

# *Punica granatum* Juice as an Oral Supplemental Therapeutic: Effect on Hemoglobin and Blood Glucose Levels among Diabetic Patients

Pradeep AN<sup>1,\*</sup>, Reena Priyadarshini S<sup>2</sup>, VeniEmilda JK<sup>3</sup>, Yashavanth G<sup>4</sup>, Harish Kumar VS<sup>1</sup>,  
Kiran LJ<sup>1</sup>, Shivashankaramurthy KG<sup>1</sup>, Pradeep BE<sup>1</sup>

<sup>1</sup>Department of Pharmacology, SS Institute of Medical Sciences and Research Centre, Davangere, Karnataka, INDIA.

<sup>2</sup>Department of Paediatrics, JJM Medical College, Davangere, Karnataka, INDIA.

<sup>3</sup>Department of Microbiology, SS Institute of Medical Sciences and Research Centre, Davangere, Karnataka, INDIA.

<sup>4</sup>Department of General Medicine, SS Institute of Medical Sciences and Research Centre, Davangere, Karnataka, INDIA.

## ABSTRACT

**Background:** Type II Diabetes Mellitus (T2DM) is one of the most common metabolic disorders and it is often associated with complications like hyper-lipidemia, anemia, cardiovascular and inflammatory disorders. The present study was conducted to evaluate the effect of consumption of *Punica granatum* (pomegranate) juice (PJ) on Fasting Blood Glucose (FBG) and haemoglobin concentration in patients with T2DM. **Materials and Methods:** The study was conducted for a period of 60 days. Twenty patients with T2DM on metformin therapy were divided into two groups. Test group with ten patients received supplementation with PJ and control group with ten patients received water with food colour similar to PJ. All patients continued with metformin treatment during the study period. FBG and haemoglobin concentration analysis was done for both groups on days 0, 30, 53 and 60. **Results and Discussion:** The test group showed a higher degree of reduction in FBG and increase in haemoglobin concentration when compared to control group. FBG levels also showed a significant ( $p < 0.05$ ) decrease over the duration of the study i.e., from days 0 to 30. Similar observations were seen on days 53 and 60 as a results of the residual effect of PJ. **Conclusion:** The present study showed that PJ supplementation had a definite improvement in reducing FBG levels and increase in haemoglobin concentration among T2DM patients on metformin treatment.

**Keywords:** Fasting blood glucose, Haemoglobin concentration, Metformin treatment, Pomegranate juice, Type II diabetes mellitus.

## Correspondence:

**Dr. Pradeep A N**

Assistant Professor, Department of Pharmacology, SS Institute of Medical Sciences and Research Centre, Davangere, Karnataka, INDIA.

Email: pradeep.amilinane@gmail.com

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## INTRODUCTION

Type II Diabetes Mellitus (T2DM) recognized as a major clinical syndrome since ancient times, has emerged as one of the largest global health emergencies in the last few decades. Currently, it is the ninth leading reason of mortality worldwide.<sup>1</sup> Diabetes accounted for nearly 1.6 million deaths globally during 2019.<sup>2,3</sup> World Health Organisation has reported increasing prevalence of T2DM in developing countries and the disease has now reached epidemic proportions in countries like India.<sup>1,4</sup> In 2019, International Diabetes Federation reported that India stood second among all countries worldwide with 77 million diabetics,

and the numbers are expected to rise to 101 million by 2030 and 134.2 million by 2045.<sup>1</sup>

Diabetes mellitus is defined as deficiency or reduced effectiveness of circulating insulin.<sup>5</sup> It is a progressive disorder associated with various complications which can either affect large blood vessels (e.g., peripheral artery disease) or present as microvascular diseases (e.g. nephropathy).<sup>5,6</sup> Such complications usually result in high rate of morbidity and mortality among patients, and are associated with increased financial burden to the individual, to health-care system and the community.<sup>7</sup> Metformin, a biguanide derivative, is one of the most widely used oral antidiabetic agents, which is known to lower the possibility of diabetes related complications.<sup>8</sup> Metformin aids in body's mechanism by restoring the action of insulin and controlling the blood glucose levels.<sup>8</sup> However, various side effects like lactic acidosis, vitamin B<sub>12</sub> deficiency resulting in megaloblastic anaemia have been reported with long term usage of metformin.<sup>8,9</sup> Patients with T2DM have an increasing interest towards dietary control and alternative therapy like yoga, acupuncture and hydrotherapy for



