Review Article

The Analysis of Published Research on Gout and Hyperuricemia from Pakistan in National Biomedical Literature

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Abstract:

Objective: This study analyzed the published research on gout and hyperuricemia in the national biomedical journals with an aim to highlight the research gaps in the management of gout and hyperuricemia in Pakistan.

Methods: An online literature survey on global databases (Medline and Google Scholar) and local Pakistani database PakMedinet was conducted from January to March 2018. Different keywords on gout and hyperuricemia in Pakistan were combined using Boolean operators. We included all kinds of manuscripts reporting work specifically related to gout or hyperuricemia from Pakistan and having the corresponding author or at least one author with an affiliation from a Pakistani institution. We also considered manuscript published on this topic in Pakistani journals by authors affiliated with other countries.

Results: Thirty-four manuscripts were selected for review and analysis. Thirty-one manuscripts were written by local authors affiliated with institutions located in different cities of Pakistan. Five manuscripts had foreign authors, out of which two were authored by all Turkish authors, but others had Pakistani co- authors too. Most of the Manuscripts were published in the category of original research article. None of them was a randomized clinical trial (RCT).

Conclusion: The number and quality of studies published on gout and hyper-uricemia from Pakistan is low. There is a need to conduct more epidemiological and interventional studies to know the actual burden of gout in the country and RCTs to compare different drug treatments for managing gout in the local population

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Key words: Literature search, serum uric acid, uric acid stones, gouty arthritis, anti-hyperuricemics, allopurinol, fenofibrate, gouty tophi, nephrolithiasis, tophaceous gout.

Introduction:

Gout is a chronic synovial inflammatory arthritis due to increase in serum uric acid level[1]. Hyperuricemia is defined as serum uric acid level exceeding 6.6mg/dl. Persistent elevation of serum uric acid can result in deposition of monosodium urate crystal deposition in soft tissues and joints, which results in manifestations of gout. Gout is considered one of the most common inflammatory arthritis and it has varied presentations. It usually presents with acute, severe painful mono articular arthritis of the first metatarsophalangeal joint. However, it has other manifestations as well including nephrolithiasis or urate neuropathy and gouty tophi on the fingertips, feet and in the olecranon and pre-patellar bursae[2,3].

The incidence of gout is on the rise specially in developed countries. This has been attributed to aging, increased global incidence of diabetes mellitus, hypertension, and renal disorders[4]. In addition, excessive consumption of red meat, beer and sugar-rich drinks is also contributing towards an increased incidence of hyperuricemia and gout[4,5].The reported prevalence of gout in

developed countries range from 1.2 −4.1% of the general population[6].

Research on gout and other similar metabolic disorders from the developing world is limited. There is no formal documentation of the quality of research and publication on gout and hyperuricemia from Pakistan. We planned to analyze the published research on gout and hyperuricemia in the national biomedical journals of Pakistan. The aim was to highlight the research gaps in the management of gout and hyperuricemia in order to increase the awareness and to device better treatment strategies in the future.

Methods:

This was an online literature-based survey and did not have any human/animal interactions or interventions. Therefore, formal ethics review committee approval was not obtained. The study was conducted from Jan – March 2018. Two Global databases (Medline and Google Scholar) and local Pakistani database PakMedinet were selected for the literature search. Two of the authors (FR and AI) independently searched these databases using different combinations of keywords. The keyword included gout, hyperuricemia, gouty arthritis, gout suppressants, febuxostat, allopurinol and Pakistan. Keywords were combined using Boolean operators (AND, OR and NOT). No time limits were set although only English language articles on humans were selected for the final analysis. The last literature search was conducted on 28th March 2018.

All types of manuscripts were included. Titles were screened for relevance to the topic and abstracts were read where needed. The full text of the articles finally selected were obtained and data extracted on the data sheet. We only included manuscripts reporting work specifically related to gout or hyperuricemia from Pakistan or having the corresponding author or at least one author with an affiliation from a Pakistan based institution.

