Endocrine (2019) 63:252–258
https://doi.org/10.1007/s12020-018-1722-1

ORIGINAL ARTICLE

Effect of metformin on blood pressure in patients with hypertension: a randomized clinical trial

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Received: 31 May 2018 / Accepted: 12 August 2018 / Published online: 21 August 2018

Abstract

Objective Part of the beneficial effects of metformin on the prevention of cardiovascular events in diabetes can be attributed to pleiotropic effects, including a blood pressure (BP)-lowering effect. In a double-blind parallel clinical trial (NCT02072382), the effect of metformin on BP evaluated by ambulatory blood pressure monitoring (ABPM) was measured.

Methods Ninety-seven patients with hypertension, but without diabetes mellitus, were randomized to receive 850–1700 mg of metformin ($n = 48$) or placebo ($n = 49$). Clinical, laboratory, and ABPM data were collected at the baseline and after 8 weeks of follow-up.

Results The sample consisted mainly of White overweight women. There was no difference in BP reduction measured by ABPM between both groups. There was no effect in BP measured in the different periods of ABP monitoring and office BP. Additionally, fasting plasma glucose, lipids, and C-reactive protein remained unchanged during the trial. There was a significant reduction in waist circumference with metformin (95.1 ± 10.4 to 89.3 ± 27.4 cm; $p = 0.02$).

Conclusion In the present trial, metformin did not reduce BP, measured by ABP monitoring, in hypertensive patients without diabetes.

Keywords Metformin · Blood pressure · Clinical trial · Ambulatory blood pressure · Hypertension

Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in patients with type 2 diabetes mellitus [1–4]. High blood pressure (BP) is a major cardiovascular risk factor in patients with type 2 diabetes, and BP-lowering treatment reduces their risk of developing cardiovascular complications [5, 6].

Metformin reduced macrovascular complications in patients with type 2 diabetes to a greater extent than other agents with similar glucose-lowering effect in the UK Prospective Diabetes Study (UKPDS) [7]. This finding suggested that the cardiovascular protection conferred by metformin could go beyond that determined by the improvement of glucose control [7, 8]. There are strong evidences that the cardioprotective effects of some anti-diabetic drugs are achieved not only by the glycemic reduction [9].

Metformin has more than one mechanism of action. Increased insulin sensitivity in skeletal muscle and the liver, improved glucose disposal, and decreased hepatic glucose production are the effects related to glucose metabolism [10]. In addition, some studies suggested that metformin could have BP-lowering effect. Animal experiments demonstrated a BP-lowering effect of metformin [11–14]. This effect could be mediated by vasodilatory actions secondary to increased nitric oxide production by vascular smooth muscle and reduction of plasma catecholamine levels [15].

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Studies of BP effects of metformin in humans have conflicting results due to methodological limitations. Among them, BP variation was not a prespecified outcome [16], the use of ambulatory blood pressure monitoring (ABPM) was infrequent [16–24], there was no control for antihypertensive drugs used during the follow-up [16–21, 23–25], lack of blinding for the different interventions [17, 19, 21, 23], and some studies were underpowered [17–19, 21, 22, 25].

We hypothesized that metformin may have beneficial effects on BP that are independent from its intrinsic glucose-lowering action. We therefore performed a randomized, double-blind, placebo-controlled trial of metformin in order to assess the effects of metformin on BP measured by ABPM in non-diabetic patients with hypertension.

Methods

This randomized controlled, double-blind parallel study was conducted in the Hypertension Clinic of the Division of Cardiology, Hospital de Clínicas de Porto Alegre (Porto Alegre, Brazil). The Institutional Ethics Committee approved the study and all patients signed an informed consent for participation. The protocol was registered in Clinical Trials.gov (Identifier: NCT02072382). The allocation of active treatment and its control was concealed, and a blind investigator distributed a numbered opaque container of identical appearance. Randomization was performed by an automated system, with stratification by systolic blood pressure (SBP) on ABPM (<130 or ≥130 mmHg).