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controlling the blood glucose levels due to the long term side effects of metformin usage and the cost associated with treatment in the long run.<sup>10</sup> Extracts of several medicinal plants and dietary supplements like chromium and magnesium have shown promising results as an alternative therapy among diabetics.<sup>10</sup>

The fruit pomegranate (*Punica granatum* Linn.) is known for its nutritional and healing properties since ancient times.<sup>11</sup> The plant grows as a small tree and different parts of it are used in indigenous Indian medicine as a cure for various conditions like cancer, Alzheimer's disease, cardiovascular diseases, arthritis, ischemia, obesity, and diabetes and more recently for complications of SARS-CoV-2 infections.<sup>12,13</sup> Pomegranate Juice (PJ) has proven to be beneficial therapeutically, especially among diabetics, due to the presence of unique bioactive compounds like polyphenols (anthocyanins, tannins, flavonoids, etc) with antioxidant, anti-inflammatory, anti-infective, antiatherogenic and anti-hyperglycaemic effects.<sup>14,15</sup> PJ can be easily incorporated in the daily diets which not only helps in improving the diabetic status of patients but also reduce the chances of debilitating complications improving the overall health of an individual. But a large knowledge gap still exists regarding the use of PJ as a supplemental therapeutic agent for the clinical management of diabetes mellitus. Though they are natural, safe and easily available studies on the consumption of PJ and its impact on healthcare are sparse. Therefore the present study was conducted to evaluate the efficacy of PJ on the Fasting Blood Glucose (FBG) and haemoglobin concentration of diabetic patients as a supplemental oral therapeutic along with the conventional metformin therapy.

## MATERIALS AND METHODS

### Study design, study setting and ethical consideration

This was a prospective study conducted at the Departments of Pharmacology and General Medicine, SS Institute of Medical Sciences and Research Centre, Davangere. The study had the approval of Institutional Ethics committee and Informed consent was obtained from each patient.

### Inclusion and Exclusion criteria

The patients were age matched and all patients between age 50  $\pm$  10 years (mean  $\pm$  SD) were selected. Among them, 20 patients with previously confirmed T2DM (FBG > 150 mg/dL) currently on metformin treatment alone were included in the study. Patients with multiple antidiabetic drug therapy; presence of diabetic complications or other systemic diseases; consumption of nutritional supplements such as vitamins, phytosterols or minerals were excluded from the study.

## Methods

Fresh pomegranate fruits were hand-picked and the seeds were removed manually. PJ was extracted using a juicer-blender and strainer. Twenty patients included in the study were divided randomly into two groups – Test group and Control group. All the 20 patients continued their metformin treatment during the entire duration of the study. After overnight fasting period of 12 hr, the test group with ten patients received supplementation with 50mL of fresh PJ while the control group received mineral water with food colour similar to PJ everyday for a period of 30 days. Both the groups were advised to take metformin tablets after 30 min of supplementation treatment and continue their normal diet during the rest of the day avoiding foods rich in polyphenols. The patients were observed for a period of 60 days.

FBG levels and haemoglobin concentration were estimated on day 1 (before initiating PJ treatment), 30 (after the last dose of PJ treatment), 53 and 60 (to detect for residual effect of PJ). Haemoglobin analysis was done by an automatic Haematological Analyser (HORIBA ABX Pentra XL<sub>80</sub>). FBG was estimated by Trinder's method (Glucose oxidase/peroxidase method) in an automated biochemistry analyser (RANDOX RX imola). Statistical analysis was done using SPSS vers 20.  $p < 0.05$  was considered statistically significant.

## RESULTS

All the participants in the test group were above 40 years of age where 17/20 patients were > 50 years (Table 1). Out of the 20 patients satisfying the inclusion criteria, 10 were males, 10 were female patients.

### Effect on FBG

Estimation of FBG levels showed that the test group had an approximately 45-50 mg/dL reduction (statistically significant -  $p < 0.05$ ) during the study period (Day 30- reduced by 49.9 mg/dL; Day 53- 50.4 mg/dL; Day 60- 45.0 mg/dL). However, the FBG of the control group did not show any statistically significant decrease (Table 2 and Figure 1). Also the test group showed lower levels of FBG compared to control group on days 30, 53 and 60. Effect on Haemoglobin Concentration The test group showed an average of 0.5 g% increase in the mean haemoglobin concentration from day 1 to day 60 (Day 30- increase by 0.6 g%; Day 53 -0.5 g%; Day 60- 0.5 g%). The mean haemoglobin concentration in the control group also showed an average increase of 0.3 g%. Though the increase in haemoglobin concentration in the test group was not statistically significant, it was slightly higher than the control group on all days of measurement (Table 3 and Figure 2).

