Epidemiology of gout and chondrocalcinosis

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SUMMARY

Gout is the most common cause of inflammatory arthritis affecting at least 1% of the population in industrialized countries. It is closely associated with hyperuricemia and is characterized by formation and reversible deposition of monosodium urate crystals in joints and extra-articular tissues. Several studies suggest that the prevalence and incidence of gout are rising. Numerous risk factors may in part explain this increasing trend including dietary and lifestyle changes, genetic factors, diuretic use and comorbid conditions such as hypertension, diabetes, cardiovascular disease, chronic renal disease and the metabolic syndrome.

Chondrocalcinosis is characterized by the deposition of calcium pyrophosphate crystals in articular tissues, most commonly fibrocartilage and hyaline cartilage. Sporadic chondrocalcinosis is a common condition in the elderly and frequently associates with osteoarthritis. Hereditary haemochromatosis, hyperparathyroidism and hypomagnesaemia are metabolic disorders that predispose to secondary chondrocalcinosis.The prevalence of chondrocalcinosis is still rather uncertain and varies depending on the diagnostic criterion used in different studies.

***Key words**: gout, CPPD, chondrocalcinosis, epidemiology, incidence, prevalence.*

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INTRODUCTION

Gout is the most common inflammatory arthritis in men and in older women (1). It is closely associated with hyperuricemia and is characterized by the formation and reversible deposition of monosodium urate (MSU) crystals in joints and extra-articular tissues (2). The gold standard for diagnosing gout is the finding of monosodium urate crystals in synovial fluid during the gout attack (2). Recent epidemiological studies have reported a rising prevalence and incidence of gout worldwide over the last two decades, especially in industrialized countries. Risk factors for hyperuricemia, such as obesity, hypertension, extensive use of diuretics and alcohol intake, may in part explain this increasing trend (3).

Calcium pyrophosphate disease (CPPD) is characterized by the deposition of calcium pyrophosphate crystals (CPP) in articular tissues, most commonly fibrocartilage and hyaline cartilage, and CPP associated arthritis is the third most common inflammatory arthritis (4, 5). Based on the recent EULAR recommendations, 'CPPD' should be adopted as the umbrella term that includes acute calcium pyrophosphate (CPP) crystal arthritis, osteoarthritis (OA) with CPPD and chronic CPP crystal inflammatory arthritis (4). Chondrocalcinosis (CC) defines cartilage or fibrocartilage calcification, most commonly due to CPP and is usually detected by conventional X-ray, but its definitive diagnosis relies on identification of CPP crystals in the synovial fluid (SF).

PREVALENCE AND INCIDENCE OF GOUT

Since hyperuricemia represents the major risk factor for gout, epidemiological data regarding these two conditions are strictly related and cannot be treated separately. However, in this review, epidemiological data have been analyzed and reported tak-

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ing gout rather than hyperuricemia as main index variable.

Prevalence

In the USA, the prevalence of gout is more than doubled between the 1960s and 1990s (6). Epidemiological studies conducted in the 1960s, such as the Framingham Heart Study (1964; subjects aged ≥42) (7) and the Sudbury Study (1972; subjects aged ≥15), showed an overall prevalence of 1.48% and 0.37%, respectively (8).

However, these were relatively small studies, carried out before the development of ACR criteria, including populations of different ages and limited to specific geographical regions (6).

Subsequent studies using self-reported information from the National Health Interview Survey (NHIS) showed an overall prevalence of 2.7%, 2.9% and 3.08% in 1988, 1992 and 1996, respectively, in people aged 65 years or over, confirming an increasing trend (6).

In the US National Health and Nutrition Examination Survey (NHANES) III, carried out between 1988 and 1994, the overall prevalence of gout in subjects aged 20 years or over was 2.7%, with a progressive rise according to age (from 0.4% in subjects aged between 20 and 29 years to 8% and 5.9% among those aged 70-79 and 80 years or over, respectively) (9).