Patients

Patients without diabetes (by history and confirmed by fasting plasma glucose <126 mg/dL tested at baseline), with controlled or uncontrolled hypertension (PAS >140 or PAD >90 mmHg), aged 18–75 years, were selected for the study. Main exclusion criteria included: diagnosis of secondary hypertension, severe hypertension by office BP (systolic blood pressure (SBP) ≥180 mmHg and/or diastolic blood pressure (DBP) ≥110 mmHg), known allergy or hypersensitivity to trial drugs; New York Heart Association grade II–IV heart failure, myocardial infarction, or stroke in the previous year; creatinine >1.5 mg/dL and pregnancy.

Procedures

Demographic and anthropometric data were collected at the baseline evaluation. Attended office BP and resting heart rate were measured with an automated device (Microlife BP3AC1-PC), with a cuff size corresponding to the circumference of the right arm before and after the experimental period. The average of two measurements was used in analysis. Participants had ABPM done at baseline and after 8 weeks of follow-up. Total cholesterol (TC), triglycerides (TGs), HDL-cholesterol (HDL-C), fasting glucose, and C-reactive protein (CRP) were determined at baseline and at end of 8 weeks follow-up period as well. The LDL-C was calculated using the Friedewald formula [26]. ABPM was registered with a Spacelabs 90207 ABPM monitor, scheduled for measurements every 15 min between 7 am and 11 pm (daytime period) and every 20 min from 11 pm to 6 am (nighttime period). Abnormal waist circumference was defined according with the International Diabetes Federation (≥90 cm for men and ≥80 cm for women) [27].

Patients were randomized to receive a pill with 850 mg of metformin or matching placebo after lunch during the first week, followed by 1700 mg (two pills), the second after dinner for seven consecutive weeks. Participants were instructed to maintain their drug and non-pharmacological treatment for hypertension, according to guideline recommendations [28].

Medication adherence was assessed by counting pills check. Use of more than 80% of the provided medication characterized good adherence. Tolerance to treatment was assessed by questioning for adverse effects by telephone interview at the fourth week and at end of the follow-up period.

In each visit, all patients received non-pharmacological recommendations according to our daily outpatient's routine [29].

Outcomes

The primary outcome was the difference in mean 24-h BP variation between the two groups after the intervention. Daytime and nighttime arterial BP, as well as the office BP, and laboratory and anthropometric differences were secondary outcomes.

Statistical analysis

Sample size was based on a standard deviation of 8 mmHg and effect size of 5 mmHg in 24-h systolic arterial BP and a two-sided significance level of 5%. A sample size of 42 patients per group provided a power of 80% to reject the null hypothesis. Considering possible 10% of losses, the final sample had 92 patients.

Baseline comparison between groups was performed using the Student's t test for continuous variables and χ^2 for categorical variables. In each group, the change in BP by 24-h daytime and nighttime arterial BP and laboratory tests was calculated by subtracting baseline values measured after the intervention period. The difference between groups

