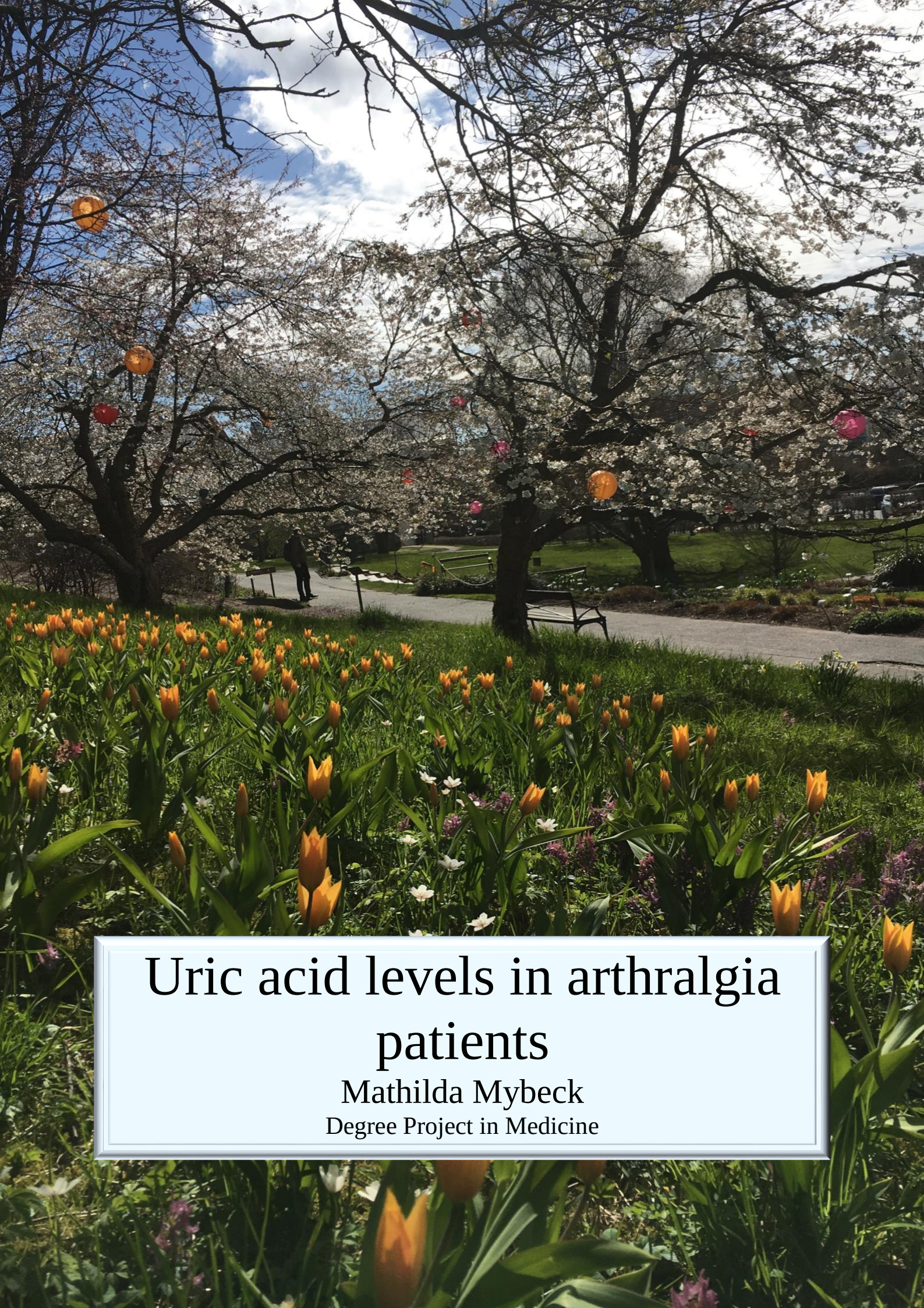

Uric acid levels in arthralgia patients

Mathilda Mybeck

Degree Project in Medicine

THE SAHLGRENSKA ACADEMY

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Programme in Medicine

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Abstract

Degree project in medicine: Uric acid levels in arthralgia patients - Mathilda Mybeck

Sahlgrenska University Hospital and Department of Rheumatology and Inflammation Research, University of Gothenburg, Sweden 2018

Background: Uric acid is often associated with gout, but recent studies have attracted attention to a potential connection between rheumatoid arthritis (RA) and uric acid. It has been shown that RA patients with hyperuricemia have a milder joint disease, and that it is more common for patients who do not have RA-specific autoantibodies to have urate crystal deposits in their joints.

Objectives: To examine the connection between uric acid and RA and to find out if there is a connection between uric acid and RA-specific autoantibodies or survivin.

Material and methods: 338 patients were collected from the material of 1743 patients with arthralgia visiting the rheumatology clinic at Sahlgrenska university hospital during one year. All patients included had at least one measured serum uric acid level. Hyperuricemia was defined by the levels >400 μmol/l for females and >480 μmol/l for males. The patients were divided into groups depending on gender, rheumatic diagnose, antibodies, survivin and uric acid level. Symptoms of gout were investigated in 152 patients.

Results: 34 % of all studied patients included had hyperuricemia. 95 % of the patients diagnosed with gout had hyperuricemia. Prevalence of hyperuricemia was higher in males than females ($P<0.0002$). Among the females with hyperuricemia, RA was the most common

diagnosis (40%). However, symptoms indicating gout, were significantly less in RA patients compared to gout (females P=0.0006, males P<0.0001). Regardless of antibodies and presence of survivin, the prevalence of hyperuricemia was similar (9/25 vs 44/114, P=0.82 for males and 11/33 vs 51/166, P=0.76 for females). There was no difference in uric acid level depending on rheumatic diagnose, except for gout which had significantly higher levels of uric acid (P<0.0001).

Conclusions: Hyperuricemia was attributed to the diagnosis of gout and showed its specificity regardless of autoantibody and serum survivin profile.

Key words: Rheumatoid arthritis, uric acid

Abbreviations

RA: Rheumatoid arthritis

ALG: Arthralgia

UA: Undifferentiated arthritis

HU: Hyperuricemia

CHU: Clinically significant hyperuricemia

RF: Rheumatoid factors

ACPA: Anti-citrullinated protein antibody

aCCP: Anti-cyclic citrullinated peptide antibody

AMP: Adenosine monophosphate

GMP: Guanosine monophosphate

DNA: Deoxyribonucleic acid

RNA: Ribonucleic acid

DECT: Dual Energy Computed Tomography

HGPRT: Hypoxanthine-guanine phosphoribosyltransferase

MTP: Metatarsophalangeal joint

Introduction

Uric acid

Metabolism

Uric acid (C5H4N4O3) is the end product of the purine metabolism in humans. Starting from AMP and GMP, purines are derived multiple times. An important step is conversion to guanine and adenine, which are two of the nucleotides in DNA and RNA [1]. Formation of DNA is one function of purines, along with signal transduction and modulation of energy metabolism. Purines are from guanine and adenine via several conversions degraded to xanthine, and then to uric acid. Humans do not have the enzyme uricase which breaks uric acid down further into allantoin in most other mammals, and therefore uric acid is the end product in humans (figure 1). Uric acid is instead excreted via the kidneys (2/3) and the gastro-intestinal tract (1/3) [2]. Uric acid has also been shown to be an important antioxidant, responsible for neutralisation of 2/3 of all free radicals [3].