In all ages, there was a clear prevalence of male gender, especially in the age group between 70 and 79 years (11.6% male and 5.2% female), with the exception of the age group between 20 and 29 years, in which there was a prevalence of female (0.5%) over male sex (0.2%) (9).

Furthermore, the overall prevalence of hyperuricemia (defined as serum urate level >7.0 mg/dL in men and >5.7 mg/dL in women) was 18.2% (9). The most recent data about the prevalence of gout and hyperuricemia in the US population confirm this increasing trend is continuing (10) (Figure 1).

In the latest US NHANES survey, conducted in 2007 and 2008, the overall prevalence of gout among US adults was 3.9% (which corresponded to an estimated 8.3

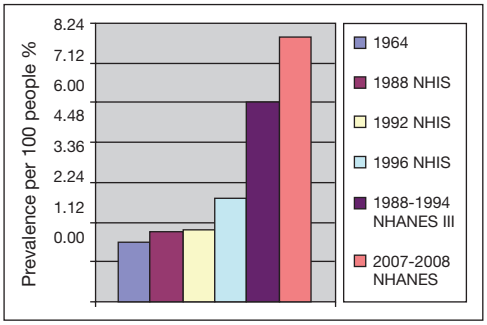

Figure 1 - Prevalence of gout in US: increasing trend from 1960 to 2008.

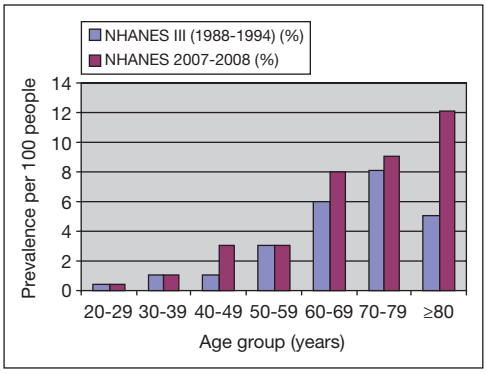

Figure 2 - Prevalence of gout among US adults: comparison between NHANES III (1988 - 1994) and NHANES 2007-2008 according to age.

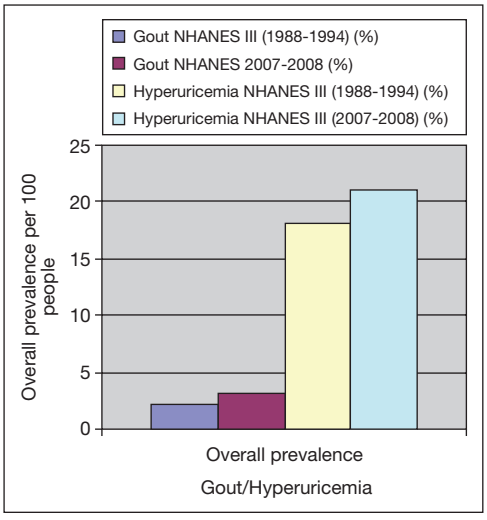

Figure 3 - Prevalence of gout and hyperuricemia (defined as serum urate level >7.0 mg/dL in men and >5.7 mg/dL in women) among US adults: comparison between NHANES III (1988-1994) and NHANES 2007-2008 according to overall prevalence.

million of people), with a clear prevalence of males (5.9%) over females (2.0%) (10). As in NHANES III, the prevalence of gout increased with age (from 0.4% in subjects aged between 20 and 29 years to 12.6% in subjects ≥80 years) (10). The overall prevalence of hyperuricemia (as defined above) was 21.4% (~43.3 million individuals).

Compared with the estimates from NHANES III, these were significantly higher, with differences of 1.2% in gout and 3.2% in hyperuricemia, although these differences were substantially reduced after adjusting for body mass index and/or hypertension (10) (Figures 2 and 3).