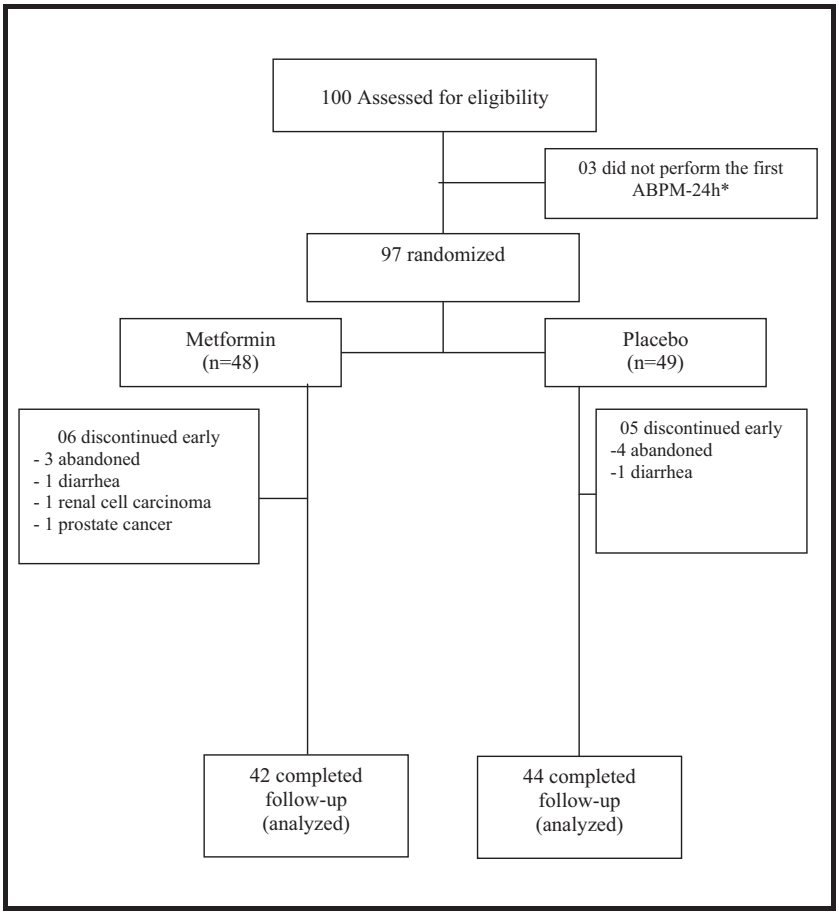

Fig. 1 Flow chart showing the patients allocated to both groups. ABPM ambulatory blood pressure monitoring

ABPM: ambulatory blood pressure monitoring

was calculated by subtracting the mean change variation observed between them (δ-values). BP variation and laboratory tests were analyzed by analysis of variance for repeated measures (MANOVA). All tests were two-tailed, and significance level was 5%. We performed a stratified analysis addressing the differences between deltas according to sex, body mass index (BMI), fasting glucose, and SBP-24 h above or below 130 mmHg. Data were analyzed using SPSS version 15.0.

Results

Between March 2013 and June 2016, 100 patients met the inclusion criteria and were invited to participate. Among them, 97 were randomized and 48 and 49 patients in the metformin and placebo groups, respectively, were effectively analyzed (Fig. 1).

Table 1 shows that there was a similar distribution of demographic characteristics, severity of hypertension measured by office and ambulatory BP, and in the proportion of patients using a combination of antihypertensive drugs in both treatment arms. There was a predominance of White overweight women in both arms. Based on an intention-to-treat analysis, randomized participants who did not complete the follow-up were included. Table 2 shows that BP measured by ABPM did not change in both treatment arms, and therefore there was no difference between metformin and placebo in their effects over BP. The absence of any effect was observed in the 24-h daytime and nighttime periods. Table 3 shows that there was no difference between metformin and placebo in the office BP. Fasting plasma glucose, lipids, and CRP remained unchanged during the trial as well. There was a significant reduction in waist circumference with metformin treatment ($p = 0.02$) (Table 4). From the whole sample, 60.5% patients had the criteria of abnormal waist circumference. There was no difference between both groups according to high or normal waist circumference (data not shown). Table 5 shows that in a stratified analysis, there was no difference in deltas relating to sex, BMI, fasting glucose, and SBP-24 h above or below 130 mmHg.

Adherence, as assessed by counting the number of tablets returned on last visit, was satisfactory in both treatment arms, but slightly higher in the placebo arm (87% versus 79% in the metformin group). The use of metformin

Table 1 Baseline characteristics of the study participants according to treatment group (mean ± SD or %)