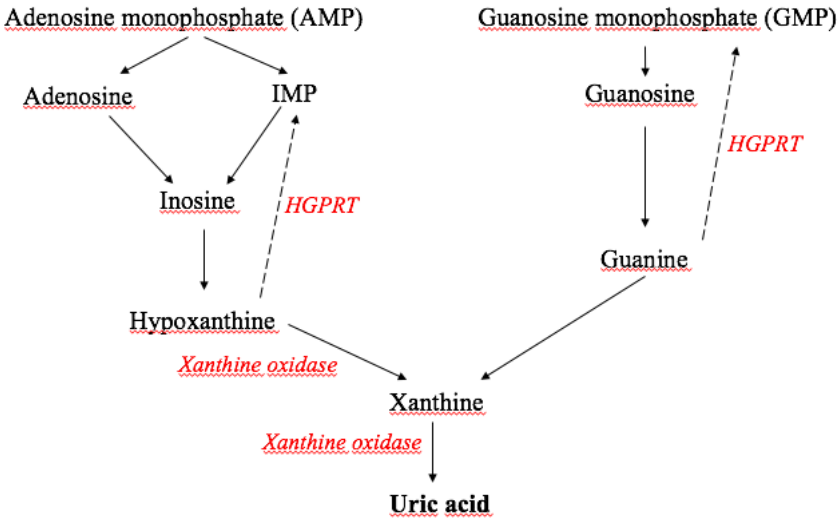

Figure 1. Metabolism of purines. Enzymes are shown in red. Purines are degraded from AMP and GMP to uric acid. IMP, inosine monophosphate; HGPRT, hypoxanthine-guanine phosphoribosyltransferase.

Causes of hyperuricemia

When the level of uric acid in the blood circulation is high, hyperuricemia occurs. This might lead to crystallisation of uric acid, and further to deposition of monosodium crystals in organs and tissues and also in joints, which got the name of gout. Gout is characterised by severe pain and joint redness, often in first metatarsophalangeal joint (MTP 1). Risk factors for gout include high consumption of alcohol and purine rich food such as red meat, as well as obesity [4]. The crystallisation of uric acid that occurs in gout is more common at a level of uric acid in the blood above 360 μmol/L [5]. There are several reasons for hyperuricemia, these can be categorised as an increased production of uric acid, a decreased elimination of uric acid or a combination of the two. Increased production of uric acid can, for instance, be a consequence of the increased cell destruction that occurs in lysis of tumour cells in leukemia [6], and it has been shown to occur after chemotherapy [7]. Decreased elimination of uric acid can be caused by acidosis, which causes decreased tubular filtration of uric acid in the kidneys due to an increase in organic acids which inhibits filtration of uric acid [8]. This can be seen in diabetes ketoacidosis, high alcohol consumption or famine. Decreased elimination of uric acid can further be due to kidney disease. Hyperuricemia can also be a consequence of genetic disorders that affects enzymes related to metabolism of uric acid. Two examples are the genetic diseases Lesch-Nyhan syndrome and Kelley-Seegmillers syndrome, which both are related to deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT). This enzyme is involved in the metabolism of uric acid as seen in figure 1, and inadequate function can cause hyperuricemia [9].

Reference range of uric acid

Currently, the reference range for uric acid used in Sweden and internationally is 155-400 μmol/L for females and 230-480 μmol/L for males. This is calculated from the healthy

population and is adjusted according to the changing uric acid levels in the population, where increasing prevalence of obesity leads to a higher mean uric acid level in the population and therefore a higher reference range for uric acid [5]. It has been debated whether the reference range for uric acid should be decreased. It has been proposed that the cut-off values for uric acid should, instead of being determined by the uric acid levels in healthy population, be determined by the physiological traits of uric acid. Zhang et. Al. proposed a cut-off value of 291 μmol/L in females and 375 μmol/L in males [10]. New evidence have shown that there is a risk for cardiovascular disease, even at a uric acid level within today's reference range [11] and this justifies a potential lowering of the uric acid reference range to open up for earlier treatment.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterised by synovial inflammation and destruction of joints. The prevalence of RA is today estimated to 0.1 to 1 percent of adults in developed countries [12]. With the discovery of disease modifying antirheumatic drugs (DMARD) and biologic agents the possibilities of treatment and the prognosis have improved substantially during the 21st century.

Autoantibodies in rheumatoid arthritis

The main antibodies used for diagnosis and disease monitoring of RA are RF and ACPA. RF is an abbreviation for rheumatoid factor and was first found in 1940. It has a specific antigen, the Fc-region of the IgG antibody molecule, and occurs in about 50 % of RA patients, but also among healthy individuals. It is a useful marker of RA, and associates with poor prognosis and severe disease. ACPA stands for antibodies against citrullinated peptides and is found in about 50 % of RA patients. It is uncommon in other diseases and in the healthy population,

and the specificity and sensitivity is high. Similarly to RF, it is also associated with a poor prognosis [13]. Clinically, the most common analysis to measure ACPA is analysis of aCCP (antibodies against cyclic citrullinated peptide). Both RF and ACPA have been shown to occur in patients for several years before symptoms of disease, and can therefore be considered important risk factors which often precedes the development of RA [14, 15].

Survivin

Survivin is an onco protein that controls cell divisions and functions as an inhibitor of apoptosis. It has recently been shown that elevated levels of survivin in serum predict development of RA. Survivin could function as an important diagnostic tool and a way to monitor patients with RA [16].

Uric acid and its connection to rheumatoid arthritis

Recent studies have drawn attention to the connection between RA and uric acid. It has been shown that hyperuricemia in patients diagnosed with RA correlates with a milder disease [17]. It has also been shown to be more common for patients negative for RF to have monosodium urate crystal deposits [18], indicating that uric acid indeed might have a connection with RA and that uric acid levels might vary depending on antibodies. Furthermore, patients diagnosed with RA have a higher risk of cardiovascular disease and mortality [19], and so does patients with hyperuricemia [20]. A possible explanation for the risk of cardiovascular disease in RA patients could be that RA patients in general have higher level of serum uric acid that elevates the cardiovascular risk [21]. It was reported that RA-patients with hyperuricemia had a higher risk of peripheral arterial events and a higher mortality rate, than patients who did not have hyperuricemia [22].

It has also been debated to what extent RA and gout coexists in the same patient. This was earlier believed to be rare, with merely 33 reported patients in scientific literature in English, but the study addressing this question found that it occurred more often than believed, though not as often as in the general population. Also, incidence of gout has increased in the general population, and therefore so has incidence of gout in RA-patients [23].

Taken together, the prevalence of both gout and hyperuricemia has been rising during the 21st century, and several studies have shown different possible connections between uric acid and RA. New knowledge is therefore important. The objective of this study was to examine the connection between uric acid and rheumatic joint diseases, and further investigate whether there is a connection between uric acid and antibodies or survivin. An additional purpose was to find out how prevalent symptoms indicating gout are among RA-patients. This was done using diagnostic rules for diagnosis of gout developed for primary care in 2010 for when joint fluid is not available [24].

Aim

To examine the connection between uric acid and RA, and to find out if there is a connection between uric acid and autoantibodies or survivin. In addition, to investigate symptoms of gout in RA-patients.

Ethics

The study was approved by the Ethics Committee of Gothenburg, in accordance to UN's declaration on human rights and the Declaration of Helsinki. Ethics committee approval number: 257-13.

Patients and Methods

Selection of the patient cohort

In total, 338 patients were selected from a larger material of 1743 patients with arthralgia visiting the Rheumatology Clinic at the Sahlgrenska University Hospital, Gothenburg during 12 consecutive months between November 2012 to November 2013 (figure 2). Inclusion criteria were, aside from having one measurement of RF and aCCP, at least one measurement of uric acid at the Laboratory of Clinical Chemistry, SU, and clinical assessment by rheumatologist in adjustment to the blood sampling.