Notably, a significant association was observed between a recently established Hmong population of Minneapolis/St. Paul and gout (11). Compared to the general US population, the prevalence of self-reported and physician-diagnosed gout was about 2-fold higher (6.5% vs 2.9% and 2.8% vs 1.5%, respectively) (11). The adoption of a westernized lifestyle may have undoubtedly played a key role in the high prevalence of gout in this population, but further investigation is important to clarify the relative roles of genetic and acquired risk factors.

Epidemiological surveys from the UK found that the prevalence of gout in the 1990s had more than tripled compared to estimates from the 1970s, increasing from 0.26% in 1975 (12) to 0.95% in 1993 (13) and 1.4% in 1999 (14). A retrospective study using medical records of general practitioners in the UK and Germany between 2000 and 2005 found the prevalence of gout to be 1.4% (mean age 60 years) (15).

The prevalence of gout has been reported to be rising also in New Zealand (16), urban African communities (17), Germany (15), China (18, 19) and Greece (20, 21). In an Italian population sample (the MAPPING study) an overall prevalence of 0.46% was found (5). An accurate and detailed summary of the prevalence of gout in different countries and regions of the world was reported in 2010 by Smith and colleagues (3).

These epidemiological trends can be explained by the high prevalence of new non-modifiable and modifiable risk factors such as increased longevity and the increased frequency of risk factors for hyperuricemia such as obesity, hypertension, extensive use of diuretics and alcohol intake (22-24). However, other possible explanations must be taken into account. In many of the epidemiological surveys, the diagnosis of gout is based on clinical assessment, patient self-report (such as in the NHANES studies), general practice diagnosis and medical record/database review rather than on microscopic identification of MSU crystals, which remains the "gold standard" for the diagnosis of gout (25). Another explanation could be a suboptimal management of gout in primary care, which may contribute to the rising prevalence of clinically significant symptomatic gout (25).

Incidence

The incidence of gout has been evaluated by several studies. In the UK general population, the incidence of gout between 2000 and 2007 was estimated using The Health Improvement Network (THIN) UK primary care database (26). The overall incidence rate was 2.68 per 1,000 person-years among subjects aged 20 years or older (4.42 in men and 1.32 in women) and increased with age, with a peak between 80 and 89 years of age (9.81 in men and 4.45 in women per 1,000 person-years) (26). If restricted to subjects aged 40 years and older, the estimate of incidence (3.5 per 1,000 person-years) was in close agreement with another recent UK study, undertaken at the Royal College of General Practitioners Weekly Returns Service between 1994 and 2007, which estimated an incidence rate of 3.2 per 1,000 person-years (27).

In a further cohort study conducted between the years 2000 and 2007 in a UK general practice database (The Health Improvement Network), in which all 18-89 year old patients with gout were included, the overall incidence rate was 2.68 per 1,000 person-years (28).

An additional study, undertaken in the UK using the General Practitioner Research Database (UK-GPRD) between 1990 and

Table I - Incidence of gout.

UK		USA		China		New Zeland Maoris		Czech Republic	
Author (Reference)		**Author (Reference)**		**Author (Reference)**		**Author (Reference)**		**Author (Reference)**	
Cea Soriano (26)	≥20 yrs: 2.68‰ ≥40 yrs: 3.5‰ 80-89 yrs: 9.8‰	Arromdee (29)	- 1977-78: 4.5‰ - 1995-96: 6.23‰	Lin (31)	18.83% (5-year cumulative)	Brauer (32)	- M: 10.3% - F: 4.3%	Hanova (33)	0.41%
Elliott (27)	≥40yrs: 3.2‰	Bhole (24)	- M: 4‰ - F: 1.4‰						
Rothenbacher (28)	- 318-89 yrs: 2.68‰	De Vera (30)	- M: 5.7-7.5‰ - F: 2.4-2.8‰						
Mikuls (14)	- 1991: 1.2‰ - 1994: 1.8‰ - 1999: 1.31‰								

1999, reported incidence of gout per 1,000 patient-years in 1991, 1994 and 1999 of 1.2, 1.8 and 1.31, respectively, with a prevalence of males (0.19%) over females (0.07%) (14). Taken together, these data show that the incidence of gout is stable in the UK.