Results:

We identified Thirty-five manuscripts published on gout and hyperuricemia from Pakistan in the national biomedical journals to March 2018. One article was published in a predatory journal and excluded from the final review. Thirty-four manuscripts were selected for review and analysis. Thirty-one manuscripts were wri-

Table 1: *Bibliographic analysis and summary of the manuscripts*

S. #	Author name	Manuscript title	Year of publication	City of first/ corresponding author	Name of the Journal	The type of manuscript	Summary points
1	Rehman A, Et al	Serum and urinary uric acid in relation to age and sex	1980	Karachi	Journal of the Pakistan Medical Association	Original article	Authors reported an increase in mean uric acid values with advanceing age. Hyperuricemia was more prevalent in males except in the sixth decade, where it was more common in females.
2	Sheikh MA, et al	Gravel passers	1985	Karachi	Journal of the Pakistan Medical Association	Original article	A retrospective study of 82 patients with symptoms similar to urinary calculus but with a normal intravenous pyelogram. They were gravel passers with raised serum and urinary uric acid. In more than 70% patients, uric acid levels and symptoms improved with allopurinol therapy
3	Nisa Z, et al	Serum uric acid in ischemic heart disease	1986	Lahore	Journal of the Pakistan Medical Association	Original article	An observational study of 150 patients with ischemic heart disease (IHD) and 30 healthy individuals as controls. Patients with IHD had 8 times higher incidence of hyperuricemia than controls. Authors suggested serum uric acid as a risk factor for IHD.

4	Zaman R, et al	The effect of Pyrazinamide on serum and urinary uric acid levels	1987	Abbottabad	Journal of the Pakistan Medical Association	Original article	The study documented the efficacy of pyrazinamide on lowering serum and urinary uric acid levels in 20 patients with tuberculosis. There was an increase in the serum uric acid and decrease in urinary uric acid during treatment and it returned to normal after stopping the drug.
5	Parvaid A et al	hyperuricemia and correlates in coronary heart disease	1987	Lahore	Journal of the Pakistan Medical Association	Original article	A case control study on the small group, which tried to establish the association of hyperuricemia and acceleration of atherosclerosis in patients with coronary heart disease.
6	Khan MS et al	Studies on normal and Abnormal excretion patterns of uric acid in Bahawalpur	1987	Bahawalpur	Journal of the Pakistan Medical Association	Original article	The study reported that uric acid concentration in serum and urine of 296 persons in Bahawalpur city. It highlighted the increasing uric acid level in males with increasing age and hypothesized that it may be due to rise in the estrogen and progesterone levels in females compared to males
7	Chugtai MN, et al	Management of Uric Acid Stone	1992	Lahore	Journal of the Pakistan Medical Association	The original article.	Sixty-seven patients having 107 uncomplicated radiolucent stone in the kidney were enrolled. They were successfully managed by sodium acid citrate or uralyt-U and reducing serum uric acid by oral allopurinol. 86.9% of the stones responded to the management.
8	Idris M, et al	Radiological manifestations of primary gout	1996	Abbottabad	Journal of the Pakistan Medical Association	Original Article	Radiological manifestations of gout were documented in 22 patients over 11 years. Most of the patients were males with tophaceous lesions on the first metatarsophalangeal joint. Few patients also had renal stones.
9	Ali NS	Evaluation and Management of Gout	1999	Karachi	Journal of the Pakistan Medical Association	Review Article	Author described the 4 phases of gout, diagnosis and management strategies, including medicine dosages and side effects.
10	Safi AJ, et al	Association of serum Uric Acid with type II diabetes mellitus	2004	Peshawar	Journal of Post-graduate Medical Institute	Original article	An observational case control study on 200 subjects to document the association between diabetes mellitus type II(DM) and obesity and hyperlipidemia. Hyperuricemia is significantly associated with diabetics, hyperlipidemia, and obese patients. Females are more prevalent.
11	al	Chemical dissolution of urinary uric acid stones by the use of Citro Soda	2004	Peshawar	Journal of Postgraduate Medical Institute	Original article	The alkalinization of urine by citro soda leads to the chemo lysis of urinary uric acid stones and it was achieved completely and partially in 93.4% and 6.6% of the patients, respectively.
12	Iqbal, et al.	Diagnosis and management of	2004	Lahore	Annals of King	Review Article	Author emphasized on the increasing incidence of uric acid