Variable	Metformin (*N*=48)	Placebo (*N*=49)	*P*[a]
Male (%)	21.6	23.7	0.75
Age (years)	57.2 ± 9.8	57.0 ± 9.7	0.93
BMI (kg/m^2)	29.2 ± 4.9	28.7 ± 5.5	0.60
White (%)	93.8	91.8	0.71
SBP office (mmHg)	141.6 ± 17.3	138.7 ± 13.8	0.35
DBP office (mmHg)	85.9 ± 8.7	86.3 ± 10.0	0.82
SBP—24 h	125.5 ± 11.4	124.3 ± 11.4	0.59
DBP—24 h	74.3 ± 9.2	76.4 ± 9.7	0.27
>2 Antihypertensive drugs (%)	25.0	28.6	0.81
Diuretics (%)	71.7	69.6	0.82
ACE inhibitors or ARBs (%)	71.7	76.1	0.63
Calcium channel blockers (%)	23.9	21.7	0.80
Total cholesterol (mg/dL)	194.6 ± 30.5	213.0 ± 46.8	0.03
Triglycerides (mg/dL)	142.2 ± 53.0	138.4 ± 74.0	0.78
Creatinine (mg/dL)	0.8 ± 0.2	0.8 ± 0.1	0.44
Current smoker (%)	8.3	12.2	0.46
Fasting glucose (mg/dL)	96.1 ± 14.1	98.6 ± 18.8	0.46
Statin (%)	16.7	4.5	0.07
10-year CV risk (%)[a]	13.0 ± 9.9	13.5 ± 10.4	0.75

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *ACE* angiotensin converting enzyme, *ARBs* angiotensin receptor blockers, *CV* cardiovascular

[a]ACC/AHA Cardiovascular Risk Calculator (2013)

Table 2 Changes in BP evaluated by ABPM by treatment

BP	Group	Baseline	Follow-up	*P*[a]
24-h SBP	Metformin	125.3 ± 11.1	124.9 ± 11.2	0.59
	Placebo	123.5 ± 10.9	124.2 ± 12.8	
24-h DBP	Metformin Placebo	74.1 ± 8.8	73.7 ± 8.4	0.77
	Placebo	75.9 ± 9.4	75.1 ± 9.4	
Daytime SBP	Metformin	129.2 ± 10.9	128.5 ± 11.0	0.64
	Placebo	127.1 ± 11.4	127.4 ± 13.7	
Daytime DBP	Metformin	77.4 ± 9.1	77.1 ± 9.0	0.44
	Placebo	79.3 ± 9.5	78.0 ± 9.9	
Nighttime SBP	Metformin	117.8 ± 13.2	117.8 ± 13.5	0.57
	Placebo	116.4 ± 11.2	117.8 ± 12.4	
Nighttime DBP	Metformin	67.6 ± 9.2	66.9 ± 8.5	0.63
	Placebo	69.2 ± 10.5	69.4 ± 10.2	

SBP systolic blood pressure, *DBP* diastolic blood pressure

[a]Interaction: time × group

Table 3 Changes in office BP by treatment group

	Group	Baseline	Follow-up	*P*[a]
SBP office (mmHg)	Metformin	140.6 ± 14.7	140 ± 16.2	0.52
	Placebo	138.9 ± 13.1	136.1 ± 15.2	
DBP office (mmHg)	Metformin	85.4 ± 8.2	84.2 ± 10.2	0.28
	Placebo	86.2 ± 9.4	84.1 ± 10	

SBP systolic blood pressure, *DBP* diastolic blood pressure

[a]Interaction: time × group

resulted in significant more adverse effects (mainly diarrhea and abdominal pain) in the metformin group ($n = 08$) versus none in the placebo group ($p = 0.003$).

Discussion

The results of this randomized placebo controlled clinical trial showed that metformin has no effect over BP assessed by ABPM in hypertensive non-diabetic patients. We also did not find any significant decrease in office BP in the metformin group. Among the several secondary outcomes investigated in the trial, metformin promoted a reduction in waist circumference.