In the US, a study carried out as part of the Rochester Epidemiology Project computerized medical records system showed that the age- and sex-adjusted annual incidence of acute gout was higher in 1995/96 (62.3/100,000) compared to 1977/78 (45.0/100,000), indicating an increased incidence from 0.03% in 1978 to 0.05% in 1996 (29). In the Framingham Heart Study, the incidence of gout per 1,000 person-years was 1.4 in females and 4.0 in males in a total of 5,209 people examined over a 52-year period (1950-2002) (24).

In a Canadian population aged 65 years or over, the incidence rates were 5.7-7.5/1,000 person-years in males and 2.4-2.8/1000 person-years in females (30).

In China, a 5-year cumulative incidence for gout (1991-1992/1996-1997) of 18.83% was reported (31). In a prospective study of gout in a New Zealand Maoris population based on a sample of 388 males and 378 females (from 1962-63 to 1974), the 11-year cumulative incidence rates were 10.3% for males and 4.3% for females (32). In a population-based study in two regions of the Czech Republic with a total population of 186,000 inhabitants (2002-2003), the annual incidence of gout was 0.41% (33) (Table I).

MORBIDITY

A large quantity of data indicate that a close relationship exists between hyperuricemia, gout and renal diseases, cardiovascular diseases and metabolic syndrome.

Renal disease

In chronic gout, renal impairment and urolithiasis were reported in 86.3% and 35-39% respectively (34, 35) and the prevalence of urolithiasis has been reported almost 2-fold higher in men with a history of gout compared with those without (15% vs 8%) (36).

Cardiovascular diseases (CVD)

There is a strong association between gout and traditional cardiovascular risk factors, such as hypertension, diabetes mellitus, obesity and hypercholesterolemia, and gout has a well-recognized association with CVD including angina, heart failure, myocardial infarction, cerebrovascular accident, transient ischemic attack and peripheral vascular disease (14, 37-39). However, there is still much debate as to whether gout is an independent risk factor for CVD, since many shared confounding factors play a significant role in all these conditions (25). Gout patients were more likely to have cardiovascular disease, hypertension, diabetes and chronic renal failure when compared with patients with osteoarthritis (14). A 2-year retrospective study examining co-morbidities and medication use among patients with gout/hype-

ruricemia across the United States reported that 57.9% had hypertension, 45.3% had a lipid disorder, 32.5% had both conditions and 19.9% had diabetes mellitus (39). A recent cohort study found an approximate 2:1 prevalence ratio of essential hypertension, hyperlipidemia, diabetes mellitus without complications and coronary atherosclerosis in patients with gout compared with those without (38). Similar co-morbidities were also seen in gout patients in other areas of the world, such as northern Thailand (3). Hyperuricemia *per se* has also been associated with an increased risk of CVD (40-43) but its role as an independent risk factor for CVD is still under debate (25). Data obtained from a review of 14 large population studies (44), and a meta-analysis of 15 other studies (45), favored hyperuricemia as an independent risk factor for CVD.

Metabolic syndrome (MS)

High prevalence of MS has been reported among gout patients (46). In a study on the relationship between the first gout attack and the diagnosis of MS it was found that the first attacks of gout may precede the diagnosis of metabolic abnormalities and associated diseases (47).

MORTALITY

An association between hyperuricemia and gout with cardiovascular mortality has been reported. Hyperuricemia is associated with an elevated relative risk of death from all causes, above all coronary heart disease, stroke, hepatic disease and renal failure (48, 49), and it is a considerable risk factor for reduced life expectancy (3). In men with gout, the increased mortality risk was primarily due to an elevated risk of cardiovascular death, especially coronary heart disease (50, 51).

