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The nomenclature of the basic disease elements of gout: A content analysis of contemporary medical journals

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Abstract

Objectives: There is currently no standardised nomenclature for the basic disease elements of gout. This study aimed to identify these elements and examine how they are labelled in contemporary medical literature.

Methods: We analysed articles from the ten highest ranked general rheumatology journals, and five highest ranked general internal medicine journals (by Impact Factor, according to 2015 Thomson-Reuters Journal Citation Reports), published between 1 January 2012 and 31 January 2017. For each journal, articles relevant to gout and hyperuricaemia were identified by the search terms ‘gout’ and/or ‘urate’ and/or ‘uric acid’ using MEDLINE. Basic disease elements were identified and their labels extracted. Labels designated ‘unique’ used different words or phrases to describe an element.

Results: A total of 549 articles were analysed. Eleven basic disease elements and 343 unique labels were identified. Labelling was imprecise for most elements. ‘An episode of acute inflammation triggered by the presence of pathogenic crystals’ was represented by a total of 162 unique labels; 33.6% of articles referring to this element used at least four unique labels. For articles referencing ‘the circulating form of the final enzymatic product generated by xanthine

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Author contributions

N.D. (the guarantor) accepts full responsibility for the work and the conduct of the project, had access to the data, and controlled the decision to publish. N.D., W.J.T. and R.T. conceived of the project. D.B. was responsible for collecting data from the literature examined and D.B. and N.D. were involved in the analysis of results. D.B. and N.D. drafted the first version of the manuscript. All authors contributed to manuscript revisions and approved the final manuscript.

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oxidase in purine metabolism in humans', the labels 'uric acid' and 'urate' were used with similar frequency (63.0% and 62.5%, respectively), and both labels were used in 25.9% of articles.

Conclusion: Labelling of the basic disease elements of gout is characterised by imprecision, inaccuracy and lack of clarity. Consensus regarding the nomenclature of these elements is required.

Keywords

Gout; Urate; Nomenclature Terminology

Introduction

Gout is a chronic disease of monosodium urate crystal deposition. Its clinical manifestations include acute inflammatory arthritis, chronic synovitis, progressive joint damage, and tophi [1-3]. The aetiology and pathogenesis of gout is well recognised, and a range of effective treatment options exist [4]. Despite this knowledge, the treatment of gout is frequently suboptimal [5,6]. The lexicon of gout, through the use of inconsistent and inaccurate terms, has been identified as a potential contributor to this treatment deficit [7-10].

We undertook a content analysis of the contemporary medical literature to identify the basic disease elements that encompass fundamental components of gout aetiology, pathophysiology and clinical presentation, and the labels used to represent these disease elements. This project was developed to provide a foundation for future consensus on the nomenclature of gout.

Methods

Search criteria

Articles about hyperuricaemia or gout from the top ten ranked general rheumatology journals, and the top five ranked general internal medicine journals were analysed. Rankings were determined according to Impact Factor (2015 Thomson-Reuters Journal Citation Reports, Table 1). For each journal, articles were identified by the search terms 'gout' and/or 'urate' and/or 'uric acid' using MEDLINE. All hyperuricaemia and gout-related articles published over a five year period, between 1 January 2012 and 31 January 2017, were analysed. There were no exclusion criteria. The journal type (rheumatology or general internal medicine) and geographic region of the first author of each article were recorded.

Results

Search results

There were 549 articles analysed from the 15 journals over the five year period, consisting of 508 articles from rheumatology journals and 41 articles from general internal medicine journals (Table 1). There were 11 basic disease elements identified, as shown in Table 2. These elements were further grouped into three categories: chemical, clinical and imaging

elements. For the 11 elements, a total of 3251 labels were extracted, of which 343 were determined to be unique.

All articles were analyzed by a single investigator(D.B.); to ensure accuracy of label extraction, the first 50 articles examined were jointly reviewed by a second investigator(N.D.) and no discrepancies were identified.

