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Research Article

Metformin Therapy in Heart Failure Patients with Pre-Diabetes and Diabetes

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Abstract

Background: Hyperglycemia, insulin resistance and type 2 diabetes mellitus (DM) are common in heart failure (HF) and associated with increased mortality. Despite a previous contraindication in HF, metformin in HF has been associated with improved outcomes but has not been studied prospectively. **Hypothesis:** Metformin therapy in HF patients with DM or pre-diabetes (preDM) may improve cardiac function and symptoms in patients with HF. **Methods:** Fifteen patients with systolic HF and DM or preDM, defined as glycosylated hemoglobin (HbA1c) ≥ 5.7%, were initiated on metformin therapy for 3 months in this single-arm, prospective, pilot/feasibility study. Other HF medications were unchanged during the study period. Pre- and post-metformin therapy examinations included echocardiography, cardiac biomarkers, a 6-minute walk test (6MWT) and a quality of life (QOL) questionnaire. **Results:** Mean age was 55 ± 9 years, with 67% NYHA class II and 27% NYHA class III. After 3 months of metformin therapy, there was a significant improvement in left ventricular ejection fraction (LVEF, 23 ± 10% to 27 ± 10%) and the trend toward improvement in left ventricular end-diastolic dimension (LVEDD, 67 ± 10mm to 64 ± 9mm). There was also a trend towards improved B-type natriuretic peptide (BNP), 6MWT distance, and QOL scores. HbA1c and renal function were unchanged after metformin therapy. **Conclusions:** Metformin therapy in HF patients with pre-DM and DM is safe and associated with improvement in LVEF. Future investigations should focus on metformin's effects in improving HF survival as well as its mechanisms of action in HF.

Introduction

Heart failure (HF) affects 5.8 million individuals in the United States, with an estimated 670,000 new cases each year [1,2]. Diabetes (DM), particularly type 2 DM, is a common co-morbidity in patients with HF, present in approximately 25% of stable outpatients and 50% of hospitalized patients with HF [3]. Several studies have shown DM in HF patients is associated with more symptoms, worsened functional status, and higher mortality [4-10].

In retrospective studies, many anti-diabetic medications including insulin, thiazolidinediones, and sulfonylureas have been associated with harm when used in patients with HF [11]. The only diabetes medication that has been associated with benefit in patients with DM and HF is metformin [12-14]. Due to the abundance of observational data, a previous black box warning regarding the use of metformin in HF was lifted, but HF still remains under "warnings" in metformin's labeling [15].

Potentially beneficial mechanisms of action of metformin in HF include improvement of myocardial energy metabolism, a decrease of potentially cardiotoxic free fatty acids, and reduced myocardial fibrosis [16-18]. This study was designed to assess metformin's tolerability and safety in HF patients as well as its effects on intermediate endpoints in HF, including cardiac structure and function, quality of life (QOL), exercise as assessed by six-minute walk test (6MWT), and cardiac biomarkers.

Methods

Participants

We studied 15 subjects with HF of both ischemic and non-ischemic etiologies and pre-DM or DM followed at a single

university center. Eligibility criteria included age ≥ 18 years, history of symptomatic HF, left ventricular ejection fraction (LVEF) ≤ 45%, glycosylated hemoglobin [HbA1c] ≥ 5.7%) and normal renal function (glomerular filtration rate [GFR] ≥ 60 mL/min, as calculated by the Cockcroft-Gault equation). Exclusion criteria were current metformin therapy, previously documented metformin intolerance, or a history of lactic acidosis.

Study Protocol

Subjects were followed prospectively in this single-arm study. Study visits were conducted at baseline (before treatment), 1 month, and 3 months (final study visit). Metformin therapy was initiated at 500 mg orally twice daily at the baseline visit. In diabetic subjects, blood sugar logs were reviewed by an endocrinologist at 1 month, and non-study anti-hyperglycemic agent doses were titrated if necessary. Metformin therapy was titrated to 1000 mg orally twice daily at the 1 month visit if tolerated, and if judged to be safe in diabetics on other antihyperglycemics. Per inclusion criteria, subjects were on stable, optimally-tolerated doses of standard HF therapy, including beta-blockers, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB); and dosing was not adjusted throughout the study period. Pre- and post-metformin therapy examinations included laboratory testing, comprehensive echocardiogram, 6MWT, and QOL questionnaire. Major safety variables (BUN, Cr, AST, ALT) were measured at baseline, 1 month and 3 months. The study protocol was approved by the UCLA Medical Institutional Review Board.

