

COMMENT

Diet and metabolism are back: The oldest known Islamic medical manuscript bridges the gap from ancient to modern gout management

STYLIANI GERONIKOLOU^{1,2}, GEORGE P. CHROUSOS^{1,2},
DEMETRIOS A. SPANDIDOS³ and ATHANASIOS DIAMANTOPOULOS⁴

¹Biomedical Research Foundation of the Academy of Athens; ²University Research Institute of Maternal and Child Health and Precision Medicine, National and Kapodistrian University of Athens, 11527 Athens;

³Laboratory of Clinical Virology, Medical School, University of Crete, 71003 Heraklion;

⁴Louros Foundation for the History of Medicine, 11528 Athens, Greece

Received May 24, 2023; Accepted September 28, 2023

DOI: 10.3892/mi.2023.114

Abstract. Gout is a chronic disease frequently associated with lifestyle; its prevalence is increasing in Western societies, as well as in the Middle East. Apart from its partial genetic features, diet accounts for 12% of the causality of the disease, while purine-rich foods contribute decisively to its development and evaluation. The influential Persian physician of the medieval ages, Abu Bakr Muhammad Ibn Zakariya al-Razi (or by his Latin name Rhazes; 860-925 AD), wrote a short book (20 chapters) entitled '*Treatise on gout*'. Rhazes adopted the Hippocratic humoralism, and suggested that the disease results from metabolic excess in the peripheral blood, presenting sex dimorphism and age-dependence. His therapeutic guidelines include a diet prescribed by a physician, the use of laxatives and emetics, counter-balancing excess or deficiency of bile or phlegm and analgesics, bloodletting, foot and steam baths, as well as salves and poultices as preventive measures. He appends differential dietary restrictions/suggestions for phlegmatic or choleric patients: Small rations and intake of good quality foods low in purine by 20% for phlegmatic and 28% for choleric patients, as well as the restriction of foods high in purine by 27% for phlegmatic and 22% for the choleric patients. Finally, the acidic to alkaloid food intake ratio suggested is 2/5 for choleric and 3/7 for phlegmatic patients.

His suggested foods and drugs are vitamin C and B-rich complexes, thereby inhibiting the accumulation of tophi.

Introduction

Gout is a chronic disease closely related to lifestyle, with an increasing prevalence in Western societies, as well as in the Middle East (1,2). It is denoted as '*the king of diseases and the disease of kings*' (3). In other words, apart from its partial genetic vulnerability features (ATP binding cassette subfamily G member 2, glucokinase regulator, capping protein regulator and myosin 1 linker 1, PDZK domain-containing scaffolding protein, solute carrier family 2 member 9 and solute carrier family 16 member 9) (4), diet also plays a critical role in its manifestations (3,5). One of the main symptoms of gout is hyperuricemia (normal uric acid levels are 2.4-6.0 mg/dl in females and 3.4-7.0 mg/dl in males); thus, sex hormones play a decisive role in its appearance as stated in the Hippocratic Aphorisms (6-8). Its reported risk factors include metabolic syndrome, alcohol intake, dietary preferences (tailored to cultural and often racial diversities) (9), decreased physical activity, and hypertension (10). Diet accounts for 12% of the causality of the disease (11), while purine-rich foods contribute to its development and progression (12-14).

Gout is one of the earliest diseases described in Egyptian scrolls, in ancient Greek literature (Homer, Lucianus, Hippocrates, Galen), in Byzantine literature (Alexander of Tralles, John Chrysostomus, etc.) (15-19), as well as in Islamic medical manuscripts and/or translations (19-22). Dietary advice (restriction mostly) for patients with gout may also be found in '*Liber de podagra*' authored by the Byzantine savant, Demetrios Pepagomenos, a 13th century AD manuscript (19,22) and in a Latin unpublished manuscript n: 98-6 of the 14-15th century AD (the manuscript was written in the 13th century AD, and transcribed in

Correspondence to: Dr Styliani Geronikou, Biomedical Research Foundation of the Academy of Athens, Soranou Ephessiou 4, 11527 Athens, Greece
E-mail: sgeronik@bioacademy.gr; sgeronik@gmail.com

Key words: gout, purine-rich foods, dietary suggestions, old manuscript, al-Razi, history of urology, history of medicine

15th century AD), entitled '*De arthetica passione*' written by Antonio Guaniero da Pavia, and found in the Toledo Biblioteca Capitulare (23).

The influential Persian physician of the medieval ages, Abu Bakr Muhammad Ibn Zakariya al-Razi (or by his Latin name Rhazes; 860-925 AD) wrote the '*Treatise on gout*', probably, as a teaching handbook for his trainees. An unpublished Latin translation of this manuscript is preserved in the Bibliothèque de l' Arsenal, 1024 (71 SAL), fol 175 vo-181. Biblioteca Alexandrina, on the other hand, published the original 40 pages in 1199 AD (595 H), transcribed by Aliy Sinān al-Sirāj al - Halabi in a multilingual translation in 2003 (21). The manuscript includes 20 chapters, where the titles have an interrogative style. A Greek translation of this manuscript was published in Athens in 2012 (19).

