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OP0171

MENDELIAN RANDOMIZATION SHOWS NO CAUSAL ASSOCIATION BETWEEN SERUM URATE OR GOUT AND TYPE-2 DIABETES

N. McCormick^{1,2}, J. Choi³, S. Marozoff², H. Choi^{1,2}. ¹Massachusetts General Hospital/Harvard Medical School, Boston, United States of America; ²Arthritis Research Canada, Richmond, Canada; ³Massachusetts General Hospital, Boston, United States of America

Background: Positive associations between gout^{1,2} or serum urate (SU)³ and risk of type-2 diabetes (T2D) have been reported in population-based observational studies, but may be due to residual confounding. As such, causal roles of SU and gout on development of T2D are unclear.

Objectives: Use two-sample mendelian randomization to estimate the causal effects of SU and gout on T2D and glycemic traits.

Methods: Aggregate data from three large genome-wide association studies were used to identify genetic variants (SNPs) associated with the exposures and outcomes. Exposure SNPs were sourced from Global Urate Genetics Consortium (> 140,000 individuals); outcome SNPs sourced from Diabetes Genetics Replication And Meta-analysis consortium (DIAGRAM; > 34,000 T2D cases and > 114,000 controls) and Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC; > 46,000 non-diabetics).

We analysed SNPs associated with SU levels (n=28) and gout (n=6) for associations with T2D and three glycemic traits (insulin resistance, fasting insulin levels, and HbA1c) using inverse variance weighted meta-analysis methods. We also specifically examined two SNPs mapping to the *SLC2A9* gene, which encodes the GLUT9 transporter (for glucose and urate), estimating Wald ratios for these individual SNPs. Analyses were performed with TwoSampleMR package in R and mRnd power calculator.

Results: Estimated effects of genetically-determined gout on each of the four outcomes (T2D, insulin resistance, fasting insulin levels, and HbA1c) were small and non-significant ($p \geq 0.18$), as were the effects of changes in genetically-determined SU levels (Table).

Although the two SNPs in the *SLC2A9* gene were strongly associated with SU (rs12498742: $R^2=2.7\%$, $\beta=0.37$ per mg/dL, $p < 10^{-700}$) and gout (rs4475146: odds ratio=0.63, $p=4.1 \times 10^{-26}$), neither was associated with T2D nor any of the glycemic traits (Table).

Applying R^2 values $\geq 1.9\%$, we had $\geq 90\%$ power to detect the increased odds of T2D (OR $\geq 1.15^{1,3}$) from observational studies.

All Risk SNPs (meta-analysis)

OUTCOME	n SNPs	Gout (vs. non-gout)		Serum urate (per 1 mg/ dL increase)	
		Effect size (95% CI)	p	Effect size (95% CI)	p
HbA1c (%)	45	0.0046 (-0.0087 to 0.0179)	0.50	-0.0046 (-0.0275 to 0.0183)	0.70
Insulin resistance (HOMA-IR: log units)	45	0.0108 (-0.0049 to 0.0265)	0.18	0.0016 (-0.0240 to 0.0272)	0.90
Fasting insulin levels (log pmol/L)	18	0.0046 (-0.0037 to 0.0129)	0.28	-0.0221 (-0.1035 to 0.0593)	0.59
Type 2 Diabetes: odds ratio	43	0.98 (0.90 to 1.07)	0.72	1.01 (0.88 to 1.16)	0.84

SNPs in *SLC2A9* Gene (single-SNP analysis)

OUTCOME	rs4475146 Gout (vs. non-gout)		rs12498742 Serum urate (per 1 mg/dL increase)	
	Effect size (95% CI)	p	Effect size (95% CI)	p
HbA1c (%)	0.0032 (-0.0139 to 0.0203)	0.71	0.0005 (-0.0205 to 0.0216)	0.96
Insulin resistance (HOMA-IR: log units)	0.0128 (-0.0073 to 0.0328)	0.21	0.0126 (-0.0121 to 0.0373)	0.32
Fasting insulin levels (log pmol/L)	0.0038 (-0.0070 to 0.0147)	0.49	0.0048 (-0.0088 to 0.0185)	0.49
Type 2 Diabetes: odds ratio	0.98 (0.87 to 1.10)	0.70	0.98 (0.85 to 1.13)	0.75

