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RESEARCH ARTICLE

TREATMENT WITH LINAGLIPTIN AND STUDY IN VARIATIONS OF SERUM URIC ACID LEVELS IN PATIENTS OF TYPE 2 DIABETES MELLITUS

Shubham Agarwal [*], **Arvind Mishra** [**], **KKGupta** [***], **Ravi Misra** [****], **Shilpa** [*****]

*Senior Resident, Department of Medicine
**Professor, Department of Medicine
***Associate Professor, Department of Medicine
****Professor, Department of Medicine
*****Senior Resident, Department of Medicine
King George's Medical University, Lucknow, UP

Correspondence
Shubham Agarwal
Department of Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India.

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ABSTRACT

Coexistent hyperuricemia with type 2 diabetes mellitus is routinely and increasingly reported and is emerging as a matter of growing concern globally. Apart from the risk of related complications, it also asks for additional strategy of management. Linagliptin, a DPP-4 inhibitor is recently reported to cause decrease in serum uric acid levels via its action on xanthine oxidase enzyme which it inhibits. Present work comprised of 172 subjects which included 90 cases and 82 controls. Case subjects were kept on Linagliptin while controls were kept on hypoglycemic agents other than DPP-4 inhibitors. Serial serum uric acid levels were observed in both groups at 3, 6 and 9 monthly intervals. In case subjects, regular decline in serum uric acid levels (mean) at 3,6 and 9 months were 6.45+/-0.28, 5.35+/-0.78 and 4.56+/- 0.47 mg/dl as accordingly. All these observations were statistically significant (p<000.1). No significant reduction in serum uric acid levels was observed in control subjects. Study advocates efficacy of Linagliptin in reducing serum uric acid levels in patients of Type 2 Diabetes Mellitus

INTRODUCTION

Hyperuricemia is observed as an association with type 2 diabetes mellitus in various studies [1]. Rise in plasma uric acid levels is attributed to increased purine catabolism [2,3,4]. Linagliptin, a selective inhibitor of DPP-4 has been observed to reduce serum uric acid levels while being used as an antihyperglycemic agent in these patients [5]. Reduction in serum uric acid levels reportedly happens due to decreased xanthine oxidase activity presumed to be occuring by Linagliptin.[6,7,8] This interesting observation is further evaluated prospectively in the present work.

METHODS AND OBSERVATIONS

Here, we have carried out a prospective study in a total of 172 patients which included 90 cases and 82 controls. Serum uric acid levels were equal or more than lower limit of normal (male: ≥4 mg/dl, female: ≥3 mg/dl) in both the groups. Case subjects were assigned to receive oral administration of 5 mg Linagliptin once a day. During the study period, subjects were instructed not to change their lifestyles and to continue taking the same dose of any concomitant oral drugs. We excluded patients with Collagen Vascular Disease, recent (<6 months) acute coronary syndromes, Acute Infections, Stroke, Malignancies, chronic alcoholics .Patients who received uric acid lowering agents such as allopurinol, febuxostat, and benzbromarone, were also excluded. All participants gave informed consent to participate in the present study A total of 90 (52.3%) of study population of diabetic patients were placed on Linagliptin for a period of 9 months from the day of enrolment and comprised the case group of study. Remaining 82 (47.7%) were patients of diabetes who were on other hypoglycemic agents than Linagliptin. This comprised the diabetic patients of control group who too were followed up for a period of 9 months.

At baseline serum uric acid levels ranged from 6.3 to 7.9 mg/dl in cases and from 5.20 to 7.50 mg/dl in controls. Mean value was 7.38±0.31 mg/dl in cases as compared to 6.70±0.63 mg/dl in controls.

Statistically, this difference was significant (p<0.001).

At 3 months serum uric acid levels ranged from 6.0 to 6.9 mg/dl in cases and from 5.20 to 7.50 mg/dl in controls. Mean value was 6.45±0.28 mg/dl in cases as compared to 6.72±0.62 mg/dl in controls. Statistically, this difference was significant (p<0.001).