Of note, Rhazes used to be proud of his Greek medical education, and his clinical point of view was humoralistic, involving the concept of four humors, as suggested by Hippocrates and further employed by Galen. In chapter IV, Rhazes clearly states that the disease results from metabolic excess in peripheral blood. This is shown by the following free translation (source language is Arabic): '*Any disorder in the blood consistency is a result of either yellow bile turning blood warm and dry, or phlegm that makes it gelatinous (thick) and phlegmatic. These two humours produce two types of gout: by choleric humour accumulation in the feet or by feet brimming with phlegm. Subjects with frail feet but lusty organs and overproduction of blood are exposed to a third type of gout, where plenty of blood attacks feet, inducing pain notwithstanding yellow bile or phlegm*'.

He notes that gout may be prevalent in adult males, rather than females before menopause ('*because before menopause their bodies are humid, aborting unhealthy humours*'), in eunuchs ('*as their bodies are cold and weak*') or male prepuberts ('*as their bodies are cold, humid and immature*'), as stated in chapters V-VII. In chapter X, he lists the treatment methods available in his time, highlighting that they supplement one another, as follows: i) Moderation of a restricted diet; ii) adopting physician-prescribed dietary guidelines; iii) the administration of laxatives and emetics; iv) bloodletting; v) application of water on feet; vi) steam baths; vii) administration of salves and poultices; viii) prevention of disease crises, ix) adopting drugs for counter-balancing excessive or excessed or deficient humors (anti-podagra) and analgesics.

All his thought is characterized by choleric vs. phlegmatic types of patients. Dietary preferences are health status moderators according to ancient Greek medicine (24). In chapters XI and XII, he provides detailed food guidelines for patients with gout, while he appends differential dietary restrictions/suggestions for phlegmatic or choleric patients.

Rhazes initiates his suggestions by emphasizing the need for small rations of high-quality foods and good hygiene standards. As ancient Greek doctors had written earlier, the undesirable effects of dietary excess may be treated with laxatives and emetics. Of note, these dietary dimorphic urges are presented as a supplement to the also humour-type targeted drug remedies. In a previous publication, the drug constituents and mode of administration (stated herein) is detailed (20).

Preferred foods

The modest consumption of cereals rich in purines (e.g., rice) for both types of patients is proposed in this work of the 9th century; the same is also recommended in modern medical research (12,25). Rhazes notes that both types of patients should prefer spinach, beetroots and wheat in boiled form, as opposed to other cooking methods. Such patients would benefit from fruits with medium levels of sweetness, such as pears, grapes and figs, as opposed to other fruits and desserts, which are high in sugar. He explains that wheat or semolina bread and fish balls should be preferred. Soups containing beetroots or wheat are, modestly allowed.

More specifically, patients suffering from phlegmatic blood are advised to consume the following: i) Only small rations of lettuce, cucumber, gourd, lentils, mushrooms, cauliflower, cuscuta, eggplants, endives, cabbage and whey (these servings are used to substitute a common meat dish named *kisk*); ii) hens, chicken, pigeons, gulls, grouses, francolins cooked in a yeast sponge and stuffed with greens and spices, stewed or prepared with onions, vinegar, leeks and honey; iii) sprouts, young lambs fried with onions, chickpeas, almonds, eggs, and herbs or cumin mixed with vinegar and spices; iv) small fish or fish balls cooked with vinegar or served with amaracus (*Origanum majorana*) sauce; v) eggs, soft-boiled. On the other hand, choleric patients are advised to prefer small fried fish (in oil) apart from fish balls (in vinegar or amaracus sauce).

Foods to abstain from

Both types of patients are recommended to avoid doves (*šafānīn*), cereals or pastries containing honey or syrup or having been fried. Greens are completely restricted, apart from those stated in the paragraph above. Almonds, raisins, pine seeds, dried dates, walnuts and peanuts are completely forbidden, and should only be consumed in very small rations. Servings containing beetroots and wheat (except boiled) and 'red color dishes' are classified as restricted by Rhazes. Rhazes clarifies that thick boiled or cooked eggs, beef, camel, sheep meat (*jupūr*) in general, and any meat and larger fish fried or salted and/or smoked and/or dried [either under the sun (*nakmasūd*) or in the oven], dairy products (except pastries containing dairy products, such as rice pudding), and almonds should be avoided by all gouty patients. Notably, all these foods have been classified to be highly or medium-rich in purines (13,26). Rhazes' remarks are unexpected, as purines were unimaginable entities in the 9th century, and his suggestions appear to be based on discerning observations. The importance of the purine concentration was evidenced a millennium later, in 2004 AD (13,14). Considering this, the restriction of foods with high purine concentrations is indicated as follows: 27% in phlegmatic and 22% in choleric patients. Accordingly, he suggests that foods low in purine to be restricted to 20% in phlegmatic and 28% in choleric patients.

