Factors Associated with Musculoskeletal Disability and Chronic Renal Failure in Clinically Diagnosed Primary Gout

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ABSTRACT. ***Objective***. To assess the association between a set of sociodemographic, clinical, and biochemical variables and the presence of musculoskeletal (MSK) disability and chronic renal failure in patients with primary gout defined using Wallace criteria.

Methods. Subjects were 90 patients with primary gout (98% male, age 54 ± 12 years, 11.3 ± 9.8 years with gout). A cohort nested case-control design was used. Analysis was done of the association between MSK disability or renal failure and a series of variables: age; duration of gout; body mass index; education level; income; serum glucose, cholesterol, triglycerides, and uric acid; Health Assessment Questionnaire score; obesity; family history of gout; high blood pressure; alcoholism; smoking habit; presence of tophi; ischemic cardiopathy; and use of colchicine, glucocorticoids, nonsteroidal antiinflammatory drug, or allopurinol.

Results. Forty-two patients (47%) had MSK disability, and 25/80 (31%) had renal failure. On logistic regression, presence of tophi (relative risk 4.3, 95% confidence interval 1.2–15.1), hypertriglyceridemia (RR 3.4, 95% CI 1.1–10), and history of ischemic heart disease (RR 8.3, 95% CI 1.6–41) were associated with MSK disability. Patient age was the only variable associated with renal failure.

Conclusion. Optimal medical control of gout and its comorbidities may improve prognosis of gout, as suggested by our findings, in which a marker for poorly controlled gout such as presence of tophi in addition to high blood triglyceride levels and ischemic heart disease were associated with MSK disability. Older age was the only factor associated with renal failure, although this may only reflect declining renal function in the elderly. (J Rheumatol 2005;32:1923–7)

Key Indexing Terms:
GOUT PROGNOSIS PROGNOSTIC FACTORS
RENAL FAILURE MUSCULOSKELETAL DISABILITY

Gout encompasses a heterogeneous group of disorders characterized by hyperuricemia, recurrent arthritic attacks, nephropathy, and aggregates of sodium urate monohydrate crystals (tophi) in and around joints[1]. It is viewed as a systemic disease, but the main organ damage targets the musculoskeletal (MSK) system and kidney. When patients with gout do not receive proper medical attention, the pattern of early intermittent arthropathy progresses to persistent and progressive joint disease and eventually to different degrees of physical disability[1,2]. In the kidney, gout can cause at least 3 types of nephropathy: nephrolithiasis, interstitial kidney disease, and uric acid crystal-mediated intrarenal obstructive uropathy. The first 2 can progress to chronic endstage nephropathy[3].

Despite gout's morbidity and mortality in the affected population, little research has been done on its prognosis. Reviews of chapters on gout in major rheumatology textbooks show no sections specifically addressing prognosis[1–5]. In addition, a Medline database search using the terms "gout," "prognosis," and "prognosis factors" in the title field produced only 9 entries, just one in English, and only 3 were original research[6-14]. One of the only studies in the area is by Darmawan, *et al*, who reported on the effects of adequate medical control and the deleterious impact of self-medication on the longterm outcome of a cohort of gout patients[15]. Clearly, the body of knowledge on gout prognosis and prognostic factors needs reappraisal and updating. In response, we used a cohort nested case-control design to evaluate the association between a set of sociodemographic, clinical, and biochemical variables and the presence of the 2 principal gout prognostic outcomes (MSK disability and

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chronic renal failure) in a group of patients with clinically diagnosed primary gout.

MATERIALS AND METHODS

Patients. Subjects were selected from the gout cohort in the Rheumatology Service of Ignacio García Téllez Specialties Hospital, Mexican Institute of Social Security, Mérida, Mexico. The cohort was assembled in 1999 by recruiting gout patients from all primary care medical units in the city of Mérida. All patients in the cohort are given a followup visit at the Rheumatology Service of García Téllez Hospital every 6 months. The main inclusion criterion was a diagnosis of gouty arthritis based on Wallace criteria[16]. Subjects with secondary gout were not included. All subjects without a categorization of MSK disability or renal failure were excluded.

