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**FEMALE GOUT. AGE AND DURATION OF THE  
DISEASE DETERMINE CLINICAL PRESENTATION.**

**TESIS**

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**P R E S E N T A**

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**TESIS DE ESPECIALIZACION EN REUMATOLOGIA DEL DR. SERGIO GARCIA MENDEZ.**

**FEMALE GOUT. AGE AND DURATION OF THE DISEASE DETERMINE CLINICAL PRESENTATION.**

La tesis fue realizada por el Dr. Sergio García Méndez, y se entrega en la modalidad de artículo, el resumen del mismo fue enviado para evaluar su presentación al Congreso anual del Colegio Americano de Reumatología (American College of Rheumatology Annual Scientific Meeting, ACR/ARH 2010), se anexa el comprobante del envío del mismo.

Como primer autor, el Dr. Sergio García Méndez realizó la parte medular de este trabajo con la ayuda de los demás colaboradores.

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De acuerdo a la política editorial de dicha revista, el número de palabras tanto en el "Abstract" como en el cuerpo del manuscrito, el número de figuras y tablas se ajustara a su normativa.

La tesis por lo tanto se presenta en el formato en que será enviada a publicación.

Atentamente,

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**Female Gout. Age and duration of the disease determine clinical presentation.**

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## **Female Gout. Age and duration of the disease determine clinical presentation.**

### **Abstract.**

**Introduction:** In previous studies, female gout has been described in post-menopausal women with higher frequency of hypertension, diuretic usage, chronic renal failure (CRF) also, they are older when compared to gout males.

**Objective:** To determine clinical data and associated diseases in female gout patients compared to males paired for age and duration of the disease.

**Methods:** Case-control study, we included all consecutive females with diagnosis of gout (ACR) and at least one control for each case (males, gout diagnosis, paired for age  $\pm$  5 years and duration of the disease  $\pm$  3 years) from the outpatient gout clinic. Variables: Demographic, clinical and para-clinical. ATP III criteria and definitions were used for metabolic syndrome variables. Renal function was determined by 3 methods: Creatinine clearance (CrC), MDRD and Cockcroft. CRF was considered in patients with CrC  $<$ 60 mL/min. Statistical analysis: t test, X<sup>2</sup>.

**Results:** 23 women and 38 men with gout were included. As expected, there were no differences in age (59.6  $\pm$ 12.5 VS 61.3  $\pm$ 15.4 years); age at onset (44.2  $\pm$  17.8 VS 46.0  $\pm$  13.1, years) and duration of the disease (14.8  $\pm$  12.5 VS 15.5  $\pm$  7.7 years). Eight (30%) female gout patients started the disease before 40 years all them were pre-menopausal at onset and none had familial history of gout. They have higher percentage (no significant) of obesity, higher glucose and triglyceride levels, but were not different to post-menopausal women in most variables. When female gout were compared with male gout patients, although there are some tendencies, there were no significant differences in percentage of patients with podagra during the first attack (61% VS 79%, p=NS) and upper limb involvement (21.7 VS 13.2%, p=NS) or associated metabolic data. None of the patients had previous diuretic use. Females had lower CrC than males (42.79  $\pm$ 23.19 VS 65.66  $\pm$ 25.53 mL/min, p=0.005) but, when CrC was calculated by methods that consider gender, there were no significant differences between females VS male gout patients (Cockcroft 63.4  $\pm$  38.9 VS 73.1  $\pm$  24.8 mL/min respectively, p=0.2) and (MDRD 63.8  $\pm$  30.9 VS 74.9  $\pm$  24.8 mL/min respectively, p=0.13). There were no differences regarding treatment.

**Conclusions:** In one third of our female gout patients, the onset is before 40 years old and do not seem related to familial history. Although some previous data associated to female gout (hypertension, metabolic abnormalities, chronic renal failure and diuretics) tend to be more frequent in them than males, they are not significant when age, duration of the disease are matched and when renal function determination consider gender.

**Key words:** Gout, hyperuricemia, renal function.

Gout is the most common form of arthritis in males and has been considered a male disease; there are around 4 males for each female with gout (1). Gout is rare in pre-menopausal women due in part to the uricosuric effect of estrogens (2); Kim et al reported a possible role of 17-beta-estradiol in the regulation of purine synthesis, uric acid metabolism and low uric acid levels (3).

After menopause serum uric acid concentrations increase as well as the percentage of patients with obesity, hypertension and other associated diseases all them, increase the risk of gout in post-menopausal women (4).

Previous studies had demonstrated that gout in women is different to the typical clinical picture well known in men. Women with gout are elder at onset and have more frequently upper limb joints involvement, previous diuretic therapy (5-7) and hypertension than males although, the frequency of these data are highly variable from one report to other.

