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The Allopurinol and Febuxostat in the Treatment of Hyperuricemic Patients and Their Impact on Lipid Fractions (Cholesterol, LDL, HDL)

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Abstract: Little is known about the role of serum uric acid and its impact on lipid fraction. The associations between hyperuricemia and much co-morbidity such as dyslipidemia and others are well recognized. This study aims to explore the impact of Allopurinol & Febuxostat on the serum lipid levels in hyperuricemia patients. An interventional clinical study was conducted in Medical OPD, Civil Hospital Karachi. The study period was six months, from September 2018 to March 2019. In this clinical trial, after ERC approval, 70 enrolled patients, 60 registered patients of serum uric acid sUA>6.8 mg/dl, after inclusion and exclusion criteria and written consent, detailed history on pro forma and patients were divided into two groups, one to receive allopurinol, 300 mg & second Febuxostat 80 mg, daily for 90-days. Patients' uric acid, cholesterol, LDL, HDL, serum creatinine, alkaline phosphatase, SGOT, and blood sugar for safety profile from baseline, repeated at day 30, 60, and 90, keep in the case record file, on follow-up visits for final analysis. Group-A (Allopurinol treated patients) baseline uric acid was changed from mean 8.79 ± 0.98 to 6.40 ± 0.86, cholesterol 195 ± 30 to 198 ± 31, LDL135 ± 20 to 137 ± 20 & HDL31 ± 07 to 31 ± 06 at day 90. Group-B (Febuxostat treated) sUA mean was 8.85 ± 0.97 to 5.96 ± 0.68, cholesterol 176 ± 36 to 164 ± 25, LDL 129 ± 09 to 124 ± 09, HDL 29 ± 06 to 36 ± 06. Mean difference ± SD change in group A & B of sUA 2.39 ± 1.15 & 2.90 ± 0.87, cholesterol - 2.90 ± 4.10 & 12.43 ± 20.76 with p-value < 0.001, LDL - 2.53 ± 6.97 & 4.63 ± 5.05 with p-value < 0.001, HDL 0.20 ± 05.87 & -7.50 ± 2.58 with p-value < 0.001. Febuxostat lowers sUA and reduces cholesterol & LDL but increases HDL, while allopurinol does not impact lipid fractions. Urate lowering drugs interventions change the risk factors and offer a practical and cheap approach to hyperlipidemia and reduce cardiovascular risk.

Keywords: allopurinol, febuxostat, serum uric acid, serum cholesterol, low-density lipoprotein, high-density lipoprotein.

别嘌醇和非布司他治疗高尿酸血症患者及其对脂质成分（胆固醇、低密度脂蛋白、高密度脂蛋白）的影响

摘要：關於血清尿酸的作用及其對脂質分數的影響知之甚少。高尿酸血症與許多合併症（如血脂異常等）之間的關聯已廣為人知。本研究旨在探討別嘌醇和非布司他對高尿酸血症患者血脂水平的影響。一項介入臨床研究在卡拉奇民用醫院醫療門診部進行。研究期限為 6 個月，從 2018 年 9 月至 2019 年 3 月。在本次臨床試驗中，經倫理審查委員會批准，入組患者 70 例，註冊患者 60 例血清尿酸>6.8 毫克/分升，經納入排除標準和書面同意，詳細病史在備考和患者分為兩組，一組接受別嘌醇 300 毫克，二組非布司他 80 毫克，每日 90 天。患者的尿酸、膽固醇、低密度脂蛋白、高密度脂蛋白。血清肌酐、鹼性磷酸酶、血清穀氨酸草酰乙酸轉氨酶和血糖從基線開始的安全性，在第 30、60 和 90 天重複，保存在病例記錄文件

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中，在隨訪中進行最終分析。一个組（別嘌醇治療的患者）基線尿酸在第 90 天從平均值 8.79±0.98 變為 6.40±0.86，膽固醇 195±30 變為 198±31，低密度脂蛋白 135±20 變為 137±20 和高密度脂蛋白 31±07 變為 31±06. 乙組（非布司他治療）血清尿酸平均值為 8.85±0.97 至 5.96±0.68，膽固醇 176±36 至 164±25，低密度脂蛋白 129±09 至 124±09，高密度脂蛋白 29±06 至 36±06. 一个組和乙組的平均差 ±标清變化 2.39±1.15 和 2.90±0.87，膽固醇-2.90±4.10 和 12.43±20.76，p 值<0.001，低密度脂蛋白-2.53±6.97 和 4.63±5.05，p 值<0.001，高密度脂蛋白 0.20±05.87&-7.50±2.58，p 值<0.001。非布索坦可降低血清尿酸並降低膽固醇和 低密度脂蛋白，但會增加 高密度脂蛋白 ，而別嘌醇不影響脂質成分。降尿酸藥物干預改變了風險因素，為高脂血症和降低心血管風險提供了一種實用且廉價的方法。