Measurements. MSK physical disability was defined as an American College of Rheumatology (ACR) functional class of II or higher[17], or a score higher than 0.5 on the physical domain of a validated Spanish-language version of the Health Assessment Questionnaire (HAQ)[18]. Renal failure was defined as moderately or severely diminished glomerular filtration rate (GFR; < 60 ml/min/1.73 m^2), based on the National Kidney Foundation criteria[19,20]. Glomerular filtration rate values were estimated using an equation as follows[21]:

$$\text{GFR} = 186.3 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ for women}) \times (1.21 \text{ if African American})$$

The variables analyzed as predictors of MSK disability and renal failure were a history of alcoholism, smoking habit, diabetes, hypertension, and ischemic heart disease (IHD), as determined by interviews with patients. Data were also obtained for hyperlipidemia (defined as abnormally high levels of total serum cholesterol or triglycerides); obesity (defined as body mass index > 30); urolithiasis (diagnosed by a history of passing kidney stones or gravel, or a kidney stone detected by ultrasound for patients with a negative history of stones); presence of tophi; use of nonsteroidal antiinflammatory drugs (NSAID); chronic colchicine and glucocorticoid treatment; family history of gout; dose of allopurinol needed to maintain a serum uric acid level < 7 mg/dl; blood uric acid levels without allopurinol treatment; total cholesterol; triglycerides and glucose; years of gout evolution; age at onset of gout symptoms; income (US dollars); and years of formal education. All these data were obtained through patient interviews or the cohort database.

Methods. All subjects were interviewed by a researcher who clinically examined them and surveyed all relevant study data. All other data were obtained from the Gout Cohort database.

Every subject gave signed informed consent and the protocol was approved by the Ignacio Garcia Téllez Specialties Hospital Research and Ethics Committee.

Statistical methods. Chi-square test with Yates' correction or Fisher's tests was used to compare categorical variables. Numerical variables were compared using the unpaired t test. Statistical significance was set at 0.05. All variables with a significant p value in the univariate analysis were entered into a stepwise logistic regression model for which all numerical variables were transformed to categorical variables. For the univariate analysis, data were collected and analyzed using SPSS for Windows (v. 7.5; SPSS Inc., Chicago, IL, USA), and multivariate analysis was done using the Epistat statistical package.

RESULTS

The study population consisted of 90 primary gout patients (88 men, 98%) with an average age of 54 ± 12 years (range 22–81). Subjects were an average age of 42 ± 11 (range 15–71) years when first clinically diagnosed with gout, and had had the disease an average of 11.3 ± 9.8 (range 2–40) years. Forty-two (47%) were found to have MSK disability, and of these, 36 (40%) were found to be in the ACR functional class II and 6 (7%) in ACR functional class III. Average HAQ score for the MSK disability patients was 0.17 ± 0.21, whereas nondisability patients had a score of 0.02 ± 0.0004 ($p < 0.0001$). Renal function could be assessed in 80 subjects, and 25 (31%) of these met criteria for renal failure. Of the renal failure patients only one had symptomatic renal failure requiring dialysis treatment.

In univariate analysis, MSK disability was associated with presence of tophi, daily requirement for NSAID, chronic glucocorticoid treatment, a history of IHD, older patient age, low formal education level, and higher serum triglyceride level (Tables 1 and 2). After these variables were entered into a logistic regression model only presence of tophi, hypertriglyceridemia, and history of IHD remained statistically associated with MSK disability (Table 3).

Older patient age was the only variable statistically associated with development of renal failure in the univariate phase analysis, meaning a logistic regression was not needed for analysis of results (Tables 4 and 5).

DISCUSSION

Although the regional prevalence of gout varies widely (1%–26%) and seems to depend on race or ethnicity, it is consistently one of the most prevalent rheumatic diseases worldwide, and the most frequent cause of arthropathy in middle-aged men[1-5]. In an open adult population survey in Mexico using the WHO-ILAR COPCORD questionnaire, gout was identified as the fourth most prevalent rheumatic disease, with a 0.4% point prevalence[22]. It leads to rheumatic symptoms and can produce significant morbidity and mortality from several forms of kidney disease. In other words, the 2 main prognostic outcomes of gout are MSK disability and renal failure. As for treatment, keeping serum uric acid concentrations lower than 5 mg/dl has been shown to change longterm prognosis in gout patients[1,4,5,15], but there is little original research assessing the influence of other nontherapeutic factors (e.g., sociodemographic, clinical, and biochemical factors) on prognosis of gout.