Basic disease elements

Articles identified through this search strategy were manually analysed for reference to the basic disease elements of gout. An a priori list of basic disease elements was generated by the authors and further elements were added during data collection as appropriate. An 'element' was considered to be any distinct concept representing the aetiology, pathogenesis or clinical presentation of gout. Definitions for these elements, when provided, were also recorded. The scope of this study did not include those elements related to kidney pathology, or more advanced concepts, such as gout staging and treatment outcomes. 'Imaging evidence' of gout was treated as a general concept; basic disease elements were included to represent the presence of pathologic crystal deposition or bone damage, independent of the imaging modality used. The scope of this study did not include modality-specific elementary lesions (such as the 'double contour sign' on musculoskeletal ultrasound).

Labelling of basic disease elements

Labels were extracted from the text, figures and tables of articles and categorised according to the identified basic disease elements. Importantly, these labels were selected only if they referred to a basic disease element and not a collection of elements that would represent a disease state. Labels were considered 'unique' if they used different words or phrases to denote an element. For each article, the use of a unique label was recorded only once. Unique modifiers for labels were captured whenever possible, with certain exceptions. The labels 'uric acid' and 'urate', for example, were typically prefixed by either 'serum', 'plasma' or 'blood'. As it was not possible to ascertain the assay method used in the vast majority of articles to confirm the validity of these prefixes, these prefixes were not included in the extracted label. The designation of labels to relevant disease elements required careful consideration of context.

Chemical elements

The chemical elements included 'the pathogenic crystals in gout', 'the circulating form of the final enzymatic product generated by xanthine oxidase in purine metabolism in humans', and 'an elevated circulating level of the final enzymatic product generated by xanthine oxidase in purine metabolism in humans' (Table 3). For element 'the pathogenic crystals in gout', there were 28 unique labels identified. The two most common labels used were 'mono- sodium urate crystals' and 'urate crystals', together representing 75.5% of the articles referencing this element.

For the element represented by 'the circulating form of the final enzymatic product generated by xanthine oxidase in purine metabolism in humans', the vast majority (99.3%) of articles used either, or both, of the labels 'uric acid' and 'urate'. These labels were used

with almost identical frequency in articles referencing this element: 63.0% and 62.5% used uric acid and urate, respectively. In addition, these labels were often used interchangeably, with over a quarter (25.9%) of articles using both labels. Geographic region of the first author also appeared to influence results. While other regions favored the use of 'uric acid', authors from Oceania predominantly (85%) used 'urate' when referring to this element (Supplementary Table 1). For the element, 'an elevated circulating level of the final enzymatic product generated by xanthine oxidase in purine metabolism in humans', there was widespread conformity, with almost universal use of the label 'hyperuric(a)emia' (99.0%).

Clinical elements

The clinical elements of gout included 'an episode of acute inflammation triggered by the presence of pathogenic crystals', 'the condition in which there is an absence of clinically evident inflammation after or between episodes of acute inflammation' and 'persistent inflammation induced by pathogenic crystals' (Table 4).

'An episode of acute inflammation triggered by the presence of pathogenic crystals' was the most inconsistency labelled element, with 162 unique labels being identified. There was also striking inconsistency within articles. The mean number of labels used per article for this element was greater than three (3.2); over a third (33.6%) of the 357 papers referencing this element used at least four different labels. Inconsistent use of labels was also seen when results were analysed according to geographic region (Supplementary Table 1). The most common labels identified were 'acute gout' (33.6% of articles), 'gout flare' (33.1%), 'gout attack' (27.7%) and 'flare' (19.9%). Further analysis of the component words within identified labels showed the common use of 'acute', 'arthritis', 'gout' or 'gouty', 'attack' and 'flare' (Supplementary Table 3). The terms 'acute' and 'gout' were important words contained within the structure of the most common labels, as demonstrated in Table 5.

'The condition in which there is an absence of clinically evident inflammation after or between episodes of acute inflammation' was represented by 16 unique labels in 57 articles that made reference to this element. Most labels (91.3%) incorporated the use of 'intercritical'; the two most common labels were 'intercritical gout' and 'intercritical period', accounting for 69.7% of all labels used.

For 'persistent inflammation induced by pathogenic crystals', a total of 34 unique labels were used to signify this element. 'Chronic gout' was the most dominantly used label (58.4% of articles), a finding that was noted across all geographic regions (Supplementary Table 1). The frequencies of other labels identified were widely distributed; 'chronic gouty arthritis', 'chronic arthritis' and 'chronic gouty arthropathy' were the only labels used in at least 5% of articles.