The results of UKPDS-34 showed that the positive effects of metformin on macrovascular outcomes could be related to some pleiotropic effect [7]. Early experimental studies had suggested that this antidiabetic drug could have some effect on BP reduction [11–14]. However, clinical studies showed some conflicting results that could be explained by methodological limitations. Among the previous studies that showed a BP-lowering effect of metformin, insufficient statistical power [17–19], analysis of BP reduction as secondary outcome [20], and absence of ABPM as a method of BP measurement are some methodologic problems that could weaken the findings. In studies that did not yield a BP effect, this variable was not analyzed as main outcome [16] or also had small samples [21–24]. The only study that used ABP monitoring did not find a BP reduction effect, but investigated only 25 subjects [25]. Our findings agree with a meta-analysis of 41 clinical trials including 3074 individuals, which found a non-significant office SBP reduction of 1.09 mmHg (−3.01–0.82) ($p = 0.3$) [30]. Conversely, a more recent meta-analysis, which included 4113 non-diabetic patients from 28 studies, showed that metformin had a significant effect on SBP (mean difference −1.98 mmHg; 95 CI; −3.61–0.35; $p = 0.02$), but not on DBP [31]. The dosage of metformin ranged from 500 to 2000 mg/day and the follow-up period was 3 months to 3.2 years. Contrary to our findings, there was an interaction between BP reduction and BMI and glucose intolerance. None of the included studies used ABPM to measure BP and this could be a limitation of the study. In an editorial about these results, Markis et al. [32] stated that meta-analyses are hypothesis-rising instruments and called for more clinical trials in this field, focusing on

the metformin BP effects in diabetic and non-diabetic patients, with controlled and uncontrolled BP and with BP measured with ABPM.

The evaluation of the possible pleiotropic effects of antidiabetic drugs may have important clinical implications. Recently, glucagon-like peptide-1 (GLP-1) agonists, a new class of incretin-based therapy used for the treatment of type 2 diabetes, had shown a cardioprotective effect independent of glucose control improvement [33, 34]. Most trials investigating the antidiabetic actions of GLP-1 agonists have reported reductions in BP [35]. Similarly, in the *EMPA-REG OUTCOME* [9], empagliflozin, an inhibitor of sodium–glucose cotransporter 2, added to standard care in patients with type 2 diabetes demonstrated cardioprotective effect. The authors infer that the mechanisms behind the cardiovascular benefit are multidimensional, including a BP reduction.

CRP is a sensitive marker of low-grade systemic inflammation and directly involved in the initiation and progression of atherosclerosis. Some studies have found a metformin-associated reduction in CRP levels [36, 37], whereas others did not [38, 39]. We also did not find any effect of metformin in lipids or in the CRP levels, but there was a significant reduction in waist circumference in the treatment group. There was also a trend in BMI in the metformin group. This finding could have occurred by chance but may explain at least part of the beneficial effects of metformin in the prevention of macrovascular events [8, 40]. Some studies have shown a positive effect of this drug on other components of the metabolic syndrome and atherosclerotic markers such as reduction of interleukin-6 (IL-6), a proinflammatory cytokine with positive association on insulin resistance, less progression on coronary artery calcification, and reduction of plasma levels of endothelial activation and coagulation [38, 41–43]. We also did not find any change in glucose and/or lipid profile in metformin group compared to placebo. This observation is in accordance with the clinical trial where 356 patients without type

Table 4 Changes in laboratory and anthropometric values

	Group	Baseline	Follow-up	P^a
Cholesterol (mg/dL)	Metformin	194.6 ± 30.6	191.6 ± 34.4	0.77
	Placebo	213.0 ± 46.9	212.2 ± 46.7	
LDL-C (mg/dL)	Metformin	120.4 ± 28.4	120.4 ± 31.1	0.70
	Placebo	138.8 ± 44.7	140.2 ± 41.8	
HDL-C (mg/dL)	Metformin	44.7 ± 08.1	43.8 ± 08.4	0.34
	Placebo	46.5 ± 11.5	46.7 ± 10.5	
Triglycerides (mg/dL)	Metformin	142.2 ± 53.0	136.9 ± 66.3	0.53
	Placebo	138.4 ± 74.1	126.5 ± 59.3	
Glucose (mg/dL)	Metformin	97.3 ± 14.9	95.2 ± 14.2	0.92
	Placebo	99.0 ± 19.5	96.7 ± 16.3	
Waist (cm)	Metformin	95.1 ± 10.4	89.3 ± 27.4	0.02
	Placebo	93.0 ± 14.1	95.0 ± 18.0	
BMI ($kg/m^{2)}$	Metformin	28.6 ± 04.8	27.6 ± 06.6	0.17
	Placebo	28.3 ± 05.3	28.3 ± 05.2	
CRP (mg/dL)	Metformin	4.7 ± 6.9	4.3 ± 6.0	0.34
	Placebo	5.6 ± 7.1	4.3 ± 5.4	