More importantly, his suggested foods and drugs are vitamin C and B-rich complexes, thereby inhibiting the accumulation of tophi, in accordance with modern treatment approaches (4,27-29). Recent literature denotes that the DASH and Mediterranean diets, and the consumption of low-fat dairy products and cherries may contribute to a decrease in serum urate levels (9,30-35).

Metabolism converts anthocyanins, contained in many of the referred foods, to anti-inflammatory elements. Finally, the acidic to alkaloid food intake ratio suggested for choleric and phlegmatic patients should be 2/5 and 3/7 accordingly; these ratios, however, merit future validation by evidence obtained from randomized controlled trials.

This ancient manuscript is of importance for medical history, due to the information conveyed herein, which has not been previously communicated, at least to the best of our knowledge. Furthermore, contemporary research may be inspired by such manuscripts that incorporate dietary ancient observations to further evaluate medical/dietary knowledge in complex disease entities. Moreover, as the prevalence of gout in specific populations of distinct racial and ethnic backgrounds largely varies (9,35,36), the quantitative suggestions of Rhazes need to be validated beyond the Persian and Arabic populations.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to the publishing rights of the publisher (Efporista), but are available from the corresponding author on reasonable request, or may be found in the e-ISBN: 978-618-80000-1-8 electronic book, or ISBN: 978-618-80000-0-1.

Authors' contributions

SG was involved in the conceptualization of the study, as well as in the investigation of relevant data, in the writing of the draft, in revising the manuscript, and in administration. All authors (SG, GPC, DAS and AD) were involved in the revising and editing of the manuscript. SG and AD confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

- World Health Organization (WHO): World Health Organization Projections of mortality and causes of death, 2016 to 2060. WHO, Geneva, 2019.
- Mattiuzzi C and Lippi G: Recent updates on worldwide gout epidemiology. *Clin Rheumatol* 39: 1061-1063, 2020.
- Richette P and Bardin T: Gout. *Lancet* 375: 318-328, 2010.
- Roman YM: Moving the Needle in Gout Management: The Role of Culture, Diet, Genetics, and Personalized Patient Care Practices. *Nutrients* 14: 3590, 2022.
- Snaith M: A (very) short history of diets for gout. *Rheumatology (Oxford)* 43: 1054, 2004.
- Diamandopoulos A, Goudas P and Oreopoulos D: Thirty-six Hippocratic aphorisms of nephrologic interest. *Am J Kidney Dis* 54: 143-153, 2009.
- Kuo CF, Grainge MJ, Mallen C, Zhang W and Doherty M: Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. *Ann Rheum Dis* 74: 661-667, 2015.
- Pagana K and Pagana TJ: *Mosby's Manual of Diagnostic and Laboratory Tests*. Elsevier, St. Louis, MI, 2014.
- McCormick N, Lu N, Yokose C, Joshi AD, Sheehy S, Rosenberg L, Warner ET, Dalbeth N, Merriman TR, Saag KG, *et al*: Racial and Sex Disparities in Gout Prevalence Among US Adults. *JAMA Netw Open* 5: e2226804, 2022.
- Fam AG: What is new about crystals other than monosodium urate? *Curr Opin Rheumatol* 12: 228-234, 2000.
- Chen LX and Schumacher HR: Gout: an evidence-based review. *J Clin Rheumatol* 14: S55-S62, 2008.
- Neogi T: Gout. *Ann Intern Med* 165: ITC1-ITC16, 2016.
- Choi HK, Atkinson K, Karlson EW, Willett W and Curhan G: Purine-rich foods, dairy and protein intake, and the risk of gout in men. *N Engl J Med* 350: 1093-1103, 2004.
- Choi HK, Atkinson K, Karlson EW, Willett W and Curhan G: Alcohol intake and risk of incident gout in men: a prospective study. *Lancet* 363: 1277-1281, 2004.
- Chrysostomus J: In *Genesium*. In: *Patrologia Graeca*. Migne PG (ed). Center of Hellenic Publications, pp82,84, 1996.
- Chrysostomus J: *De paenitentia*. In: *Patrologia Graeca*. Migne JP (ed). Center of Hellenic Publications, pp312,332, 1996.
- Chrysostomus J: In *acta apostolorum*. In: *Patrologia Graeca*. Center of Hellenic Publications, pp333,358, 1996.
- Chrysostomus J: *Scr Eccl* (2062) *De Anna* (sermons 1-5) (114) Occurrence 1: vol 54 p, ln45: *De Anna* (sermons 1-5) (114). In: *Patrologia Graeca*. Migne JP (ed.), pp674,645. https://books.google.gr/books?redir_esc=y&hl=el&id=fWfTbyBHD6sC&q=De+anna#v=snippet&q=De%20anna&f=false.
- Geronikolou S: Translation to Greek, and Study of the 'Treatise on Gout by Rhazi'. Efporista, Public Health NPO, Athens, 2012.
- Geronikolou SA: Treatment of gout in a recently published 9th century manuscript of Rhazes. *Vesalius* 20: 95-98, 2014.
- al-Razi ABMiZ: *Treatise on Gout (Maqala fi al naqras)*. Biblioteca Alexandrina, Alexandria, 2003.
- Pepagomenus D: *Liber de podagra graece et latine ope MS*. Guillaume Morel, Paris, 1558.
- Guainiero da Pavia: *De arthetica passione*, ms n 98-6. Biblioteca Capitolari di Toledo. sec XV, 62 ff in folio Med in volg14-15th century AD.
- Littre E: *Oeuvres complètes d' Hippocrate*. Baillière, Paris, 1838.
- Li R, Yu K and Li C: Dietary factors and risk of gout and hyperuricemia: a meta-analysis and systematic review. *Asia Pac J Clin Nutr* 27: 1344-1356, 2018.
- Kaneko K, Aoyagi Y, Fukuuchi T, Inazawa K and Yamaoka N: Total purine and purine base content of common foodstuffs for facilitating nutritional therapy for gout and hyperuricemia. *Biol Pharm Bull* 37: 709-721, 2014.
- Zhang M, Zhang Y, Terkeltaub R, Chen C and Neogi T: Effect of Dietary and Supplemental Omega-3 Polyunsaturated Fatty Acids on Risk of Recurrent Gout Flares. *Arthritis Rheumatol* 71: 1580-1586, 2019.
- Bae J, Shin DH, Chun BY, Choi BY, Kim MK, Shin MH, Lee YH, Park PS and Kim SK: The effect of vitamin C intake on the risk of hyperuricemia and serum uric acid level in Korean Multi-Rural Communities Cohort. *Joint Bone Spine* 81: 513-519, 2014.
- Zhang Y and Qiu H: Folate, Vitamin B6 and Vitamin B12 Intake in Relation to Hyperuricemia. *J Clin Med* 7: 210, 2018.
- Chen JH, Wen CP, Wu SB, Lan JL, Tsai MK, Tai YP, Lee JH, Hsu CC, Tsao CK, Wai JP, *et al*: Attenuating the mortality risk of high serum uric acid: the role of physical activity underused. *Ann Rheum Dis* 74: 2034-2042, 2015.