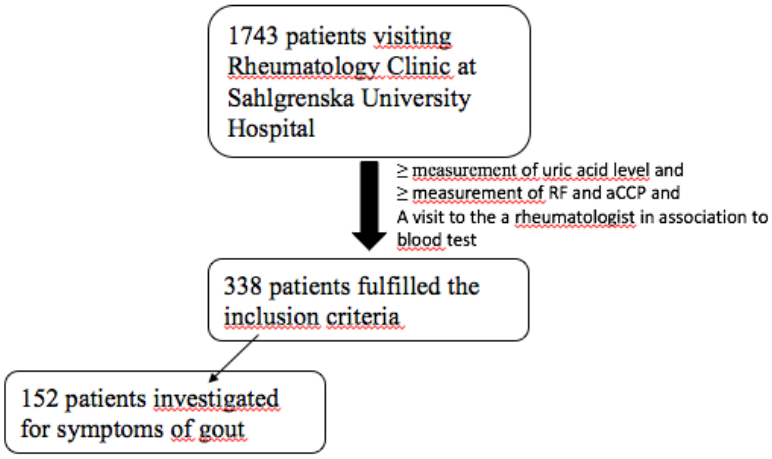

Figure 2. Chart flow diagram of the patients included. Of 1743 patients visiting the Rheumatology Clinic at Sahlgrenska University Hospital, 338 were included in the study and analysed in respect of uric acid. 152 patients of the 338 patients were investigated for symptoms of gout.

All patients were labelled with gender, age, diagnosis and positive or negative RF, aCCP and survivin-protein. Serum uric acid levels were noted. The patients were further divided into six groups depending on diagnose and formed the groups with 1) rheumatoid arthritis (RA), 2) gout, 3) undifferentiated arthritis (UA; which included monoarthritis, oligoarthritis, polyarthritis and reactive arthritis), 4) spondyloarthritis and psoriasisarthritis (SpA/PsA) 5)

arthralgia (ALG) (table 1). In addition, one group contained the patients with other diagnoses and it included osteoarthritis, polymyalgia rheumatica, systemic lupus erythematosus, tendinitis or uncertain diagnose. This subdivision into groups was based on diagnoses set at the first visit and classified according the International Classification of Diseases.

Collection of clinical material from medical records

Medical records from 152 patients diagnosed with gout, RA or categorized as "other diagnose" were carefully reviewed for the signs and symptoms of gout, using the diagnostic rules for diagnosis of gout (table 3). It includes the following parameters: Uric acid level above 350 μmol/L (3.5 points), male gender (2 points), previous gout attack (2 points), debut of symptoms within 24 hours (0.5 points), joint redness (1 point), involvement of the first MTP joint (2.5 points) and hypertension or one or more cardiovascular diseases (1.5 points). The points were added and a "gout-score" was calculated. The information was collected from medical records, Sahlgrenska University Hospital.

Measurement of the uric acid in serum

Uric acid was measured at the Laboratory of Clinical Biochemistry at the Sahlgrenska University Hospital. Clinically significant hyperuricemia (CHU) was defined as serum uric acid level >400 μmol/L for females and 480 μmol/L for males, this is the range used by the laboratory of Clinical Chemistry, SU. In addition, serum uric acid values above 300 for females and 400 for males were labelled as hyperuricemia (HU), due to recent findings suggesting that even an increase in uric acid level that is within the reference range can have consequences in health.

Measurement of RA specific antibodies: aCCP and RF

RA specific antibodies were measured at the accredited laboratories of the Clinical Immunology at the Sahlgrenska University Hospital. aCCP was measured using an automatic multiplex method (anti-CCP2, BioRad, Hercules, CA), with cut-off value 3.0 U/ml. RF was measured by rate nephelometric technology (Beckman Immage 800, Beckman Coulter AB, Brea, CA), with a cut-off value of 20 U/ml.

Measurement of serum survivin

Serum survivin was measured using ELISA (DY647, R&D Systems, Minneapolis, MN). The cut-off value was calculated from 104 healthy individuals and set to 450 pg/ml [25].

Statistical analysis

For statistical analyses, various methods were used, depending on what was investigated. Graphpad prism version 7 were used for ANOVA and Chi square tests. ANOVA stands for "Analyses of variance" and was used to compare means and medians among groups. Chi square tests were used for comparison of prevalence among two or more groups. Www.openepi.com was used for two by two tables when comparing prevalence in two groups. Descriptive results are presented as median [1^{st} quartile – 3^{rd} quartile].

Results

Clinical and demographic characteristics of the patient cohort

In total, 338 patients were included in the study, 198 females and 140 males. The median age was 60 years (range 48-68). Characteristics of all patients included are presented in Table 1.

Table 1. Patients characteristics. Results are showed as median and 1st and 3rd quartile. Categorical variables showed as n (%). Other diagnoses include for example arthrosis, polymyalgia rheumatic, systemic lupus erythematosus, tendinitis or uncertain diagnose. SpA, spondyloarthritis; PsA, psoriasisarthritis; IQR, interquartile range.

	All participants **n=338**	Females **n=198**	Males **n=140**
Age, years, median [IQR]	60 [48-68]	56 [45-67]	61 [52-69]
Uric acid, umol/L median [IQR]	300 [244-376]	267 [223-316]	373 [301-458]
Hyperuricemia, n (%)	114 (34%)	61 (31%)	53 (38%)
Clinically significant hyperuricemia, n (%)	44 (13%)	15 (8%)	29 (21%)
Rheumatoid arthritis (%)	84 (25%)	55 (28%)	29 (21%)
Gout (%)	42 (12%)	11 (6%)	31 (22%)
Undifferentiated arthritis (%)	46 (14%)	24 (12%)	22 (16%)
Arthralgia (%)	55 (16%)	46 (23%)	9 (6%)
SpA/PsA (%)	26 (8%)	14 (7%)	12 (9%)
Other diagnoses (%)	87 (26%)	48 (24%)	37 (26%)

The median levels of uric acid in serum were 300 μmol/L (range 244 to 376). As expected, among the male patients the median level of uric acid was significantly higher than among the female patients (median 373 μmol/L vs. 267 μmol/L, $p<0.0001$. Table 1). Due to the

difference in uric acid level between males and females, the groups were mostly analysed separately.

The diagnoses differed in male/female ratio (figure 3). Females were more common in the ALG group, and males were more common in the gout-group. Remaining groups were more similar, but RA had a tendency towards the female gender.

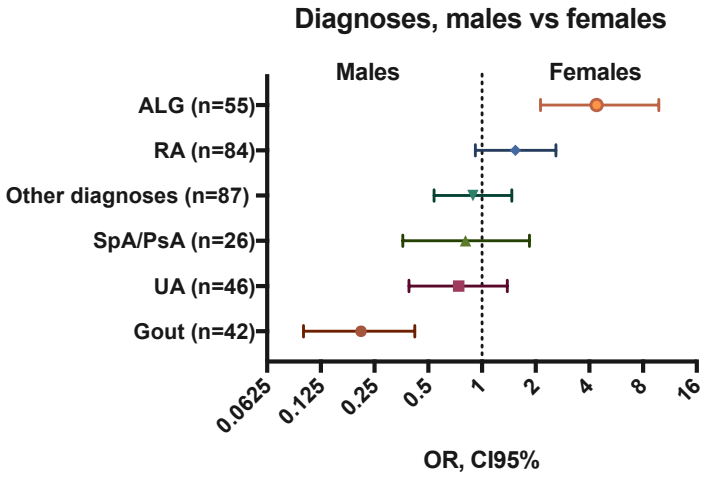

Figure 3. Gender distribution within the diagnoses. Number of females 198, number of males 140. ALG, arthralgia; RA, rheumatoid arthritis; SpA, spondyloarthritis; PsA, psoriasisarthritis; UA, undifferentiated arthritis.

