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Review Article

Niqras (Gout) from Antiquity to Present Scenario and Contribution of Greco-Arab Physician

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Abstract

Background: The history of Niqras (Gout) dates back to early human era. Due to continuous alteration in demography of this ancient disease, clinicians of 21st century faced a lot of difficulties to understand it.

Method: In this article we reviewed how the perception about the aetiogenesis, symptomatology, diagnosis and management of gout including myths have advanced and also discussed about the inference thereof.

Results: Niqras (Gout) has been reported as a clinical entity as far back as the 5th century BC by Hippocrates (Buqrat, 460 - 377 BC), who devoted his aphorism regarding the gout between the 1st - 6th century AD, the role of heredity and the relationship of gout with a rich diet and wealth men who overindulged in food and drinks. The term gout is derived from the Latin word "Gutta" probably around 1200 AD and the microscopy of uric acid crystals and gout symptomatology were the focal point of the studies between the 17th to 18th centuries. Several drugs like salicylates, probenecid, and allopurinol were discovered for the treatment of gout between the 19th -20th centuries. Gout as a risk factor for several diseases like cardiovascular diseases, metabolic disorders and type 2 diabetes is the challenge for the twentieth century clinicians and so forth.

Conclusion: The history of our understanding of gout parallels with the human development but how to deal with gout associated cardiovascular co-morbidities is still a challenge for the future.

Keywords: *Allopurinol; Gutta; Metabolic Disorder; Niqras*

Niqras (Gout) in ancient civilizations (Eras)

People have recognized gout as a specific disease for thousands of years. Many ancient writers clarified gout in ways that still make sense to us today. The history of our understanding of gout parallels the history of scientific knowledge. The initial written reference to gout dates back to 2600 BC, when Ancient Egyptians first described Podagraor gouty arthritis, typically of the big toe (1st metatarsophalangeal joint), and at present understood it as uric acid arthropathy [1,2]. The initial reference in this regard lies in the Ebers Papyrus (1500 BC) in which a drug, probably matching with colchicines was described. Both Ancient Greek and Roman (Romi) medical writers included gout in their books [3-6].

Diocles of Carystusin in 4th century B.C considered gout as an inflammatory disease which occurs due to accumulation of bad humors (raddiakhlat) in the joint of feet [7].

Although there is definite evidence of the presence of gout in Egyptian mummies almost 4,000 years ago via detection of uric acid crystals in their body joints, the disease was first described in detail by Hippocrates during the 5th century BC, who referred to it "the unwalkable disease and the arthritis of rich, because it mostly affects the rich and blame it on an excess of wine, food and sex [2,6,8-11].

Hippocrates (Buqrat 460- 377 BC), the father of Medicine recommended that gout was the result of an excess of one of the four humors (akhlat) setting in the joints. This is derived from his belief that every person's body contained four humors (akhlat) - which in equilibrium were thought to maintain health- would, under certain circumstances, drop into a joint, causing pain and inflammation. He referred to gout as podagra (meaning severe pain grabbing the leg), cheiragra, gonagra or omagra depending on whether the big toe, hand, knee or shoulder was involved. In addition, he described the association between sexual hormones and gout [2,3,5,8,10,12-19].

Hippocrates further explained that gout mainly affect the persons who are aged, have tophi in their body parts, passing a hard life, and whose bowels are constipated are beyond the power of medicine to cure [2]. The noteworthy clinical perceptions of Hippocrates in relation to gout are preserved in the form of aphorisms, which are as accurate today as they were 2500 years ago [10] (Table 1).

- Eunuchs do not take the gout, nor become bald.
- A woman does not take the gout until their menses be stopped.
- A youth does not get the gout before sexual intercourse.
- In gouty affections, inflammation subsides within forty days.
- Gout affected more people in spring and autumn.

In Roman physicians Celsus (25 BC- AD 50) used the Latin word podagra (seizure in the foot) and chiragra (seizure in the hand) to explain a gout-like disease [20]. Historically, gout has been considered to be primarily a male disease.

Seneca, a Roman senator of first century A.D, first recognized that women can also develop gout during the reign of Nero (54- 68 A.D) [10]. Seneca also highlighted the role of genetics in gout [2,6,21]. In 1st century A.D, Aretaeus (81- 138 AD)described polyarticular gout [8] and suggested that there was a toxic substance in the blood of gouty patients [20]. Dioscorides, renowned Greek scholar of Roman era and the author of famous book ''De universa medicina'' (kitab-ul-Hashaish in Arabic) described about the gout in his book while discussing the properties of colchicum in first century AD [14]. Roofas-Al-Afsi, (100 AD) famous scholar of Roman era, wrote about 60 books on different topics and discussed causes, symptoms and treatment of gout separately in his treatise "Kitab-Fi-Auja-ul-Mafasil" [22]. Galen (Jalinoos, 129 - 200 AD), was the first physician to describe the tophi in longstanding gout sufferers around 200 AD- lumps of crystallized uric acid under the skin [1,2,10,22]. According to Galen, major cause of gout is coitus hence Eunuch and Young man do not involved in gout [12]. Galen associated gout with debauchery and intemperance, but also distinguished gout as a hereditary trait that had formerly been referred to by the Roman senator Seneca [10,12].

