gout, urate, and crystal deposition disease

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Review

Gout in Paleopathology: A Review with Some Etiological Considerations

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Abstract: Gout has been part of human history for thousands of years. Skeletal evidence of the disease among past people in Europe is often associated with high-status individuals whose lifestyles comprised risk factors for gout, including increased sedentism and greater access to rich, high-caloric, food. A growing body of evidence, however, has shown that multiple factors other than lifestyle also contribute to gout development. In 2011, Buckley presented a review of modern and pre-modern gout cases in which she proposed that selective pressures may partly underlie the high prevalence of gout in the population history of the Pacific region. In this paper, we provide an update on Buckley's 2011 review of gout in human history. We also review early life stress as a potential underlying factor to consider for gout development, particularly among small prehistoric communities where opulent lifestyles traditionally associated with gout were unlikely to have occurred.

Keywords: gout; hyperuricaemia; prehistory; archaeology; paleopathology; early life stress; metabolic syndrome

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1. Introduction

Over the past several decades, gout cases have risen at an alarming rate causing a significant global health burden [1,2]. However, more than just a recent phenomenon, gout is an erosive arthropathy that has afflicted humanity since ancient times, and assessing the history of this disease can be informative of the etiology of this issue today. Gout is a monosodium urate crystal deposit disease resulting in inflammation and, in the absence of modern treatment (that has been considered curative by dissolving the crystals), can cause joint damage and early death [3,4]. Given that gout is such a painful and debilitating disease [5], its impact would have been similarly detrimental in the past, with potential social and economic consequences for individuals suffering from this disease and also for the wider community. In 2011, Buckley [6] reported on the long history of gout by synthesizing published paleopathological studies of the disease from various parts of the world. In this review, she suggested that selective pressures could influence the high occurrence of gout among modern and ancient populations in the Pacific, thereby challenging the conventional view of gout purely as a lifestyle disease often linked with affluent groups in European history [7–9].

The purpose of this current paper is to update Buckley's [6] review of gout in paleopathology. We extend this review by offering several points of discussion that relate to gout etiology in the past and the criteria used to identify gouty erosive lesions. Specifically, we consider gout cases in the prehistory of the Asian mainland whose inhabitants are ancestrally connected to Pacific groups through the Austronesian expansion with a high prevalence of gout [10]. We consider the role of early life stress in gout susceptibility, particularly among small prehistoric communities where skeletal evidence for the disease cannot be explained by affluent living. In past European societies, affluence was widely associated with greater access and consumption of rich, high-caloric, food and alcohol, as well as

increased sedentism. Finally, we reflect on the challenges of diagnosing gout in the skeleton and offer some ways to develop the methods used to identify gouty erosive lesions.

2. Epidemiology of Gout in Brief

Affecting mainly adults, gout is a condition that is considered part of a cluster of chronic metabolic disorders that tend to co-occur [11,12]. Metabolic disorders associated with gout include the Metabolic Syndrome (MetS) and its individual components [13–15], cardiovascular diseases [16–18], type 2 diabetes [19–22], psoriasis [23], chronic kidney disease [24,25], and diffuse idiopathic skeletal hyperostosis (DISH) [26]. Gout primarily occurs in older males and postmenopausal females [27]. Gout in children is rare and caused by genetic disorders such as Lesch-Nyhan syndrome [28] and Von Gierke disease [29]. Children and pre-menopausal women have lower serum urate levels compared with men [30]. These levels increase as children age. From puberty, levels continue to rise among men, but only slightly among women until menopause when their values become more comparable with men.

Hyperuricaemia, or an elevated serum urate level, is a prerequisite for gout [31], but having hyperuricaemia does not necessarily lead to gout [32]. The hallmark of the condition is the presence of urate crystals in the body, which can form into chalk-like nodules called tophi, primarily in the joints [31]. Initial urate crystal deposits occur on the surface of the cartilage of affected joints and tendons, which can develop into large tophi with advanced gout. Over time, significant bone damage can occur where a tophus comes into contact with bone. Chhana and colleagues [33] found that monosodium urate crystals reduce osteoblastic formation, while greater osteoclastic activity causes bone erosion at the joint site. For gout sufferers, inflammation of affected joints can cause disability, negatively impacting overall quality of life [5].

Although gout prevalence is increasing globally, this varies among regions. In a recent review of the Global Burden of Disease Study data from 1990 to 2019, Jeong and colleagues [1] found greater frequencies of gout cases in Australasia, high-income North America, and countries with high socioeconomic indices. In contrast, regions such as Asia, Africa, and Central and South America reported low to mid-range prevalence rates for the condition [2]. According to Dehlin and colleagues [2], review of gout prevalence rates range from <1% up to 6.8% across multiple countries, with even higher prevalence in some ethnic groups, particularly in the Asia-Pacific [34–36].