Several previous reports had compared the clinical data between females and males with gout in all them the age, age at onset and duration of the disease in females were significantly different compared to men (4-7, 13-17).

The present study is a case control design, we included female patients with gout and matched them with male gout patients paired for age and duration of the disease, we looked for the clinical differences between both groups related to gout and associated diseases.

### **Patients and methods**

We included consecutive gout patients with diagnosis of gout (8) according to ACR criteria and chronic gout diagnosis criteria (CGD), attended in the gout outpatient clinic from the Rheumatology department in our hospital.

Cases were all the females with gout diagnosis attended in the last 10 years and from whom there are complete clinical records.

Controls were males with gout diagnosis (8) from the same clinic and attended in the same years. We looked for at least one control for each case, matched for age ( $\pm 5$  years) and duration of the disease ( $\pm 3$  years).

We included demographic and clinical data at onset and during the disease. We also looked for the presence or absence of obesity, diabetes, hypertension, hyperlipidemia and metabolic syndrome as defined in Adult Treatment Panel III (ATP III) (9). Ischemic heart disease was considered in patients with a previous diagnosis of ischemia, myocardial infarction or angina diagnosed by a physician and that required specific treatment. Additionally we registered all the medications that each patient received for gout or associated diseases.

Glomerular filtration rate (GFR) was calculated by adjusted creatinine clearance in 24 hours urine and also by Cockcroft-Gault method ( $GFR = (140 - \text{age}) \times \text{weight (kg)} / (\text{creatinine in plasma mg/dL} \times 72) \times 0.85$  if females (10) and MDRD method (Modification of Diet in Renal Disease)  $GFR = 186 \times (\text{creatinine})^{-1.154} \times (\text{age})^{-0.203}$  ( $\times 1.21$  in African American) or ( $\times 0.742$  in females) (11). GFR  $< 50$  mL/min or when serum creatinine was  $\geq 1.5$  mg/dL was considered as chronic renal failure.

Statistical analysis included Student's t test,  $\chi^2$  and Fisher exact test.

## **Results**

Twenty three females and 38 males with gout were included. Current age was  $59.6 \pm 12.5$  years in females VS  $61.3 \pm 15.4$  years in males; age at onset was



44.2 ± 17.8 VS 46.0 ± 13.1, years and duration of the disease at inclusion, 14.8 ± 12.5 VS 15.5 ± 7.7 years respectively.

### ***Pre-menopausal VS post-menopausal gout.***

Eight (30%) female gout patients had their first acute attack before 40 years, all them were pre-menopausal at onset and none had familial history of gout. They have higher percentage (although not significant) of obesity (22.2% VS 14.28%; p=0.624), hyperglycemia (22.2% VS 14.28%; p=0.624), and hypertriglyceridemia (22.2% VS 42.8%; p = 0.311) compared to post-menopausal women.

### ***Female VS male gout***

Seventy six percent of males had history or current alcohol intake compared to females (26%, p=0.000). Although some variables tend to be different, there were not significant differences in the percentage of patients with podagra during the first attack (Females: 61% VS Males: 79%, p = NS), upper limb joints attacks (22% VS 13%, p = NS). Also although not significant, women had more acute attacks per year (2.1 ± 2.9 VS 1.0 ± 2.7; p = 0.153); less tophi than men (2.7 ± 3.6 VS 3.6 ± 4.2; p = 0.391), but there were no differences in the size of the larger diameter tophi (3.6 ± 2.0 VS 3.8 ± 3.5 cm; p = 0.882). All the other variables related to gout were similar in both groups.

Regarding associated diseases, mean systolic and diastolic blood pressure values were similar among females VS males with gout (Systolic: 126.1 ±17.2 VS 126 ±16.5 mm/Hg; p = 0.969; diastolic 77.4 ± 7.4 VS 80.8 ±11.9 mm/Hg; p = 0.217); mean blood pressure was significantly higher in women (92.5 ± 9.4 VS

86.6 ± 11.5 mm/Hg; p = 0.042). Patients with the diagnosis of hypertension according to ATP III criteria were more frequent –although not significant- in females than males (table 1).

Mean body mass index (kg/m<sup>2</sup>) was higher in males (27.8 ± 7.1 VS 38.9 ± 8.0; p= 0.000), but when abdominal circumference was considered, there were not significant differences (Females 97.7 ± 13.2 cm VS 103.4 ± 11.8 cm in males, p = 0.185), nor in the frequency of obesity according to ATP III criteria (17.4% VS 36.8%, p = 0.150) (table 1).

There were not differences in the frequency of diabetes or hyperglycemia, hypertriglyceridemia, hypercholesterolemia, ischemic heart disease, metabolic syndrome, chronic renal failure and lithiasis (table 1).