Niqras (Gout) between 4th to 7th century AD

Faligaroos (4th - 5th century AD) a renowned unani scholar of Byzantine era, compiled a booklet ''Risala-fi-Auja-Niqris'' on gout and pointed out that injury is a central cause of gout. Rhazes (Rhazi, 850- 923 AD) has extensively referred to this booklet while discussing gout in his books "Al-Hawi" "Al-Mansoori" "and Al-Fakhir" [22].

Colchicum: A remedy for gout through the ages

Alexander of Tralles (6th century AD), a Byzantine physician, introduced a plant called *Colchicum autumnale*, commonly known as meadow or autumn crocus, as a specific remedy to alleviate the pain and inflammation of gout. He was the first person who used the corm (bulb) of it for the treatment of podagra (gout), in the 6th century AD. This drug was first suggested by Dioscurides and later used by Jacob Psychristus, the personal physician of Emperor Leon I (457-474 AD), and it was broadly used as analgesic or laxative during the Byzantine era. Although colchicines was discarded from the market for centuries, and reintroduced by physician Anton Storck in Vienna in 1763, for the management of gout and now today consider it as a first-line remedy for acute gouty arthritis [2,8].

Paul of Aegina in 7th century AD, used infusion of the whole plant (*Colchicum autumnale*) to treat the gout [20].

Prevalence

Lascaratos has widely deliberated the prevalence of arthritis in a large cohort of Byzantine emperors (326 - 1453 AD) and found that 14 out of 86 emperors suffered from gout. He also points out that there are no signs of any kind of inheritance because emperors belong to the different dynasty, but its etiology was almost certainly due to overconsumption of meat and alcohol. Theophylactus Simocattes in 6th century AD explained that gout was highly prevalent among the inhabitants of Constantinople [8].

Gout during the Arab period: Contribution of Arab Physicians

During the Arab period of Unani Medicine gout was described by most of the great medical authorities of medieval word and physicians such as Al-Tabbari (Al-Tabbari, 838 - 870), Rhazes (Al-Rhazi, 860 - 923), Albucasis (Al-Zahrawi, 936 - 1013), Al-Biruni (Al-Biruni, 973 - 1050), Avicenna (Ibn Sina, 980 - 1037), Alhacen (Ibn al-Haitham, 960 - 1040), Ibn al-Nafis (Ibn al-Nafis, 1213 - 1288), Ibn Khaldun (Ibn Khaldun, 1332 - 1395), Ibn al-Baitar (Ibn al-Baitar, 1197 - 1248), and Avenzoar (Ibn Zuhr, 1091 - 1161) and their textbooks were used in European Universities up to the 16th century. These Arab and Muslim physicians were among the first to make accurate diagnosis of gout [13,22-24]. Johannes Damascenus (Ibn Masawaih, 777 AD - 857 AD), famous physician of Arab period, mentioned that Aloe barbadensis (Sibr) and Castor oil (Roghan-e-Arandi) is beneficial for gout while describing the treatment of gout [12].

In 8th century AD, Qusta Ibn Luqa (820 - 912 AD) a renowned physician and translator of Abbasi Period, mentioned detailed etiology, clinical feature, and management of gout in his book "Risalah-FI-auja-Al-Niqris'' [22,25,26]. Andin 9th century AD, Ya'qub Ibn Ishaque (also known as Philosopher of Arab) and Sabit Bin Qarrah, renowned translators of Baitul-Hikmat, wrote the book "Kitab Fi Wajul- Maida Wa Al- Niqris" and '' Kitab Fil Waja-ul-Mafasil Wa Al- Niqris''on gout respectively. Sabit Bin Qarrah described that right-side gout is khafeef (weak) and better than left side [12,22].