ELDERLY-ONSET GOUT

Since epidemiological data demonstrate an increased prevalence and incidence of gout among elderly people, it is of interest to briefly review some particular aspects related to this subset of patients.

Elderly-onset gout (EOG) is defined as a disease with onset at 65 years of age or over, and represents a special issue with notable epidemiological, clinical and therapeutic differences from the typical middle-aged form (52). In the US, among subjects aged 65 years or older, the prevalence of gout and hyperuricemia was 9.8% (~3.5 million US citizens) and 31.4% (~10.7 million US citizens), respectively (10). Although the prevalence of gout is higher in men than in women (6), after the age of 65 this gender difference is less evident, and after the eighth decade, EOG is found almost exclusively in females (29, 53). At onset, women are generally ten years older than men (54, 55). From a clinical point of view, the main differences from the middle-aged form are the more frequent subacute/chronic polyarticular onset with hand involvement, the unusual localization of tophi superimposed on ostheoarthritis (OA) nodes, and the frequent association with drugs that reduce renal urate excretion (diuretics and low-dose aspirin) and/or with primitive renal impairment (52). Because of the frequent atypical presentation, EOG can easily be confused with other diseases (i.e. rheumatoid arthritis, OA, pseudogout and spondyloarthritides) (56) thus often remaining misdiagnosed or diagnosed later in its clinical course (52). Even when recognized, its treatment is often difficult or unsatisfactory (52).

RISK FACTORS FOR THE DEVELOPMENT OF GOUT

Hyperuricemia

As mentioned above, hyperuricemia is considered the most important risk factor for the development of gout (25) and the risk of gout increases dramatically with increasing serum urate level (24, 29, 31, 57, 58). However, a large majority of people with hyperuricemia do not have gout while hyperuricemia is much more common, implying that other factors must be involved in the pathogenesis of gout (59).

Genetic factors

Although a strong familial predisposition to primary gout has been recognized for centuries, especially in males, the genetic basis remains largely unknown (1). Renal mechanisms involved in urate handling and transportation appear to play a central role in determining hyperuricemia. More than 70% of the body's uric acid is eliminated by the kidneys, while approximately only 30% is excreted into the intestine (25). The usual mechanism of hyperuricemia in primary gout relates predominantly to a relative inefficiency in excretion rather than overproduction (25). In addition, twin studies support the hypothesis that genetic factors exert an important control on the renal clearance of urate (60, 61). These data explain the deep interest recently focused on genes regulating renal urate transport (62, 63). SLC2A9 (GLUT9) and ABCG2 are urate transporters located in the proximal renal tubules which are involved in the renal excretion of urate and are, to date, considered the two major regulators of serum uric acid (SUA) levels (64-66). Several studies have reported that individuals with GLUT9 or ABCG2 polymorphisms were associated with higher SUA concentrations and gout risk (67-69). Polymorphisms in the *SLC17A1* gene, which encodes for NPT1, a sodium-dependent phosphate co-transporter (68) and in the *SLC17A3* gene (encoding NPT4, a proximal tubule sodium/phosphate co-transporter) (65) have also been shown to be associated with gout. A polymorphism of *SLC22A12* gene encoding for human urate transporter 1 (URAT1), which is critical in controlling reabsorption of uric acid from the proximal renal tubules (25, 70) has been associated with hyperuricemia in German Caucasians (71).

Other genetic associations with hyperuricemia have been recently reported, such as the 677T allele of the methylene tetrahydrofolate reductase (*MTHFR*) gene (66) and the 64Arg variant of the β3-adrenergic receptor (*ADRB3*) gene (72).

It is likely, although not yet proven, that individuals with a greater number of urate-associated genes develop gout at a younger age than average (73, 74).

