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EVALUATION OF GOUT DIAGNOSIS AND MANAGEMENT IN PRIMARY HEALTH CARE CENTERS

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Abstract:

Background: *Gouty arthritis is a type of metabolic disorder that is associated with joint inflammation as a result of accumulation of monosodium urate in the synovial fluid. It's considered as one of the commonest presentations in primary care centers, in which a patient's present complaining of rapid pain development, redness and swelling of the effected joint. Objective: In our review, we focused upon discussing the clinical presentation of gouty arthritis, and recent updates in diagnosis and management in primary health care center.* ***Methodology:*** *A comprehensive search was done using biomedical databases; Medline, and PubMed, for studies concerned with assessment of Gouty Arthritis. Keywords used in our search through the databases were as; —Gout arthritis evaluation‖, —Diagnosis‖, —Management‖, and —Primary health care center‖. Conclusion: Acute gouty arthritis attacks occur as a result of accumulation of monosodium urate crystal deposits into the joint space which associated with inflammatory reaction development. The condition can cause severe pain at the start of the attacks, later on as the condition progress a patients may develop deformity in the effected joint and functional impairment. Primary health care physicians should have a full knowledge regarding gouty arthritis diagnosis, evaluation, and management options. Gout management aims to reduce serum urate level below 6mg/dL, to avoid/ prevent formation of new crystals and promote the dissolution of existing crystals. In general gout management can be difficult as a result of patient's incompliance, poor medical care provided by the health care system, and the presence of comorbidities. A physician should inform the patients about their condition, and the importance of patient's compliance with management plan to prevent attacks development.*

Key words: *Acute gouty arthritis, inflammatory reaction, urate crystal, joint space, management, primary health care centers.*

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INTRODUCTION:

Gouty arthritis is considered as a metabolic disorder that occurs as a result of accumulation of uric acid in the synovial fluid and cartilage in a form of monosodium urate crystals, which finally result in arthritic inflammation (1). Gouty arthritis described for the first time by the ancient Egyptians, then in the fifth century BC Hippocrates identify it and referred to it as

―The Un-walkable disease‖ (2). Gout also was described as a ―Disease of Kings‖, because of the relation between eating and drinking certain foods and beverages that mostly can be offered by affluent people (2).

Gout acute attacks are triggered by the accumulation of sufficient amount of monosodium urate crystals inside the joint space. Clinical symptoms are characterized by rapid onset of pain that is very difficult to bear. Other signs and symptoms include redness, swelling, warmness of the effected joint. In most of the time the acute attacks involve the first metatarsophalangeal joint of the great toe. Most often the attacks are self- limiting lasting 3-14 days (4). With time, the attacks become less painful, but last longer and tend to involve more than one joint and tendons1. The chronic deposition of crystals damage the joints, and lead to formation of tophi (urate crystal deposits in tissues), with chronic stiffness and swelling of the joints (1). With the chronic inflammation and swelling of the joints gouty arthritis can resemble rheumatoid arthritis and lead to intense inflammation, deformities, tophi, stones formation in the kidney, and renal insufficiency (5).

Gouty arthritis considered as the most common type of inflammatory arthritis in Western countries1. According to the National Health and Nutrition Examination Survey (NHANES 2007-2008), the prevalence of gout US adults were 3.9% (7). The results showed that there was a significant increase in the prevalence of gout compared to the same study done in 1988-1994 which accounted for 2.7%. Most of the escalation in the prevalence was observed in men and elderly (6). The significant escalation in the prevalence explained by the increased in the rates of obesity and metabolic syndrome (7).

Gouty arthritis is associated with a substantial impact on the quality of patients' life. Also, it has a huge economic burden. As a result of unbearable pain and restriction of joint movement the patient will be unable to perform his or her daily activity or going to work. In addition, gouty arthritis is associated with various comorbidities that substantially have an impact on morbidity and mortality. As mentioned by Choi HK et al. a history of gouty arthritis is associated with 28% increase in the risk of death, 38% increase in the cardiovascular disease related death, and 55% increase in the risk of coronary heart disease related death (8).