Rhazes (Rhazi, 860 - 923) also known as "Jalinoos of Arab" wrote the book "Kitab Fi Alal Al-Mafasilwa Al-Niqriswa Urqun-Nisha'' in the 9th century AD [12,22] and described the treatment of gout in detailed in Al-Hawi-Fit-Tibb and stated that "Niqris and Waja-ul-Mafasil cured very rarely if it is caused by Ghaleez Ratubat and involve old people [13,25]. After Rhazes, Avicenna (Ibn Sina, 980 - 1037), worked on gout and explained the etiology, clinical features and treatment of gout in his famous treaties "Canon of Medicine" (Alqanoon-fit-tib). Avicenna also wrote "Risala Niqris'' on gout and mentioned that gout is a Balghami disease [27] and in 10th century AD Abu Sahel Maseehi, author of well-known book "Kitabul Miat'' also elaborated some risk factors responsible for developing gout [22]. In 11th century A.D Averroes (Ibn Rushd) in his famous book "Kitabul Kulliyat'' described the changes which occur in gout according to Kammiyat (Quantity) and Kaifiyat (quality) and in 12th century AD, Ismail Jurjani author of Zakheera Khwarzam Shahi described other key points related with etiology, symptoms and management of gouts in detail [28]. During the 12th and 13th century AD., Unani system of Medicine reached the Indian sub-continent where majority of the scholar described the gout in the light of explanation given by their predecessor.

Gout and Poetry

Michael Psellus's Poem about gout

In different cultures and civilizations, poetry and music has been merging with medical conditions. Michael Psellus (1018 - 1078 AD), a Byzantine monk, philosopher and politician, composed a poem and included fifteen lines regarding the pathogenesis and clinical picture of gout in his poem titled "An excellent medical work in the iambic manner". In this poem, Michael Psellus described the main clinical symptoms of gout, for example painful joint, swelling, he also recommends that the disease originates from the accumulation of several waste products (pathologic humors) circulating in the body. He also claims that gout can not only affect the feet but also many other joints of the body (polyarthritis). Michael Psellus views were parallel with Hippocrates' theory about the imbalance of humors which were the main factor for the genesis of all diseases [8].

The term "gout"

The term 'gout' is derived from the Latin word "gutta", meaning drop of liquid, probably first used by Dominican monk, Randolphus of Bocking around 1200 AD [1,3,6,10,20]. Randolphus, in accordance with Hippocrates theory about humors, thought that proper balance of humors is necessary to maintain good health and gout resulted when one of the humors (fluids) "dropped" into a joint causing pain and inflammation. Therefore, a large number of population still carry on to tracking the ancient remedies of bleeding, sweating and purging to try to restore this balance [2,8,20].

Gout between 17th and 18th century AD

In 1679, Anton von Leeuwenhoek, one of the pioneers of microscope, first saw urate crystal, but it was about several hundred years before the great English Physician Alfred Garrod affirmed that urate was the cause of gouty inflammation. In 1683, the modern history of gout started with Thomas Sydenham, who himself suffered from gout [1,3,6,15]. Thomas Sydenham (1624 - 1689), an English physician in England, also known as the English Hippocrates, and father of English Medicine, distinguished gout from rheumatism [29]. Sydenham first described the acute attack of gout in his treatise On Gout in1683 [6]. Thomas Sydenham was sometime referred to as Shakespeare of gout, some of his Quotes regarding the gout are shown in table 2 [19,30].

- Gout kills more rich men than poor, more wise men than simple.
- Gout produces calculus in the kidne. The patient has frequently to entertain the painful speculation as to whether gout or stone be the worse disease. Sometimes, the stone, on passing, kill the patient, without waiting for gout.
- Gouty patients are, generally, either old men, or men who have so worn themselves out in youth as to have brought on a premature old age.
- Gout generally attacks those aged persons who use too much wine and other spirituous liquors.

In 1700s, spa treatments to ease the symptoms of gout were most popular and were recommended by foremost physicians including Willian Cadogan in A dissertation on the gout, and all chronic disorders in 1771 AD. Most of the physicians in the 1700s as well as Dr William Stukeley thought that diet and exercise could play a key role to alleviate the symptoms and that a balanced lifestyle was also important [20]. William Stukeley in 1734 described the crystals from a tophaceous joint and in 1763, colchicines was reintroduced by Prof. Baron von Stock in Vienna [2,8]. Swedish Chemist, Scheele in 1776 discovered chemical identity of uric acid as a constituent of renal calculus and in 1797, English Chemist Wollaston demonstrated urate in a tophus from his own ear [3,6,10].

Gout in the 19th and 20 centuries:

Although gout was infrequent among the South Africans black, Mody and Naidoo stated that a case report on South Africans black sufferer was published as early as 1807 by Andrew. Later, Cassim., *et al*. also established an association between the South Africans black with gout and increase HLA B14 antigen level compared to those without gout [2].