When comparing uric acid levels among the groups with different diagnoses, patients with gout (31 males and 11 females) had significantly higher level of uric acid than all other groups ($P<0.0001$ for both males and females, figure 4). Few patients diagnosed with gout were positive for RF and/or aCCP (10% of the males and 18 % of the females). There was no significant difference in age between the groups.

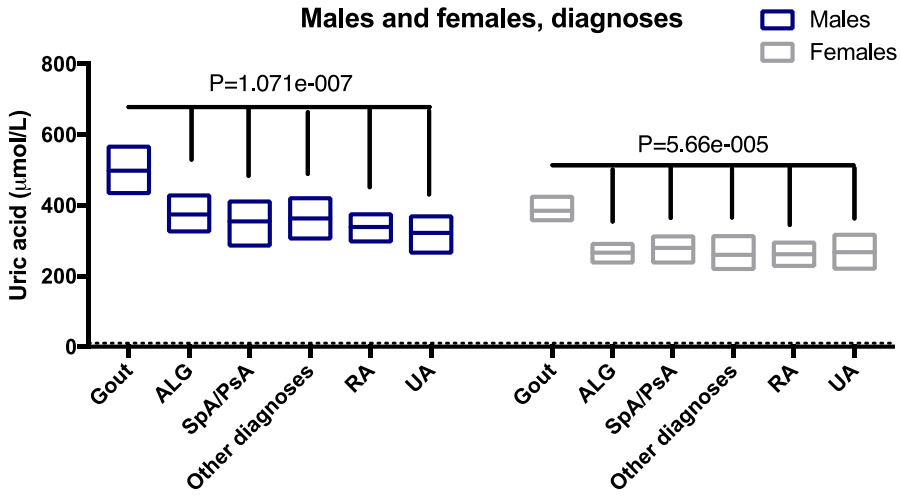

Figure 4. The levels of uric acid in patients with different diagnoses. Male patients (n=140) had higher levels of uric acid compared to females (n=198). The patients with gout had significantly higher levels of uric acid compared to all other groups (ANOVA, p<0.0001).

Prevalence of CHU is higher among males than females

Males have higher absolute levels of uric acid in general and that was also the case in this material (table 1). Therefore, males and females have separate reference intervals for uric acid levels, with different threshold limits for HU (see method). In total, 53 of 140 males (38 %) and 61 of 198 females (31 %) had HU. Males had significantly higher prevalence of CHU than females, 21% (29 of 140) compared to 8 % (15 of 198) (p=0.0005, OR 3.18, [95% CI 1.64-6.33]. Figure 5). There was no significant difference in prevalence of HU (53/140 vs 61/198, P=0.18, OR 1.37, [95% CI 0.87-2.16]).

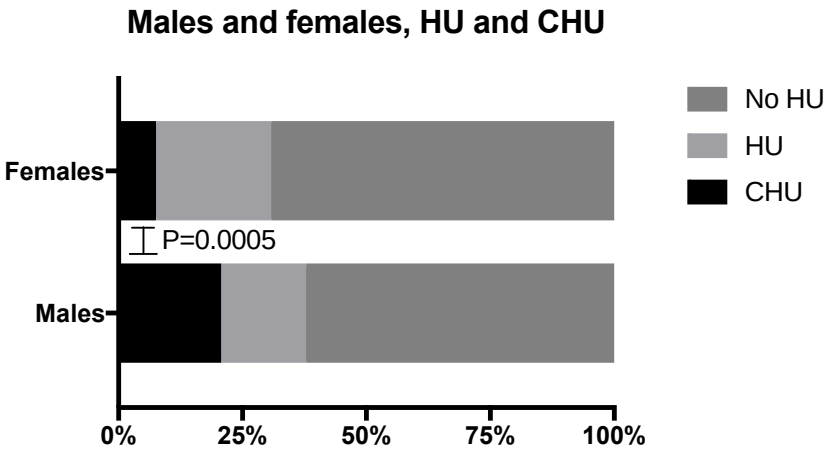

Figure 5. Hyperuricemia (HU) and clinically significant hyperuricemia (CHU) among the male and female patients. Number of males 140, number of females 198. Tested with Chi Square. Significant difference in prevalence of CHU between males and females. P=0.0005.

The difference in CHU was due to high number of patients with gout among the males. The prevalence of HU or CHU was similar between males and females with non-gout diagnosis (HU: 28/110 vs. 51/187, P=0.74. CHU: 12/110 vs. 11/187, P=0.13).

Prevalence of HU and uric acid levels is similar in RA and other rheumatic diseases, with the exception for gout

When comparing the prevalence of HU in RA to other rheumatic diseases, there was no significant difference, except for gout. Patients diagnosed with gout had higher prevalence of HU than patients diagnosed with RA (P<0.0001, for both males and females, figure 6). Male patients with gout also had higher prevalence of CHU than male patients with RA. There was no such significant difference in CHU seen among females with gout compared to females with RA (6/56 vs 4/12, P=0.079).

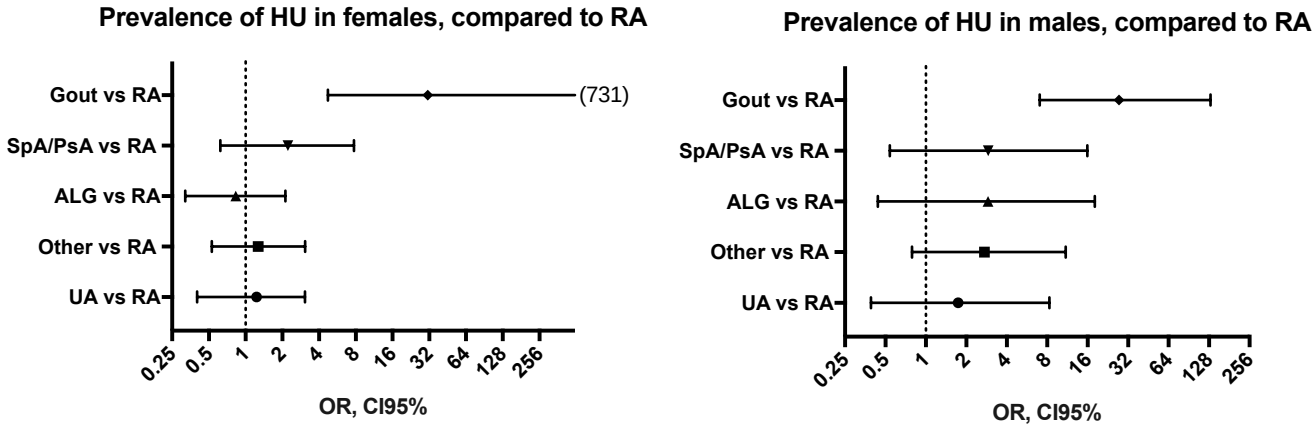

Figure 6. Prevalence of hyperuricemia (HU) in patients with different diagnoses. HU was significantly more prevalent in gout compared to RA. Other diagnoses were similar in prevalence of HU compared to RA. Males (n=140), females (n=198). RA, rheumatoid arthritis; Spa, spondyloarthritis; PsA, psoriasisarthritis; ALG, arthralgia; UA, undifferentiated arthritis; OR, odds ratio; CI, confidence interval.