Early discovery of the disease help in providing the patients with a good management plan and better outcomes. In this paper we reviewed the recent diagnostic and management plans that can be used in the primary health care centers.

METHODOLOGY:

Sample

We performed comprehensive search using biomedical databases; Medline, and PubMed, for studies concerned with evaluation of GERD published in English language. Keywords used in our search through the databases were as; (Gout Diagnosis, Gout History, Gout Management, Goutin Primary Care). More relevant articles were recruited from references lists scanning of each included study

Analysis

No software was used to analyze the data. The extracted data were based on specific form that contains (Title of the study, name of the author, Objective, Summary, Results, and Outcomes), these data were reviewed by the group members. Double revision of each member's outcomes was applied to ensure the validity and minimize the errors.

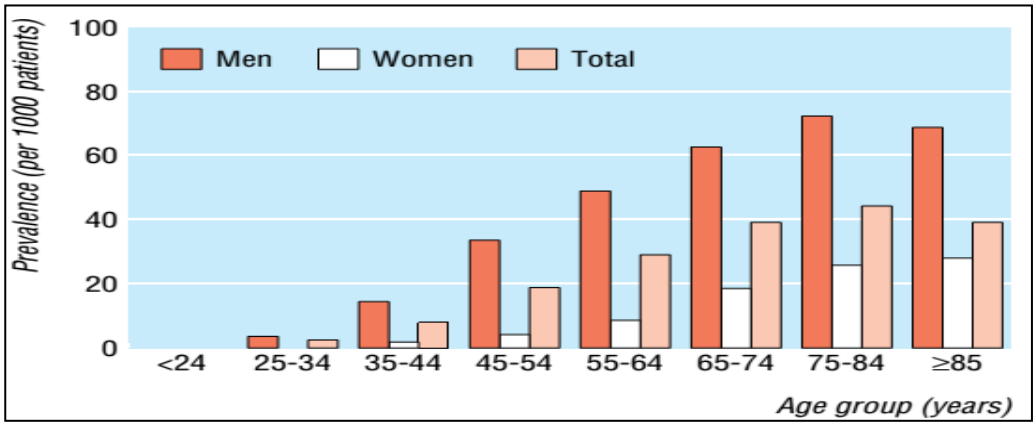
Results of the survey studies and data extracted from the literatures outcomes and analysis of the collected databases on the various aspects of the disease have to be presented in summary such as those illustrated in graphs and tables. Then we will discuss these results with the results of the similar studies.

Discussion

Gouty arthritis or (The Un- Walkable Disease) according to Hippocrates was identified for the first time by the ancient Egyptians (2). Gouty arthritis is considered as a metabolic disorder that occur as a result of accumulation of uric acid in the synovial fluid and cartilage in a form of monosodium urate crystals, which finally result in arthritic inflammation(1).

In Western countries gout is considered as the most common cause of inflammatory arthritis. In a period between 1988- 1994, the National Health and Nutrition Examination Survey (NHANES) found that the gout prevalence accounted for 2.7% (7). Another survey was done by (NHANES) between 2007- 2008 and found that gouty arthritis prevalence accounted for 3.8% which is considered as a significant escalation in the percentage. The survey attached the increase in gouty arthritis rate in the population by

increase in the incidence rate of obesity and metabolic syndrome (8). In Saudi Arabia, Al-Arfaj AS et al. study population accounted for 8.4% discovered to have hyperuricemia with no case of gout was found (9). Wallace KL et al. mentioned that the prevalence of gout increase with advancing age, being a male (Figure 1), and is associated with the use of low dose aspirin, diuretics, and the presence of comorbidities such as hypertension, cardiovascular disease, chronic renal insufficiency, and metabolic syndrome (10) (Figure 2). Also, it was documented that both diet with higher levels of meat and seafood and alcohol intakes (Figure 3) are risk factors for development of gout as well as triggers the recurrence attacks in patients who are already diagnosed with gouty arthritis. Numerous risk factors have been identified for the development of gouty arthritis (Box 1).