At 6 months serum uric acid levels ranged from 5.0 to 6.2 mg/dl in cases and from 5.30 to 7.60 mg/dl in controls. Mean value was 5.53±0.28 mg/dl in cases as compared to 6.73±0.59 mg/dl in controls. Statistically, this difference was significant (p<0.001).

At 9 months serum uric acid levels ranged from 4.0 to 6.0 mg/dl in cases and from 5.20 to 7.60 mg/dl in controls. Mean value was 4.56±0.40 mg/dl in cases as compared to 6.74±0.61 mg/dl in controls. Statistically, this difference was significant (p<0.001). (Table 1)

Table 1: Within Group Comparison of Change in Uric Acid levels in Cases at different time intervals

	Mean Change	**SD of change**	**% Change**	**t'**	**p'**
BL to 3 months	-0.93	-0.36	-12.66	24.59	<0.001
BL to 6 months	-1.85	-0.44	-25.05	39.64	<0.001
BL to 9 months	-2.83	-0.60	-38.28	44.88	<0.001
3 to 6 months	-0.91	-0.43	-14.18	20.38	<0.001
3 to 9 months	-1.89	-0.54	-29.33	33.52	<0.001
6 to 9 months	-0.98	-0.37	-17.65	24.74	<0.001

BL- BaseLine

In Group I, as compared to baseline a reduction of 0.93±0.36, 1.85±0.44 and 2.83±0.60 mg/dl was seen at 3, 6 and 9monthsshowing a mean % change of -12.66%, -25.05% and -38.28% respectively. Maximum change between two subsequent periods was observed between 6 and 9 months (reduction of 0.98±0.37 mg/dl). For all the between follow-up comparisons, the change was significant statistically.(Figure 1)

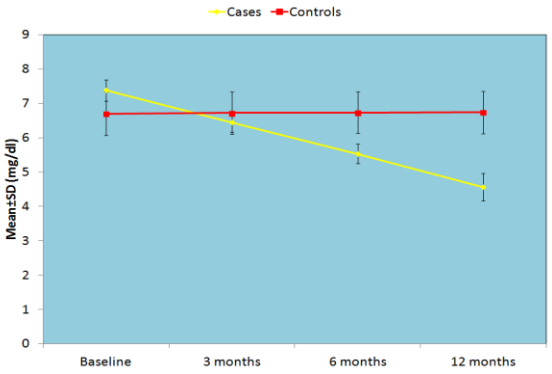

Figure 1. Mean Reduction in serum Uric acid levels.

In control group, a mean change of 0.02±0.14, 0.03±0.13 and 0.04±0.11 mg/dl respectively as compared to baseline was observed at 3 months, 6

months and 9 months intervals respectively. Correspondingly, a percentage increase of 0.24, 0.47 and 0.60 was observed. For other intervals too, the mean change ranged from 0.01±0.22 mg/dl (6 to 9months) to 0.02±0.16 and 0.02±0.20 mg/dl (3 to 6 and 3 to 9 months). Statistically, none of the changes were significant (p>0.05). (Table 2)

Table 2: Within Group Comparison of Change in Uric Acid levels in Controls at different time intervals

	Mean Change	SD of change	% Change	t'	p'
BL to 3 months	0.02	0.14	0.24	-1.02	0.308
BL to 6 months	0.03	0.15	0.47	-1.91	0.060
BL to 9 months	0.04	0.19	0.60	-1.89	0.062
3 to 6 months	0.02	0.16	0.24	-0.88	0.381
3 to 9 months	0.02	0.20	0.36	-1.09	0.279
6 to 9 months	0.01	0.22	0.13	-0.35	0.724