Uric acid was not connected to RF, aCCP and survivin

In total, 25 males and 33 females were positive for the RA-specific antibodies RF and/or aCCP (AB+), and 98 females and 55 males were positive for survivin (Surv+). The patients were divided into groups based on antibody and survivin positivity and the levels of uric acid were compared. The groups were very similar, there was no connection seen between aCCP, RF, survivin and prevalence of hyperuricemia in non-gout patients or gout-patients (figure 7). There was further no connection between antibodies, survivin and uric acid levels (ANOVA for males P=0.80, for females P=0.97).

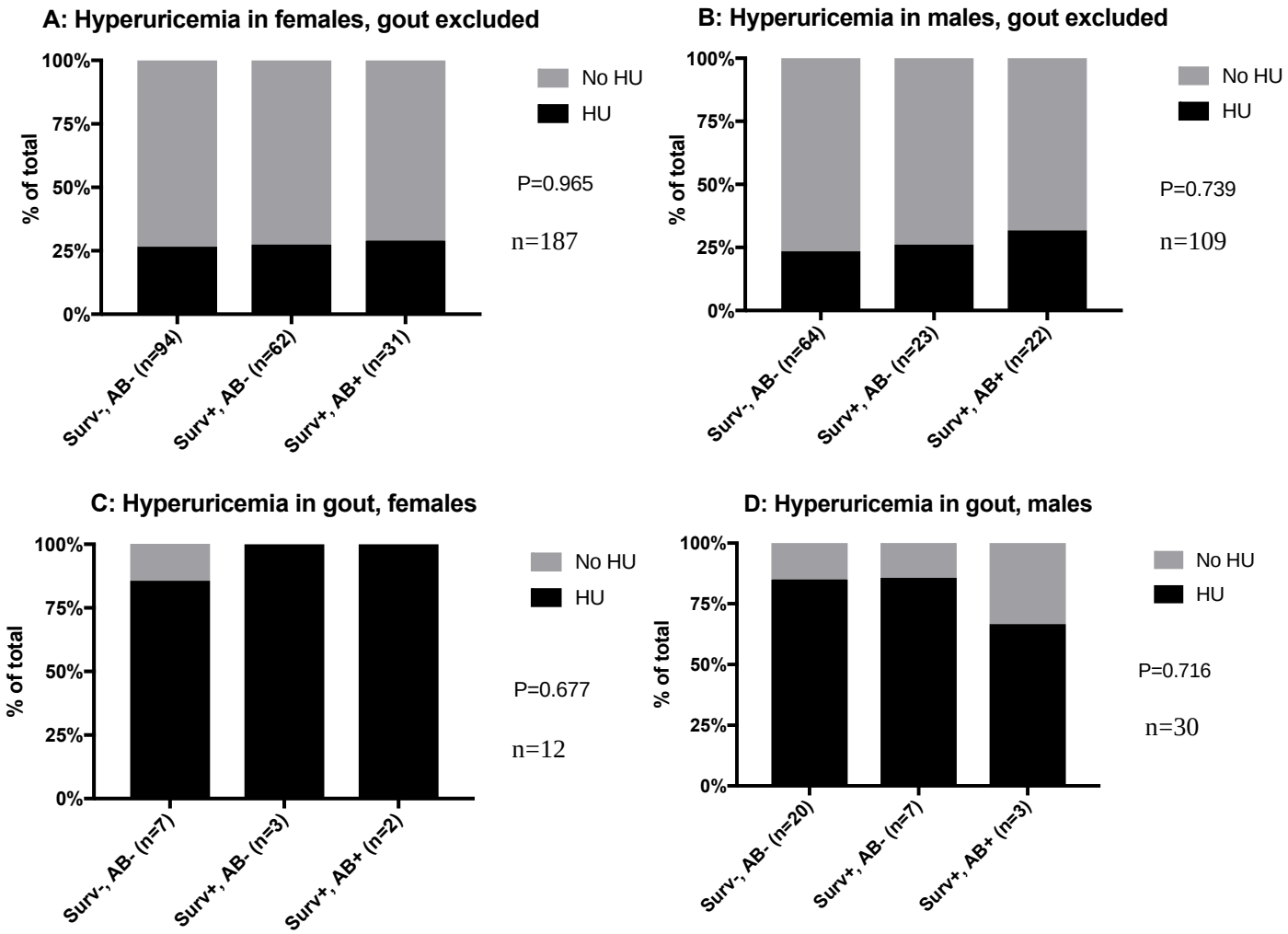

Figure 7. Prevalence of hyperuricemia (HU) depending on antibodies and survivin. Males and females are analysed separately. Patients with gout are not included in picture A and B. No significant difference in prevalence of HU was seen, Chi square test for males P=0.739, for females P=0.965. C and D shows gout-patients. Surv, survivin; AB, antibodies; HU, hyperuricemia.

Among the 84 patients diagnosed with RA were 65% females, and 37 patients (44 %) were positive for RF and/or aCCP. 51 patients (61 %) were positive for survivin. There was no significant difference in uric acid levels (ANOVA for males P=0.56, for females P=0.57) or prevalence of HU (Chi Square test, P>0.05 for both males and females) in the groups with high and low levels of antibodies or of survivin.

All seropositive patients were divided into groups depending on antibodies (positive RF or positive aCCP, both positive RF and aCCP and negative) (table 2). There was no significant difference in uric acid levels depending on antibodies (ANOVA for males P=0.49, for females P=0.62). Moreover, there was no significant difference in prevalence of HU (Chi Square test for males P=0.72, for females P=0.53) or CHU (Chi Square test for males P=0.81, for females P=0.80).

Table 2. Comparing patients positive for aCCP or RF (n=40), patients positive for aCCP and RF (n=18) and patients negative for aCCP and RF (n=280). HU, hyperuricemia; CHU, clinically significant hyperuricemia; AB, antibodies; RF, rheumatoid factor; aCCP, anti-cyclic citrullinated peptide antibody; IQR, interquartile range.

	Males			Females		
	Uric acid, median [IQR]	HU, n/total	CHU, n/total	Uric acid, median [IQR]	HU, n/total	CHU, n/total
aCCP+ or RF+ n=40	386 [308-440]	7/17 (41%)	4/17 (24%)	285 [240-334]	9/23 (39%)	1/23 (4%)
aCCP+ and RF+ n=18	336 [296-380]	2/8 (25%)	1/8 (13%)	238 [223-283]	2/10 (20%)	1/10 (10%)
AB- n=280	373 [300-459]	44/114 (36%)	24/114 (21%)	267 [224-316]	51/166 (31%)	13/166 (8%)

Uric acid level and age correlates in females

In females there was a significant correlation between uric acid level and age (figure 8). At a higher age the uric acid levels tended to be higher as well (P<0.0001 and R=0.355). There was no significant correlation between uric acid and age seen among males.