关键词：別嘌醇、非布索坦、血清尿酸、血清胆固醇、低密度脂蛋白、高密度脂蛋白。

1. Introduction

Over a period, hyperuricemia is considered gout but is currently significantly associated with metabolic syndrome parameters. Hyperuricemia prevalence is high in hypertensive patients. Hyperuricemia should be acknowledged and monitored as a risk factor for cardiovascular disease [1]. Hyperuricemia is reported in developed countries, but evidence comes up in low and middle-income countries, and incidences are also increasing. The final oxidation product of purine degradation is uric acid. In humans, uric acid is mainly derived from endogenous production and food intake, with 70% being excreted by the kidneys and the remainder being primarily eliminated by the intestine [2].

Epidemiological studies showed that only hypertriglyceridemia is a component that increases the risk of hyperuricemia. In addition, hyperuricemia increases the risk of metabolic syndrome by more than two-fold. It seems that high uric acid can be considered as a predisposing factor for metabolic syndrome; thus, it is recommended to measure serum uric acid in routine tests [3].

In previous studies, increased cardiovascular morbidity & mortality in the general adult population is associated with elevated serum uric acid. Asymptomatic hyperuricemia over decades in the Asian region has been increasing [4].

Recent epidemiological studies show that hyperuricemia may be involved in hypertension, diabetes, atherosclerosis, chronic kidney disease, atrial fibrillation [AF], and cardiovascular events [5].

Uric acid synthesis and excretion are balanced in the body. Once this balance is disturbed, it leads to hyperuricemia. It is estimated that the total number of patients with hyperuricemia was 170 million in the population of China [6].

Past studies of raised uric acid levels related to the development and progression of metabolic, renal, and cardiovascular disease are presented in [7].

Uric acid is the end oxidative product of purine catabolism in humans. Hyperuricemia presented sUA above 6.8 mg/dl [8].

Breakdown of a purine by xanthine oxidase synthesizes uric acid in the intestine, liver & muscles, are the intrinsic source, while uric acid synthesis from organ meat, fatty meat, and seafood are outside sources [9].

Serum uric acid levels were positively associated with serum TG, TC, LDL, cholesterol, and the ratio of TG to HDL cholesterol. There was an inverse association between sUA and HDL cholesterol level regardless of adjustment for gender and several potential confounders, indicating a uric acid crucial role in regulating dyslipidemia [10].

Elevated uric acid, considered pro-inflammatory, results in an endocrine imbalance in the adipose tissues, an important factor for dyslipidemia. Although allopurinol remains the most frequently prescribed urate-lowering therapy, studies observed that less than 50% of patients taking the drug attain an sUA level <6 mg/dL at an allopurinol dose of 300 mg/day [11].

Allopurinol is considered a golden therapy due to its efficacy and tolerability in hyperuricemia. Allopurinol is a xanthine oxidase inhibitor, largely significant due to dual mechanism by reduction of oxidative stress and uric acid, which can likely reduce the risk of cardiovascular disease [12].

Febuxostat used in managing hyperuricemia, studies have shown non-inferiority in reducing sUA compared to allopurinol, the most commonly used sUA lowering agent. Compared to allopurinol, whether febuxostat improves cardiovascular outcomes remains controversial [13].

Febuxostat is a selective, non-purine derivative for prolonged duration action & potent drug Febuxostat

has clinical efficacy in serum urate-lowering, and long-term use leads to improved outcomes such as gout flare frequency and tophus burden [14].

Febuxostat structural difference from allopurinol can inhibit both the oxidized and reduced forms of xanthine oxidase, thus resulting in more potent inhibition of uric acid and production of reactive oxygen species [15].