A cohort design study assessing factors associated with gout prognostic results would be ideal. However, this type of study is difficult because of the challenge of assembling an incipient cohort and the longterm followup time needed for meaningful results. Given these difficulties, we decided to address the issue using subrogates, such as a cohort nested case-control design.

A wide array of variables was analyzed, including sociodemographic, clinical, and biochemical factors that are clearly gout related or have been associated with other diseases. Clinical features such as blood uric acid level, tophi, nephrolithiasis, gout duration, and age at onset of gout, as well as non-gout features such as alcoholism, have been suggested as direct or indirect markers of more severe, protracted disease or interference with treatment[1-5]. As a result, they were included in our evaluation of gout prognostic fac-

Table 1. Analysis of categorical variable association with MSK disability in gout.

Variable	Disability (%)	No Disability (%)	p
Obesity	33/42 (78)	34/48 (70)	0.27
Family history of gout	13/42 (30)	16/48 (33)	0.49
Diabetes	3/42 (7)	3/48 (6)	1.00
High blood pressure	21/42 (50)	19/48 (39)	0.21
Urolithiasis	17/42 (40)	14/48 (29)	0.24
Alcoholism (moderate/severe)	41/42 (98)	44/48 (92)	0.22
Smoking habit	14/42 (33)	17/46 (40)	0.44
Hyperlipidemia	29/42 (69)	29/48 (60)	0.26
Presence of tophi	18/42 (42)	8/48 (17)	0.006
Colchicine use	27/42 (64)	23/48 (48)	0.08
Chronic glucocorticoid treatment	14/42 (33)	6/48 (12)	0.01
NSAID daily requirement	8/42 (19)	1/48 (2)	0.009
Allopurinol > 300 mg/day to maintain serum urate < 7 mg/dl	8/42 (19)	7/47 (15)	0.79
Ischemic heart disease	16/42 (38)	3/48 (6)	0.0001

Table 2. Analysis of association of numerical variables with MSK disability in gout*.

Variable	Disability (%)	No Disability (%)	p
Patient age, yrs	57 ± 11	52 ± 12	0.01
Age at clinical diagnosis of gout, yrs	45 ± 10.8	40 ± 11.5	0.33
Gout duration, yrs	12.5 ± 11	10.3 ± 8.6	0.31
Body mass index	31 ± 4.6	30 ± 5.3	0.36
Years of formal education	7.3 ± 2.7	9.5 ± 3.9	0.003
Monthly income, US$	441 ± 118	478 ± 150	0.26
Serum glucose, mg/dl	108 ± 30	96 ± 13	0.39
Total cholesterol, mg/dl	210 ± 46	198 ± 42	0.23
Serum triglycerides, mg/dl	331 ± 218	221 ± 113	0.005
Serum uric acid, mg/dl	7.8 ± 1.9	7.2 ± 1.8	0.14

* Mean ± standard deviation.

Table 3. Analysis of variable association with MSK disability in gout; results after logistic regression.

Variable	Relative Risk	95% CI
Presence of tophi	4.3	1.2–15.1
Chronic glucocorticoid use	1.7	0.4–6.5
Daily NSAID requirement	1.6	0.3–78
Ischemic heart disease	8.3	1.6–41
Patient age	1.0	0.3–3.0
Education level	2.7	0.8–8.7
Hypertriglyceridemia	3.4	1.1–10

tors. Sociodemographic variables have been shown to influence prognosis of a group of chronic rheumatic and nonrheumatic diseases. For instance, low formal education level correlates with a poorer prognosis for back pain, hypertension, cardiovascular diseases, peptic ulcer, diabetes, and chronic lung diseases[23,24]. In rheumatoid arthritis, low formal education level has been identified as an independent prognostic factor for mortality and poor functional outcome[25-28], in addition to biological factors such as number of swollen joints, functional status at onset, and acute phase reactants[29]. Another example is that sociodemographic variables such as sex, race, income, and lack of medical insurance, as well as disease-specific biologic variables, are correlated with prognosis in systemic lupus erythematosus[30-35]. These findings justify inclusion of relevant sociodemographic variables in the prognosis assessment of a chronic rheumatic disease such as gout. Finally, assessments of chronic comorbidities such as diabetes, hypertension, IHD, and obesity are required variables in any chronic disease prognosis evaluation study and were included in this evaluation.