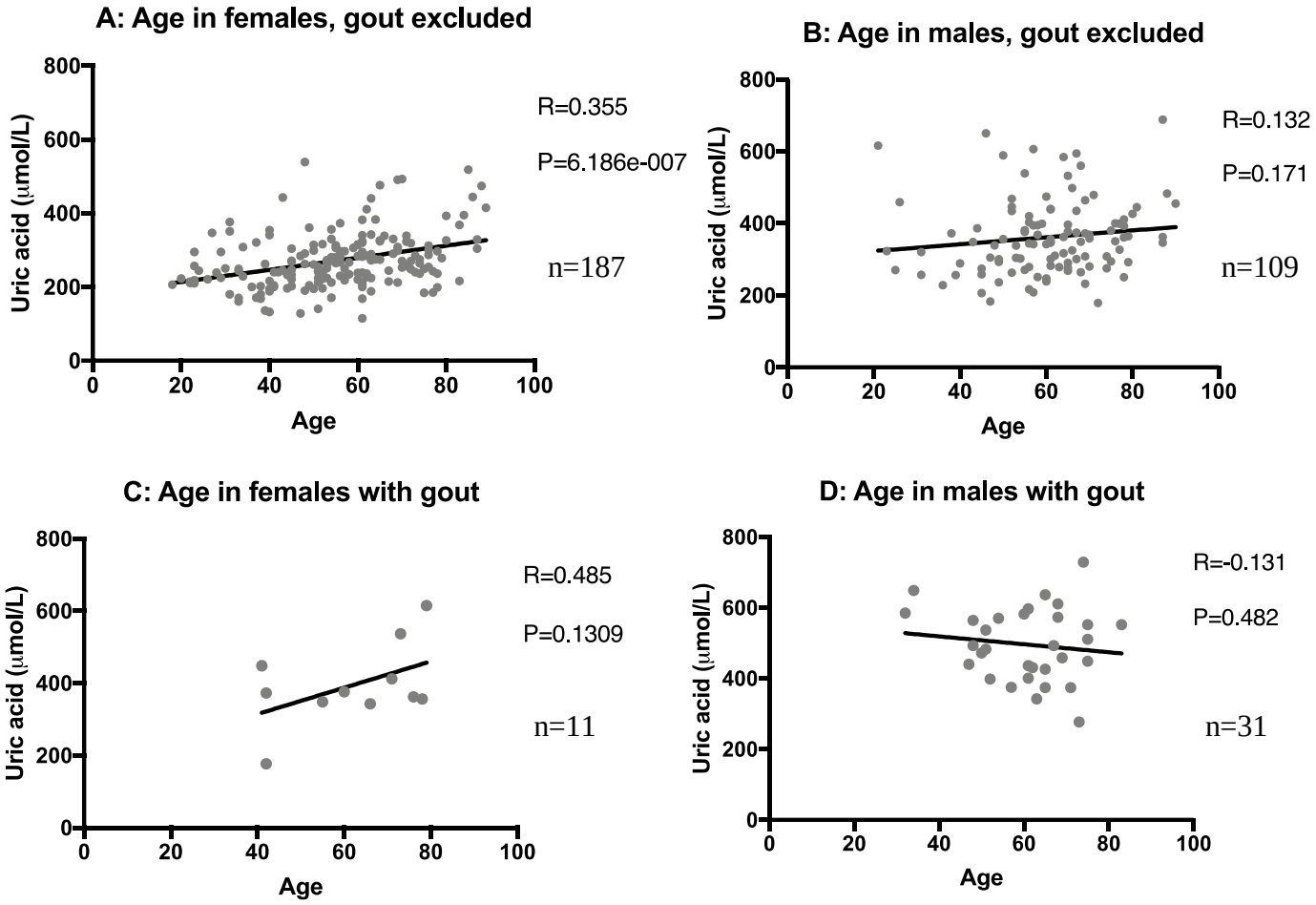

Figure 8. Male and female patients, serum uric acid level and age, correlation tested with Pearson. In A and B, gout-patients are excluded, in C and D, only gout-patients are included. A significant correlation was seen in A (R=0.355, P<0.0001). N, number of patients.

RA was the most common diagnosis among the female patients with CHU

Among all patients with CHU, gout was the most common diagnosis among males, but not among females (figure 9). Among females, instead, RA was the most common diagnose. 40 % of all female patients with CHU were diagnosed with RA, this compared to 27 % of the female patients who were diagnosed with gout. Furthermore, 20% of females and 24 % of males with CHU had other diagnoses.

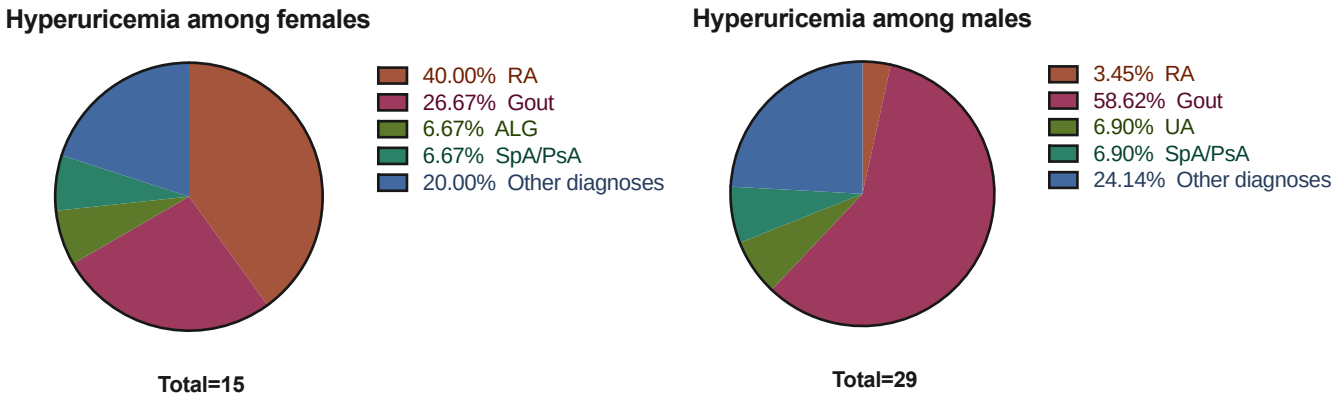

Figure 9. Distribution of patients with clinically significant hyperuricemia by diagnoses. Females (n=198) to the left and males (n=140) to the right. The most common diagnosis was gout among males (59 %) and RA among females (40 %). RA, rheumatoid arthritis; UA, undifferentiated arthritis; ALG, arthralgia; SpA, spondyloarthritis; PsA, psoriasisarthritis.

Clinical symptoms in gout and rheumatoid arthritis

Using the symptoms of gout collected from medical records, patients diagnosed with gout were compared to patients diagnosed with RA (Table 3). The gout patients had significantly higher gout score than RA-patients, both males and females ($P=0.0006$ for females, $P<0.0001$ for males, figure 10). It was not possible to retrieve information about all patients in the medical records. To investigate whether the information about the patients from the medical records were representative for the whole material, the patients included and the patients not included at the medical records were compared by age, gender, uric acid levels and presence of autoantibodies. There was no significant difference between the groups in any aspect.

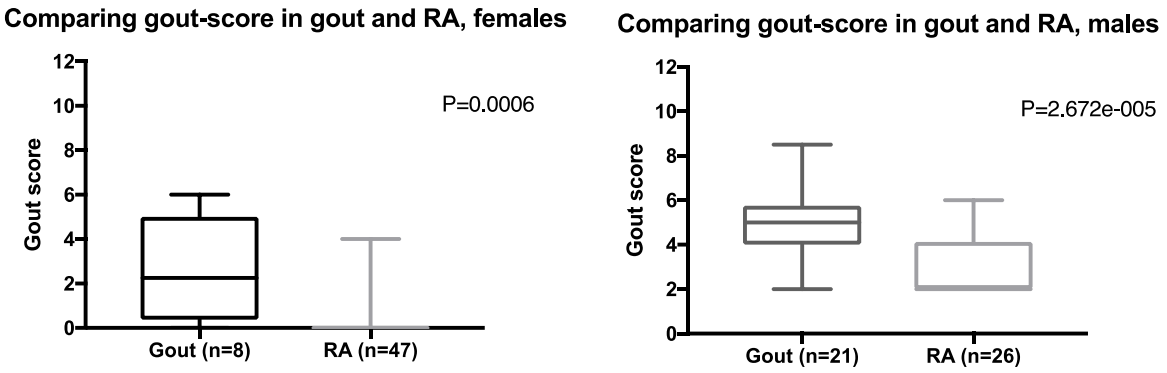

Figure 10. Comparing gout score in gout and RA patients using Mann-Whitney test. Significantly higher points in gout-patients, females P=0.0006, males P<0.0001. RA, rheumatoid arthritis.