2. Materials and Methods

This interventional clinical study design, conducted from September 2018 to March 2019, consisted of sixty adult participants recruited from Medical OPD Civil Hospital Karachi. All the participants were healthy without any cardiovascular diseases. Informed consent was obtained from all participants prior to inclusion in the study approved by the BASR and permission from the ERC Department of Pharmacology, Hamdard University Karachi.

With consent, diagnosed patients of either sex, ages varying from 38 to 69 years, were registered after applying inclusion and exclusion criteria and serum uric acid concentration >6.8 mg/dL. Initially, 70 patients were interviewed, ten patients dropped out due to irregular visits and poor adherence to the study drugs, only 60-patients completed the study duration of 90-days. They were divided into two groups, A & B, with 30 patients in each group. All information about the patients' health status entered in design pro forma at enrollment, i.e., Day-0 and collected data 0n schedule visits day 30, 60 & 90 entered in case recording file (CRF) for final statistical analysis.

Group-A was treated with Allopurinol 300 mg once daily for 90 days.

Group-B was treated with Febuxostat 80 mg daily for 90 days.

Patient details, along with baseline serum uric acid, cholesterol, HDL, LDL, patient's safety profile of serum creatinine, serum, blood sugar, SGPT, and serum alkaline phosphate, were collected from baseline (day-0) to completion of treatment (90-days).

3. Results

3.1. Comparison between Groups A & B

Patients of both groups were discussed in detail about the disease's prognosis and directed to report any adverse reaction at a scheduled visit or inform the investigator. On follow-up days, the investigator kept a case record to enter the data for the final evaluation of the study outcome.

Group-A registered thirty patients with the following baseline characteristics: male 22 (73.3%) & female 8 (26.7%) with a mean age of 57.60 ± 6.11 years (range 45 to 68 years). Mean body weight 63.27 ± 5.74, and 16 (53.3%) were smokers. Patients mean serum uric acid of 8.79 ± 0.98 (mg/dL) (Table 1).

Group-B registered thirty patients, have baseline characteristics; 21 (70%) male & 9 female (30%) of mean age 54.30 ± 8.66 years (range 40 years to 69 years), 13 (43.3%) smokers, and body weight mean 65.03 ± 7.22. The baseline sUA mean was 8.85 ± 0.97 (Table 1).

Table 1 Comparison of baseline characteristics between Group-A & Group-B in hyperuricemia patients

	GROUP-A Allopurinol n=30	GROUP-B Febuxostat n=30
Female	**8(26.7%)**	**9 (30%)**
Male	**22(73.3%)**	**21 (70%)**
Age in years (Mean±SD)	**57.60±6.11**	**54.30±8.66**
Smokers	**16 (53.3%)**	**13 (43.3%)**
Non-Smokers	**14 (46.7%)**	**17 (56.7%)**
Body Weight Kg	**63.27±5.74**	**65.03±7.22**
Serum Uric Acid mg/dl	**8.79 ± 0.98**	**8.85 ± 0.97**
Serum Cholesterol mg/dl	**195±30**	**176±36**
Serum LDL mg/dl	**135±20**	**129±09**
Serum HDL mg/dl	**31±07**	**29±06**

Notes: Group-A - Allopurinol 300 mg once daily
Group-B - Tab Febuxostat 80 mg daily
N - number of patients

Drugs of Group-A & B belong to the same class of xanthine oxidase inhibitors but of different sources. Allopurinol is a purine, and Febuxostat is a non-purine derivative; both prevent the production of uric acid.

Group-A (Allopurinol 300 mg/daily): The changes of serum uric acid from day-0 to day-90 were mean from 8.70 ± 0.98 to 6.40 ± 0.86, with a percentage change of 27%. Serum cholesterol change from 8.79 ± 0.98 to 198±31with p-value < 0.001, no significant change in LDL & HDL (Table 2, Fig.1 and 2).

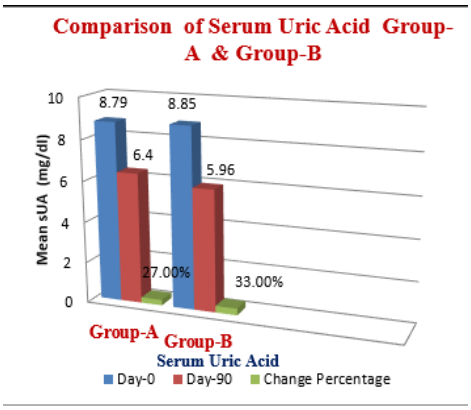
Group-B (Treated with Febuxostat 80 mg/daily): The change mean serum uric acid 8.85 ± 0.97 to 5.96 ± 0.68, percentage change was 33%; statistically results are significant with p-value >0.001.