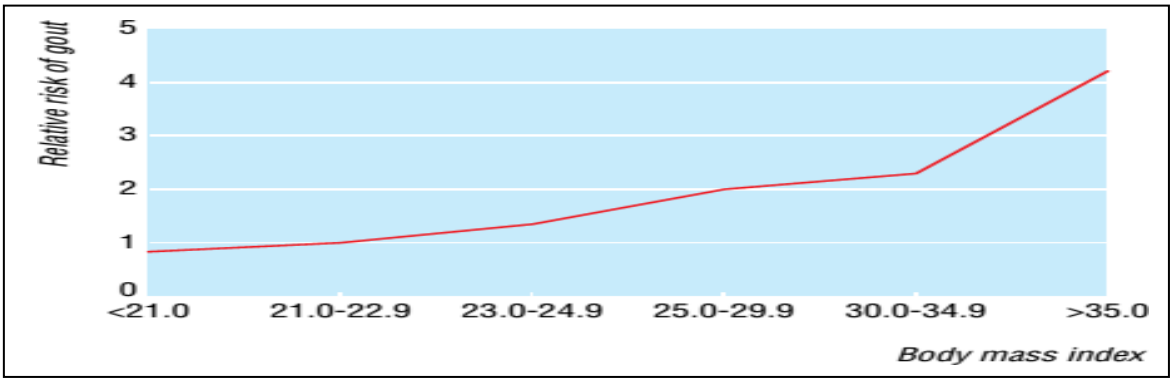
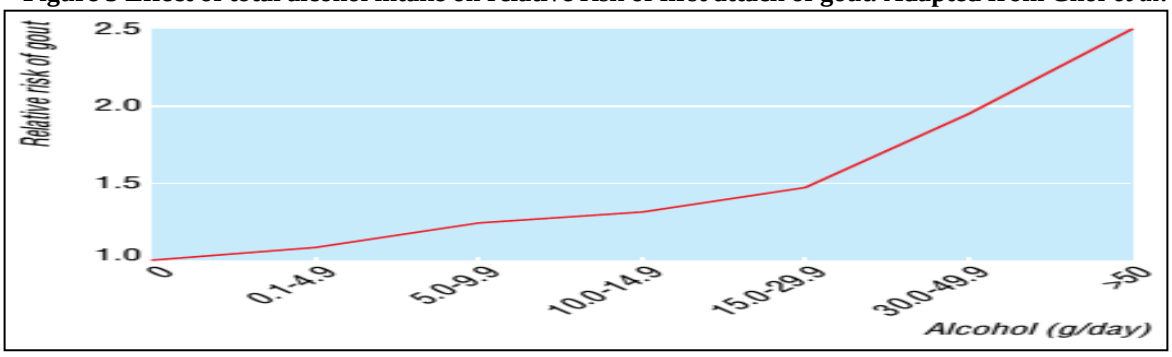


Figure 1 Prevalence of gout. Adapted from Mikuls et al.[3]

Figure 2 Effect of obesity on incidence of first attack of gout. Adapted from Choi et al. [11].

Figure 3 Effect of total alcohol intake on relative risk of first attack of gout. Adapted from Choi *et al*.[11]



Gouty arthritis clinical symptoms manifested by rapid onset of severe pain in the affected joint. Other

signs and symptoms include swelling, redness, and warmness. These clinical manifestations occur in response to the accumulation of monosodium urate (MSU) crystals. In every patient with gout, a number of pathophysiological points are required to present before development of the disease. First, increase in the levels of urate concentrations which can occur either by overproduction or under- excretion of urate levels (Box 2). Overproduction occurs as a result of alterations in purine synthesis and degradation. Urate under- excretion occur as a result of alterations in renal tubules function.