DISUSSION

Linagliptin is a highly potent, selective and long-acting DPP-4 inhibitor, having a xanthine scaffold structure that defines this unique property. [9] It has been seen that linagliptin directly inhibited xanthine oxidase activity in vitro and reduced serum uric acid levels in type 2 diabetic patients. Xanthine Oxidase have been shown to have a pathological role in mediating oxidative stress generation in ischemia/reperfusion injury. It binds to the surface of vascular endothelial cells by sulfated glycosaminoglycans causing oxidative damage which gets further potentiated by generation of free radicals.[10,11] In Type 2 Diabetes, associated hyperuricemia is considered to be happening from stimulated xanthine oxidase activity.[12,13] Uric acid, an end product of purine metabolism, has been shown to be associated with an increased risk of hypertension , cardiovascular disease, peripheral arterial disease, insulin resistance and chronic kidney disease along with progression of diabetes mellitus. It is likely then, that Linagliptin being an xanthine oxidase inhibitor, might exert an protective influence against organ damage in patients of diabetes mellitus along with combating increase in uric acid levels. Studies on Linagliptin have reported reduced infarct size after myocardial ischemia/reperfusion in Type 2 Diabetes as its beneficial effects on vascular injury via glucose-lowering-independent, anti-oxidative properties.[14,15,16,17]

Studies performed to demonstrate relation between Linagliptin and levels of uric acid are sparse. Yamagishi et al (2014) have drawn attention with their observation of reduction in uric acid levels with use of Linagliptin in the patients of diabetes mellitus[18]. They performed an open labeled prospective 24 week study including26 patients(18 male and 8 female, 69.4 ± 12.4 years old with body mass index: 24.7 ± 3.6).Total study subjects were divided into two groups, one receiving oral Linagliptin (case study group) and another kept on other antidiabetic agents not including any DPP 4 inhibitor. Serumuric acid levels measured were equal or more than lower limit of normal (male: ≥4 mg/dl, female: ≥3 mg/dl) at the start of study.Cases on Linagliptin were examined for its effect on xanthine oxidase activity in vitro. They observed significant decrease in mean uric acid levels ($p < 0.05$) at 3 month, 6 month and 9 month interval from 5.5±1.2 to 5.1±1.2 mg/dl. It was accompanied by significant improvement in glycemic levels(mean fasting-9.9 mg/dl, mean post prapandial-42.0mg/dl , $p<0.05$) in studied subjects and all these observations were significant as compared to subjects with similar characteristics not on DPP 4 inhibitors. It was concluded that though Linagliptin appears to have a mechanism related to xanthine oxidase activity resulting in reduction in serum uric acid levels, other mechanisms leading to this reduction cannot be excluded [19,20]. A prospective study for further elaboration of these results is recommended by authors.

In the present work, we tried to evaluate this observation of reduction in uric acid levels using Linagliptin in our patients of Type 2 Diabetes. Study comprised of 172 subjectsincluding 90 cases and 82 controls. Case subjects of the study were kept on Linagliptin for a period of 9 months from the day of enrolment. Remaining 82 (47.7%) were taken as controls and these were patients of diabetes on other hypoglycemic agents than Linagliptin. They too were followed up for a period of 9 months. At initiation of the study, serum uric acid levels ranged from 6.3 to 7.9 mg/dl in cases and from 5.20 to 7.50 mg/dl in controls. At 3

months follow up, serum uric acid levels ranged from 6.0 to 6.9 mg/dl in cases (mean vlue-6.45±0.28 mg/dl)and from 5.20 to 7.50 mg/dl(mean value-6.72±0.62 mg/dl) in controls. At 6 months follow up, serum uric acid levels ranged from 5.0 to 6.2 mg/dl (5.53±0.28 mg/dl) in cases and from 5.30 to 7.60 mg/dl (6.73±0.59 mg/dl) in controls. At 9 months follow up, serum uric acid levels ranged from 4.0 to 6.0 mg/dl (4.56±0.40 mg/dl) in cases and from 5.20 to 7.60 mg/dl (6.74±0.61 mg/dl)in controls. The differences in serum uric acid levels in case subjects in all these three time intervals were statistically significant ($p < 0.001$).