Cholesterol 176 ± 36 to 164 ± 25, LDL 129 ± 09 to 124 ± 09 & HDL 29 ± 06 to 3 6 ± 06, all results are statistically significant (Table 2, Fig. 1 and 2).

Compare Group-A & B with the mean difference ±SD of serum uric acid from 2.39 ± 1.15 to 2.90 ± 0.87, serum cholesterol -2.90± to 16.80 ± 14.84, Serum LDL - 2.53 ± 6.97 to 15.13 ± 2.69, serum HDL 0.20 ± 05.87 to -6.03 ± 2.87 results statistically highly significant (Table 3).

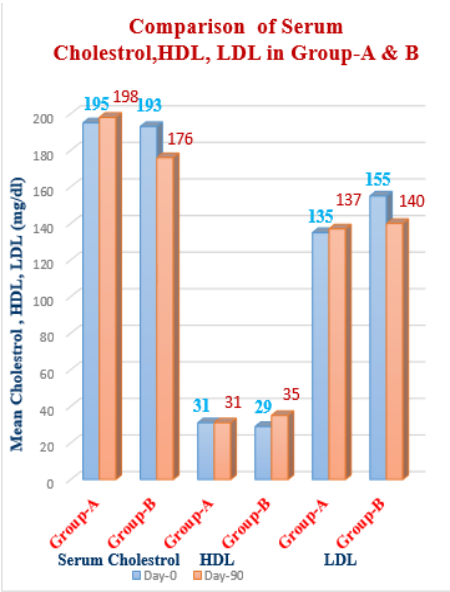
Table 2 Comparison of Groups-A & Group-B in hyperuricemia patients (Day -0 and Day -90)

Group A (Allopurinol)	Day	MEAN ± SD	P-value*
Serum Uric acid mg/dl	Base line (Day – 0)	8.79 ± 0.98	< 0.001**
	After treatment (Day – 90)	6.40 ± 0.86	
	Percentage Change	27%	
Serum Cholesterol mg/dl	Baseline (Day-0)	195±30	< 0.001**
	After treatment (Day-90)	198±31	
Serum LDL mg/dl	Baseline (Day-0)	135±20	0.056
	After treatment (Day-90)	137+20	
Serum HDL mg/dl	Baseline (Day-0)	31+07	0.853
	After treatment (Day-90)	31±06	
Group-B Febuxostat			
Serum Uric acid mg/dl	Base line (Day – 0)	8.85 ± 0.97	< 0.001**
	After treatment (Day – 90)	5.96 ± 0.68	
	Percentage Change	33%	
Serum Cholesterol mg/dl	Baseline (Day-0)	176+36	< 0.003**
	After treatment (Day-90)	164±25	
Serum LDL mg/dl	Baseline (Day-0)	129+09	< 0.001**
	After treatment (Day-90)	124+09	
Serum HDL mg/dl	Baseline (Day-0)	29+06	< 0.001**
	After treatment (Day-90)	36+06	



- Group-A: Allopurinol treated 300mg/d
- Group: B Febuxostat treated 80mg/d
- sUA: Serum Uric Acid

Fig. 1 Comparison of serum uric acid in Groups A and B



- Group-A: Allopurinol (300 mg) treated Patients
- Group-B: Febuxostat (80mg) treated Patients
- n: Total number of Patients

Fig. 2 Comparison of serum cholesterol, HDL, LDL in Groups A and B

Table 3 Compare group A & B for change mean difference ± SD blood assays (Day-0 and 90)

Group A & B	Mean Difference ± SD	P-value*
Serum Uric Acid		
Group A	2.39 ± 1.15	0.061
Group B	2.90 ± 0.87	
Serum Cholesterol		
Group A	-2.90 ± 04.10	< 0.001**
Group B	16.80 ± 14.84	
Serum LDL		
Group A	-2.53 ± 6.97	< 0.001**
Group B	15.13 ±2.69	
Serum HDL		
Group A	0.20 ± 05.87	< 0.001**
Group B	-6.03 ± 2.87	