**Table 1: Age and sex distribution of T2DM patients.**

Age (in years)	Groups						Total
	Test Group			Control Group			
	Male	Female	Total	Male	Female	Total	
40-50	0	0	0	2	1	3	3
50-55	2	3	5	2	2	4	9
50-60	2	3	5	2	1	3	8
Total	4	6	10	6	4	10	20

**Table 2: Comparison of FBG levels among test and control groups on days 1, 30, 53, and 60.**

Days	FBG (mg/dL)		p value
	Test Group Mean (SD)	Control Group Mean (SD)	
Day 1	187.6 (73.3)	164.6 (21.8)	0.363
Day 30	137.7 (47.6)	166.6 (49.6)	0.200
Day 53	137.2 (42.8)	159.7 (34.9)	0.214
Day 60	142.6 (46.4)	171.8 (40.8)	0.153
p value	0.011*	0.337	

\* $p < 0.05$ , statistically significant.

**Table 3: Comparison of mean haemoglobin concentration of test and control group on days 1, 30, 53 and 60.**

Days	Haemoglobin concentration (g %)		p value
	Test Group Mean (SD)	Control Group Mean (SD)	
Day 1	11.90 (1.59)	12.40 (1.174)	0.436
Day 30	12.50 (1.65)	12.30 (1.337)	0.769
Day 53	12.40 (1.57)	12.00 (0.943)	0.502
Day 60	12.40 (1.57)	12.00 (0.943)	0.502
p value	0.377	0.092	

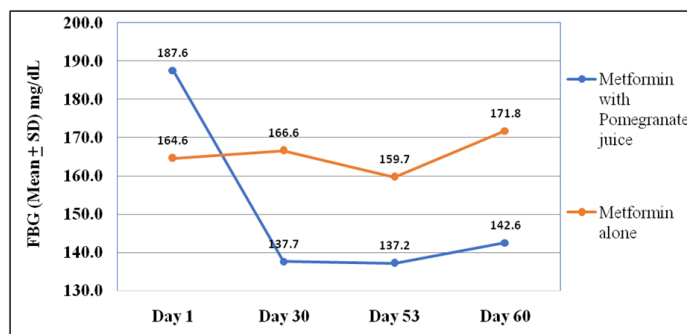
\* $p < 0.05$ , statistically significant.

## DISCUSSION

Glucose, which serves as a primary fuel for the optimum functioning of the human body, is broken down from complex sugars in the diet with the help of insulin. T2DM occurs when glucose is poorly metabolised either due to decreased levels of insulin or cell response resulting in elevated blood glucose levels. Also food with higher glycemic index results in sudden increase in blood glucose levels.<sup>16</sup> Hypoglycemic agents are the first choice of therapy to treat T2DM which act by either inhibiting gluconeogenesis or glucose absorption or stimulate or sensitize insulin secretion.<sup>16</sup> Bioactive compounds present in food can also act as hypoglycaemic agents and have a potential implication as a alternative or supplemental therapeutic agent to control blood glucose levels.<sup>16</sup>

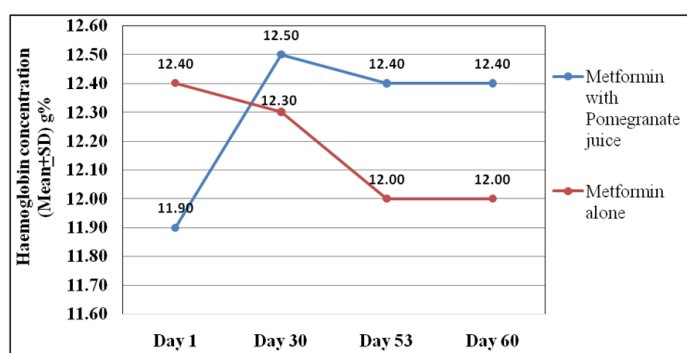
PJ can help in improving the diabetic status of patients by decreasing oxidative stress, intestinal absorption of glucose,