The multivariate analysis showed that presence of tophi, high blood triglyceride levels, and a history of IHD were independent factors associated with development of MSK disability in patients with primary gout. The association found between presence of tophi and MSK disability may be explained as the result of inadequate disease control, because development of tophi is known to be a consequence of persistent hyperuricemia[1]. Darmawan, *et al*[15] support this in a recent report on a Malayo-Polynesian gout patient cohort with a 10-year followup, in which they found an association between lack of patient compliance with a urate-lowering therapeutic regime and increased morbidity, mortality, and disability.

Table 4. Analysis of categorical variable association with renal failure in gout.

Variable	Renal Failure (%)	No Renal Failure (%)	p
Obesity	18/25 (72)	43/55 (78)	0.54
Family history of gout	7/25 (28)	20/55 (36)	0.46
Diabetes	1/25 (4)	4/55 (7)	0.57
High blood pressure	14/25 (56)	23/55 (41)	0.23
Urolithiasis	12/25 (48)	17/55 (30)	0.14
Alcoholism (moderate/severe)	24/25 (96)	52/55 (94)	0.78
Smoking habit	9/25 (36)	20/54 (37)	0.92
Dyslipidemia	16/25 (64)	38/55 (69)	0.65
Presence of tophi	9/25 (36)	13/55 (23)	0.25
Chronic colchicine use	11/25 (44)	35/55 (63)	0.10
Chronic glucocorticoid use	5/25 (20)	15/55 (27)	0.48
Daily NSAID requirement	4/25 (16)	5/55 (9)	0.36
Allopurinol > 300 mg/day to maintain serum urate < 7 mg/dl	6/25 (24)	9/55 (36)	0.41
Ischemic cardiopathy	6/25 (24)	12/55 (21)	0.82

Table 5. Analysis of numerical variable association with renal failure in gout*.

Variable	Renal failure	No Renal Failure	p
Patient age, yrs	59 ± 11	52 ± 11	0.03
Age at clinical diagnosis of gout, yrs	45 ± 13	42 ± 10	0.34
Gout duration, yrs	13 ± 10	10 ± 9	0.24
Body mass index	29 ± 3	30 ± 4	0.35
Years of formal education	7.9 ± 3.0	8.8 ± 3.6	0.34
Monthly monetary income, US$	442 ± 97	464 ± 149	0.55
Serum glucose, mg/dl	108 ± 37	99 ± 14	0.10
Total cholesterol, mg/dl	201 ± 44	205 ± 46	0.73
Serum triglycerides, mg/dl	319 ± 220	263 ± 166	0.21
Serum uric acid, mg/dl	7.2 ± 2.1	7.7 ± 1.8	0.28
HAQ score	0.14 ± 0.29	0.08 ± 0.07	0.15

* Mean ± standard deviation.

Several reports suggest a pathogenetic link between IHD, hyperlipidemia, and gout[36-38], but no published data exist on the association between IHD and hyperlipidemia and a gout prognosis outcome such as MSK disability. Given the lack of data, this prognostic association can only be explained as the result of a subrogated prognostic marker phenomenon, or coincidence.

Older patient age was the only variable shown to be associated with chronic kidney failure in this study. This finding probably does not indicate a real prognostic association with gout because previous reports show a decline in kidney function as patient age increases[20].

Some qualifying factors may affect this study. The results may have a certain bias because gout diagnosis was not based on synovial fluid analysis, and due to some of the variable definitions (i.e., diagnosis of IHD by case history). The study population can also be seen as a survival cohort (inherent to the study design), and the results may be exposed to type II error, particularly in the case of small sample size in the association of gout and kidney failure. Nonetheless, the findings are still valuable if treated as an initial approach to analytic research of primary prognostic factors in gout.

The cohort-nested case control design used here revealed that presence of tophi, hypertriglyceridemia, and a previous diagnosis of ischemic heart disease are independent factors associated with development of musculoskeletal disability in patients with clinically diagnosed primary gout. Older patient age was the only variable associated with development of renal failure. Our results also highlight the need for studies using larger sample sizes and, if possible, a prospective design to determine the prognostic factors associated with development of musculoskeletal disability and chronic renal failure in primary gout, one of the most prevalent rheumatic diseases worldwide.

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