Dietary factors

The close link between diet and gout has been well known for centuries and several studies have highlighted not only the predisposing but also the protective role of certain foods towards the development of gout. A recent study of 5,003 subjects randomly recruited from 5 coastal cities of Shandong province in Eastern China showed a higher prevalence of hyperuricemia and gout in urban than in rural residents, and in the more developed than in the less developed cities, suggesting the possibility that dietary and lifestyle changes may be directly responsible for these variations in the prevalence of gout (18).

Foods associated with an increased risk of gout include meat and seafood (75), sugar-sweetened soft drinks, fruits with high fructose content and fruit juices (76, 77).

Conversely, dairy products (75), coffee (78) and higher total vitamin C consumption (79) were seen to be protective against the risk of hyperuricemia and gout.

Results of recent studies may explain the lowering of the risk of gout in individuals consuming dairy products. It has been reported that full cream milk has an acute urate-lowering effect by increasing the fractional excretion of uric acid (80), and both lipid and protein fractions of dairy products may inhibit the inflammatory response to monosodium urate crystals in animal models (81). However, the protective effect against high SUA levels intake was seen for low-fat dairy products but not for high-fat dairy products (75).

As far as coffee is concerned, a modest inverse association between decaffeinated coffee intake and SUA levels was shown, while total caffeine from all sources and tea intake were not associated with hyperuricemia or the risk of gout (78).

Consumption of purine-rich vegetables appeared not to be associated with hyperuricemia and gout (75).

Alcohol consumption

Several studies and recent epidemiological data support the important relationship between alcohol consumption and risk of incident and/or prevalent gout (24, 31,

73, 82-88). In a study carried out over a period of 12 years (1986-98) using twice yearly questionnaires, a strong association between alcohol intake and gout was reported, with the greatest risk for beer consumption and, albeit to a lesser degree, for spirits; moderate wine drinking did not, however, increase the risk (86). Excessive alcohol intake is an important risk factor for gout also in women; in the Framingham Heart Study cohort, alcohol use was associated with a 3-fold higher risk of incident gout among women and a 2-fold higher risk in men (24). Furthermore, it has been reported that alcohol intake may trigger attacks of acute gout typically within 24 h after its consumption (89), besides being associated with a higher risk of gout flares per year (73). Notably, it was found that alcoholism was significantly increased in gouty patients compared with non-gouty patients (84). The intake of alcoholic beverages may predispose to gout by several mechanisms, such as increasing the availability of the substrate for urate production (accelerated degradation of purine, high purine content of beer) or reducing renal urate excretion through lactic acidosis (90).

Metabolic factors

Gout has an important association with the metabolic syndrome, the prevalence of which is significantly higher in individuals with gout (62.8%) compared with those without gout (25.4%) (46), obesity (24) and diabetes mellitus (14, 91). Hyperuricemia is a common finding in patients with metabolic syndrome (92) and SUA levels are usually more elevated (by 0.5-1.0 mg/dL) in subjects with metabolic syndrome than in controls (93, 94). It has been hypothesized that insulin-resistance syndrome could be the common denominator shared by these conditions. Previous studies have shown a close relationship between hyperuricemia and the insulin resistance syndrome (95-97), and higher insulin levels are known to reduce renal excretion of urate (98-100).

Medications

Diuretics, including thiazide and loop diuretics are a significant risk factor for gout and for gout flares (14, 24, 101, 102), as they may induce hyperuricemia trough inhibition of renal urate excretion (103, 104). Cyclosporine use has been associated with an increased risk of new-onset gout after renal transplantation (105). The risk is higher than that observed with tacrolimus, and the incidence of new-onset gout appears to be increasing even while the dosage of cyclosporine is decreasing (104).
Aspirin is known to have a bimodal effect on SUA levels, high dosages (>3 gm/day) being uricosuric while low dosages (1-2 gm/day) cause UA retention (106). One study showed that low-dose aspirin (75mg a day) may also be a risk factor for gout, causing significant changes in uric acid management in a group of elderly patients (107).

