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Original article

Effect of metformin combined with lifestyle modification versus lifestyle modification alone on proinflammatory-oxidative status in drug-naïve pre-diabetic and diabetic patients: A randomized controlled study

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ABSTRACT

Background: Targeting biomarkers of oxidative-proinflammatory stress may result in improvement of modifiable metabolic syndrome, pre-diabetes and diabetes risk factors and subsequent risk reduction.
Methods: 64 newly diagnosed antihyperglycemic treatment-naïve prediabetic and type 2 diabetes mellitus (T2DM) patients were randomly assigned using block design to either metformin combined with therapeutic lifestyle changes (TLC) or TLC alone. Body mass index (BMI), waist circumference, blood pressure, fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), fasting lipid profile, plasma oxidative status and tumor necrosis factor (TNF)-α were measured at baseline, after 3 months and after 6 months from baseline.
Results: Except for HbA1c, baseline values did not differ significantly between the two groups. The post 3-months relative reductions in BMI ($P = 0.014$) and HbA1c ($P = 0.037$) in metformin combined with TLC intervention were significantly greater than those in TLC alone group. TNFα plasma levels were decreased significantly vs. baseline by metformin combined with TLC intervention ($-22.90 \pm 46.76\%$, $P = 0.01$). Conversely, TLC alone basically worsened proinflammatory status (42.40 ± 40.82 %), $P < 0.001$. Metformin with TLC treatment effected a therapeutic decrement of the oxidative stress ($-15.44 \pm 35.32\%$, $P = 0.029$ vs. baseline) unlike TLC alone ($61.49 \pm 122.66\%$, $P = 0.01$ vs. baseline). Both interventions' effects were sustained in the 6-month follow up periods.
Conclusion: In both intervention groups, the relative changes in plasma TNFα were significantly correlated ($P < 0.01$) with systolic blood pressure and the relative changes in oxidative stress were markedly correlated ($P < 0.05$) with total cholesterol.

1. Introduction

Diabetes mellitus (DM) is associated with chronic microvascular, macrovascular and neuropathic complications [1]. Pre-diabetic state can be diagnosed via impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). Importantly, about one third of IFG patients develop diabetes eventually [2]. Patients with heart disease, metabolic syndrome (MetS) and T2DM have high concentrations of inflammatory adipocytokines such as tumor necrosis factor α (TNFα) [3]. TNF-α is principally expressed by adipocytes and have a key role in promoting atherosclerosis and, therefore, cardiovascular disease. [4]. TNFα has been also involved in obesity-related insulin resistance (IR) [3]. Apparently, with particular interventions, high-risk individuals for developing T2DM may substantially decrease the risk of onset of diabetes [5]. Highly recommended and well-structured programs to emphasize lifestyle changes with regular physical activity and moderate weight loss, incorporating dietary strategies with reduced calories and dietary fat but increased intake of protein and polyunsaturated fatty acid (PUFA). Collectively, they can drop on the risk for developing diabetes. The ADA recommended the following for prevention and management of pre-diabetic stage:

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those with HbA1c of 5.7–6.4% should increase physical activity to at least 150 min/week of moderate activity such as walking. Furthermore, they are advised to be placed on weight loss programs targeting 7% of body weight. For guaranteed success, follow-up counseling appears to be important [1,6]. Meftormin has evolved as an absolute reference drug for primary treatment of T2DM [7]. It improves the glycemic control by insulin sensitization [8,9]. It also reduces postprandial elevations of plasma glucose either by partly inhibiting intestinal glucose absorption, by increasing glucose utilization or by increasing glucose uptake/storage in peripheral tissues. At the level of the intestine, metformin has a negligible effect on glucose absorption but slightly delays the absorption process. However, due to the accumulation of metformin in the gut wall, metformin favors glucose metabolism to form lactate. The combination of these two phenomena reduces postprandial glycemic peaks [2]. Oral anti-hyperglycemic agents were evidenced with anti-inflammatory pharmacologies [10–12]. In an in vitro study, the influence of metformin on lipopolysaccharide (LPS)-induced increase in TNF production and tissue factor (TF) activities in isolated human monocytes was examined [13]. Interestingly, metformin inhibited the increase in both TNF and TF production through the inhibition of ERK1/2-Erg-1 (extracellular signal-regulated protein kinase (1/2) and early growth response factor-1) pathway in human monocytes after LPS stimulation, thus exerting an anti-inflammatory pharmacology in vitro. Further supportive evidence of metformin anti-inflammatory effect was proven via direct inhibition of TNFα [14–23]. Moreover, metformin was found to suppress NF-κB activation [24] and, thus, attenuate the TNF α-induced expression of proinflammatory and adhesion molecule genes via AMPK activation in vascular endothelial cells [25].