In control group, there was a slight variation in uric acid levels at 3 ,6 and 9 monthly intervals which was not statistically significant ($p<0.1$). Observations in present study support the findings of Yamagishi et al in relation to decrease in serum uric acid levels in patients of type 2 diabetes mellitus on Linagliptin therapy. This decrease was observed to be a consistent finding as reflected by serum uric acid levels noted at different time intervals. These two studies indicate towards an added therepeuatic benefit of Linagliptin in addressing coexistent hyperuricemia and providing protection against vascular complications. A clear recommendation of use of Linagliptin in this regard may only be made after further studies but usefulness of this compound in reduction of uric acid levels is certain to be accounted in diabetic management in coming time.

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BL to 9 months	-2.83	-0.60	-38.28	44.88	<0.001
3 to 6 months	-0.91	-0.43	-14.18	20.38	<0.001
3 to 9 months	-1.89	-0.54	-29.33	33.52	<0.001
6 to 9 months	-0.98	-0.37	-17.65	24.74	<0.001

BL- BaseLine

Table 2: Within Group Comparison of Change in Uric Acid levels in Controls at different time intervals

	Mean Change	**SD of change**	**% Change**	**t'**	**p'**
BL to 3 months	0.02	0.14	0.24	-1.02	0.308
BL to 6 months	0.03	0.15	0.47	-1.91	0.060
BL to 9 months	0.04	0.19	0.60	-1.89	0.062
3 to 6 months	0.02	0.16	0.24	-0.88	0.381
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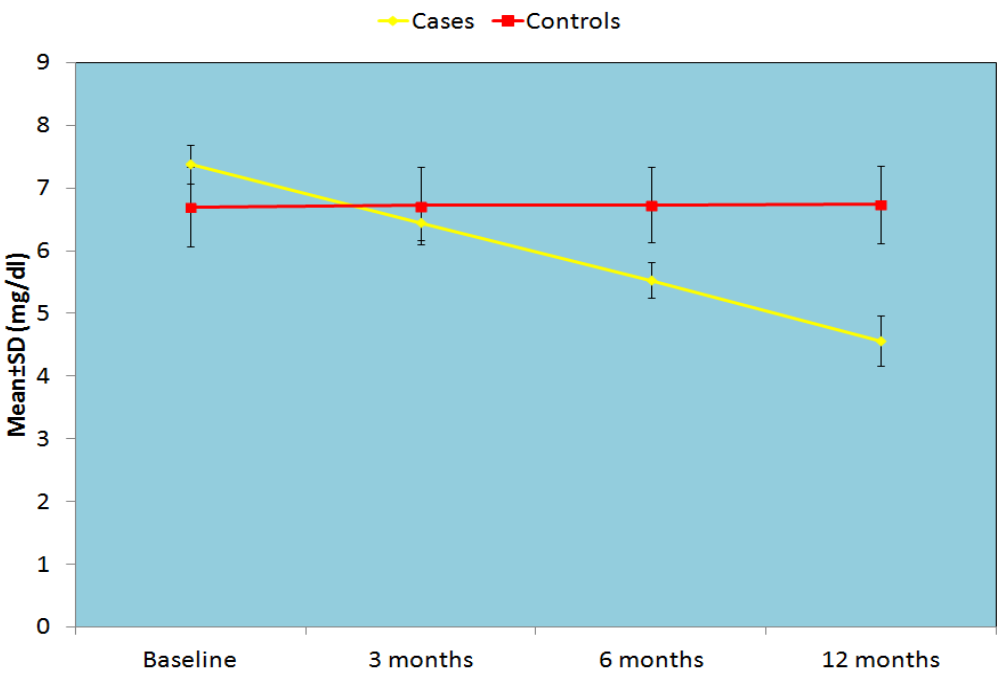

Figure 1. Mean Reduction in serum Uric acid levels.