Drugs and substances which can induce hyperuricemia (CANTLEAP)

- Cyclosporine
- Alcohol
- Nicotinic acid
- Thiazides
- Lasix (Furosemide) or other loop diuretics
- Ethambutol
- Aspirin
- Pyrazinamide

Renal disease

Chronic renal disease is an important risk factor for gout (14, 101). In a retrospective study, the incidence of gout was 5.4% in the first year of dialysis and 15.4% in the first five years (108).

PREVALENCE OF CHONDROCALCINOSIS

The prevalence of chondrocalcinosis (CC) is still rather uncertain and varies depending on the diagnostic criterion used in different studies, i.e. X-ray or synovial fluid examination. In the Framingham Knee Osteoarthritis Study, a large population based study of the elderly, the prevalence of radiological knee CC was 8.1% in a sample of 1,425 subjects aged over 63 years (109).

In a Spanish primary care-based study, the crude prevalence of CC in subjects aged over 60 years was 10%, as confirmed by both knee and wrist X-rays (110).
In a large UK community study (1727 individuals; 1,084 women, 643 men, mean age 63.7 years), a prevalence of CC of 7% was reported, with a strong age association (from 3.7% in people aged 55-59 years to 17.5% in those aged 80-84 years). There was no difference according to gender (111).
In a population of elderly Italian subjects from Northeastern Italy, the prevalence of radiological chondrocalcinosis of the lower limbs was 10%, and this increased with age, rising from 7.8% in subjects aged 65-74 years, to 9.4% in those aged 75-84 years, and to 21.1% in subjects aged over 85 years (112) (Figure 4).
The prevalence of CPPD is much higher when SF is examined for crystals: 25-43% of SF obtained from patients undergoing total knee arthroplasty contain CPPD crystals (113-115).
In a recent study, the comparison of CC prevalence between Chinese subjects (Beijing residents, ages >60 years) and US white subjects in Framingham (MA, USA) showed a much lower prevalence of knee CC in Chinese subjects (1.8% in men, 2.7% in women) than in white subjects (6.2% in men, 7.7% in women) (116). Moreover, wrist chondrocalcinosis was very rare in elderly Chinese subjects (prevalence 0.3% in men and 1.0% in women) (116).
Data on CPPD incidence are lacking. Some information comes from studies which analyzed the seasonal pattern of occurrence of acute attacks of CPPD and these will be reported below.

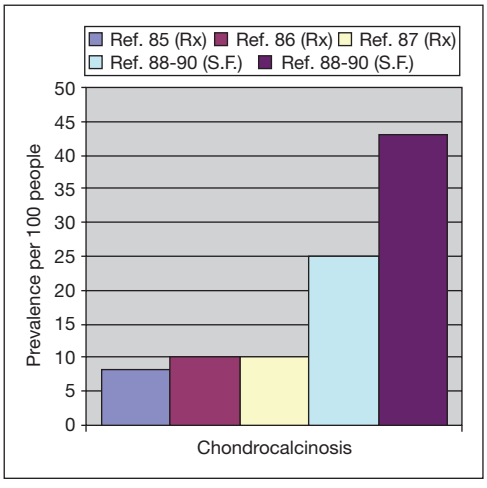

Figure 4 - Prevalence of CC in various epidemiological studies (Ref: reference; S.F.: synovial fluid).

RISK FACTORS FOR THE DEVELOPMENT OF CHONDROCALCINOSIS

Genetic factors

A familial form of chondrocalcinosis has now been widely recognized and two genetic locations have been identified: the CCAL1 locus, located on the long arm of chromosome 8 and associated with severe osteoarthritis; and the CCAL2 locus, which has been mapped to the short arm of chromosome 5 and identified in families from the Alsace region of France and the United Kingdom (117).
The responsible gene at the CCAL2 locus has been identified as the *ANKH* (ankylosis human) gene, whose mutations are believed to cause familial CC (117). In contrast, the role of genetic factors in sporadic forms of CC has not yet been fully established (118).