Within the Asia-Pacific region, high prevalence rates are observed among the indigenous peoples of Taiwan [35,37] and Polynesians [36,38]. In Taiwan, Chang and colleagues [37] reported a three-fold greater prevalence of gout among indigenous groups compared with non-indigenous groups. Moreover, family history of gout among the general Taiwanese population and indigenous groups also increases the risk of gout [39,40]. In the Pacific, studies have historically shown that some Polynesian groups, such as New Zealand Māori, are more susceptible to gout than other ethnic groups living in the same region [38,41]. Winnard and colleagues [42] found a significantly higher prevalence of gout cases among Māori and Pacific peoples compared with Europeans and Asians, residing in the same country based on the 2009 data from the Aotearoa New Zealand Health Tracker. These studies also report the high prevalence of hyperuricaemia in Polynesian groups from other regions of the Pacific [43,44].

Genetic predisposition for gout is one factor contributing to its high prevalence within these ethnic groups such as Polynesians and indigenous Taiwanese [45]. The recent proliferation of genetic studies has led to the discovery of population-specific variants that appear to increase the risk for hyperuricemia or gout in Polynesians. For example, Tanner and colleagues [46] identified ABCC4 rs4148500 as a risk factor for gout among Polynesians, which is absent in New Zealand Europeans. The same study also identified a population-specific variant, ABCC4 P1036L, in a small group of Western Polynesians with hyperuricaemia [46]. Among Pacific Islanders of Western Polynesian ancestry, hyperuricaemia and gout are also associated with genetic variants associated with urate transporter proteins, such as ABCG2

rs2231142, which reduces uric acid clearance from the body [47]. In another study, Phipps-Green and colleagues [48] reported associations between four known genetic variants with gout, in addition to two genetic variants that may protect against gout in individuals of Polynesian ancestry. Genetic variants associated with early gout onset (<40 years old) and tophi development have been found among indigenous Taiwanese [49], New Zealand Europeans, and Polynesian groups [50].

In addition to genetics, a diet high in purines and alcohol consumption are well-known risk factors for gout. Ancient Greek documents, for example, describe treatments that include increasing the amount of vegetables consumed and decreasing alcohol intake to manage the condition [9]. Modern studies have confirmed this association, demonstrating that excessive consumption of food, particularly meat and seafood products that are high in purines, as well as alcohol, can lead to gout [51,52]. Obesity is also associated with increased serum urate levels, which increases the risk for the condition in some groups [40]. Related to this, current strategies to decrease risk include dietary changes, in combination with weight loss [53–55].

A special form of gout, termed saturnine gout, is caused by chronic lead exposure [56]. Saturnine gout was primarily thought to occur from drinking tainted alcoholic beverages stored in lead vessels. Cases of lead poisoning have been mentioned in European history, such as in ancient Rome, but have also occurred in more recent times, particularly among groups that tend to brew homemade alcohol [56,57]. In a clinical study of lead toxicity, Emmerson [58] found there were no age or sex differences in affected individuals chronically exposed to lead.

3. Gout among Pre-Modern Populations

3.1. Criteria for Diagnosing Gout in the Skeleton

Paleopathologists primarily rely on the examination of skeletal material to identify gout in past populations. The presence of abnormal bone proliferation or erosion indicates a pathological state, which arises due to the disruption of normal physiological processes [59]. Skeletal evidence for gout is characterized primarily by lytic bone lesions (Figure 1) with well-defined erosions that form at the margins of synovial joints often along the long axis of the bone [60,61]. These erosive lesions appear punched-out or scooped out and are round or ovoid in shape on the cortical surface of the bone. These lesions also feature a layer of remodeled, dense, bone, lining the internal lytic cavity (sclerosis on radiographs) that distinguishes gouty lesions from other erosive arthropathies such as rheumatoid arthritis (RA). The overhanging edges that extend from the cortex around the lesion opening are also characteristic of bone changes with gout. With time, the erosive lesions can extend into the subchondral bone or move into the diaphysis [62,63].

Standard recording practices are conducted as part of assessing individual skeletons for disease in paleopathology (see [64]). A skeletal inventory, for example, is taken to determine the completeness of each individual skeleton. To assess gouty erosive lesions, an inventory of skeletal regions that are part of the synovial joints is most relevant. Estimates of biological age (young, mid, and old adults) and sex are also assessed using morphological landmarks on the skeleton. For sex estimation, this is conducted most reliably using the skull and os coxae (pelvis) because they demonstrate strong sexual dimorphic features [64]. Given gout is an adult-onset disease, only adults are included in the assessment for the condition. Individual skeletons are considered adults when their skeletal growth is complete ([65]; see also [64,66] for age estimation methods). Bones showing severe degenerative pathology and postmortem taphonomic changes alternations that have compromised the structural integrity of the bone are omitted from the analysis. In addition to these bone recording/inventory methods, gout prevalence data can be presented by 'individual' or by bone type. An 'individual' is defined by a bone count threshold (e.g., a minimum of five complete metacarpals and five complete metatarsals [67]). Conducting the initial recording outlined above, in concert with an accepted paleopathological assessment of erosive lesions, provides more comprehensive knowledge of each individual and how

pathology has affected the skeleton, increasing the probability of a true gout diagnosis and prevalence at an archaeological site. Prevalence of differentially diagnosed disease at archaeological sites, however, is based on the number of recovered skeletal individuals (a cemetery sample) which does not represent the total cemetery sample. In addition to gross assessment of erosive lesions, methods to diagnose gout from the presence of urate crystals are used in paleopathology. These methods include microscopic or biochemical techniques that require additional parameters of preparation, of which the details are beyond the scope of this review but are described in other studies [68–70].