Two-dimensional echocardiography was performed by experienced technicians using Phillips iE33 Echocardiography System at baseline and final study visits. LVEF was quantified by the modified Simpson biplane method [19]. Diastolic measurements were also obtained including early diastolic filling velocity (E), late diastolic atrial filling velocity (A), mitral valve deceleration time (MVDT), and diastolic tissue Doppler velocities (E', A' and E/E' ratio). Echocardiograms were interpreted by physicians blinded to whether the study was from baseline or final visit. Blood was collected and processed by UCLA Clinical Laboratory and Pathology services.

The 6MWT was conducted on flat ground and the distance patients walked was recorded. Patients were asked to quantify their level of shortness of breath and level of fatigue using the Borg Rating of Perceived Exertion scale and indicate any chest discomfort, dizziness and/or palpitations they were experiencing before and after completion of the 6MWT.QOL was measured using the Minnesota Living with Heart Failure Questionnaire (MLHFQ), a 21-item disease-specific measure [20].

Statistical Analysis

Variables were reported as mean ± standard deviation for continuous variables and % total for categorical variables. Paired-samples *t*-tests were used to compare baseline to post-treatment variables within groups. Statistical comparisons were performed using 2-sided significance tests and a $p \leq 0.05$ was considered to be statistically significant.

Results

Study Population

Seventeen patients were enrolled in the study and fifteen patients completed the study. One subject did not complete the study because he was noncompliant with his other HF medications resulting in a decline in his clinical status. The other subject failed to show up for his final study visit due to transportation problems. The mean patient age was 55 ± 9 years and patients were predominantly male (80% male, 20% female). The average duration of HF was 6 ± 5 years with 6% of patients classified as NYHA class I, 67% as NYHA class II and 27% as NYHA class III. Table 1 shows the results of baseline and final study visit evaluations.

Metformin Therapy and Glycemic Control

Thirteen patients (87%) were on a target dose of 1000 mg BID at 3 months. At the end of the 3-month study period, there was no significant change in HbA1c (Table 1).

	Pre-Metformin (Baseline)	Post-Metformin (3 Months)
Age, years	55.3 ± 9.410	N/A
Male, n (%)	12 (80%)	N/A
Duration of cardiomyopathy, years	5.7 ± 4.9	N/A
Ischemic cardiomyopathy, n	8 (53%)	N/A
Heart failure medications, n (%) Beta-blocker ACEI/ARB Aldosterone antagonist Loop Diuretic	 15 (100%) 14 (88%) 13 (75%) 13 (75%)	 15 (100%) 14 (88%) 13 (75%) 13 (75%)
BMI, kg/m²	31.7 ± 6.0	31.3 ± 6.1
Waist circumference, cm	110 ± 14	110 ± 13
NYHA class, n (%) I II III IV	 1 (6%) 10 (67%) 4 (27%) 0	 2 (13%) 94 (60%) 43 (27%) 0
HbA1c, %	7.7 ± 2.2	7.6 ± 2.5
BNP, pg/mL	237 ± 259	167 ± 192
hsCRP, mg/L	4.7 ± 5.9	4.7 ± 6.1
LVEF, %	23 ± 10	27 ± 10*
LVEDD, mm	67 ± 10	64 ± 9
E, cm/s	85 ± 31	85 ± 24
E/A	1.2 ± 1.4	0.6 ± 0.7
MVDT, ms	220 ± 69	229 ± 1194
E/E'	16 ± 9	15 ± 8
MLHFQ score	47 ± 31	46 ± 33
6MWD, m	1250 ± 230	1330 ± 260

Table 1: Characteristics of subjects a baseline and after three months of metformin therapy;

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; NYHA, New York Heart Association; HbA1c, glycosylated hemoglobin; BNP, B-type natriuretic peptide; hsCRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fracture; LVEDD, left ventricular end-diastolic dimension; E, early diastolic filling velocity; A, late diastolic atrial filling velocity; MVDT, mitral valve deceleration time; E/E' diastolic tissue Doppler ratio; MLHFQ, Minnesota Living with Heart Failure Quality of Life Questionnaire; 6MWD, 6 minute walk distance *$p < 0.05$.

In the cohort of patients with DM, there were significant reductions in dosages of other antihyperglycemic agents, particularly insulin, after initiation of metformin therapy in 6 of the 8 patients (Table 2), with two patients no longer requiring insulin therapy after the initiation of treatment with metformin.