		uric acid nephrolithiasis			Edward Medical University		stones in Pakistan compared to the Western world and he mentioned the sensitivity of computerized tomography and intravenous urography for detecting renal and ureteric stones due to uric acid stone's radiolucent properties.
13	Shujat et al	A rare case of co-existent Rheumatoid Arthritis and Tophaceous Gout	2004	Rawalpindi	Pakistan Armed Forces Medical Journal	Case Report	A single case report of 53 years old male having coexisting rheumatoid arthritis and tophaceous gout. Authors concluded that hyperuricemia delays the appearance of Rheumatoid Arthritis in susceptible individuals. Hypouricemic therapy in such patients may precipitate the attack of Rheumatoid Arthritis, which may be mistaken as a complication of hypouricemic therapy in chronic gout.
14	Ahmed N, et al	Obesity, hyperlipidemia and hyperuricemia in young and old hypertensive patients	2009	Abbottabad	Journal of Ayub Medical College	Original article	This cross-sectional study was conducted on 86 adult patients. Hypercholesterolemia, hypertriglyceridemia, and Hyperuricemia was not associated with the age of the hypertensive patients. Increased BMI was more frequent in the young compared to the old hypertensive patients
15	Ullah I, et al	Dermatological manifestation of gout	2009	Lahore	Journal of Postgraduate Medical Institute	Case Report published under the heading of Original article.	A 32 year old male presented in dermatology with tophi dischargeing white cheesy material on unusual sites such as palmer surfaces of fingers and planter surfaces of feet in addition to the lesions on the extensor surfaces of elbows.
16	Haq A, et al	Association of serum uric acid with obesity	2009	Peshawar	Journal of Pakistan medical Institute	Original article	An observational case control study on 200 subjects to observe the significant association between obesity and raised serum uric acid levels.
17	Bano U, et al	High serum uric acid levels as a marker of poor cardiovascular outcome and high mortality	2009	Rawalpindi	Journal of Pakistan Medical Institute	Original article	A descriptive cross-sectional study was conducted on congestive heart failure patients. A positive correlation of serum uric acid and raised cardiovascular mortality was observed.
18	Haq A, et al.	Association of serum uric acid with blood urea and serum creatinine	2010	Peshawar	Pakistan journal of physiology	Original article	A case control study was conducted to study the association between serum uric acid and renal functions tests such as serum urea and creatinine. Serum uric acid was raised in 33 patients out of 80 patients with impaired renal function tests.
19	Saeed M, et al	Lesch-Nyhan syndrome	2011	Inter Taif, KSA	Pakistan Pediatric Journal	Case Report	Six years old male child with a rare X linked recessive disorder of HPRT gene mutation was reported with the characteristics

							of features of self-mutilation, spasticity, mental retardation, and hyperuricemia.
20	Yorulmaz E, et al	Relationship between uric acid levels and impaired glucose tolerance in subjects with metabolic syndrome		International Turkey	Pakistan journal of Medical sciences	Original article	An observational study on 83 patients with metabolic syndrome was conducted to measure the relationship between serum uric acid level, MetS criteria and oral glucose tolerance test.
21	Waseem, et al	Tumor lysis syndrome in hematological malignancies	2012	Oman	Journal of Liaquat University of Medical and Health Sciences	Original article	Tumor lysis syndrome is a disease-related emergency, reported in 5–20 percent of patients with cancer, in which tumor cell turnover releases their contents into the blood stream, resulting in hyperuricemia, hyperkalemia, hypophosphatemia and hypocalcemia. Hyperuricemia leads to acute uric acid nephropathy, which needs to be treated aggressively to prevent fatal complications.
22	Zafar I, et al	Efficacy and safety of fenofibrate in patients with hyperuricemia	2012	Karachi	Journal of the Dow University of Health Sciences	Original article	Research on 60 adult patients divided into two groups. Group A was given allopurinol and Group-B fenofibrate for hyperuricemia. Fenofibrate was an effective drug in the management of hyperuricemia.
23	Qureshi AE, et al	Relationship of serum uric acid level and angiographic severity of coronary artery disease in male patients with acute coronary syndrome	2013	Lahore	Pakistan Journal of Medical Sciences	Original article	Hyperuricemia has an association with the severity of coronary artery disease.
24	Qamar MM, et al	Gout: Causing Factors and Counter Strategies	2013	Sweden Sargodha	Annals of KEMU, King Edward Medical University	Review Article	A review of the Incidence, prevalence, pathophysiology, diagnosis, complications, pharmacological and non-pharmacological strategies to manage gout and hyperuricemia.
25	Malik MI	Comparison of hyperuricemia in type 2 diabetics on low dose aspirin and not on low dose aspirin	2013	Rawalpindi	Pakistan Armed Forces Medical Journal	Original article	A quasi-experimental study was conducted on patients with type2 diabetics. Group A taking low dose aspirin and group B was not on aspirin. Significant hyperuricemia was observed in the group A patients.
26	Ahsan N, et al	Association of high serum uric acid with risk factors of cardiovascular disease in the rheumatology clinic of a tertiary care hospital of Karachi	2014	Karachi	Annals of Abbasi Shaheed Hospital and Karachi Medical and Dental College	Original article	Hyperuricemia, diabetes, hypertension and dyslipidemia are risk factors of cardiovascular disease. Fasting lipid profile was significantly deranged in patients with raised uric acid levels.