'A discrete collection of pathogenic crystals with associated host-response material' represented the general concept of pathogenic crystal deposition and the chronic inflammatory tissue associated with this. The deposits in this case may be either detectable by physical examination, or evident only with the use of imaging. Labelling of this element was consistent, with the label 'tophus' used by the vast majority of articles (92.5%). The

deposition of crystals ‘detectable on clinical examination’ was treated as a separate element due to reflect the increasing use of advanced imaging modalities in clinical practice to detect the presence of intra-articular pathogenic crystal deposits and tophi. The labelling of this element was more variable, with 27 unique labels identified; subcutaneous tophus (44.1%), subcutaneous nodule (11.8%) and visible tophus (11.8%) were the most frequently used.

Excluding the conventional use of ‘mono/oligo/polyarticular arthritis’, ‘podagra’ was the only label used to represent ‘clinical patterns of articular involvement by gout’ with any meaningful frequency. A total of 31 articles (5.6% of all papers reviewed) used ‘podagra’ to refer to an acute inflammatory arthritis of the first metatarsophalangeal joint due to gout. Other labels, such as ‘axial gout’ or ‘gonagra’ were identified in no more than two articles each.

Imaging elements

The imaging elements identified included ‘the presence of pathogenic crystal deposition on imaging’ and ‘the presence of structural bone damage due to gout’ (Table 6). The labels used to represent crystal deposition on imaging were diverse, although the majority (63.3%) of articles mentioning this element referred to imaging evidence of ‘urate deposition’. Labels referring to imaging evidence of ‘monosodium urate crystal deposition’, ‘urate’, ‘urate crystal deposition’ and ‘monosodium urate deposition’ were each present in at least 10% of articles.

For ‘the presence of structural bone damage due to gout’, 30 unique labels were identified in the 50 articles that made reference to this element. ‘Erosion’ was the most common label, present in 54% of articles. Other commonly used labels included ‘bone erosion’ (34% of articles), ‘radiographic erosion’ (12%), ‘erosive gout’ (10%)

Discussion

This content analysis of the contemporary medical literature highlights a number of important deficiencies in the terminology currently used to describe the basic disease elements of gout. These deficits can be broadly characterised as problems of precision, accuracy and clarity. Most of the elements examined showed marked variability in the labels used, with two notable exceptions. The element, ‘an elevated circulating level of the final enzymatic product generated by xanthine oxidase in purine metabolism in humans’ was denoted by the label ‘hyperuric(a)emia’ in 99.0% of relevant articles. Similarly, the label ‘tophus’ was used in 92.5% of articles that described the disease element of ‘a discrete collection of pathogenic crystals with associated host-response material’.

The most prominent example of imprecise terminology was observed in the labels used to express the element ‘an episode of acute inflammation triggered by the presence of pathogenic crystals’. Marked variability in labelling was evident, both between and within articles. Other elements with inconsistent labelling included ‘persistent inflammation induced by pathogenic crystals’ (34 unique labels), ‘presence of structural bone damage due to gout’ (30 unique labels) and ‘the pathogenic crystals in gout’ (28 unique labels). The elements implied by this multitude of labels are likely to be recognisable to most physicians

and non-physician researchers. However, the lack of precision in gout-related publications has the potential to obscure the interpretation and impact of their results. Consistent labelling and definitions are important when comparing outcomes in clinical trials. A lack of uniformity in terminology is also likely to be a source of confusion to patients and may have implications for their health literacy and subsequent treatment outcomes.

This study has also demonstrated the common use of inaccurate labels for the basic disease elements of gout. The use of 'uric acid' is an important example of this. Due to its characteristics as a weak acid, uric acid exists predominantly in its anionic form, urate, in the circulation. Therefore, 'urate' is the correct term in the context of serum or plasma, unless referring to renal uric acid transport or kidney stones, in which case 'uric acid' is the pathophysiologically correct label. Conventional laboratory assays likewise measure concentrations of urate, not uric acid, despite this misnomer frequently perpetuated by pathology reports. While the difference may seem a minor one, the labels are not interchangeable. Again, this inaccuracy has the potential to cause misunderstanding in communications between health care providers and their patients with gout.