In 1814, Want first time revealed the colchicines specialty in acute gout treatment and in 1820 colchicines listed in USA pharmacopaedia [2,31]. In 1848, Sir Albert Garrod discovered the association between hyperuricemia and gout and in 1859 he wrote the book "The Nature and Treatment of Gout and Rheumatic Gout". He also described his famous "thread test", a semi quantitative method, for the measurement of uric acid in urine and serum. It was the first clinical chemical test ever undertaken [6,10,20]. Between 1894 and 1897, Haig (being a gout sufferer), was conducted several experiments on himself and explained that hyperuricaemia could be lowered by decreasing the intake of purine-rich foods [2], and likewise Freudweiler in 1899, experimentally proved that injecting crystal of sodium urate into joints and subcutaneous tissue precipitated gout and tophi respectively [2,10,31].

In 1896, Huber gave first radiological description of gout and in 1898; Emil Fischer proposed pathogenic mechanism of gout. In 1913, Folin and Denis identified the measurement of serum urate and Talbot, Gutman, and Yu identified the uricosuric effect of probenecid in 1950. Several uricosuric agents were also introduced towards the end of 19th century and used to treat gout [2,6] and in 1931, Garrod's son Archibald, author of first clinical genetics textbook, declared gout to be an "inborn error of metabolism" [1].

By the 1940s, aspirin was used for the treatment of gout and probenecid was introduced in 1951 and in 1963, Gertrude Elion and George Hitching Introduced Allopurinol, first xanthine oxidase inhibitor, which even today is the most broadly used drug for gout treatment and in 1988, George Hitchings and Gertrude Elion were rewarded the Nobel Prize for developing allopurinol, azathioprine and some other drugs [1-3,6,33].

In 1961, Mc Carty and Hollande reidentified monosodium urate (MSU) crystals in the synovial fluid of patients with acute gout and hence represented the initial recognition of arthritis associated with articular crystal deposition [1,6,15,32]. The midpoint of the 20th century was perhaps the golden age of gout therapy, with the introduction, in rapid succession, of ACTH (1948, adrenocorticotropic hormone), prednisolone (1995), and indomethacin (1963) [1]. Seegmiller, Rosenbloom and Kelly, in 1967discovered first enzymatic defect (HGPRT deficiency) responsible for one subtype of adult primary gout and after five years, in 1972, Sperling and his colleagues discovered the second enzymatic defect (PRPP synthetase over activity in urate overproduction) [5,6]. Klinenberg, in 1977, suggested that gout cases are equally distributed into three categories of over-production, under-excretion, or a combination of the two defects [34].

Between 1980 and 1990, various new drugs were discovered for the treatment of gout, but allopurinol remains the most broadly used drug. In 1996, Oxypurinol was released into US. market. In 1998, clinical trials were started on new anti-hyperuricemic drugs in Japan [31]. Recently, the estimation of salivary urate as a noninvasive method of diagnosis and monitoring gout has been recommended [35]. From the Cold War until the end of 20th century, there was no more significant advance in gout therapy [1].

Gout in 21st century: An emerging challenge for physicians

During first few years of 21st century, the understanding and treatment of gout and hyperuricemia has begun to advance once more [1]. Later, gout become the most common inflammatory arthritis in men above forty years of age and incidence and prevalence increases across all races. This is mainly because dietary changes, increasing longevity, renal insufficiency, excessive use of diuretics and some other drugs leads to hyperuricaemia. The incidence of metabolic syndrome, hypertension, renal stones, renal insufficiency, type 2 diabetes and coronary artery disease (CAD) also increasing in gouty subjects [2,3,5,6]. Gout was associated with a 60% increased risk for CAD in men in Framingham heart study and a 26% increased independent risk of myocardial infarction. Gouty men have a 41% increased risk for type 2 diabetes and gouty men also have an increased risk of death from all causes[6]and this constitutes a serious concern within the context of a global epidemic of type 2 diabetes and coronary artery diseases [2]. In the same light, increased consumption of sugar sweetened soft drinks and fructose has been associated with an increasing risk for gout [2,6].

The lenient lifestyles that predispose to gout are also risk for the majority cardiovascular diseases, although a higher intake of dairy products have a protective role against the development of gout because of the uricosuric urate-lowering effect of dairy protein6. In the same way, a prospective study on coffee consumption suggests that it appears to be protective against the development of gout and this protection depends on the number of cups of coffee consumed per day, with maximum protection at 6 cups, irrespective of caffeine content [2].

Conclusion

With a history spanning more than 2600 years, People recognized gout as a specific oldest disease. Its profound impact on patient's quality of life has been influenced historical events. The changing trends in gout epidemiology can be safely attributed to dietary changes, increased longevity and increasing number of individuals with metabolic syndrome and organ transplants. Hence the challenge for the future physicians will not be limited to the management of pain and lower increased serum uric acid levels successfully, but also the linked cardiovascular co-morbidities condition in patients with gout. During the past years advances in understanding the etiology and pathology of gout, have lead to the development of effective treatment.

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