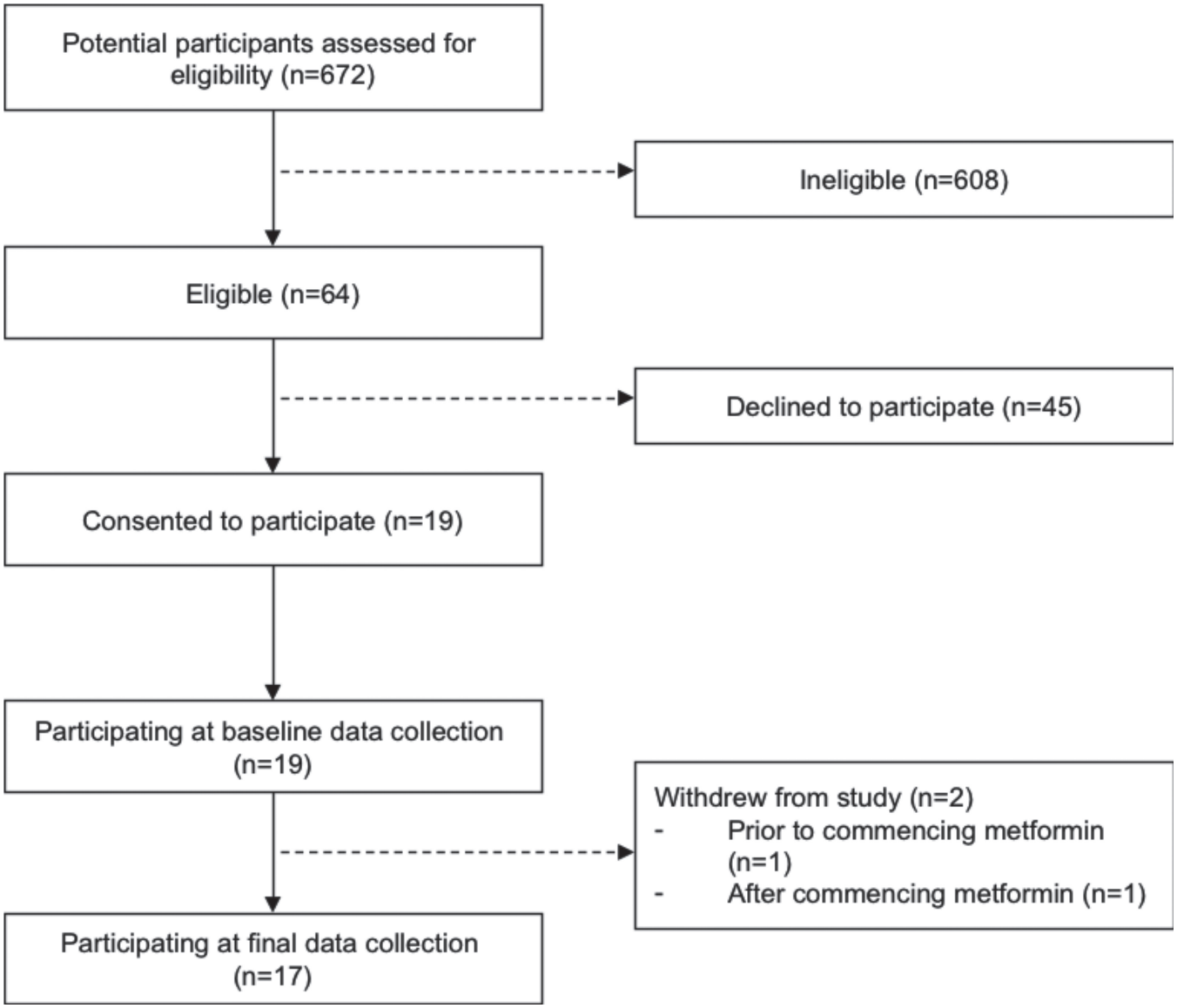

Figure 1. Flow chart depicting participant recruitment and study design.