Aging and osteoarthritis (OA)

Age and OA are major risk factors for CC (4). It is well known that age is a common risk factor for both OA and CC, and age-related alteration of cartilage matrix encourages deposition of calcium crystals (119). However, the precise relationship between OA and CC is unclear, since it is also known that CPPD could be a primary factor that causes or worsens joint damage in OA.

Injury

Previous joint injury may predispose to CPPD. The best evidence comes from studies of post-meniscectomy knees in which the risk of CC is five times greater than in contralateral unoperated knees (120).

Hyperparathyroidism
Patients with hyperparathyroidism are three times more likely to have CPPD than controls (121, 122).

Hemochromatosis (HH)
Although there is some evidence to support the association between hemochromatosis and CPPD, the relationship between them has not been defined. In a hospital series of 54 patients with idiopathic hemochromatosis, 31 had arthropathy, which had a significant association with CC (123). In another study of 178 patients with hemochromatosis, the prevalence of CC was 30% and the number of joints with CC correlated positively with age, ferritin level and serum PTH 44-68 (124).
In contrast, in a hospital case-control study, no significant association was found although patients with hemochromatosis developed CC at a younger age (<60) than those without (125). Furthermore, the frequency of HH in patients with sporadic CC is very low, so systematic genetic testing for HH in patients with CC is not recommended (126).

Hypomagnesemia
Hypomagnesemia associates with increased risk of CPPD. In a recent cross-sectional study, the prevalence of CC was found to be markedly higher in patients with intestinal failure, in whom severe hypomagnesemia often develops despite magnesium supplementation, than in controls (127).
In one community study, use of diuretics was a risk factor for CC, and this might be explained by hypomagnesemia consequent to increased urinary magnesium loss induced by thiazides (111).

Other metabolic and endocrine diseases
Gout, ochronosis, familial hypocalciuric hypercalcemia, X-linked hypophosphatemic rickets, Wilson's disease and acromegaly have been reported to predispose to CC but these are only anecdotal observations (128). Diabetes mellitus and hypothyroidism, initially reported as predisposing factors for CC, were not confirmed by controlled studies involving age-matched controls (128).

SEASONAL VARIATION IN THE ONSET OF GOUT AND CHONDROCALCINOSIS

Some studies have shown a temporal variation in the onset of gout and CCPD (129-132). In our 1999 study, we showed that the occurrence of gout attacks had a circannual distribution, characterized by a spring peak in April (132). These results were consistent with other studies on chronobiological evaluation of gout (129, 131), with the exception of one single report in which a summer peak was found in July (130). Analysis of the distribution of events by gender confirmed such a pattern only for males, whereas the extreme scarcity of females did not allow any valid statistical analysis to be carried out (132). On the contrary, no significant seasonal variation in pseudogout attacks has been demonstrated (131, 132), although in our study pseudogout events showed a higher frequency peak in autumn (132). Overall, the analysis of the distribution of events by season showed a significant difference between gout and pseudogout attacks (132). There are still no convincing explanations for this particular seasonal pattern.

CONCLUSIONS

Gout is a very common form of arthritis, and prevalence and incidence rates are rising worldwide, especially among industrialized and elderly populations. Risk factors such as obesity, hypertension, extensive use of diuretics and alcohol intake may in part explain this increasing trend. Hyperuricemia is the central risk factor for gout, a key component of the metabolic syndrome and an independent risk factor for cardiovascular disease. High prevalence of cardiovascular diseases, renal impairment and metabolic disease has been reported among gout patients.
Chondrocalcinosis defines cartilage calcification, most commonly due to CPPD.

Definitive CPPD diagnosis relies on identification of SF CPP crystals. The prevalence of chondrocalcinosis is still uncertain and varies depending on the diagnostic criterion used in different studies. When X-ray is used as diagnostic criterion, CC overall prevalence is similar to gout. When SF is examined for crystals, the prevalence of CPPD may be much higher than that of gout, ranging between 25 to 43%.

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