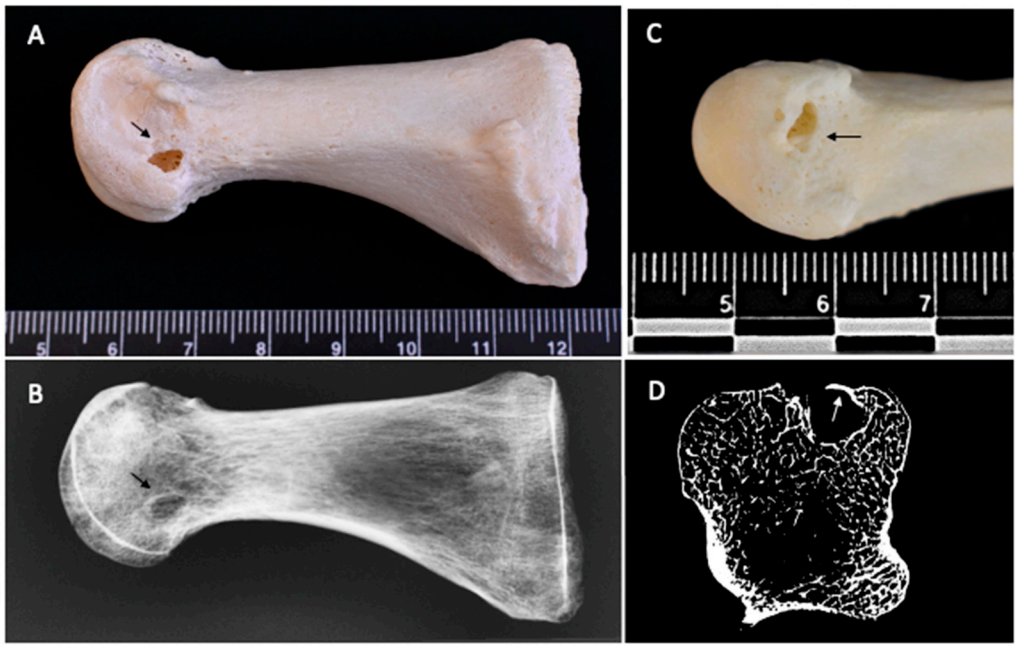

Figure 1. Examples of gouty lesions from a modern male individual from the Anatomy Museum, University of Otago. (**A**,**B**): Photograph and radiograph of right first metatarsal showing an erosive lesion (black arrow) with scooped-out appearance and evidence for sclerosis. (**C**,**D**): Photograph and microCT image of the distal end of left second metacarpal showing erosive lesion (black arrow) and evidence for overhanging edge (white arrow) on palmer side.

Bone affected by tophaceous gout can be polyarticular but the condition is usually monoarticular [63]. The first metatarsophalangeal joint is most frequently affected [31,32,71], though crystal deposition can build up around other joints in the body [72]. Gouty lesions have a predilection for the lower half of the body, but to a lesser extent, in the lower spine and hips. The elbow and hand joints are also commonly involved [63]. Asymmetrical expression of lesions is characteristic of the disease, however, more joints can be affected when the disease is severe, increasing the likelihood of symmetrical patterning [73,74]. Asymmetry, however, is an important feature to consider for differential diagnosis because it is not characteristic of RA. Differential diagnosis of erosive lesions in paleopathology also includes seronegative spondyloarthropathies, osteoarthritis, and hallux valgus.

On rare occasions, urate crystals have been found in archaeological assemblages making it possible for a definitive gout diagnosis. These crystals, for example, have been identified as white chalky masses on bone, as well as in the soft tissue of mummified remains [68,75]. As mentioned above, methods using polarized light microscopy [69], scanning electron microscopy [68], biochemical analysis using uricase [68], and high-performance liquid chromatography [70] have been used to confirm the presence of urate crystals in skeletal remains. Often, however, paleopathologists are restricted to diagnosing gout by assessing the characteristics of erosive lesions around the joints and their distribution in the skeleton and as a result, a diagnosis of gout is much less certain. When visual observation of the bone is limited, radiographs can offer essential information [76–78]. In

these images, sclerosis and overhanging edges can be seen more clearly. Further still, in our experience, microCT can help to identify gouty features on very small erosive lesions not shown on radiographs. These erosive lesions are often associated with the small bones of the hands and feet.