Patient	Baseline antihyperglycemic agents	3-month antihyperglycemic agents
1	Humulin 40 units SC qAM Humulin 35 units SC qPM	Humulin 25 units SC BID Novolog 10 units SC qAC Metformin 1000 mg BID
2	Glyburide 5 mg daily Novolog 8 units SC qAC NPH 15 units SC qAM NPH 7 units SC qPM	Glyburide 10 mg daily Novolog 10 units SC qAC NPH 18 units SC qAM NPH 8 units SC qPM Metformin 1000 mg BID
3	Lantus sliding scale Pioglitazone 15-30 mg prn	Lantus discontinued Pioglitazone discontinued Metformin 750 mg BID
4	Humalog 15 units SC qAC Lantus 30 units SC qAM	Humalog 10 units SC qAC Lantus 15 units SC qAM Metformin 500 mg PO BID
5	Lantus 32 units SC qAM Novolog 12 units SC qAC	Lantus 26 units SC qAM Novolog 8-10units SC qAC Metformin 1000 mg BID
6	Lantus 40 units SC BID Novolog 40 units SC qAC	Lantus 50 units SC BID Novolog 40 units SC qAC Metformin 1000 mg BID
7	Lantus 35 units SC daily Novolog sliding scale	Lantus discontinued Novolog discontinued Metformin 1000 mg BID
8	Humalog 4 units SC qAC Lantus 20 units SC daily	Humalog discontinued Lantus 15units SC daily Metformin 1000 mg BID Sitagliptin 50 mg BID

Table 2: Antihyperglycemic agents at baseline and at the end of the study in patients with DM.

Effect of Metformin on Cardiac Function

Systolic function improved as measured by LVEF after metformin therapy (Table 1, Figure 1).

