

DOI: <http://dx.doi.org/10.18203/2319-2003.ijbcp20201769>

Letter to the Editor

Effect of metformin on fibrinolysis in type 2 diabetes mellitus: an explorative study

Sir,

Type 2 diabetes mellitus (T2DM) is associated with a high incidence of vascular disease which can cause significant morbidity and mortality. The risk of cardiovascular mortality in T2DM patients is observed to be more compared to the age-matched subjects.¹ This is attributed to depression of the fibrinolytic system which maintains patency of blood vessels. Endogenous inhibitors such as plasminogen activator inhibitor-1 (PAI-1) inhibit the activation of plasminogen and thus prevent the degradation of fibrinogen. In T2DM there is increased levels of PAI-1. Such a state of altered fibrinolysis is attributed to insulin resistance.² A previous study done at our institute demonstrated higher euglobulin lysis time (ELT) in T2DM patients than controls, suggesting altered fibrinolytic activity in the former group. D-dimer is a degradation product of fibrin. Its presence indicates a state of hypercoagulability. In a study by Nwose et al rise in D-dimer levels were observed in diabetics, especially with cardiovascular complications as compared to controls indicating D-dimer could be a useful marker for predicting the complications in T2DM.³

Metformin, the drug of choice in T2DM, in addition to its effects on blood glucose, has shown improvement in fibrinolysis by reducing insulin resistance. It has shown to reduce the PAI-1 levels. Recent studies also indicate that metformin has direct effects on fibrin structure/function and stabilization of platelets, the two important components of arterial thrombus formation.⁴

However, not many studies were found in literature that showed the beneficial activity of metformin on fibrinolysis in the newly diagnosed T2DM patients. Hence study was undertaken as a pilot study to evaluate the fibrinolytic activity of metformin in this scenario.

The study commenced after obtaining the Institutional ethics committee approval (VIEC/2016/APP/012). Newly diagnosed T2DM patients of either sex, aged 30-65 years were included in the study. Patients with history of cardiovascular diseases, hypertension, kidney or liver dysfunction, history of surgical procedures within four weeks, pregnant or breastfeeding, history of malaria or tuberculosis, history of psychiatric illnesses or patients on anticoagulant therapy were excluded.

The eligible patients were subjected to plasma D-dimer, fasting blood glucose (FBG) and postprandial blood

glucose (PPG) level measurement after obtaining a written informed consent. They were prescribed 500-1000 mg of metformin sustained release preparation after dinner. The dose was decided by the endocrinologist based on the FBG levels. They were followed up by phone every 10-15 days to remind them about compliance to medication and to enquire about adverse effects if any. At the end of three months, the investigations were repeated.

The D-dimer test was done at our central laboratory using a single use fluorescence immunoassay method which was designed to determine the concentration of D-dimer in EDTA anticoagulated whole blood or plasma specimens.⁵ The results were analysed using Mann Whitney U test.

Twenty-five T2DM patients who were willing to participate in the study were screened, out of which fourteen eligible patients were enrolled. After 3 months, 4 patients were found to be non-compliant and one patient's sample could not be tested in time. As a result, the samples of nine patients could be tested for a final reading.

Mean age of the study group was 48 years. There were 5 males and 4 females. As shown in Table 1, metformin reduced both FBG and PPG which was statistically significant. As compared to the baseline, the mean D-dimer values were lowered by 23.92% after 3 months of metformin therapy though statistically insignificant.

Our study indicates that metformin may reduce D-dimer levels and improve fibrinolytic activity in T2DM, in addition to decreasing the blood glucose levels. It was also observed that the fibrinolytic activity changed regardless of the age group or gender of the patient, as long as they were compliant with metformin treatment.

The results of our study are similar to Gin et al who demonstrated that in T2DM patients with secondary oral treatment failure, insulin had no effect on the fibrinolytic activity; addition of metformin improved the fibrinolytic parameters. However, PAI-1Ag was used as marker of fibrinolytic activity in their study. The authors concluded that controlling hyperinsulinemia by decreasing insulin resistance seems to be an effective way of improving fibrinolysis.⁴

Table 1: Effect of metformin on FBG, PPG and D-dimer test.

	FBG (mg/dl±SD)	PPG (mg/dl±SD)	D-dimer (mg/dl±SD)
Mean baseline	132.56±15.84	206.11±37.12	138.96±52.89
Mean final	110.44±11.36*	140.33±10.64*	105.71±10.18
Change in percentage (%)	16.68	31.91	23.92

*P<0.05 as compared to baseline.

Preliminary observations in this study suggest that controlling insulin resistance to improve fibrinolysis is of importance. If the function of fibrinolysis is to maintain vascular patency, the possibility of enhancing its action pharmacologically by decreasing insulin resistance may permit a fresh approach to the problem of occlusive vascular disease.

A study repeated in a larger population may confirm these findings. Since hyperinsulinemia is also a feature in prediabetics, it would also be worthwhile to study the effect of metformin on fibrinolysis in prediabetics.

Financial support

The study was supported by the scholarship from Short Term Studentship (2016-02945) of Indian Council of Medical Research, New Delhi, India. The authors are thankful to the ICMR, the management and Principal of our institution for their support and encouragement.

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Cite this article as: Reddy SK, Nadig P, Andra R, Sarathi V. Effect of metformin on fibrinolysis in type 2 diabetes mellitus: an explorative study. Int J Basic Clin Pharmacol 2020;9:833-4.