The next pathophysiological point is formation monosodium urate (MSU) crystals. As a result of MSU deposition in the joint synovial fluid the symptomatic gout develops. Most often the attacks are self- limiting lasting 3- 14 days5. With time, the attacks become less painful, but last longer and tend to involve more than one joint and tendons (1). The chronic deposition of crystals damage the joints, and lead to formation of tophi (urate crystal deposits in tissues), with chronic stiffness and swelling of the joints (1) .As mentioned earlier a typical gout patient will complain of a rapid and sudden onset of unbearable pain, swelling, and tenderness in a single joint with complete resolution of flares in a few days to 2 weeks. As gouty arthritis progress and the acute attacks still uncontrolled, the hands and more proximal joints might be involved. Females present differently than males, in which they are more likely to have more than one joint to be effected during the attacks.

Age
- >50 years at onset

Race
- African American > White

Sex
- Male > female

Genetics
- Amount of uric acid excreted by kidneys influenced by genetics

Lifestyle factors
- Heavy consumption of alcohol (especially beer)
- Red meat, seafood
- Purine-rich foods
- Obesity

Medications
- Diuretics (thiazides, loop diuretics)
- Low-dose aspirin
- Ciclosporin
- Niacin
- Ethambutol

Comorbidities
- Metabolic syndrome
- Hypertension
- Cardiovascular disease, Thromboembolic disorders (myocardial infarction, peripheral artery disease), Heart failure
- Chronic kidney disease
- Hyperuricemia without gouty arthritis

Box 1Risk factors for the development of gouty arthritis

For a definitive diagnosis of gout, identifying urate crystals in the aspirated fluid from the effected joint is considered the gold stander test. In medical practice most of the time patients with gout are diagnosed according to the American College of Rheumatology criteria (ACR) for the clinical diagnosis of gout (Box 3) without using this test. Choi et al. (11) mentioned that in only about 11% of gout patients are diagnosed by joint fluid aspiration in a health professionals study. The sensitivity of ACR was 84.8%, but the specificity was lower because 7.3% of patients with pseudogout, 2.5% with septic arthritis, and 1.7% with rheumatoid arthritis also met the criteria. Thus, if infection is possible

or suspected (ie, septic arthritis), aspiration is recommended. Various clinical variables can be used by a family physician to determine whether joint fluid aspiration is necessary. These include male sex, previous patient- reported arthritis attack, onset within 1 day, joint redness, metatarsophalangeal involvement, hypertension or ≥1 cardiovascular diseases, and an Uric Acid level >5.88 mg/dL. Janssens et al. (13) analyzed a total of 328 patients presented to a family physician with monoarthritis. They found that the presence of ≤4 of these variables ruled out gouty arthritis in 100% of enrolled patients. The presence of ≥8 variables confirmed gouty arthritis in 80% of the patients. In order to apply the ACR a physician must do a complete physical examination of the joints and looks for the cardinal signs of inflammation such as erythema, warmth, swelling, tenderness, and for presence of tophus.

Factors that decrease serum urate concentration:

- **Diet:** low fat dairy products
- **Drugs:** xanthine oxidase inhibitors (allopurinol, febuxostat), uricosuric drugs (sulfinpyrazone), uricas
- e drugs (rasburicase), coumarin anticoagulants, and oestrogen

Factors that increase serum urate concentration:

- **Diet:** meat, fish, alcohol (particularly beer and spirits), obesity, and weight gain
- **Drugs**: including diuretics, low dose salicylates, pyrazinamide, ethambutol, cytotoxics, and lead poisoning

Box 2 Factors affecting serum urate

Six or more of these criteria are needed to make a diagnosis:

- More than one attack of acute arthritis
- Maximum inflammation developed within one day
- Attack of monoarthritis
- Redness over joints
- Painful or swollen first metatarsophalangeal joint
- Unilateral attack on first metatarsophalangeal joint
- Unilateral attack on tarsal joint
- Tophus (proved or suspected)
- Hyperuricaemia
- Asymmetric swelling within a joint on radiograph
- Subcortical cysts without erosions on radiograph
- Joint fluid culture negative for organisms during attack

Box 3 American College of Rheumatology preliminary criteria for the clinical diagnosis of gout [12].