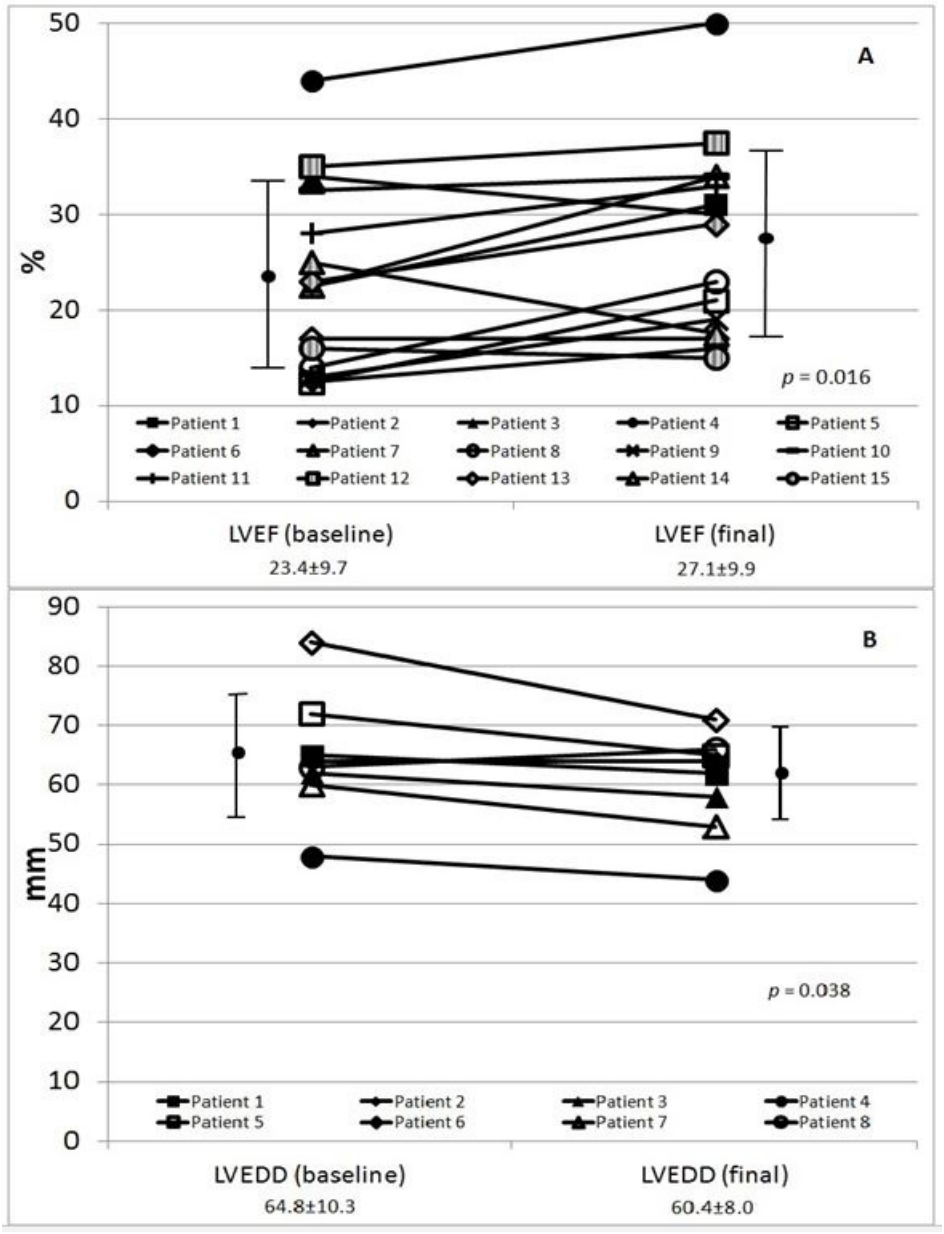


Figure 1: Metformin and cardiac function after 3-months of therapy; (A) Left ventricular ejection, LVEF in subjects (n = 15); (B) Left ventricular end-diastolic dimension, LVEDD in DM cohort (n = 8).

LVEF at baseline was 23 ± 10% and after 3 months of metformin therapy was 27 ± 10% (p = 0.016). Mean LVEDD was decreased from 67 ± 10 mm at baseline to 64 ± 9 mm after therapy (p = 0.096). There were no significant differences in diastolic measurements after metformin therapy (Table 1).

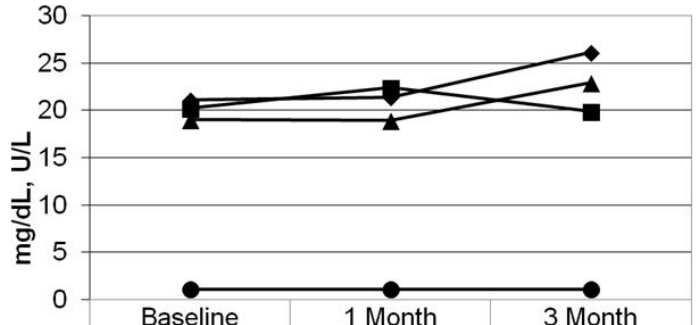
When the cohort was stratified by etiology, a greater degree of improvement in LVEF from baseline to 3 months was seen in the non-ischemic cohort (LVEF, % 19 ± 7 to 25 ± 7, p = 0.006) *vs* the cohort with ischemic etiology (LVEF, % 27 ± 10 to 29 ± 12, p = 0.38). After stratifying the cohort by DM *vs* preDM, a greater improvement in LVEF was seen in the DM cohort (x to x, p = x) *vs* those with preDM (x to x, p = x) (appendix).

Cardiac Biomarkers, Exercise Tolerance and Quality of Life

After 3-months of metformin therapy, there was a trend towards decreased BNP values (237 ± 259 to 166 ± 192 pg/ml, p = 0.06). The patients with non-ischemic etiology had more pronounced decrease in BNP, pg/ml (276 ± 260 to 167 ± 224, p = 0.06) compared to those with ischemic etiology (203 ± 271 to 176 ± 62, p =1.0). There was no significant change in hs-CRP after metformin therapy when compared to baseline values (Table 1). There was a non-significant trend towards improvement in 6-minute walk distance and MLHFQ score with metformin therapy. NYHA classification was either unchanged or improved in all patients at the end of the study period (Table 1).

Major Safety Variables

There were no statistically significant differences in any major laboratory tests done for safety (BUN, Cr, AST and ALT) measured pre-and post-metformin therapy (Figure 2). There were no adverse events.



	Baseline	1 Month	3 Month
BUN	20.2	22.4	19.9
Cr	1.1	1.1	1.1
AST	19	18.9	22.9
ALT	21.1	21.4	26.1

Figure 2: Safety variable monitoring (renal and liver function tests) during 3 months of metformin therapy.

Discussion

Metformin has been a mainstay of treatment for patients with DM type 2 for decades [24]. DM is a common comorbidity in patients with HF and is associated with a poor prognosis [25]. Until recently, HF was considered by the FDA to be an absolute contraindication to metformin use, mostly due to a theoretical risk of lactic acidosis which was seen with the older biguanide, phenformin; HF is still listed as a warning on metformin's labeling [17,26]. However, retrospective and observational studies have consistently demonstrated improved morbidity and mortality in HF patients with DM who are treated with metformin when compared to other anti-hyperglycemic agents. In Canada, a randomized double-blinded placebo-controlled trial was attempted, but aborted due to the inability to enroll patients, as the majority of diabetic HF patients in Canada were already treated with metformin [17]. This was the first prospective study to demonstrate that metformin is not only safe and well-tolerated in advanced HF patients with DM or pre-DM, but is also associated with improvement in cardiac function.