Disease element labelling has an important effect on the clarity with which key concepts of gout pathophysiology are conveyed to health practitioners and their patients. While the natural history of gout involves hyperuricaemia and the deposition of pathogenic crystals, treatment is often based on the level of clinically-evident inflammation resulting from this process; correcting the underlying pathology is often neglected. The labels 'acute gout' and 'chronic gout', the two most common labels used for their respective elements, may reinforce this misperception. A failure of these labels to reflect chronic crystal deposition may lead to therapeutic inertia with regards to the implementation of, and adherence to, urate lowering therapy.

In conclusion, this content analysis of the contemporary medical literature has shown that labelling of the basic disease elements of gout is characterised by imprecision, inaccuracy and lack of clarity. It is hoped that these findings will provide impetus for further work establishing consensus on the nomenclature used for gout.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Statement of clinical significance**What was already known**

- The language used to describe gout lacks standardization with no widely accepted nomenclature.

What was learned from this study

- This study has provided a detailed overview of the range and frequency of labels used to denote the basic disease elements of gout.
- These results indicate key deficits in the consistency, accuracy and clarity of labels used for these basic disease elements.

Table 1

Journals used in a content analysis of gout-related literature. The top-ten ranked general rheumatology journals and top-five ranked general internal medicine journals – ranked according to Impact Factor (2015 Thomson-Reuters Journal Citation Reports) in descending order – and the number of relevant articles identified between the 1 January 2012 and 31 January 2017

Specialty	Journal	Number of gout-related articles identified
General rheumatology journals	Annals of the Rheumatic Diseases	109
	Nature Reviews Rheumatology	37
	Arthritis and Rheumatism/Arthritis and Rheumatology	45
	Rheumatology	82
	Current Opinion in Rheumatology	23
	Arthritis Research and Therapy	55
	Seminars in Arthritis and Rheumatism	32
	Best Practice and Research in Clinical Rheumatology	6
	Journal of Rheumatology	70
	Arthritis Care and Research	50
General internal medicine journals	The New England Journal of Medicine	3
	Lancet	3
	Journal of the American Medical Association	5
	British Medical Journal	11
	Annals of Internal Medicine	18
Total		549

Table 2

The basic disease elements of gout. Labels used to denote elements in 549 gout-related articles

Element category	Element	Number of unique labels	Articles referencing element Number of articles (% of total articles, $n = 549$)	Total number of labels identified	Number of different unique labels per article
Chemical	The pathogenic crystals in gout	28	309 (56.3%)	420	1.4
	The circulating form of the final enzymatic product generated by xanthine oxidase in purine metabolism in humans	9	397 (72.3%)	506	1.3
	An elevated circulating level of the final enzymatic product generated by xanthine oxidase in purine metabolism in humans	7	301 (54.8%)	315	1.0
Clinical	An episode of acute inflammation triggered by the presence of pathogenic crystals	162	357 (65.0%)	1152	3.2
	The condition in which there is an absence of clinically evident inflammation after or between episodes of acute inflammation	16	57 (10.4%)	69	1.2
	Persistent inflammation induced by pathogenic crystals	34	149 (27.1%)	212	1.4
	A discrete collection of pathogenic crystals with associated host-response material	18	240 (43.7%)	290	1.2
	A discrete collection of pathogenic crystals with associated host-response material, detectable on physical examination	27	68 (12.4%)	92	1.4
	Clinical patterns of articular involvement by gout	17	37 (6.7%)	48	1.3
Imaging	The presence of pathogenic crystal deposition on imaging	11	49 (8.9%)	70	1.4
	Presence of structural bone damage due to gout	30	50 (9.1%)	94	1.9

Table 3

Chemical elements of gout. Labels used in at least 5% of articles referencing each element

Element	Number of referencing articles element	Most common unique labels	Number of articles using label ^a	% of articles element labelling
The pathogenic crystals in gout	309	Monosodium urate crystals	226	73.1%
		Urate crystals	91	29.4%
		Monosodium urate monohydrate crystals	30	9.7%
		Uric acid crystals	21	6.8%
The circulating form of the final enzymatic product generated by xanthine oxidase in purine metabolism in humans	397	Uric acid	250	63.0%
		Urate	248	62.5%
An elevated circulating level of the final enzymatic product generated by xanthine oxidase in purine metabolism in humans	301	Hyperuric(a)emia	298	99.0%

^aRecorded as a single occurrence for each article using this label.