3.2. Gout in the 'Old World'

Paleopathological studies of gout in the 'Old World' primarily involve skeletal assemblages from parts of Europe where the archaeological record has been well documented. Many of these studies highlight the association between gout and high social status, the latter often being linked to individuals whose lifestyle allows for a rich, high-purine diet and sedentary living. Individual case studies of gout often describe prominent figures in history, such as the Holy Roman Emperor Charles V (1516–1556 AD) [68], Federico of Montefeltro, Duke of Urbino (1422–1482 AD) [79], and Ferdinand I, Grand Duke of Tuscany (1549–1609 AD) [77], all of whom suffered from gout. In these studies, Charles V's fifth distal phalanx contained urate crystals, while the Dukes, Federico and Ferdinand, had erosive lesions characteristic of gout on the first proximal metatarsal of the right foot, and at the fourth distal interphalangeal joint of the left foot, respectively. Historical documents written by or about these men describe the impacts that painful acute gout attacks had on their lives.

Evidence for gout has also been found in skeletal assemblages from European cemeteries post-BC. Particularly representative are studies from British sites dating from the 1st century AD onwards where many reports from these sites have also drawn a connection between gout and lifestyle. Dittmar and colleagues [80] identified six individuals with gout associated with an Augustinian friary, a parish church, and a hospital from the medieval period in Cambridge. Half of these cases came from the Augustinian friary, which is a cemetery associated with clergymen and high-status members of the community. Two cases came from the hospital and one from the parish church. The same study, however, did not find evidence for gout at a parish cemetery described to be for the rural poor. An osteobiographical report of an old man from the same hospital in Cambridge included an isotopic analysis that suggested that he had a richer diet, probably of meat or fish, compared with the average person from the medieval period [81]. In the Romano-British archaeological site of Cirencester, Wells [82] found skeletal evidence for gout in three individuals and wrote a case report on one of the individuals who displayed the most severe skeletal manifestation of this disease [83]. This individual was described as an old adult male who lived around AD 150, exhibiting gouty lesions in numerous regions of the upper and lower limbs, with large osteolytic lesions, particularly around his ankles and feet. Wells [83] speculated, based on the man being entombed within a stone sarcophagus (one of only two from the site), that this person might have been wealthy, and that his lifestyle, which may have included a rich diet, may have contributed to the development of gout.

Waldron [84] found high lead concentrations at Cirencester. Despite this, the low number of gout cases found here suggests lead poisoning may not have been a contributing factor as we would expect that this would have been evident in the wider community. Rothschild and colleagues [85] also investigated the possibility of lead poisoning at several archaeological sites in Italy dating from the 1st to 3rd centuries AD. Among these sites, however, it was found that only two individuals with possible evidence for gout among several hundred skeletal individuals. Evidence for gout in prehistoric Europe is scarce. One case from the Middle Bronze Age (4000–3600 Before Present [BP]) from Lerna, Greece, has been found in a young to middle-aged male [86].

Few published studies have explored gout outside of Europe. From Egypt, Smith and Dawson [75] describe an elderly man from an Early Christian burial (exact date not known) near the temple of Philae, who was found with large amounts of urate crystals in his upper and lower limbs. In Asia, skeletal evidence for gout was discovered in people who do not have the type of indulgent lifestyle as some individuals found in Medieval Europe. For example, Inoue and colleagues [87] encountered one individual with evidence

for gout from the Middle Jomon period (4500–3500 BP) in Japan. The Jomon were sedentary hunter-gatherers who lived prior to the transition to intensive agriculture [88]. In another study, Pietrusewsky and Douglas [89] identified gouty lesions in two individuals from the late Bronze Age (2900–2400 BP) at Ban Chiang, an archaeological site in Thailand.

3.3. Gout in the Pacific

Of the small number of studies that have explored gout in the prehistory of the Pacific region, a common thread among them is the high number of individuals who have been found with evidence for this disease (Table 1). One exception is a study by Suzuki [90] that reported only one individual with possible evidence for gout from 349 individuals from the Mokapu site in Hawai'i. Rothschild and Heathcote [78] reported fifteen cases of gout from a skeletal assemblage dating between 950–1450 AD in Guam. Specifically, gouty lesions were recorded in the upper and/or lower limbs of seven females and eight males. Those who could be assigned an age estimate were mostly young to middle-aged adults. Similarly, Buckley and colleagues [76] found skeletal evidence for gout in seven of twenty adults from a 3000-year-old Lapita period site from Teouma, Vanuatu. At this site, all affected individuals were male. A later study by Buckley and colleagues [91] reported six of 42 individuals with evidence for gout from a settlement dating from 1288–1300 AD from Wairau Bar, New Zealand. These affected individuals were all males ranging in age from young to old adults.

Table 1. Reported cases of gout in ancient skeletal samples.