A family physician assessment for a suspected patient with gout should include a complete history and risk factors assessment. Also, a physician should ask for sUA level, glomerular filtration rate, erythrocyte sedimentation rate, and C-reactive protein level given that elevations in these markers are associated with monosodium urate crystals. The presence of persistent hyperuricemia (ie, sUA >6.8 mg/dL) can be indicative of gouty arthritis in a patient who reports a history of previous monoarticular arthritic attacks. However, studies have found that sUA levels during the acute gouty arthritis attacks are not

accurate and they tend to be lower than the actual levels before the attacks. This reduction in the sUA levels is explained by the increase in urinary excretion of uric acid that accompanies the acute inflammatory events associated with flare (14).

It is important as mentioned earlier for a family physician to roll out septic arthritis in a patient suspected with gout. A physician should keep in mind that during early presentation of a patient suspected with gout it may present with no fever or leukocytosis. When these features are present, gram stain and culture of synovial fluid or blood are needed to exclude infection (15). Another important differential diagnosis for gouty arthritis is Pseudogout which has a similar presentation. A physician can rely on lab microscopic reports, Pseudogout crystals are positively birefringent and rhomboid shaped, while urate crystals are negatively birefringent and needle-like in appearance. Also, in most of the time Pseudogout attacks affect the large joints and old females.

Management and Treatment

Management a patient with gout is difficult and requires a good compliance from the patients. A physician should take in consideration the presence of comorbidities, patient's medications, potential impact on lifestyle, and complications of continued medication.

Treatment of acute gout attack

The immediate goals for management of patient with acute gouty arthritis attack is to relive the pain flares, intensity, and to improve the function with the use of nonsteroidal anti- inflammatory drug [NSAID] of choice, colchicine, and/or corticosteroids. Ice, rest, and elevation are useful nonpharmacologic adjunctive therapies. Treatment of the attacks does not have any relation or impact on crystal formation or deposition. Physicians should keep in mind that they cannot start uric acid- lowering therapy (ULT) during an acute attack as it can further propagate the attack.

• Non-steroidal anti-inflammatory drugs

In general, Non-steroidal anti-inflammatory drugs (NSAIDs), specifically indomethacin (a non-selective Cox1 and Cox2 Inhibitor) are the most popular treatment for reliving of gouty arthritis acute attacks symptoms. A lot of clinical done to assess if there are any differences in the outcomes of using selective versus no selective NSAIDs. Their final results have failed to show any difference in the outcomes (16). Their potential gastrointestinal and cardiovascular side effects are well documented and a physician should use it carefully in patients with these comorbidities.

• Colchicine

Colchicine is approved for treatment of gout acute flares and as a prophylaxis (17). A randomized AGREE (Acute Gout Flare Receiving Colchicine Evaluation) trial found that there is no difference in the outcomes between using a high dose of colchicine (4.8 mg total over 6 hours) and a low dose (1.8 mg

total over 1 hour). As a result of this study the USA federal and drugs administration approved for the use of Colchicine with maximum recommended daily doses of 1.2 mg for prophylaxis and 1.8 mg for treatment of flare (18). In patients with hepatic and renal impairment the use of Colchicine is contraindicated.

• Steroids and adrenocorticotrophic hormone

Oral, parenteral, and intra-articular steroids and adrenocorticotrophic hormone are all used to treat acute gout. According to our search we were not able to find any placebo controlled trials that wanted to assess the effect of steroids or adrenocorticotrophic hormone on acute gout. A physician might use a short course of oral steroid in patients with contraindication of using NSAIDs or colchicine to avoid unwanted adverse effect. However, a physician should put in mind to taper the oral steroid dose before stopping the drug to avoid rebound flares on withdrawal.