Table 4

Clinical elements of gout. Labels used in at least 5% of articles referencing each element

Element	Number of referencing articles element	Most common unique labels	Number of articles using label ^a	% of articles element labelling
An episode of acute inflammation triggered by the presence of pathogenic crystals	357	Acute gout	120	33.6%
		Gout flare	118	33.1%
		Gout attack	99	27.7%
		Flare	71	19.9%
		Acute gouty arthritis	67	18.8%
		Acute gout attack	63	17.6%
		Acute attack	57	16.0%
		Acute gout flare	52	14.6%
		Attack	48	13.4%
		Acute flare	44	12.3%
		Acute attack of gout	28	7.8%
		Gouty arthritis	27	7.6%
		Attack of gout	18	5.0%
		Intercritical period	24	42.1%
The condition in which there is an absence of clinically evident inflammation after or between episodes of acute inflammation	57	Intercritical gout	22	38.6%
		Intercritical phase	6	10.5%
		Intercritical joint	3	5.3%
Persistent inflammation induced by pathogenic crystals	149	Chronic gout	87	58.4%
		Chronic gouty arthritis	19	12.8%
		Chronic arthritis	14	9.4%
		Chronic gouty arthropathy	10	6.7%
A discrete collection of pathogenic crystals with associated host-response material	240	Tophus	222	92.5%
		Gouty tophus	25	10.4%
		Tophaceous deposit	20	8.3%
A discrete collection of pathogenic crystals with associated host-response material, detectable on physical examination	68	Subcutaneous tophus	30	44.1%
		Subcutaneous nodule	8	11.8%
		Visible tophus	8	11.8%
		Clinical tophus	7	10.3%
		Palpable tophus	6	8.8%
		Clinically evident tophus	6	8.8%
		Soft tissue tophus	4	5.9%
		Podagra	31	83.8%

^aRecorded as a single occurrence for each article using this label.

Table 5

The structure of the most common labels used to denote ‘an episode of acute inflammation triggered by the presence of pathogenic crystals’. Breakdown of the words used within labels according the presence of ‘acute’ and/or ‘gout’

Presence of ‘acute’ and/or ‘gout(y)’						
Labels		p	Acute	Gout(y)	Acute and gout(y)	Neither acute nor gout(y)
						Totals (%), N ¼ 1150
Acute gout	Acute gout	–	–	120	–	120 (10%)
Gout flare	Attack	57	117	91	48	313 (27%)
Gout attack	Flare	44	118	52	71	285 (25%)
Flare	Arthritis	–	27	67	–	94 (8%)
Acute gouty arthritis						
Acute gout attack	Totals (%), N¼ 1150	101 (9%)	262 (23%)	330 (29%)	119 (10%)	
Acute attack						
Acute gout flare						
Attack						
Acute flare						
Acute attack of gout						
Gouty arthritis						
Attack of gout						

Table 6

Imaging elements of gout. Labels used in at least 5% of articles referencing each element

Element	Number of referencing articles element	Most common unique labels	Number of articles using label ^a	% of articles element labelling
The presence of pathogenic crystal	49	Imaging evidence of urate deposition	31	63.3%
		Imaging evidence of monosodium uratecrystal deposition	11	22.4%
		Imaging evidence of urate	8	16.3%
		Imaging evidence of urate crystal deposition	6	12.2%
		Imaging evidence of urate crystal deposition	5	10.2%
		Imaging evidence of uric acid deposition	3	6.1%
Presence of structural bone damage due to gout	50	Erosion	27	54%
		Bone erosion	17	34%
		Radiographic erosion	6	12%
		Erosive gout	5	10%
		Gouty erosion	5	10%
		Gouty arthropathy	4	8%
		Gout related joint damage	3	6%
		Radiographic damage	3	6%

^a Recorded as a single occurrence for each article using this label.