inflammation and increasing insulin sensitivity.<sup>16,17</sup> PJ also has an acute hypotensive effect which can be helpful in the treatment and prevention of hypertension, an important co-morbidity with T2DM.<sup>18</sup> In addition, it improves wound healing, an important complication of T2DM.<sup>17</sup> Various *in vitro* and *in vivo* studies have been conducted to understand the benefits of PJ, especially in diabetes.<sup>19,20</sup> PJ has been reported with significant antioxidative stress in patients with diabetes mellitus.<sup>19</sup> Studies have also shown that PJ was able to significantly reduce the postprandial blood glucose levels in individuals after consuming foods with high glycemic index.<sup>21</sup> A single dose intake of PJ during fasting can result in significant increase in insulin levels.<sup>22</sup> Although there have been numerous studies reporting the benefits of PJ on T2DM and various other diseases, the effects of PJ adjuvant to metformin therapy on diabetic patients is sparse. PJ is known to possess significant synergistic effect along with oral antidiabetic agents. Both the agents can produce a pronounced antioxidant



**Figure 1:** Comparison of FBG levels (Mean±SD in mg/dL) of test and control groups.

(Test group – Metformin with pomegranate juice; Control group – Metformin alone).



**Figure 2:** Comparison of mean haemoglobin concentration (g %) among test and control groups.

(Test group – Metformin with pomegranate juice; Control group – Metformin alone).

effect reducing diabetes-associated complications.<sup>20</sup> Therefore, the purpose of the present study was to examine the effects of PJ on blood glucose levels and haemoglobin concentration in diabetic patients along with continuation of conventional metformin therapy.

We observed that PJ consumption in diabetic patients consuming metformin significantly reduced the mean FBG levels. This is in accordance with the previous studies.<sup>23,24</sup> The possible mechanism for the reduction in blood glucose levels may be due to increased absorption of glucose by peripheral tissues, which is associated with the presence of polyphenols in pomegranate, decreased insulin resistance after PJ administration and increased beta cell function or regeneration of beta cells in pancreas.<sup>25</sup> The present study did not show any notable complications such as hypoglycemia or hypersensitivity reactions. The residual effects of PJ was persistent for about 3 weeks which was in accordance with the previous studies.<sup>26</sup> We also found that there was a gradual improvement in the mean FBG levels of test group during the last week of the study period showing residual effect of PJ even after its consumption was stopped. A mild improvement in mean haemoglobin concentration was found in the test group in comparison with the control group. The observed difference

was not statistically significant as the mean RBC lifespan is 115 days and our study period was for 60 days.<sup>27</sup> However, increase in haemoglobin concentration is expected to become significantly evident on continuation of PJ supplementation. Haemoglobin concentration improvement was consistent with the results of Manthou *et al.* and Harikrishnan *et al.*<sup>28,29</sup> These beneficial hematological effects may be observed as PJ is a good source of nutrients and minerals like calcium, iron, magnesium, ascorbic acid, tannins, anthocyanins and ellagic acid.<sup>30</sup> The study had a few limitations. It involved small number of subjects, as it is difficult to identify diabetic patients on metformin monotherapy. The results of this study can be extrapolated to general population using larger study sample. Further extensive and long term studies are required to reiterate the study findings.

## CONCLUSION

Treatment of T2DM without any side effects still remains a challenge to the medical field. The present study shows that combination of pomegranate juice and oral metformin may prove more effective in the treatment of diabetes compared to metformin monotherapy. Incorporating PJ in daily diets can help diabetic patients in controlling blood glucose levels and also reduce chances of most of the complications associated with diabetes.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**T2DM:** Type 2 Diabetes mellitus; **FBG:** Fasting Blood Glucose; **PJ:** Pomegranate Juice; **SD:** Standard Deviation; **RBC:** Red Blood Cell.

## SUMMARY

Diabetes mellitus is an increasingly challenging metabolic disorder due to complications associated with prolonged hyperglycaemic status. Various therapeutic options are available to control the blood sugar level in such patients. However, most commonly used antidiabetic drugs like metformin are associated with complications like megaloblastic anaemia. Safer and easily



available therapeutic options like pomegranate juice have proven to possess significant anti-hyperglycaemic effect. In the present study, pomegranate juice was used a supplemental therapeutic along with conventional metformin treatment and the effect of PJ on FBG and haemoglobin concentration was noted. The results of the study prove that individuals treated with PJ along with metformin had an improved diabetic status (decreased FBG and increased haemoglobin concentration) when compared with control group treated with metformin alone. PJ can be used as an effective supplement along with conventional metformin treatment and easily incorporated in daily diets.

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