27	Akram M et al	Comprehensive review on therapeutic strategies of gouty arthritis	2014	Rawalakot	Pakistan Journal of Pharmaceutical Sciences	Review article	The role of traditional Greek (unani) medicines extracted from the plants and herbs along with modern medicine was highlighted. Introduction, classifycations, epidemiology, and management of gouty arthritis were described in detail.
28	Khaleeq A	Hyperuricemia as a Predictor of Poor Fetal Outcome in Pre-Eclamptic Women	2015	Lahore	Journal of Rawalpindi Medical College	Original article	Correlation between raised serum uric acid levels and fetal growth retardation in terms of small for gestational age (SGA) was observed in hyperuricemic pre-eclamptic patients as compared to the normo-uricemic pre-eclamptic patients.
29	Siddiqui, et al	Association of Hyperuricemia with Metabolic Syndrome	2015	Lahore	Pakistan Journal of Medical Research	Original article	A cross-sectional analytical study was carried out on 600 patients to evaluate the association of hyperuricemia with metabolic syndrome. In this study, no association was observed between hyperuricemia and metabolic syndrome.
30	Inayat N, et al	Hyperuricemia and arthralgia during Pyrazinamide therapy in patients with Pulmonary tuberculosis	2016	Jamshoro	Pakistan Journal of Chest Medicine	Original article	A trend of increasing serum uric acid was observed in patients taking pyrazinamide. More than 20% patients in this study developped knee, ankle and shoulder pain, which resolved with oral aspirin. This study demonstrated the positive effects of aspirin on hyperuricemia and arthralgia due to PZA.
31	Qidwai W	Hyperuricemia and its management: an emerging public health and clinical practice challenge	2016	Karachi	Journal of Liaquat University of Medical and Health Sciences	Editorial	Hyperuricemia is an independent risk factor for hypertension, diabetes, cardiovascular diseases and renal impairment. Newly diagnosed hypertension in middle aged (adolescents) when treated with allopurinol resulted in blood pressure control.
32	Khan A, et al	Serum uric acid level in the severity of congestive heart failure (CHF)	2017	Peshawar	Pakistan Journal of Medical Sciences	Original article	An observational study on 285 patients with a diagnosis of CHF. Hyperuricemia was observed in 59.29% of patients with male predominance. Serum uric acid can be considered a factor to identify high risk patients with CHF.
33	Resorlu H, et al	Cubital tunnel syndrome secondary to gouty tophi: a case report	2017	Inter Canakale, Turkey	Journal of the Pakistan Medical Association	Case Report	Sixty-three years old male with multiple comorbidities and diagnosed case of gout for the last 15 years presented with numbness in the left ulnar nerve distribution but no muscle weakness. MRI left elbow showed the ulnar nerve compression, which resolved after surgery.

34	Latif H, et al	Correlation between Serum Uric Acid Level and Microalbuminuria in Type-2 Diabetic Nephropathy	2017	Lahore	Pakistan Journal of Medical Sciences	Original article	A cross-sectional study was conducted on 200 patients with type 2 diabetes having nephronpathy. A significant correlation was observed between serum uric acid and microalbuminuria. Serum uric acid can be used as a prognostic marker in the diabetic nephropathy.

tten by local authors affiliated with institutions located in different cities of Pakistan. Five manuscripts had foreign authors, out of which two were authored by all Turkish authors, but others had Pakistani co- authors too and were included in the final analysis.

Most authors were affiliated with institutions from Lahore, Karachi, and Peshawar. In addition, there were contributions from authors based in Abbottabad, Bahawalpur, Jamshoro, Rawalakot, Rawalpindi and Sargodha.

Most of the Manuscripts (64.5%) were published in the category of original research article None of them was a randomized controlled trial (RCT). They were either cross sectional surveys, case control studies, observational studies, interventional, cohort studies and quasi-experimental studies. One article was an editorial, and the remaining were case reports and review articles.

Discussion:

The incidence and prevalence of hyperuricemia and gout is increasing in the whole world due to an increase in the prevalence of obesity and metabolic syndrome. A 2012 epidemiological study documented that one in 40 British and one in 16 Taiwan residents has gouty arthritis[8]. Similarly according to the NHANES survey of 2008, the prevalence of hyperuricemia in the US population is 3.9%[8]. The same is the case in the SAARC countries such as India and Bangladesh where a high prevalence of gout and hyperuricemia has been reported[9].