3.2. Safety Profile

Assesses the safety profile by adverse effects & blood analysis of S. Creatinine S. Alkaline phosphatase, SGPT, and Blood sugar in both groups were carried out for the study duration of 90-days. Adverse reactions were reported in Group-A, 9 & in Group-B 4 out of 30 patients. Reported adverse effects were Palpitation Two (6.7%) in group-A, headache 1 (3.3%) in Group-B, numbness one (3.3%) in Group-B, abdominal pain three (10%) in Group-A. Two patients reported hematuria in group-A, but one case (3.3%) in Group-B, hypersensitivity cases two (6.7%) in group-A, vomiting one patient (3.3%) reported in Group-B. No reported case of fever and fatigue in any study groups of patients. No patients were discontinued from the study due to any serious side effects (Table 4).

Table 4 Tolerability/Safety of the drugs: Group-A & B

Adverse effect of drugs	Response	Group-A		Group-B	
		No.	%	No.	%
Palpitation	Yes	02	6.7	00	00
	No	28	93.3	30	100
Headache	Yes	00	00	01	3.3
	No	30	100	29	96.7
Numbness	Yes	00	00	01	3.3
	No	30	100	29	96.7
Abdominal pain	Yes	03	10	00	00
	No	27	90	30	100
Hematuria	Yes	02	6.7	01	3.3
	No	28	93.3	29	96.7
Hypersensitivity	Yes	02	6.7	00	00
	No	28	93.3	30	100
Vomiting	Yes	00	00	01	3.3
	No	30	100	29	96.7
Fever	Yes	00	00	00	00
	No	30	100	30	100
Fatigue	Yes	00	00	00	00
	No	30	100	30	100

Both study groups were ensured the safety of the drugs, blood analysis for renal function by measuring serum creatinine, liver functions, notably the serum alkaline phosphate and SGPT, and blood sugar, compared from baseline to Day-90.

Group-A treated patients change mean from Day-0 to Day-90, serum creatinine from 1.54 ± 0.39 to 1.42 ± 0.30 with p-value 0.019 statistically significant, serum alkaline phosphatase from 142 ± 20 to 143 ± 20 & SGPT from 30 ± 05 to 31 ± 05 no significant change, blood sugar means changes from 117 ± 14 to 117 ± 14 with p-value <0.001** results are highly significant.

Group-B treated patient's serum creatinine mean difference from 1.48 ± 0.40 to 1.45 ± 0.31, serum alkaline & SGPT mean change from 157 ± 13 to 158 ± 14 & 33 ± 07 to 34 ± 06 respectively statistically showed significant difference from baseline to day-90, blood sugar mean change was highly significant (Table 4).

Compare Group-A & B with the mean difference± SD of serum creatinine 0.11±0.25 & -0.03 ± 0.20 statistically significant with p-value 0.061, Serum

Alkaline phosphatase change -0.83 ± 3.13 & -4.10 ± 4.0 with p-value < 0.001, SGPT & Blood sugar mean difference ±SD in both groups is insignificant (Table 5).

Table 5 Blood parameters analysis for safety profile among Group-A and Group-B

BLOOD PARAMETERS	DAY-0	DAY-90	p-value
GROUP-A (Allopurinol Therapy)			
Serum Creatinine	1.54 ± 0.39	1.42 ± 0.30	0.019**
Alkaline Phosphatase U/L	142 ±. 20	143±20	0.156
SGPT U/L	30±05	31±05	0.223
Blood Sugar	117±14	109±14	<0.001**
GROUP—B (Febuxostat Therapy)			
Serum Creatinine	1.48 ± 0.40	1.45 ± 0.31	0.258
Alkaline Phosphatase U/L	157±13	158±14	0.037**
SGPT U/L	33±07	34±06	<0.005**
Blood Sugar	122±12	111±13	<0.001**

Table 6 Comparing Groups A and B for mean difference ± SD for safety (Day -0 and Day -90)

Group A & B	Mean Difference ± SD	P-value*
Serum Creatinine		
Group A	0.11 ± 0.25	0.061**
Group B	-0.03 ± 0.20	
Serum Alkaline Phosphatase		
Group A	-0.83 ± 3.13	< 0.001**
Group B	-4.10 ± 4.0	
Serum SGPT		
Group A	-0.76 ± 3.37	0.110
Group B	-1.97 ± 2.24	
Blood Sugar		
Group A	08.60 ± 7.18	0.675
Group B	09.43 ± 8.10	

4. Discussion

Hyperuricemia often correlates with dyslipidemia and prevents dyslipidemia by treating hyperuricemia patients [16]. An attempt was made to study the lipid fractions, specifically serum cholesterol, LDL, HDL, during serum uric acid-lowering therapy, to evaluate any significant difference in serum uric and lipid fraction in apparently healthy adults.