Adverse events

No severe metformin-related adverse events occurred during the study. One participant dropped out after approximately 6 weeks, owing to gastrointestinal adverse effects of metformin. Another four participants experienced moderately troublesome gastrointestinal side-effects which resolved after lowering their metformin dose to 1 g daily. Thus, 5 participants (28%) experienced gastrointestinal side-effects sufficient to alter management, but only 1 (6%) exited the study.

Health status and symptoms

The SGRQ total score improved by a median of 5 points ($p = 0.005$), exceeding the minimal clinically important difference of 4 points (16) (Table 2, Figure 2). The impacts subscore fell by 4 points and and there was a trend to a reduction in the symptoms subscore. Dyspnoea also improved: at the final visit, total TDI and the "task magnitude" and "effort magnitude" subscores showed statistically and clinically significant (17) improvements.

Exercise capacity

There was a trend to a small improvement in the median incremental shuttle walk test (ISWT) (Table 2). The Borg score at test end improved by a median of 1 point.

Lung function

Baseline severity of AFO was moderate for most participants (Table 1), and gas trapping was common (Table 4). No significant changes in spirometry or gas transfer were seen during the study. There were trends towards reductions in TLC, RV and the RV/TLC ratio ($p < 0.15$).

Muscle function

Inspiratory mouth pressures (PI_{max}) increased during the study (Table 3 and Figure 3). PI_{max} increased among all but

Table 1. Baseline characteristics of study participants

	Median (range)
n	17
Male (%)	65
Age (years)	61 (42–74)
Height (cm)	173 (153–187)
Weight (kg)	89.4 (69.6–153.8)
BMI (kg/m^2)	29.1 (25.2–55.1)
Pack years (smokers only)	30 (14–114)
Diagnosis of asthma (%)	47
eGFR (mL/min)	83 (58–117)
Impaired fasting glucose (%)	88
Impaired glucose tolerance (%)	12
Type 2 diabetes mellitus (%)	13
HbA_{1c}, mmol/mol	42 (37–61)
FEV_1 (% predicted)	63 (33–78)
FVC (% predicted)	88 (50–114)
FEV_1/FVC ratio	0.53 (0.26–0.73)
FEV_1/FVC ratio (% predicted)	69 (34–92)
GOLD stage II	65
GOLD stage III	35
DLCO (L)	21.0 (10.7–38.1)
DLCO (% predicted)	84 (52–137)
Baseline dyspnoea index (BDI)	7 (3–10)

two participants, by a median of 7.5 cm H_2O. No significant changes were observed in expiratory mouth pressures, and grip strength decreased slightly (median loss of 1.4 kg).

Airway and systemic inflammation

There were trends to reductions in CRP and total and LDL cholesterol (not shown). No significant changes were seen in other lipid markers, or ENO (Table 4).

Changes in other variables

Participants lost a median 2.4 kg during the study, with corresponding small decreases in fat mass, BMI (median 0.9 kg/m^2) and WC. Metformin produced a median 3 mmol/mol decrease in HbA_{1c}. Fasting insulin and HOMA insulin resistance scores were stable. Reported daily physical activity was unchanged over the study, apart from small increases in frequency of moderate exercise (without changes in moderate-intensity caloric expenditure). None of the observed endpoint changes discussed above was statistically related to changes in body weight, BMI, or central obesity.

Discussion

This prospective observational study demonstrated beneficial effects of 6 months of oral metformin on health status, dyspnoea and physiological parameters in a group of adults with COPD and abnormal glucose homoeostasis.

Metformin was considered an ideal investigational agent for studying antidiabetic therapy in respiratory disease. It is an oral medication which acts through several mechanisms to control hyperglycaemia and increase end-organ insulin sensitivity. Metformin acts through AMP-associated protein kinase (AMPK), an energy-sensing enzyme present in all cells (19), to mimic the effects of caloric restriction, activate antioxidant defenses, and inhibit target of rapamycin. Metformin has effects beyond glucose metabolism: it has been associated with reduced incidence of, and mortality from, several cancers in epidemiological studies (20). Metformin has a well-established safety record, and the most serious biguanide-associated adverse event (lactic acidosis) appears to be extremely rare (21). As an oral agent, administration is more convenient than insulin. Finally, it is off-patent and inexpensive.