31. Juraschek SP, Gaziano JM, Glynn RJ, Gomelskaya N, Bubes VY, Buring JE, Shmerling RH and Sesso HD: Effects of vitamin C supplementation on gout risk: results from the Physicians' Health Study II trial. *Am J Clin Nutr* 116: 812-819, 2022.
32. Juraschek SP, Miller ER 3rd, Wu B, White K, Charleston J, Gelber AC, Rai SK, Carson KA, Appel LJ and Choi HK: A Randomized Pilot Study of DASH Patterned Groceries on Serum Urate in Individuals with Gout. *Nutrients* 13: 538, 2021.
33. Stamostergiou J, Theodoridis X, Ganochoriti V, Bogdanos DP and Sakkas LI: The role of the Mediterranean diet in hyperuricemia and gout. *Mediterr J Rheumatol* 29: 21-25, 2018.
34. Teng GG, Pan A, Yuan JM and Koh WP: Food Sources of Protein and Risk of Incident Gout in the Singapore Chinese Health Study. *Arthritis Rheumatol* 67: 1933-1942, 2015.
35. Díaz-Torné C, Pou MA, Rodríguez-Díez B and Pujol-Ribera E: Living with gout. Experiences, impact and challenges of the disease. Qualitative study through focus groups. *Reumatol Clin (Engl Ed)* 19: 150-158, 2023.
36. Safiri S, Kolahi AA, Cross M, Carson-Chahhoud K, Hoy D, Almasi-Hashiani A, Sepidarkish M, Ashrafi-Asgarabad A, Moradi-Lakeh M, Mansournia MA, *et al*: Prevalence, Incidence, and Years Lived With Disability Due to Gout and Its Attributable Risk Factors for 195 Countries and Territories 1990-2017: A Systematic Analysis of the Global Burden of Disease Study 2017. *Arthritis Rheumatol* 72: 1916-1927, 2020.



Copyright © 2023 Geronikolou et al. This work is licensed under a Creative Commons Attribution 4.0 International (CC BY 4.0) License.