BMI body mass index, *CRP* C-reactive protein

Table 5 Stratified analysis by treatment group showing the deltas adjusted by basal pressure in participants that completed follow-up

	Variable	Group	Baseline	Follow-up	*P*	Deltas[a] (CI 95%) Adjusted	*P*
Sex	Male, $n = 38$	Metformin	124.3 ± 9.3	123.0 ± 4.9	0.66	1.3 (−3.9–6.4)	0.61
		Placebo	124.4 ± 11.9	124.3 ± 13.2			
	Female, $n = 48$	Metformin	126.2 ± 12.4	126.4 ± 14.2	0.72	0.35 (−5.6–6.3)	0.90
		Placebo	122.8 ± 10.3	124.1 ± 12.7			
BMI	≥25, $n = 61$	Metformin	127.4 ± 11.4	126.3 ± 12.5	0.51	0.13 (−5.0–4.7)	0.95
		Placebo	125.5 ± 9.9	124.7 ± 12.5			
	<25, $n = 25$	Metformin	119.6 ± 8.4	121.1 ± 5.5	0.52	2.3 (−4.8–9.3)	0.51
		Placebo	119.2 ± 12.2	123.1 ± 13.7			
Fasting glucose	≥100 mg/dL, $n = 28$	Metformin	130.0 ± 10.9	131.2 ± 12.0	0.76	0.35 (−7.6–8.3)	0.93
		Placebo	125.3 ± 10.7	127.6 ± 14.5			
	<100 mg/dL, $n = 53$	Metformin	123.0 ± 11.0	122.3 ± 9.4	0.81	0.84 (−3.8–5.5)	0.71
		Placebo	123.7 ± 11.3	123.5 ± 12.1			
SBP-24H	>130 mmHg, $n = 21$	Metformin	141.3 ± 7.9	134.5 ± 12.9	0.21	5.6 (−3.6–14.8)	0.22
		Placebo	137.3 ± 4.4	135.7 ± 10.0			
	<130 mmHg, $n = 65$	Metformin	121.0 ± 7.2	122.3 ± 9.4	0.92	0.7 (−5.3–3.8)	0.75
		Placebo	118.4 ± 7.6	119.9 ± 11.0			

Less participants with complete fasting plasma glucose owing to missing data

BMI body mass index, SBP systolic blood pressure

[a]Delta of BP between the baseline and follow-up visits in the metformin group minus the delta in the placebo group

2 diabetes, taking metformin compared with those taking placebo, had no significant differences for TC, HDL-C, non-HDL-C, TGs, high sensitivity CRP, or fasting glucose [44].

Some limitations of our study deserve mention. First, the follow-up period of 8 weeks may have been insufficient to demonstrate an effect of metformin over BP, particularly if this effect is mediated by other actions of metformin, as the reduction of waist circumference. A longer duration of treatment may reduce insulin resistance that could affect BP. However, experimental and clinical studies demonstrated a rapid vascular effect with the administration of metformin [13, 15, 45]

The meta-analysis of Wulffelé et al. [30]. included trials with at least 6 months follow-up period, and was negative regarding effects of metformin over office BP. Second, the sample size of the present trial precluded a meaningful stratified analysis to assess the differences in the effects of metformin on mean change variation of BP according to the baseline severity of BP, especially in those severe hypertensive patients. A significant BP reduction in patients with severe hypertension cannot be ruled out. Third, the effect of metformin over BP could express only in patients with diabetes. And finally, the single-center trial, with predominance of middle-aged overweight women, diminishes the external validity of our results.

In conclusion, metformin does not reduce BP measured by ABPM in hypertensive non-diabetic subjects.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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