2. Experimental

In this randomized controlled trial, using block design by age, gender and BMI, we compared the effect of metformin (850 mg thrice a day) combined with therapeutic lifestyle changes (TLC) [regular daily dietary intake (1500 cal/day for men and 1200 cal/day for women) coupled to physical activity (daily moderate exercise for 30 min–1 h)], vs. TLC alone, on oxidative status and pro-inflammatory (TNFα) level in new-onset prediabetes or type 2 diabetes antihyperglycemic-treatment-naïve patients over the period of six months.

2.1. Study sample size

Based on the results of Esteghamati, et al. [26], the sample size was calculated by the formula:

$N = 2^{*}SD2\ (Z\alpha + Z\beta)^{2}/\Delta^{2}$ [27]

where: N: Sample size; Zα: Type one error = 1.96 when α = 5%; Zβ: Type two error = 1.28 when β= 10% SD = Standard deviation of the ferritin-reducing ability of plasma (FRAP) baseline and equals 250 μmol/L [26]; Δ = the ambitious difference yielded between FRAP baseline and after 3 months treatment and equals to 280 μmol/L [26] and, based on this equation, the number = 17 patients per each study arm. The patients were recalled for follow up after 3 month and 6 month from first visit.

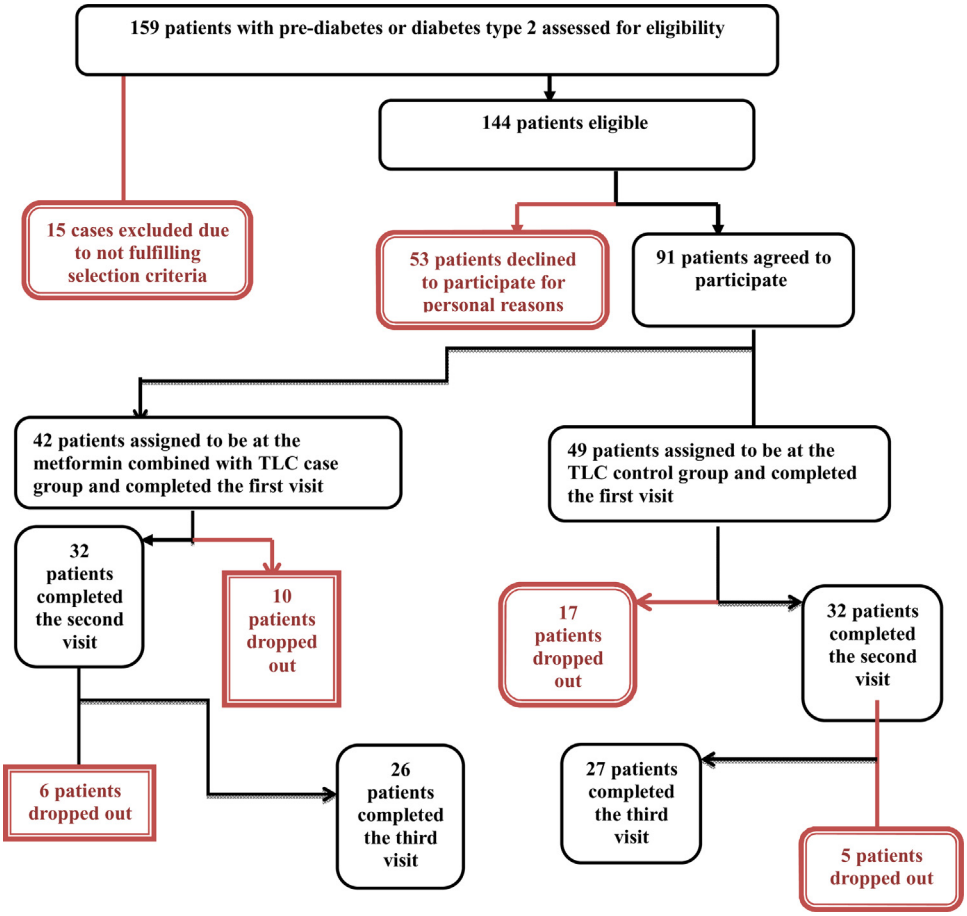

Fig. 1. The study flow chart.

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