Clinical respiratory effects of metformin

The first aim of this study was to assess whether treatment with metformin was associated with clinical benefit

Table 2. Changes in health status and symptoms

Variable	Baseline Median (range)	Week 26 Median (range)	Change Median (range)	*p* value
SGRQ score (total)	45 (11–72)	39 (3–66)	–5 (–29–6)	0.0051
SGRQ score (symptoms)	65 (6–100)	50 (6–84)	–11 (–59–22)	0.0936
SGRQ score (activity)	54 (18–86)	48 (0–85)	–1 (–54–15)	NS
SGRQ score (impacts)	32 (0–77)	28 (0–58)	–4 (–32–4)	0.0042
Transitional dyspnoea index (total)	–	2 (–3–5)	–	0.0114
Transitional dyspnoea index (functional impairment)	–	0 (0–1)	–	0.0369
Transitional dyspnoea index (magnitude of task)	–	1 (–2–2)	–	0.0283
Transitional dyspnoea index (magnitude of effort)	–	1 (–1–2)	–	0.0120
Shuttle walk distance (m)	250 (90–530)	340 (130–630)	15 (–70–150)	0.1137
Borg score at test end	4 (1–7)	3 (1–7)	–1 (-4–2)	0.0441

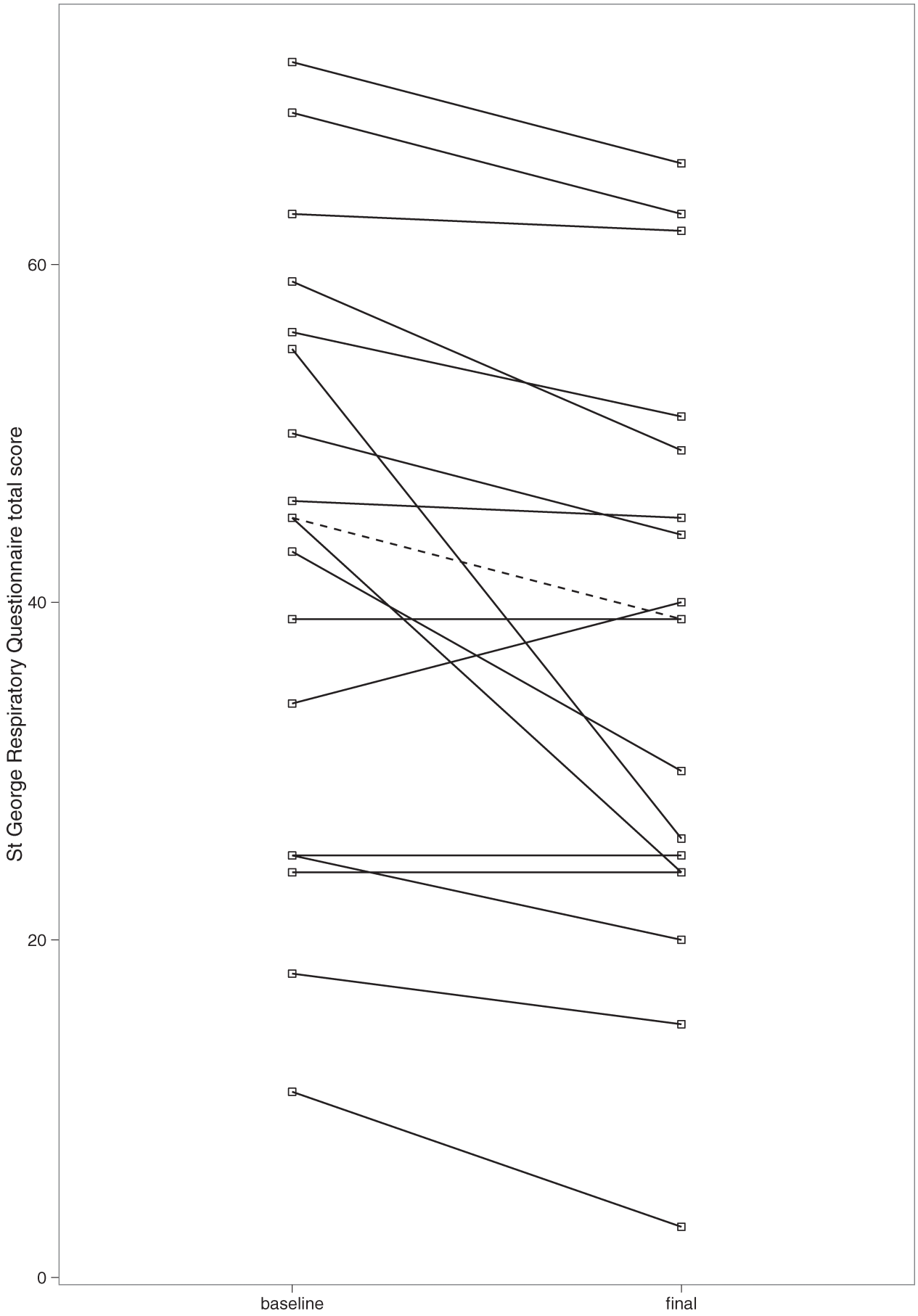

Figure 2. Change in St George's Respiratory Questionnaire total score. The dashed line shows change in the median score.