Location	Study	Date/Period	Gout Cases (n/N *)	Individual/s	References
El Escorial, Spain	Individual	1516–1556 AD	1	Holy Roman Emperor Charles V	[68]
Rome, Italy	Individual	Roman Imperial Period	1	Tomb 75, old adult female	[92]
Urbino, Italy	Individual	1422–1482 AD	1	Federico of Montefeltro, Duke of Urbino	[79]
Florence, Italy	Individual	1549–1609 AD	1	Ferdinand I, 3rd Grand Duke of Tuscany	[77]
Florence, Italy	Individual/also collection	1618–1659 AD	1	Anton Francesco Maria, adult male	[93]
Rome, Italy	Individual	1st–2nd century AD	1	Adult female, 35–45 yo	[94]
Cambridge, UK	Individual	1195–1511 AD	1	Old male	[81]
Herculaneum, Italy	Collection	1st century AD	1/75	No information	[85]
Porto Recanati, Italy	Collection	1st century BC–3rd century AD	1/79	No information	[85]
Cirencester, UK	Collection	Romano-British period, ~150 AD	3/384	Males	[82,83]
Trowbridge, UK	Collection	Saxon period, 9–11th century AD	1/50	Male	[95]
Poundbury, UK	Collection	Roman Period	5	3 males, 2 females	[96]
St. Peters' Church, Barton-on-Humber UK	Collection	950–1855 AD	10/1938 (15 yo+)	4 males, 3 females, 3 unknowns	[97]
Various, UK	Individuals	14th–19th century AD	5	4 old adult males, 1 old adult female	[70]

Table 1. *Cont.*

Location	Study	Date/Period	Gout Cases (n/N *)	Individual/s	References
Cambridge, UK	Collection	Medieval	6/177	4 young to old adult males, 1 female middle adult, 1 adult unknown sex	[80]
Hartlepool, UK	Collection	13th to 16th century AD	1/93	Middle-aged male	[98]
Northallerton, UK	Collection, Carmelite Priory	14th to 16th century AD	1–2/7	2 adult males	[99]
Messene, Greece	Collection	5th–7th century AD	2/74	2 young adults, unknown sex	[100]
Lerna, Greece	Collection	Middle Bronze Age, 2000–1600 BC	1/102	35 yo, Male; 70 LER, Burial BE-18	[86]
Egypt	Individual	Early Christian	1	Old adult, Male	[75]
Ohta, Western Japan	Collection, Kiyono	4500–3500 BP, Middle Jomon	1/45	Middle-aged, adult male	[87]
Ban Chiang, Thailand	Collection	2100 BC to 200 AD	2/104 (15 yo+)	20–25 yo female, 45–50 yo male	[89]
Mokapu, Hawai'i	Collection	"pre-European"	1/349	Male, mid-thirties	[90]
Teouma site, Vanuatu	Collection, Lapita	~3000 BP	7/20	Males	[76]
Chamorro, Guam	Collection	950–1450 AD	15/268	7 females, 8 males	[78]
Wairau Bar, New Zealand	Collection	~1288–1300 AD	6/42	3 young to middle adult males, 3 middle to old adult males	[91]

* Total number of individuals assessed (if data are available).

If we consider that the skeletal assemblage from an archaeological site is demographically representative of the population who inhabited it, then it appears that gout was prevalent at the settlements in Teouma, Wairau Bar, and Guam. Rothschild and Heathcote [78] suggest that the high prevalence of gout in Guam could be related to genetic factors, rather than solely to dietary factors. This is because the gout cases were distributed equally among both males and females and included individuals from younger adult age groups rather than the more at-risk group comprising older males and post-menopausal females. Buckley and colleagues [76,91] also discuss the possible genetic predisposition for hyperuricaemia and gout for the individuals at Teouma and Wairau Bar, combined with a diet that included purine-rich seafood, which may have provided the appropriate conditions for gout development in this community.

4. Discussion

4.1. Gout Etiology in Past Populations

The paleopathological literature reviewed in the previous section considers genetic predisposition and the environment as etiological factors underlying gout development in the various regions and chronological periods of human history. However, the environment appears to be a primary trigger for gout [101–103]. By studying gout among male twins, Krishnan and colleagues [104] found gout prevalence was similar between monozygotic twins and dizygotic twins, suggesting that although genes may primarily determine the risk for hyperuricaemia, it is the environment that largely determines the onset of the condition.

The traditional association of gout with lifestyle indicates the importance of locality as a driver for the condition. In the medieval period, wealthy individuals from urban societies were at greater risk for gout because only the wealthy could afford rich, high-caloric food, such as meat and alcohol. Supporting this connection are the case studies of past European nobility who suffered from gout [68,77,79] and gout cases being linked to high-status and wealthy burials, particularly from medieval cemeteries [80,83]. The

association between wealth and increased gout risk, however, does not occur in all instances. Minozzi and colleagues [94] described a small 35–45-year-old female with a simple burial who had skeletal evidence for polyarticular gout from Imperial Rome between the 1st to 2nd centuries AD. The authors proposed hypothyroidism as the underlying cause of her gout, a condition that may also explain her remarkably small size compared with the average stature (15–20 cm shorter) of the other women buried in the cemetery. If her lack of funerary assemblage is considered a marker of status, then she does not appear to have been a high-status member of her community. Compared with Imperial Rome, early farming settlements were smaller and less stratified, making it less likely that gout was caused by affluent living in these communities. Hunter-gatherer and horticulturalist communities with skeletal evidence for gout make the link between lifestyle (e.g., overeating, and sedentary living) and gout even less compelling.