When comparing the individual criteria of the gout diagnostic rule there was significant difference between gout and RA in five of seven criteria (table 3, figure 11).

Table 3. Comparing the individual criteria of the gout diagnostic rule among patients diagnosed with gout (n=29) and RA (n=73). RA, rheumatoid arthritis; MTP, metatarsophalangeal joint.

	Gout	RA
Previous gout attack	20/29 (70 %)	1/73 (1 %)
Serum uric acid level>350 µmol/L	26/29 (90 %)	18/73 (25 %)
Joint redness	3/29 (10%)	1/73 (1 %)
Male sex	21/29 (72 %)	26/73 (36 %)
Hypertension or ≥ cardiovascular diseases	10/29 (34 %)	8/73 (11 %)
Onset within 24 h	9/29 (31 %)	7/73 (10 %)
MTP1 involvement	9/29 (31 %)	10/73 (14 %)

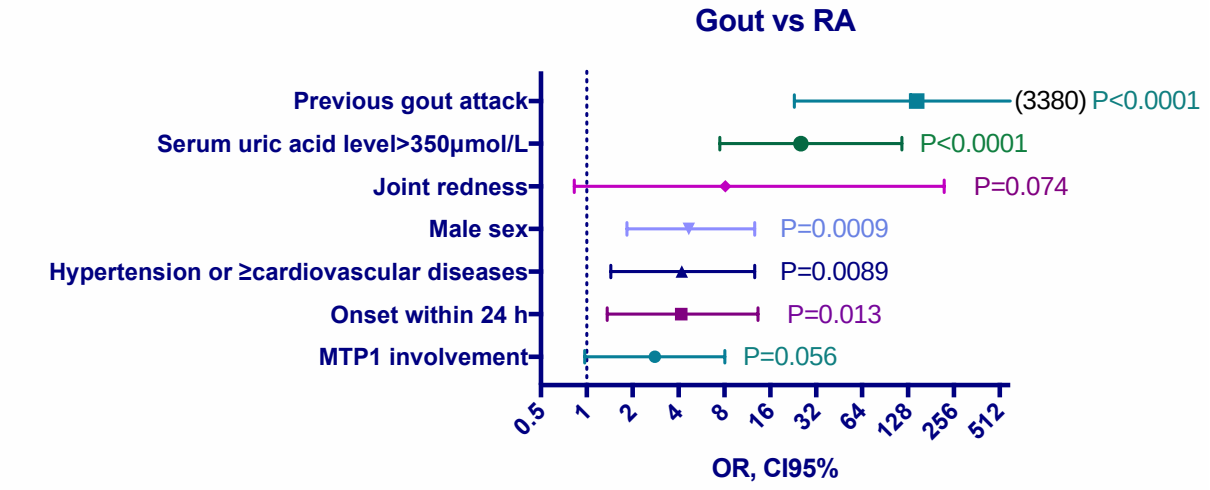

Figure 11. Comparing gout diagnostic rule among patients diagnosed with gout (n=29) and RA (n=73). RA, rheumatoid arthritis; MTP, metatarsophalangeal joint.

Among RA patients there was a significant correlation between uric acid level and gout score (P<0.0001, R=0.7479, figure 12). Among gout patients it was more common with higher gout score at a higher uric acid level as well, but this correlation was not significant (P=0.0534, R=0.362).

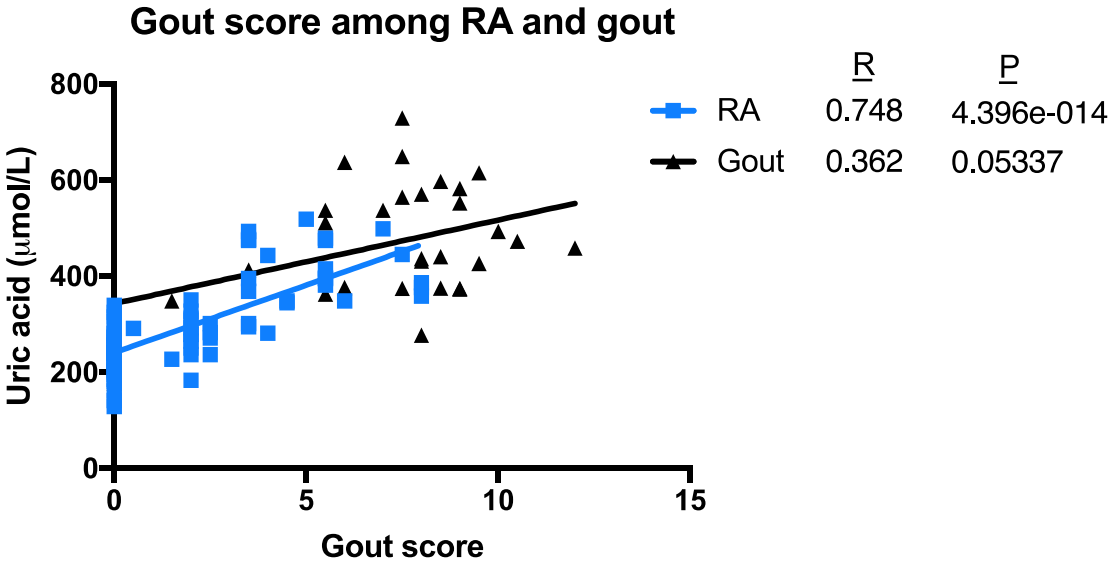

Figure 12. Correlation between gout score and uric acid in RA and gout, tested with Pearson. RA shown in blue and gout in black. R value 0.748 for RA, 0.362 for gout. RA, rheumatoid arthritis.

In total, nine patients diagnosed with gout medicated with allopurinol at the time their uric acid level was measured. When comparing gout score among gout-patients who medicated with Allopurinol with gout-patients who did not medicate with allopurinol there was no significant difference between the groups (Mann Whitney, P=0.356). According to medical records, none of the patients diagnosed with RA were using allopurinol at the time of the blood test.

Discussion

In this study the levels of uric acid were investigated in respect of gender, age, diagnosis, autoantibodies and survivin, particularly in connection to RA. Taken together, the analysis showed that RA patients had neither significantly different levels of uric acid than patients diagnosed with other rheumatic diseases, with the exception for gout, nor did the uric acid levels vary depending on aCCP, RF or survivin. Although RA was the most common diagnosis among female patients with hyperuricemia, the symptoms indicating gout were significantly more common among patients diagnosed with gout.

In contrary to the results reported by Petsch et al. [18], we observed no significant difference in uric acid levels depending on autoantibodies. Patients positive for RF had a prevalence of HU comparable to the patients negative for RF. Neither were there any difference depending on aCCP or survivin. However, this study did not include assessment of urate deposits in tissues, which had been found more often in patients negative for RF than in RF-positive [18]. One hypothesis was that even marginally elevated uric acid levels, but within today's reference range, could correlate with autoantibodies or survivin, but we did not see this either.