Metformin has several properties that are potentially cardioprotective and may account for the positive effects of metformin observed in the HF population. Metformin's actions are mediated, at least in part, by metformin's activation of AMP-activated Protein Kinase (AMPK), a protein kinase that is essential in regulating cellular metabolism for sustaining energy homeostasis under stress conditions [29-31]. When activated, AMPK stimulates fatty acid oxidation, promotes glucose transport, accelerates glycolysis and inhibits both triglyceride and protein synthesis [32-34]. Since glucose is more efficient than alternative substrates (i.e., fatty acids and lactate), metformin may act by improving the efficiency of myocardial energy utilization [27]. Metformin's inhibition of cardiac remodeling also may stem from the inhibition of fibrosis. Experimental data demonstrate that metformin reduces cardiac fibrosis by inhibiting the action of transforming growth factor (TGF)-β1 in cardiac fibroblasts [36].

A number of retrospective/observational studies in HF patients have demonstrated that metformin's use in HF patients is safe and well-tolerated, and associated with improved clinical outcomes in patients with HF and DM [13-15]. In a cohort of elderly HF patients, prescription of an insulin-sensitizing agent (metformin or thiazolidinedione) was independently associated with improved survival [13]. MacDonald et al. performed a case-control study of patients with newly diagnosed HF and T2DM and we found the use of metformin monotherapy or metformin combination therapy was associated with lower mortality. Finally, our group previously demonstrated that metformin therapy was associated with improved one-year survival as well as improved left ventricular function in patients with advanced HF and T2DM

followed at a single university center [15].

One recently published prospective study by Wong et al. investigated metformin therapy in insulin-resistant HF patients, with cardiopulmonary exercise testing as a primary endpoint. The study demonstrated that metformin was associated with reduced insulin resistance and improved exercise tolerance as evidenced by VE/CO_2 slope on cardiopulmonary exercise testing; however, LVEF was not significantly changed in the metformin *vs* the placebo group. This raises the possibility that the improvement in LVEF seen in our study stemmed from the lowering of dosages of potentially cardiotoxic antidiabetic agents in our subjects with clinical DM. However, a minority (13 of 49) of subjects in Wong's study had non-ischemic etiology, the subgroup in which we saw the largest increase in LVEF Further investigation into the types of HF patients who may benefit from metformin is clearly needed.

Furthermore, although metformin is being investigated as an agent to improve myocardial ischemic and reperfusion injury, several animal models have shown beneficial effects of metformin in non-ischemic systolic dysfunction. A study by Sasaki et al. examined the effects of 4-week oral metformin therapy in a pacing-induced HF model in dogs and found that compared with placebo, metformin improved LVEF, slowed HF progression, and decreased myocardial apoptosis via an AMPK-dependent mechanism [38]. Finally, in a genetic model of spontaneously hypertensive, insulin-resistant rats, metformin resulted in attenuation of left ventricular remodeling as evidenced by decreased left ventricular volumes, wall stress, and fibrosis as well as improved systolic and diastolic function [39].

Limitations

We acknowledge several limitations of our study. The study population was small, yet despite the small size, we found a significant improvement in LVEF and a trend toward improvement in LVEDD. The investigation was a single-arm pilot/feasibility study. Due to the limited study duration of 3-months, long-term effects of metformin therapy were not observed. It should also be noted that these patients were closely monitored in a comprehensive HF management program and these findings may not apply to patients who are followed in other settings. Nonetheless, this study has further confirmed a potential role for metformin in the management of pre-DM or T2DM in patients with advanced HF. We cannot rule out that the observed increase in LVEF and decrease in LVEDD were due to decreased dosing of other anti-diabetic agents in the DM cohort over the study period rather than due to the introduction of metformin. However, most outcomes other than LVEF were similar in the DM and pre-DM cohort (see appendix). However, All the patients enrolled in our study were on a stable HF regimen prior to initiating metformin therapy. There was no titration of standard HF medications during the study period to account for the improvement in cardiac function observed.

Conclusions

In patients with pre-DM or DM and advanced HF, metformin therapy is safe and well-tolerated despite warnings on use in HF on metformin's labeling. Short-term metformin treatment in 15 humans with advanced systolic HF of multiple etiologies on optimal medical therapy is associated with a significant improvement in cardiac remodeling, as demonstrated by improvement in LVEF. Additional investigation of metformin therapy in HF patients, with further exploration, is warranted to determine which subgroups of patients may derive the most benefit.

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