Females and males with gout seem to receive similar treatment for gout and associated diseases. Females receive colchicine more frequently than males (71% VS 44%, p = 0.033), and allopurinol doses >300mg/day are more frequent among males (55% VS 26%, p=0.036). Interestingly, none of the women included in this study received previous or current diuretic therapy.

**Renal function.** Adjusted creatinine clearance in 24h urine determination, is significantly lower in females than in males (42.7 ± 23.1 VS 65.6 ± 25.5, p = 0.005); but when the estimation is made with Cockcroft-Gault and MDRD formulas that consider gender, there were not significant differences (Cockcroft-Gault: Females 63.4 ± 38.9 VS 73.1 ± 24.8 in males, mL/min/1.73 m<sup>2</sup>, p = 0.2) and MDRD: Females 63.8 ± 30.9 VS 74.9 ± 24.8 in males, mL/min/1.73 m<sup>2</sup>, p = 0.13). (Figure 1).

## **Discussion**

In one third of our female gout patients, the onset is before 40 years old and do not seem related to familial history. Previous studies reported that gout females are post-menopausal although the percentages are highly variable (66-95%) (7).

Although some previous data reported that gout in females is more frequently associated to hypertension, metabolic abnormalities, chronic renal failure and diuretics, the differences are not so important and they are not significant when age and duration of the disease are matched and when the method to calculate renal function consider gender.

Probably, we do not have enough number of patients to detect the differences, although we attend a big population of gout patients, only 5% of the patients with gout in our country are females. This is a smaller percentage than previously reported in other countries, as European countries or from USA, but similar than those from Taiwan (7, 12).

Also we reported previously, that the age of onset in gout patients –most of them males- in our country is younger, this is also the case of our female gout patients, whom mean age at onset was 44 years old (2, 13).

One previous study reported the association of pre-menopausal female gout with familial history of the disease (14), but we could not find this association, only 17.4% of our patients had familial history of the disease and in those with familial history none was pre-menopausal at onset.

Some studies had reported a higher frequency of podagra in men as the first acute attack (45% males and 23% females) (5, 15), in our group of patients

podagra is more frequent as the first attack in males as well as in females (61 and 79%).

Also we had lower frequency of upper limbs arthritis than previously reported but our gout female patients had more acute attacks per year than men (5, 15).

Previous reports, including the Framingham Heart Study, found more frequency of CRF, diabetes and hyperglycemia, hypertension and previous diuretic usage in females with gout compared to males, but in all them there were significant differences in age and duration of the disease (2, 5, 6, 13, 16, 17); in our study, when matched patients were included, although there is a tendency to find some differences, these do not seem very clear; additional studies with enough number of patients but controlled by age and duration of the disease, could clarify which differences are secondary to age itself and duration of the disease and which others are characteristics of female gout.

The Cockcroft-Gault and MDRD methods for GFR determination consider adjustment for females and afro-american patients because creatinine clearance determined by 24h urine could under evaluate GFR in these group of patients; for these reasons, these methods are recommended for the renal function evaluation in patients with several diseases (18-20) and should be recommended also in gout patients.

## GOUT AND ASSOCIATED DISEASES

	<b>Women (n = 23)</b>	<b>Men (n = 38)</b>	<b>P</b>
Uric Acid (mg/dL, mean $\pm$ SD)	6.4 $\pm$ 2.7	7.2 $\pm$ 1.8	0.188
Urea (mg/dL, mean $\pm$ SD)	46.4 $\pm$ 19.1	38.4 $\pm$ 19.9	0.141
Creatinine (mg/dL, mean $\pm$ SD)	1.1 $\pm$ 0.5	1.2 $\pm$ 0.5	0.869
Abdominal circumference (cm, mean $\pm$ SD)	97.7 $\pm$ 13.2	103.4 $\pm$ 11.8	0.185
Obesity (%)	4 (17.4)	14 (36.8)	0.150
Hypertension (%)	16 (69.6)	18 (47.4)	0.115
Diabetes or hyperglycemia (%)	4 (17.4)	8 (21.1)	1.000
Hypertriglyceridemia (%)	8 (34.8)	19 (50.0)	0.295
Hypercholesterolemia (%)	7 (30.4)	14 (36.8)	0.782
Chronic renal failure (%)	9 (39.1)	12 (31.6)	0.587
Lithiasis (%)	1(4.3)	0	0.190

**Table 1. Gout and associated diseases.**

**Comparison between Females VS males.**

## Figure Legends

### Figure 1. GFR in patients with gout by several methods.

#### Females VS males

24h urine: Females:  $42.7 \pm 23.1$  VS Males:  $65.6 \pm 25.5$  mL/min.

MDRD: Females:  $63.8 \pm 30.9$  VS Males:  $74.9 \pm 24.8$  mL/min.

Cockcroft-Gault: Females:  $63.3 \pm 38.9$  VS Males:  $73.1 \pm 24.8$  mL/min

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