Prevention of recurrent gout

A symptomatic hyperuricemia rarely require management except in, patients who are treated for malignancy and people with high urate concentration (> 0.8 mmol/l) and high renal excretion of urate, to prevent formation of renal stones. A physician should take in consideration that increased urate concentration and recurrent joint pain is not sufficient for starting a lifelong uric acid lowering drugs with potential side effect. To decide whether to use or not a prophylactic therapy a physician must take in consideration the patient's decision. In general a physician can offer this medication for patients who experience more than two acute attacks per year, have tophi, or have radiological changes. As a role, a physician should not start urate lowering drugs during the acute flares of gout. During the first

3 month of using urate lowering drugs a physician must add NSAIDS or Colchicine to prevent a rebound increase in acute gout.

The target of interventions to reduce serum urate is to decrease the serum urate concentration to be below 0.36 mmol/l, well below the level at which urate crystallises (19).

• Medication review

As a side effect, few drugs may cause hyperuricemia such as diuretics; a physician should review all the drugs of gout patients.

• Xanthine oxidase inhibitors

Xanthine oxidase inhibitors, such as allopurinol and febuxostat, reduce the production of uric acid by inhibiting the enzyme those catalyses the final steps in uric acid synthesis.

Allopurinol is used for treatment of patients with acute attack of gout, tophi and joint destruction. The desirable sUA in gout should be below 6 mg/dl, and this is reached at initial dose of Allopurinol 100 mg/day then increased in 100 mg every week but not exceeding 800 mg/day. Dose adjustments in patients with renal dysfunction are necessary. Allopurinol has several adverse reactions. The most common and important side-effect is skin rash. The sever life threating reactions include hypersensitivity, Stevens-Johnson syndrome, generalized vacuities, irreversible hepatotoxicity and Allopurinol should be stopped immediately when the skin rash is noticed. There are several drugs that have a drug-drug interaction with Allopurinol such as mercaptopurine, theophylline, and azathioprine and the doses should be reviewed when administered with Allopurinol (20).

Febuxostat is a nonpurine xanthine oxidase inhibitor that is highly selective for xanthine oxidase. It is approved for the management of symptomatic hyperuricemia in patients with gout. The desirable sUA goal of 6 mg/dL and this is reached at initial dose of 40 mg/day. If the sUA goal not reached within 2 weeks the dose should be increased to 80 mg/day. Febuxostat is metabolized in the liver; as a result it doesn't need any dose adjustment in case of patients with renal dysfunction. The use Febuxostat is associated with have GIT side-effects such as abnormal liver function tests, nausea, and arthralgia representing the most frequently reported adverse events (21, 22).

• Uricosurics

Uricosuric medications such as Probenecid are substances that increase the excretion of uric acid in the urine, thus reducing the concentration of uric acid in blood plasma.

Probenecid is a potent uricosuric drug used as alternative to allopurinol for treatment of hyperuricemia in gout and gouty arthritis. Probenecid is not used in management of acute gout and alternative symptomatic therapy such as colchicine could be used. probenecid is less effective than allopurinol, and the recommended dose is 250 mg twice daily for 1 week and 500 mg twice daily thereafter.

Probenecid may not be effective in patients with CrCl ≤30 mL/min.Hydration is important, and alkalization of urine by sodium bicarbonate (3-7.5 g/day) or potassium citrate (7.5 g/day) is essential to decrease the uric acid stone formation associated with increase the uric acid clearance. Other side-effects include headache, dizziness, hepatic necrosis, nausea, and vomiting (23).

• Pegloticase

Pegloticase is used in cases of refractory chronic gout that doesn't respond to the other management options. The drug is administered by infusion intravenously every two weeks. The use of Pegloticase is associated with development of infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis, and vomiting. It should be noted that the risk of infusion reaction and anaphylaxis is significant enough for the physician to start a course of antihistamines and corticosteroids before treatment. One of the important problems regarding to Pegloticase is that a proportion of the patients might develop antibodies which increase the drug failure rate (24, 25).

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