One of our initial hypotheses was that hyperuricemia in RA could be a sign of the underlying cell cytotoxicity occurring in RA, similar to cell destruction in tumour lysis syndrome [26]. To investigate this, we compared the uric acid levels among six groups with different rheumatic diagnosis. The results from this study shows that HU does not seem to be an essential part of cell destruction in RA more than other rheumatic diseases. On the contrary, there was no significant difference in uric acid level or prevalence of hyperuricemia depending on disease, apart from gout. Some patients with RA have hyperuricemia, but not more than patients with, for instance, arthralgia. Thus, the levels of uric acid do not seem to

be a marker for cell destruction or a part of a destruction mechanism in RA. To be noted, this study did not measure on going cell damage. To understand how uric acid might be connected to cell damage it would have to be further investigated, for example by measuring a marker for on going cell destruction. One potential marker could be lactic dehydrogenase which is released from damaged cells and was proposed to predict joint damage in RA [27], but this marker is not reliable in clinical practice. Further studies are needed in this subject to investigate it. Another interesting aspect would be to include a group of healthy individuals to compare with.

Among all patients with hyperuricemia, RA was the most common diagnosis among females. Although it is to be noted that the number of females with RA was higher than the number of female patients with gout included in this study, this was an interesting find. We hypothesized that it could potentially mean that patients diagnosed with RA are less prone to be examined for the signs of gout. Therefore, gout might be underdiagnosed in patients with RA. Also, symptoms of RA may mask symptoms of gout, and further postpone the diagnosis. It has been reported that coexisting RA and gout in the same patient is more common than what was previously believed, and that gout does occur in RA patients, but at a lower incidence than the general population [23].

An underlying hyperuricemia/gout in a patient with RA is problematic, it could postpone the diagnosis of RA for years if the symptoms are interpreted as gout [28]. To address this issue, we performed a retrospective analysis of the medical records of the first visit of patients with RA and gout. The purpose of the medical records analysis was to investigate whether clinical symptoms of gout were similar in patients diagnosed with RA and with gout. The result of this analysis clearly showed that the patients diagnosed with RA had significantly less

symptoms of gout, than patients diagnosed with gout. When comparing the criteria of separately, all seven criteria of the gout diagnostic rule showed less symptoms of gout in RA, with significantly less symptoms in five criteria. In conclusion, RA patients did not have similar symptoms as gout. However, RA-patients with a higher uric acid level had more symptoms of gout, with a significantly higher gout score. Therefore, one can hypothesise that uric acid has an impact on the symptoms in RA-patients, even with no gout-diagnosis. We can also conclude that uric acid level is a good predictor of gout score in RA-patients.

The correlation between age and uric acid found in this study could only be seen among females. This correlation allows suggestion that age, and not the clinical signs, is the major indicator for hyperuricemia in female RA-patients. The correlation between age and uric acid is also in line with previous studies, reporting that females have a difference in uric acid levels depending on age, with lower oestrogen level at a higher age resulting in higher uric acid level. It has been proposed that a decline in oestrogen levels could be connected to hyperuricemia [29]. This would explain why only females showed an age correlation between uric acid and age in our study (figure 8), and why this correlation was not seen among males.

Methodological considerations

Several limitations of this study should be appreciated. First, in this study hyperuricemia was the measured outcome, via measurement of uric acid levels in serum. Hyperuricemia does not necessarily mean that crystallization of uric acid has occurred, and therefore it is unclear if the symptoms are caused by uric acid, even if the uric acid level is elevated. A recently introduced way to diagnose gout is Dual Energy CT (DECT). DECT uses X-ray beams of two types of energy and can detect monosodium crystal deposits in tissue non-invasively with a low radiation dosage. It was reported to be a very good and effective screening method for

crystal deposits [18]. DECT was not used in this study, and to be sure of which patients have monosodium crystal deposits, and which symptoms are due to gout, DECT should be used. Secondly, according to the inclusion criteria, all patients were required at least one measured uric acid level, therefore the material might have been biased to patients who one way or another had a blood test analysed in respect of uric acid. Also, the diagnosis was determined in association to the blood test which means that later development of the disease was not taken into consideration. Moreover, the diagnoses were based on the ICD-code which was determined by each treating doctor, and the basis for selection of ICD-code is not fully standardised. Lastly, we did not have information about all factors which potentially could affect uric acid levels, for example body mass index and current medicines. It has been proposed that therapy with methotrexate might lower uric acid levels, due to an inhibition of enzymes in the purine metabolism, and an accumulation of adenosine as a consequence. It has been shown that patients treated with methotrexate had lower uric acid levels. It was also found that the patients with lower uric acid levels due to methotrexate treatment had better clinical status [30]. Information about the use of methotrexate was not collected for this study, and since this was a cross sectional study, collecting the data retrospectively would not produce any useful result. This might be a source of error and is also an interesting aspect of the connection between uric acid and RA which should be investigated further in future studies.

Conclusions

Prevalence of HU and uric acid levels are similar in RA and other rheumatic diseases, with the exception for gout. Moreover, there was no significant connection between levels of uric acid and RF, aCCP and survivin. Prevalence of CHU is higher among males than females and in the female patients with CHU, RA was the most common diagnosis. The levels of uric acid also correlated positively to the age of female patients.

In a wider perspective, this study contributes to the research field of rheumatoid arthritis and its connection to uric acid which was previously rather unexplored with only a few studies addressing the issue. Our study also supports the use of gout diagnostic rule for clinical diagnosis of gouty arthritis in primary care when joint fluid analysis is not available, which can be a helpful tool in the clinic.

Populärvetenskaplig sammanfattning på svenska: Uratvärden hos patienter med ledsjukdom

Gikt och reumatoid artrit är två reumatiska sjukdomar som båda drabbar allt fler människor i Sverige. Gikt beror på att ämnet urat ansamlas i blodet vilket kan göra att kristaller av urat bildas. Om dessa kristaller ansamlas i leder kan detta leda till snabbt påkommande rodnad, svullnad och svår smärta. Det är framförallt vanligt att stortån drabbas. En gikt-attack går i regel över inom några veckor. Reumatoid artrit beror på att immunsystemet reagerar mot strukturer i kroppens egna celler och detta orsakar svullnad, ömhet, stelhet och smärta i leder. Vid reumatoid artrit är det vanligt att ha autoantikroppar, vilka är proteiner som ingår i kroppens immunförsvar och som riktar sig mot strukturer i kroppens egna celler vilket orsakar skada. I denna studie undersöktes kopplingen mellan urat-värde i blodet, ledsjukdomar såsom reumatoid artrit och gikt, samt autoantikroppar. Man har i tidigare studier sett att patienter med reumatoid artrit och högt urat kan ha en något lindrigare sjukdom. Man har även sett att det är vanligare med förhöjt uratvärde i blodet hos patienter med reumatoid artrit som är positiva för autoantikroppar än patienter som är negativa för autoantikroppar.

Totalt 338 patienter inkluderades i studien. Samtliga patienter hade någon typ av ledbesvär och hade besökt reumatolog på Sahlgrenska universitetssjukhuset. Alla hade dessutom minst ett uppmätt uratvärde. Patienterna analyserades utifrån diagnos, kön, uratvärde och förekomst av autoantikroppar. Utöver detta studerades symtom vid besök till reumatolog hos 152 patienter utifrån det diagnostiska hjälpmedlet för giktdiagnos för att ta reda på vilka patienter som hade symtom tydande på gikt.

Enligt våra resultat har inte urat-värden någon koppling till autoantikroppar vid reumatoid artrit. Man kan inte heller se att patienter med reumatoid artrit skulle ha högre urat-nivåer i blodet än patienter med andra ledsjukdomar. Däremot sågs, som förväntat, högre uratnivåer hos män än hos kvinnor samt hos patienter diagnosticerade med gikt. Bland kvinnliga patienter med förhöjda uratnivåer var den vanligaste diagnosen reumatoid artrit, men det diagnostiska hjälpmedlet för giktdiagnos visade inte på att det skulle vara vanligare med gikt-symtom bland patienter med reumatoid artrit än patienter med gikt.

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