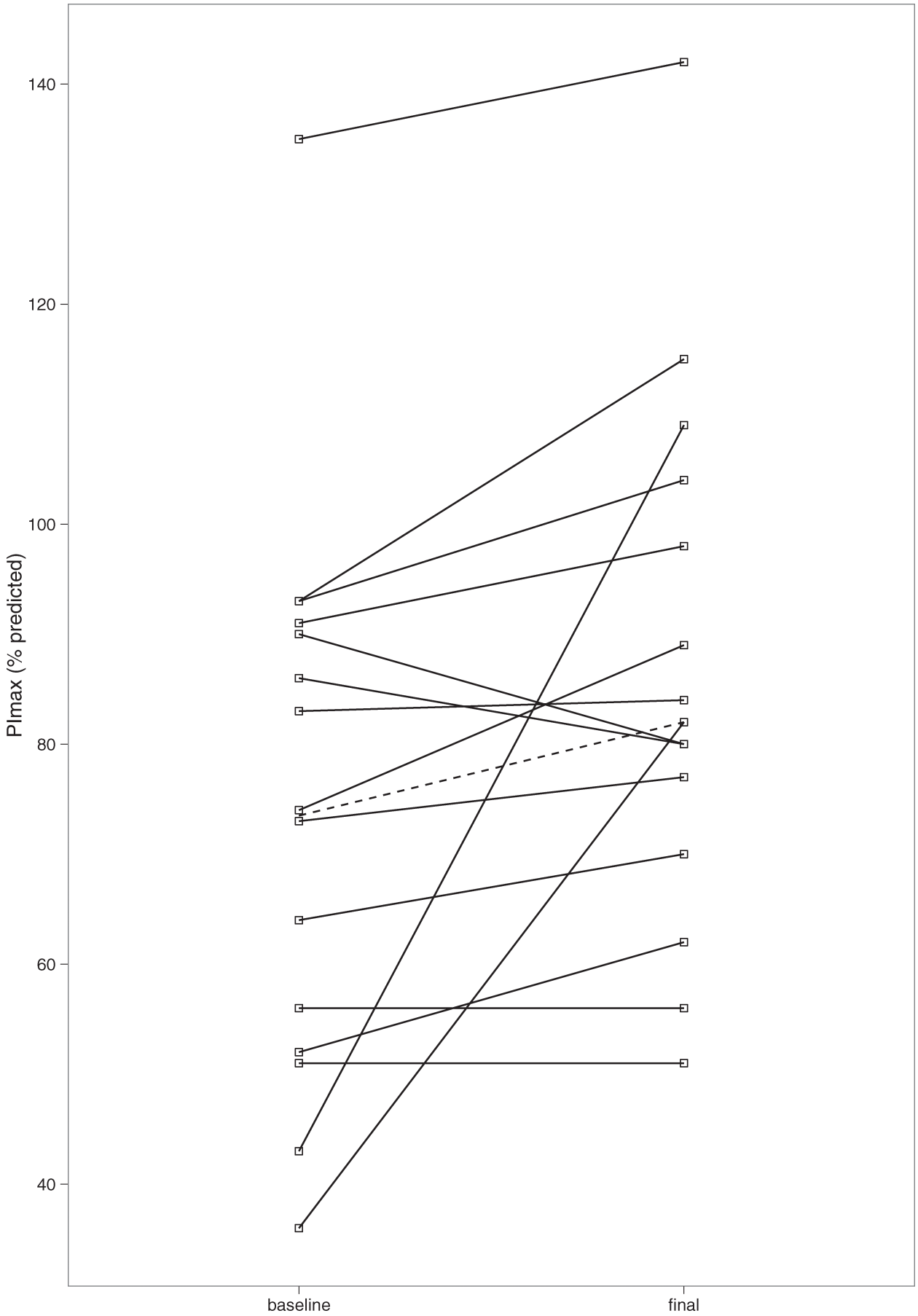

Figure 3. Changes in inspiratory mouth pressures (PI_{max}). The dashed line shows change in median PI_{max}.

Table 3. Changes in lung function, gas transfer and exhaled nitric oxide

Variable	Baseline Median (range)	Week 26 Median (range)	Change Median (range)	*p* value
FEV_1 (L)	1.54 (0.87–3.02)	1.66 (0.83–3.41)	0.03 (–0.34–0.65)	NS
FEV_1 (% predicted)	63 (33–78)	63 (29–81)	1 (–9–19)	NS
FVC (L)	3.43 (2.02–5.58)	3.48 (2.16–5.36)	0.07 (–0.65–0.89)	NS
FVC (% predicted)	88 (50–114)	92 (59–107)	2 (–12–20)	NS
FEV_1/FVC ratio	0.53 (0.26–0.73)	0.56 (0.27–0.67)	0.01 (–0.11–0.10)	NS
FEV_1/FVC ratio (% predicted)	69 (34–92)	73 (35–89)	1 (–15–12)	NS
TLC (L)	6.53 (4.31–9.94)	6.35 (4.16–9.84)	–0.16 (–0.57–0.42)	0.0995