In 2011, Buckley [6] proposed a genetic predisposition to hyperuricaemia as a potential risk factor to explain the high prevalence of gout found thus far in the prehistory of the Pacific [76,78,91]. Buckley [6] considered genetic predisposition within the context of the 'Thrifty Genotype Hypothesis', which proposes that in past times the body increased insulin production to process and store energy during periods of food abundance in preparation for times of famine [105]. Although the human body's ability to store energy during times of food scarcity was a crucial survival mechanism in our human history, it can have negative consequences for health when food becomes more readily available. This shift towards a more stable food environment has led to an increased risk of diseases such as obesity, diabetes, and hypertension. The high prevalence of gout among Pacific groups today may be explained by the mismatch between the challenges faced by their ancestors and the relative ease with which their descendants can access food [106]. However, it should be noted that modern groups residing in the locality today may not share the same genetics as groups who also resided there in the past. Gosling and colleagues [107] built on this proposal by considering other factors, such as founder effects from inter-island voyages and infectious diseases, that may have driven the selective pressures for hyperuricaemia in the region. Gosling and colleagues [108] have argued that high levels of serum urate can increase the rate of inflammatory response and clearance of malaria-infected cells that increase the likelihood of survival, but this hypothesis remains untested. In support of a genetic basis for metabolic disorders in the history of the Pacific, a study by Knapp and colleagues [109] found a genetic variant associated with insulin resistance in an individual from the early prehistoric New Zealand site of Wairau Bar who also demonstrated skeletal evidence of gout.

Although gout can provide a proxy to investigate metabolic disorders in past populations, DISH is another condition that has also been used for a similar purpose in paleopathology ([6]; see also [110,111]). Understanding the epidemiology of DISH can potentially tell us more about gout. DISH is a proliferative state and presents on dry bone as abnormal flowing, bulbous ossifications along the vertebral column, accompanied by extraspinal enthesophytes [63]. Evidence for gout and DISH comorbidity has been found in several individuals in history [70,76,77,80]. Although the skeletal manifestations of gout and DISH are different, the two conditions have some similarities epidemiologically. For example, gout and DISH are considered diseases of lifestyle in Europe. Among Medieval groups, a high frequency of DISH cases is associated with high-status burials and monks [112,113]. Monastic life was thought to have been very comfortable in many ways, particularly with access to high-caloric foods among the clergy of high rank [112,114,115]. Although the Lapita people from the site of Teouma in the Pacific relied on both marine and terrestrial resources, the result of stable isotope analyses does not support the link between DISH and a high protein diet at the site [116]. Stable isotope analyses, however, do support this relationship in medieval Europeans [117]. Skeletal evidence for DISH in hunter-gatherer communities such as a man who lived 7500–6500 years ago from Lake Baikal in Russia [118], and two Jomon individuals (one male and one of unknown sex) dating to 3500 to 2300 years ago from Rebun Island, Japan [119], present some of the earliest

cases of the condition. These individuals would have relied on terrestrial resources and aquatic species from nearby lakes or sea. In the latter study of the Jomon, the researchers considered maternal stress as a risk factor for DISH, albeit briefly. DISH development appears to have various pathways, some of which likely overlap with gout. Similar to gout, Polynesians today also have a high prevalence of DISH [120]. In comparison with gout, DISH is not clinically significant and has received less attention in the literature. The condition, however, is particularly relevant because it can be identified in the archaeology record. More research of DISH in antiquity can help to understand the history of the condition and its underlying mechanisms, and by extension MetS and other related conditions.

4.2. Gout and the Austronesian Link

If a genetic predisposition to hyperuricemia in the Pacific is accepted as a legacy of the past, then it is possible that this susceptibility may extend further back in antiquity, especially when the population history of the larger Asia-Pacific region is considered. As mentioned above, indigenous Taiwanese and Polynesians both demonstrate high frequencies of gout today. These two groups are part of the Austronesian-speaking language family and are considered descendants of the early farmers who migrated from East Asia approximately 4000 years ago [10]. From East Asia, they expanded into Taiwan, moving into Island Southeast Asia and the Pacific. At the same time, farming groups also moved from East Asia southwards into Mainland Southeast. The migratory routes were complex, but genetic studies of modern-day populations support a close ancestral link between people from mainland Asia and the Pacific [121,122].

