IDENTIFICATION OF NEW AND RARE VARIANTS IN THE ROLE OF NSAIDS IN THE ASSOCIATION BETWEEN ALL-CAUSE MORTALITY AND CARDIOVASCULAR DISEASES: A POPULATION-BASED COHORT STUDY

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Background: Early-onset or juvenile gout (EOG) without hypoxanthine-guanine phosphoribosyltransferase enzyme deficiency (HPRT, OMIM 300323) and not related to familial juvenile hyperuricemic nephropathy (UMOD, OMIM 300323) is a rare gout phenotype characterised by a first flare in adolescence or in young adulthood. While numerous genome-wide association studies (GWAS) have been done on classical late-onset gouty patients, very few studies have been performed in EOG patients. Moreover, until now most genetic studies only assess association between predefined single nucleotide polymorphisms (SNP) and gout.

Objectives: Our aim was to identify the genetic variants of clinically confirmed EOG by screening all exons of gout-associated genes with targeted Next-Generation Sequencing (NGS) approach.

Methods: Twenty-six urate crystal-proven gout patients with first flare occurring before the age of 30 years were included. Gout history, comorbidities and patient characteristics were recorded. All participants provided written informed consent to genetic analysis. After DNA extraction from total blood samples, the NGS libraries were prepared with sureselect QXT (Agilent) and sequencing was performed with miseq (Illumina).

The multigene panel included 80 genes described in GWAS and genes involved in rare diseases such as primary hyperparathyroidism, x-linked agammaglobulinemia, and Hunter syndrome. In all, 130,598 variants were prepared with sureselect QXT (Agilent) and sequencing was performed with miseq (Illumina). The multigene panel included 80 genes described in GWAS and genes involved in rare diseases such as primary hyperparathyroidism, x-linked agammaglobulinemia, and Hunter syndrome. In all, 130,598 variants were prepared with sureselect QXT (Agilent) and sequencing was performed with miseq (Illumina).

Results: Six patients had a molecular anomaly (26.9%). Six patients harboured one rare or novel variant in SLC22A11 (one African patient) and ABCG2 (two Caucasian patients). The other patients (one Caucasian and one African) carried an association of variants in both SLC22A11 and ABCG2. All variants had a Minor Allele Frequency (MAF) below 0.3% or were never described in public databases. All variants were considered as probably pathogenic according to in silico predictive algorithms. Interestingly, the well-known p.Gln141Lys SNP of SLC22A11 was identified in 3 Asian patients (11.5%) at homozygous level.

Conclusions: Our finding of very rare and novel pathogenic variants in SLC22A11 and ABCG2 in EOG patients highlights the involvement of yet undetermined genes in this population.

Disclosure of Interest: None declared


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Treatments: friend or foe?

THE ROLE OF NSAIDS IN THE ASSOCIATION BETWEEN OSTEARTHROPATHIES AND CARDIOVASCULAR DISEASES: A POPULATION-BASED COHORT STUDY

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Background: Worldwide, osteoarthritis (OA) is a major musculoskeletal disorder. Recent research suggests that OA is an independent risk factor for cardiovascular disease (CVD). The relationship is complicated because non-steroidal anti-inflammatory drugs (NSAIDs), a proven risk factor for CVD, are frequently used for the treatment of OA. Researchers have hypothesised that NSAID use in the causal pathway between OA and CVD is what may ultimately impact these patients to develop CVD, this pathway has yet to be studied.

Objectives: The objective of this study was to disentangle the role of NSAID in the increased risk of CVD among OA patients.

Methods: This longitudinal study was based on linked health administrative data from British Columbia, Canada. From a population-based cohort of 720,055 British Columbians, we matched on age and sex to assemble 7,743 OA patients and 23,229 non-OA controls (1:3 ratio). We used multivariable Cox proportional hazards models to estimate the risk of developing incident CVD (primary outcome) as well as ischaemic heart disease (IHD), congestive heart failure (CHF) and stroke (secondary outcomes). To estimate the mediating effect of NSAIDs, defined as current use of NSAID using linked prescription dispensing records, in the OA-CVD relationship, we implemented a marginal structural model.

Results: People with OA had 23% higher risk of developing CVD compared to people without OA after adjusting for SES, BMI, hypertension, diabetes, hyperlipidemia, COPD, and Romano comorbidity score, adjusted HR (95% CI) was 1.23 (1.17, 1.29). Adjusted HR (95% CI) was 1.42 (1.33, 1.52), 1.17 (1.10, 1.27), 1.14 (1.08, 1.24) for CHF, IHD and stroke, respectively. Approximately 67.51% of the total effect of OA on the increased risk of CVD was mediated through current NSAID use. Among the secondary outcomes, approximately 44.77% of increased CHF risk was mediated through current NSAID use. More than 90% of the total effects on IHD and stroke was mediated through the current NSAID use.

Conclusions: Our study is the first to evaluate the mediating role of NSAID use in the OA-CVD relationship based on population-based health administrative data. The results of this study also indicate that OA is an independent risk factor for CVD. Our findings suggest that the mediating role of NSAID use substantially contributes to the OA-CVD association.

REFERENCES:


Disclosure of Interest: None declared


ALL-CAUSE MORTALITY AND CARDIOVASCULAR DEATH IN HYDROXYCHLOROQUINE USERS IN RHEUMATOID ARTHRITIS PATIENTS – A POPULATION BASED DANISH COHORT STUDY

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Background: Rheumatoid arthritis (RA) is associated with a marked increase in cardiovascular comorbidity and mortality.1 The increased risk is present from the earliest stages of the disease and evidence suggests an overlap in the pathogenic features leading to RA and atherosclerosis.

Hydroxychloroquine (HCQ) is used to treat RA in combination with methotrexate and has been associated with decreased risk of type II diabetes and dyslipidaemia among RA patients. Also HCQ has improved survival rates when used to treat other inflammatory diseases, e.g. systemic lupus erythematosus.2 The evidence regarding RA patients is scarce.

Objectives: We wish to examine whether HCQ would affect the incidence rates of cardiovascular diseases, type II diabetes, cardiac – and all-cause mortality among Danish RA patients in an observational cohort study.

Methods: We identified all incident RA patients during the period of 2004 through 2014 in Denmark. HCQ initiators were compared with non-users of HCQ, stratified on rheumatoid factor positivity. Each HCQ initiator was matched to a non-HCQ initiator by their propensity score (PS). In the PS all relevant available cardiovascular drugs and comorbidities were included. All together we had 3,742 RA patients in each group.

Results: We found a significant reduction in all-cause mortality and cardiovascular related death among HCQ initiators, with a hazard ratio of 0.83 (95% confidence interval [CI] 0.71–0.97) and 0.78 (95% CI: 0.61 to 0.99), respectively. We did not find any association between HCQ use and development of type II diabetes or specific ischaemic events (myocardial infarctions and ischaemic strokes).