Hyperuricemia was still associated with increased hypertension, dyslipidemia, chronic kidney disease, and overweight/obesity.

The study [17] must be considered another brick in the wall that supports the role of sUA as a risk factor for cardiometabolic diseases.

In experimental animal [18] and human [19] studies, manipulation of uric acid levels showed modification both in uric acid & lipid levels. The mechanism regulates unknown but proposed suppression of lipid peroxidase & lipase activity decreases. Previously published studies evidence-based with the current study, evidenced the association between uric acid and dyslipidemia or its components [20].

Our study showed improvements in serum cholesterol, statistically significant but clinically within the limit, LDL & HDL showed no change during allopurinol therapy with uric acid normalization, agree with research study [21, 22], proposed that prolonged studies may show offhand relation between uric acid and lipid fraction levels.

Our study agrees with [23] that in sixty hyperuricemia patients, estimated cholesterol, HDL, and LDL to determine the impression between uric acid and lipid fraction proves a significant positive interrelation between uric acid and cholesterol and LDL and a significant negative correlation between uric acid and HDL. Studies showed that hyperuricemia is associated with dyslipidemia.

Febuxostat is a highly potent xanthine oxidase inhibitor. This inhibition resulted in an antioxidant action that reduces reactive oxygen species and oxidative stress, the important factor of vascular inflammation in hyperlipidemia. Febuxostat significantly reduces low-density lipoprotein & cholesterol. These proposed mechanisms of the anti-hyperlipidemic events of Febuxostat imply antioxidant and anti-inflammatory outcomes [24].

In a retrospective study, urate-lowering drugs, Febuxostat, allopurinol, and benzbromarone showed mild influence on serum cholesterol and triglyceride levels in hypercholesterolemia patients. Cholesterol levels significantly decreased in Febuxostat treated patients who did not receive any other lipid-lowering drugs.

Allopurinol and benzbromarone's effect on cholesterol levels were not seen. Febuxostat markedly influences the cholesterol, LDL, HDL that agree with our study [25], although urate-lowering treatments in several studies showed the association of lipid fraction likely serum cholesterol, high-density lipoprotein, and low-density lipoprotein. CARES trial-based initial results, FDA alert regarding Febuxostat safety compared with allopurinol. The study showed no difference in overall cardiovascular events, but the Febuxostat group had an increased risk of cardiovascular mortality. Our study did not exhibit any such complication except a few cases of palpitation, which respond well after rest [12].

A study showed no significant differences in cholesterol, HDL and LDL of the patients in the allopurinol group than the Febuxostat group, but Febuxostat 80 mg once daily lower the levels of sUA and as well as lipids fraction [LDL, TC] and increase the level of HDL. Allopurinol and Febuxostat's effectiveness in treating hyperuricemia showed a certain effect on concentrations of lipid fractions [21].

5. Conclusion

Hyperuricemia management should be an important aspect in planning the treatment strategy for dyslipidemia to reduce cardiovascular morbidity.

Febuxostat effectively improved serum cholesterol levels compared to allopurinol in patients with hyperuricemia.

Febuxostat lowered the sUA levels in hyperuricemia patients and impacted the lipids fraction, but there was no significant difference in cholesterol, LDL & HDL in the allopurinol group of patients.

Clinical therapeutic interventional studies investigating hyperuricemia play a pathophysiological role in co-morbidities, many of which are important public health challenges. These analyses were limited by the lack of a standardized approach for defining hyperuricemia and by duration and size. Despite that, the results are provocative enough to go head further studies with randomized controlled trials on the larger dimension to establish the role of uric acid as a likely target for novel therapeutic interventions in the management of co-morbidities. Indeed, there have been eminence efforts to standardize medical approaches regarding outcome measures, staging, and management, but some reasonable gaps exist.

The study limitations were a small number of patients in only one location and a short duration (3 months).

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Ethical Approval

Ethical approval was taken from the institutional ethical review board (Reference number ERB-19-03).

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