Given this ancestral link, we may expect similar high frequencies of hyperuricemia or gout in the Asian mainland today. Current reports do not show a high prevalence of gout among modern groups in Mainland Southeast Asia compared with those from the Pacific [1]. These data, however, do not consider the possible variation in prevalence rates within countries and if studies were to be conducted among ethnic groups, these prevalence rates may look different from the national statistics. To date, Pietrusewsky and Douglas' [89] skeletal report of Ban Chiang contains the only two published cases of gout in prehistoric Mainland Southeast Asia. Based on this limited information, the susceptibility to hyperuricemia and gout observed in Island Southeast Asia and the Pacific is not similarly reflected in the Asian mainland. Rather, the high prevalence of gout among Taiwanese aboriginals and some Pacific groups could be a health legacy of the Austronesian expansion from East Asia. Alternatively, selective pressures for hyperuricemia and gout may have occurred separately in Taiwan and the Pacific, and not at the beginning of the so-called Austronesian expansion. That said, published information on gout in the archaeology of mainland Asia is limited. More research into this topic may help to clarify the condition's history in this region and its possible connections to other places in the Asia-Pacific.

4.3. Early Life Stress as a Contributor to Gout Development

The Developmental Origins of Health and Disease hypothesis refers to the relationship between early life stress and the increased risk for chronic metabolic disorders in adulthood. Within this field, Hales and Barker [123] proposed one of the earlier explanations for this relationship that they termed the Thrifty Phenotype Hypothesis. They hypothesized that during periods of chronic fetal and/or infant stress from undernutrition, the body will allocate the limited resources to important organs, particularly the brain while compromising the growth of other organs. Hales and Barker [123] used the pancreas as an example of an organ that could be compromised, arguing that restrictions placed on its growth can permanently impair its function, increasing susceptibility to type 2 diabetes in later life. Alternative models were later established that build on the Thrifty Phenotype Hypothesis. Gluckman and colleagues [124], for example, proposed the Predictive Adaptive Response, which focuses on the ability of the fetus to adapt to its most likely postnatal surroundings based on cues taken from the intrauterine environment. If the fetus adapts to a resource-poor environment, but the opposite is true and they experi-

ence a resource-rich environment, they are at greater risk of chronic metabolic diseases in adulthood. More recently, Wells [125] proposed the metabolic capacity-load model that centers around the concept of metabolic equilibrium, a state where the body is functioning optimally. Metabolic capacity is defined as the theoretical amount of nutrition (metabolic load) a body can process without disrupting the metabolic equilibrium. This capacity-load model posits that a person whose growth is impaired is at greater risk for disease because they have a small metabolic capacity and therefore can only process a smaller metabolic load in later life than a person who experienced normal growth.

Famines in recent history have provided opportunities to investigate the long-term consequences of early life stress. For example, Roseboom and colleagues [126] found that individuals who were gestationally exposed to the Dutch Famine (1943–1947) were at greater risk of developing one or more metabolic disorders in later life, including glucose intolerance, dyslipidemia, obesity, and cardiovascular disease with individuals who were exposed to the famine in early gestation having a risk of the development of more metabolic disorders. Similar findings have also been reported among individuals exposed to the Chinese Great Famine (1959–1961) who demonstrated a greater risk of developing cardiovascular disease [127,128], chronic kidney disease [129], and non-alcoholic fatty liver disease [130].

A study conducted by Eriksson and colleagues [131] on the Helsinki Birth Cohort, born between 1934 and 1944, found that individuals with low birth weight or who were small in infancy, both used as a measure of early life stress, demonstrated a greater risk of coronary heart disease in adulthood. Poor growth and dysfunction of the liver from early life stress was considered one underlying risk factor for later disease development given the role of the liver in lipid metabolism [132]. Studies have also found that individuals born small, who then experienced rapid growth in childhood, were more likely to develop metabolic-related disorders as adults compared with those who maintained a consistent size throughout their growth [131,133]. Evidence of rapid growth suggests that these individuals were experiencing better postnatal environments and potentially more nutrition than their bodies could process.

During later postnatal development, the body is also vulnerable to growth restrictions, which can be linked to morbidity in adulthood. In a Guatemalan cohort, for example, childhood morbidity appears to be a predictor of elevated glucose levels and central obesity among young adults [134]. Stunting among children in Ethiopia has been linked to seasonal and temperature changes which determine food availability and disease risk among agricultural groups [135]. Children from poor families in lowland Nepal were more likely to be stunted, and had smaller and weaker organs, compared with children who had grown up in better socioeconomic conditions [136]. Among animal studies, it was found that undernourished pups weighed less, had smaller organs, and were more likely to develop impaired glucose intolerance and obesity in later life [137,138]. Smallness from stress also extends to linear growth. For example, rural children from the Peruvian highlands who grew up more stressed had shorter limbs than urban children living on the coast [139]. Poor growth and function of the body appear to be a biological cost of chronic stress exposure.