TLC (% predicted)	105 (85–136)	101 (80–138)	–3 (–8–9)	0.1475
RV (L)	3.24 (1.77–4.42)	2.87 (1.49–4.30)	–0.28 (–0.91–0.52)	0.1208
RV (% predicted)	136 (89–171)	123 (60–170)	–13 (–36–28)	0.0833
RV/TLC ratio	0.44 (0.35–0.67)	0.45 (0.27–0.55)	–0.03 (–0.13–0.07)	0.1167
RV/TLC ratio (% predicted)	115 (88–159)	111 (65–146)	–6 (–30–18)	0.1297
FRC (L)	3.85 (2.36–5.60)	3.32 (2.20–5.82)	–0.09 (–0.72–0.34)	NS
FRC (% predicted)	116 (83–161)	109 (85–170)	–2 (–19–9)	NS
VC (L)	3.50 (2.17–5.61)	3.51 (2.16–5.54)	0.04 (–0.46–0.69)	NS
DLCO (L)	21.0 (10.7–38.1)	19.0 (10.1–34.5)	–0.6 (–5.5–2.7)	0.0883
DLCO (% predicted)	84 (52–137)	80 (49–140)	–3 (–22–13)	0.0736
ENO (ppb)	34 (8–220)	28 (10–135)	–4 (–85–52)	NS

in patients with COPD. To this end, respiratory health status, dyspnoea, and exercise capacity were assessed.