We located thirty-four articles published on the topic of hyperuricemia and gout in the biomedical literature of Pakistan. Pakistan has a population of 220 million people with an underdeveloped healthcare system, which is not universally accessible to all residents. The incidence of non-communicable and mus-culoskeletal disorders is on the rise. Considering the rising burden of the disease, the number and quality of articles published on hyperuricemia and gout is extremely low. There is no RCT on management of gout and hyperuricemia from Pakistan published in the local literature. There is a lack of large-scale epidemiological studies. This is further complicated by the absence of a national disease registries for metabolic and musculoskeletal disorders in Pakistan. Therefore, it is difficult to accurately estimate the disease burden of gout in Pakistan. In our clinical practice we have observed that anti-hyperuricemia drugs are frequently misused and over prescribed in Pakistan. Patients are often prescribed uric acid lowering drugs even on mild elevation of serum uric acid detected incidentally or even for knee and back pain without any justification. There can be many reasons for this practice. One of them may be a lack of national guidelines. The current guidelines for the evaluation and management of gout and hyperuricemia were created by professionals based in the developed countries[10]. These guidelines are usually meant for their own population and do not consider the unique dynamics and disease pattern of a developing country like Pakistan[11]. The treatment of gout is based on clinical experience by most of the physician's[9] which leads to the misuse of anti-gout medications. However, biogenetics of Pakistani population is different from that of developed countries populations due to the diff-erences in the lifestyles and genetic makeup. Therefore, there is a need to conduct randomized control trials on the different management strategies of gout and hyper-uricemia in Pakistan.

Thirty-one articles were authored by Pakistani authors, while two articles had international authors. One of the manuscripts was a literature review on the risk factors and management of gout, while the other was a descriptive observational study on tumor lysis syndrome due to tumor cell death, which leads to hyperuricemia, hyperkalemia, hypophosphatemia and hypocalcemia[12]. It is a disease-related emergency in hemolytic cancers due to

acute uric acid nephropathy. There is a need to collaborate with international researchers to improve the quality and quantity of publications from Pakistan. A case report on lesch-nyhan syndrome and cubital tunnel syndrome secondary to gouty tophi was published in Pakistan pediatric journal and journal of Pakistan medical association, respectively, the authors of both articles had international association and those case reports were from Saudi Arabia[13] and Turkey[14].

A case report on the dermatological manifestations of gout was published in the journal of postgraduate medical institute, but that was erroneously labeled as an original article[15].

The review articles on gout and hyperuricemia described the epidemiology, classification, risk factors, diagnosis management and complications of gout[16]. This review article also highlighted the non-availability of specific guidelines for the diagnosis and management of gout and hyperuricemia for Pakistani population.

All the manuscripts in the category of original research articles were observational studies, except two, which were interventional studies[17]. One was on 30 patients as a quasi-experimental study with the no control group, explaining the significant role of citrus soda in the dissolution of urinary uric acid stones, while others compared the efficacy and safety of fenofibrate with allopurinol on 60 patients only. These number of cases is very low to make generalizable conclusions.

Most of the observational studies identify hyperuricemia as an independent risk factor for diabetes type II[18], hypertension, hyperlipidemia[19], coronary artery disease, congestive heart failure[20], obesity, and metabolic syndrome. Many Observational studies have been conducted in other SAARC countries that also correlate with their results. Such as, in the recent literature on Bangladeshi population observed the significant association between metabolic syndrome and its components with hyperuricemia[10]. Another study on the same population documented the direct relation of obesity with hyperuricemia[11]. Also, a retrospective study in India, a neighbor country of Pakistan mentioned the high prevalence of hyperuricemia in patients with other comorbidities such as diabetes types II and hypertension.

The quality of the research also lacks behind the global standards. For example, Idris et al in 1996, published the radiological manifestations of primary gout in a series of 22 patients[22]. They only described the X-ray findings in these patients. In the same year, Computer Tomographic (CT) scan and magnetic resonance imaging (MRI) findings of gout were being published in the international biomedical literature[23,24].

Patients with elevated serum uric acid and 24 hour urinary uric acid levels having symptoms suggestive of calculus but normal intravenous pyelogram were described as "gravel passers" by Sheikh and Naqvi[25]. Pakistan lies in the strongest calculus belt areas of the world. Haq et al suggested that the increase in serum uric acid has a direct association with impaired renal function tests such as serum urea and creatinine[26].

It has been postulated that gout and hyperuricemia increase with increasing age, especially in the male population due to change in androgen levels. A study on 296 patients was conducted in Bahawalpur to document the normal and abnormal excretion patterns of uric acid[27]. It highlighted that rise in the uric acid level in males with increasing age and hypothesized that it may be due to raised estrogen and progesterone levels in females as compare to males.

Conclusions:

The number and quality of studies published on gout and hyper-uricemia from Pakistan is low. There is a need for better quality studies on epidemiology and RCTs to compare different drug treatments for managing gout in the local population. This will identify the clinical features unique to our population and identify the most appropriate treatment protocols to manage different forms of gout and hyperuricemia.

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