Given the connection between early life stress and chronic metabolic disorders [140], as well as the connection between gout and the same disorders [11], it is reasonable to consider a possible connection between early life stress and gout. This is because chronic stress exposure can compromise organ growth and function, such as the liver, kidney, and gut, which are responsible for purine and uric acid metabolism [141]. This scenario may explain gout cases where a rich lifestyle or genetic predisposition may be unlikely factors. The small woman from Imperial Rome [94] is one example where stunted growth, thought to be from hyperthyroidism, may also have increased her risk for gout. It is also possible that early life stress events might have contributed to the development of gout present in the small number of cases present among the small communities of Jomon hunter-gatherers [87], and the early farmers of Ban Chiang [89]. Jomon foragers [142] and Ban Chiang farmers [143]

both showed evidence for multiple skeletal indicators of childhood stress. Although these indicators are non-specific and could have a variety of causes, the researchers considered events such as infectious diseases and seasonal food shortages (specifically among the forager groups) which are linked to nutritional deficiencies and elevated physiological stress exposure in these groups. Individuals with smaller, compromised, metabolic capacity are at greater risk of disease such as gout if their metabolic load surpasses what their body could process [125].

4.4. Difficulties of Diagnosing Gout in the Skeleton

Unlike clinicians who can draw on a broad range of methods to diagnose gout [31], paleopathologists are limited to a narrow set of criteria that relates to the skeleton [60]. Assessing archaeological material for gout comes with additional challenges. First, a full assessment may not be possible because skeletal remains can come in different states of completeness and preservation. This increases the probability of misdiagnosis. Second, individuals with skeletal evidence for gout represent only a subset of cases. These are individuals who suffered from chronic tophaceous gout resulting in erosive lesions whereas gouty individuals with no skeletal manifestations cannot be considered in paleopathological assessment. Lastly, small erosive lesions may be overlooked or mistaken for foramina (or vice versa). Consequently, large erosive lesions with clear gouty features are often recorded. Although these types of lesions present strong evidence for gout in the skeleton, not accounting for early-stage lesions further reduces the quantification of the true number of gout cases in an archaeological population.

A stronger set of diagnostic criteria for gout in bone is essential to address the challenges of assessing skeletal assemblages in the field. Imaging techniques (e.g., radiographs, microcomputed tomography) can help broaden the scope of analysis in archaeology. However, access to these technologies can be limited or difficult to access if skeletal remains are kept in remote repositories. The high costs to use some of the equipment can also limit the number of individuals that can be assessed. This becomes challenging when analysis involves large or multi-site skeletal collections. In addition to these tools, gout has been definitively diagnosed from the presence of urate crystal deposition using technologies such as double energy computed tomography [32,144,145], ultrasound [144,145], and Raman spectroscopy [146], in a modern clinical and research setting. These technologies could potentially be applicable in the archaeological context, particularly in well-preserved bodies with soft and skeletal tissues intact. Finding crystal deposits in human remains, however, has not received much attention because the skeleton (dry bone) is usually what is recovered from archaeological sites. Assessing bone for the presence of urate crystals requires additional processes for approval given a sample must be extracted for analysis. Non-destructive methods are generally preferred to maintain the preservation of skeletal material in archaeology. That said, multi-technique approaches have been applied to individual gout cases, which can provide a more nuanced assessment of gout in skeletal or mummified remains [68].

Given that paleopathologists often rely on the analysis of dry bone for evidence of gout, lesion appearance, and distribution become essential features for diagnosing the disease. Little, however, is yet known about the different stages of osseous gout development. Specifically, the early formation of gouty lesions before they become large enough for visual or radiographic identification by paleopathologists is unclear. For this reason, it is difficult to identify erosive lesions associated with tophaceous gout at an early stage. It is also unclear if there are any changes in patterns in lesion distribution in the skeleton with disease progression. To date, clinical research has explored in-depth how gout manifests in the skeleton from a cross-sectional sample, but not with disease progression [32,71,72,74,147]. More information on how tophaceous gout affects bone over time, from early to late stage, can help build stronger diagnostic criteria for gout in the skeleton, while also reducing the probability of misdiagnosis.

5. Conclusions

Today, gout is a common condition with prevalence rates that are increasing globally. In this review, we provided a synthesis of paleopathological studies that highlight the long history of gout worldwide. From this synthesis, we consider how variations in gout prevalence and etiology can vary between regions. These studies have identified lifestyle and genetics as risk factors for gout. There is a significant body of evidence that has linked early life stress with several metabolic-related disorders, indicating a potential association with gout, though no direct evidence has been found. We can investigate this potential association by considering the biocultural context of an archaeological site in combination with skeletal evidence of gout and skeletal markers of specific and non-specific stress experienced during growth. Knowing the type and degree of stress a person experienced growing up, as well as their surrounding environment (cultural and physical) in adulthood, can help us understand the underlying factors that may have led to gout development.

By improving the diagnostic criteria for gout in the skeleton, paleopathologists can strengthen their assessments and better account for the different stages of gout in these ancient groups. It is well known that gout is a debilitating condition, and we expect that prehistoric people with the disease were faced with similar experiences of pain and suffering. With further studies of gout in the past, we may learn more about the impact of this disease on the lives of people in ancient communities. These studies could also tell us more about how gout has progressed over the course of human history to become the widespread condition it is today, and what risk factors may underlie gout development at different places and times.

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