Health status and symptoms

The St George's Respiratory Questionnaire (SGRQ) is a well-established, self-administered health status questionnaire developed for use among patients with chronic airways disease (16). In this study, the SGRQ total score showed highly clinically and statistically significant improvements over the followup period, comparable in magnitude to the improvements seen in randomised trials of long-acting bronchodilators for COPD (16). The transition dyspnoea index (TDI) also showed clinically significant improvements (17). Taken together, the changes in SGRQ and TDI suggest that metformin produces meaningful symptomatic benefits in COPD.

Exercise capacity

The ISWT is a measure of maximal exercise capacity that has low intra-subject variability and close correlation with maximal oxygen uptake among patients with COPD (22). Although the increase in shuttle walk distance was statistically nonsignificant, it was consistent with the statistically significant increase in Borg dyspnoea scores at test end. A definitive study should reassess the effect of metformin on exercise, either using the ISWT or the 6-minute walk test.

Pathophysiological insights

The other aim of the present study was to gain insight into the mechanisms underlying any benefit. The most plausible mechanisms include reduced tissue glycosylation, reduced airway inflammation, and improved skeletal muscle function.

Table 4. Changes in general and respiratory muscle strength

Variable	Baseline Median (range)	Week 26 Median (range)	Change Median (range)	*p* value
PI_{max} (cmH_2O)	68 (26–157)	76 (53–165)	7.5 (–8.0–50.0)	0.0090
PI_{max} (% predicted)	74 (36–135)	82 (51–142)	7 (–10–66)	0.0130
PE_{max} (cmH_2O)	94 (54–173)	108 (58–235)	3 (–31–48)	NS
PE_{max} (% predicted)	56 (33–89)	59 (34–106)	1 (–16–35)	NS
Mean grip strength, dominant hand (kg)	31 (20–59)	30 (17–61)	–1.4 (–9.5–2.2)	0.0448
Mean grip strength, dominant hand (% predicted)	83 (64–122)	77 (58–120)	–2.8 (–30.6–5.4)	0.0395
Maximum grip strength, dominant hand (kg)	33 (20–62)	32 (19–62)	–1.2 (–10.3–3.5)	0.0244

Tissue glycosylation

The hypothesis that chronic glycosylation of pulmonary tissue accounts for the adverse effects of DM on respiratory function is supported by histopathological studies showing microangiopathy (4) with basal laminar thickening, increased synthesis and deposition of collagen and elastin, and unusual patterns of fibrosis (5).

However, an expected corollary is that DM-associated respiratory abnormalities should be slight at first, worsening with increased DM duration or with worse blood sugar control. In fact, lung function impairment is detectable *before* DM develops (6), and seems unrelated to control or duration of diabetes (2).

The present study was able to assess glycosylation only indirectly, by using changes in DLCO to reflect changes in severity of pulmonary microangiopathy. The lack of improvement in DLCO suggests that the pulmonary microvasculature did not respond to metformin within the followup period. However DLCO must be interpreted cautiously in small studies given its high intra-subject variability.

Airways disease

Despite the frequency with which DM coexists with COPD and asthma, little evidence specifically supports a causative role for DM in airways disease. The lung function impairment associated with insulin resistance is almost always restrictive rather than the expected obstructive pattern (7). The literature on airway inflammatory markers in DM is nonexistent for ENO, and minimal for other exhaled substances (23). Despite *in vitro* evidence that hyperinsulinaemia causes proliferation and hypercontractility of smooth muscle (24), the diabetic response to bronchoconstrictor challenge appears to be normal or blunted (25).

In the present study, ENO did not change significantly with metformin treatment, suggesting that insulin sensitisation does not affect allergic airway inflammation. However, ENO was generally within normal limits at baseline, and most participants were taking inhaled corticosteroids, which are known to suppress ENO (26). No effects were seen on spirometry, but there were nonsignificant trends to reductions in TLC, RV, and RV/TLC ratio, possibly reflecting reduced hyperinflation and gas trapping. Overall, the evidence for airway-specific effects is weak, but the hints of improvements in static lung volumes are worthy of further study.

Muscle function

General skeletal muscle function is abnormal in DM (27), and handgrip strength correlates negatively with insulin resistance (8). Inspiratory muscle strength is abnormal in diabetic subjects (28) and metformin has improved diaphragmatic function in animal studies (29). There is no published literature on the effects of antidiabetic treatment on respiratory muscle function in humans.

In this study, the observed 11% increase in inspiratory muscle strength (PI_{max}) was highly statistically significant. The change was independent of changes in daily caloric expenditure, and was not accompanied by improved grip strength. The clinical significance of this result is unclear as literature on minimum clinically important differences in respiratory muscle strength is lacking. In a small trial of inspiratory muscle training, a 29% increase in PI_{max} was associated with clinically significant improvements in dyspnoea scores (30).

Hyperinflation can impair respiratory muscle function by altering diaphragmatic force-length relationships (31). However, we found no correlation between change in PI_{max} and change in RV (Spearman $p > 0.5$). Perhaps insulin resistance affects the diaphragm differently from other skeletal muscle. The results of the present study should prompt further examination of respiratory muscle function in glucose-intolerant subjects.

Adverse events and participant withdrawal

One participant discontinued the study (due to constipation); another 4 participants reported moderately troublesome gastrointestinal side effects which resolved after their metformin dose was reduced to 1g daily. However, the risk of attenuating any treatment effect must be considered before allowing dose reductions in any future study. If the 4 dose-reduced participants are counted as dropouts, the dropout rate is comparable to larger randomised trials of metformin (32). Other than gastrointestinal effects, no serious metformin-related adverse effects were recorded.

Limitations

The study lacked a control group. The ideal study design would have been a randomised placebo-controlled trial, which would have allowed us to measure the influence of placebo effects on SGRQ results, and of learning effects on PI_{max}. However we felt that available information was insufficient to allow confident selection of a primary endpoint. The single-arm design also maximised the number of participants exposed to metformin, maximising the chance of observing any treatment effect.

A longer follow-up period may have identified responses which were slower to appear. On the other hand, a longer study duration increases costs and dropout rates. Six months of followup was felt to be reasonable as evidence exists from other studies that diabetic complications begin appearing within this time frame (33).

The reduced dose of metformin taken by some participants may have been subtherapeutic. A larger randomised placebo-controlled study should require participants to withdraw if they cannot tolerate the full dose.

Data were not collected on COPD exacerbations, which are an important clinical outcome measure. More detailed assessment of airway function (bronchodilator reversibility, respiratory mechanics) and inflammation (exhaled breath condensate, sputum examination) may have produced additional pathophysiological insights.

Conclusions

In this prospective study of the effects of six months of metformin therapy in COPD, statistically and clinically significant improvements were observed in symptoms, health status, and inspiratory muscle function. The changes remained significant after correction for small changes in BMI, arguing against confounding by obesity. These observations are sufficiently encouraging to require confirmation in a larger, definitive study.

Such a study should be powered to observe a clinically significant increase in SGRQ score (not enough is known about the clinical effects of changes in PI_{max} to use it as a primary outcome). It should also aim to reexamine the other outcomes examined by the present study as secondary endpoints. A 6-minute walk test should be considered as a more directly clinically relevant alternative to the ISWT.

A longer study duration would be ideal. Diabetes or glucose intolerance may affect lung function through multiple mechanisms, some of which might take longer than 6 months to respond to normalisation of glucose metabolism. Continued observation might also reveal larger degrees of improvement in those endpoints which began to change in the present study.

Declaration of Interest Statement

This study was funded by a grant from the Greenlane Research and Educational Fund. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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