HOMA-IR=homeostasis model assessment of insulin resistance

Conclusion: Evidence from this instrumental variable analysis suggests gout and SU are signals for future T2D, but neither SU or gout itself are causally associated with the development of this condition. As such, interventions targeting SU levels alone are unlikely to lower the risk of T2D.

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OP0172

EFFECT OF WEIGHT LOSS AND LIRAGLUTIDE ON SERUM URATE LEVELS AMONG OBESE KNEE OSTEOARTHRITIS PATIENTS: SECONDARY ANALYSIS OF A RANDOMISED CONTROLLED TRIAL

K. Zobbe^{1,2}, S. M. Nielsen^{1,3}, R. Christensen^{1,3}, A. Overgaard¹, H. Gudbergensen¹, M. Henriksen¹, H. Bliddal¹, L. Dreyer^{1,4}, L. Stamp⁵, F. Krag Knop^{6,7}, L. E. Kristensen¹. ¹The Parker Institute, Bispebjerg-Frederiksberg Hospital, University of Copenhagen, Frederiksberg, Denmark; ²Center for Rheumatology and Spine Diseases, Rigshospitalet Gentofte, Hellerup, Denmark; ³Department of Rheumatology, Odense University Hospital, Odense, Denmark; ⁴Department of Rheumatology, Aalborg University Hospital, Aalborg, Denmark; ⁵Department of Medicine, University of Otago, Christchurch, New Zealand; ⁶Center for Clinical Metabolic Research, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark; ⁷Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Background: There is a strong association between gout and obesity. Lowering urate is the cornerstone of gout management [1] and urate levels correlate strongly with central obesity. Previous studies suggest that weight loss has a positive effect on serum urate, however, the studies are sparse and small [2].

Objectives: To assess the impact of an initial low-calorie diet-induced weight loss and subsequent randomisation to the body weight-lowering drug liraglutide (a glucagon-like peptide 1 receptor agonist) or placebo on serum urate levels.

Methods: In the LOSE-IT trial (NCT02905864), a randomised, double-blinded, placebo-controlled, parallel group, single-centre trial [3], 156 obese individuals with knee osteoarthritis, but without gout, were offered an initial 8-week intensive diet intervention (week -8 to 0) on Cambridge Weight Plan (800-1000 kcal/day) followed by a weight loss maintenance period in which participants were randomised to either liraglutide 3 mg/day or placebo for 52 weeks. We conducted a secondary analysis of blood samples collected at week -8, 0 and 52. The primary outcome measure was change in serum urate. We used paired t-test for the change from week -8 to 0, and for change from week 0 to 52 we used an ANCOVA model adjusted for stratification factors (sex, age category and obesity class), and the level of the outcome at baseline. Data were analysed as observed (i.e. no imputation of missing data).

Results: 156 individuals were randomised and 155 had blood samples taken at baseline. In the initial intensive diet intervention period (week -8 to 0) they lost a mean of 12.5 kg (95% CI -13.1 to -11.9, n 156). In the following 52 weeks, the liraglutide group lost an additional 4.1 kg (SE 1.2, n 71) whereas the control group was almost unchanged with a weight loss of 0.2 kg (SE 1.2, n 66). Looking at the main outcome of serum urate levels change, the initial intensive diet resulted in a mean decrease of 0.21 mg/dL (95% CI 0.35 to 0.07, n 155) for the entire cohort. In the following year (week 0 to 52) the liraglutide group exhibited a further mean decrease in serum urate of 0.48 mg/dL (SE 0.11, n 69), whereas the placebo group exhibited a slight decrease in mean serum urate of 0.07 mg/dL (SE 0.12, n 65) resulting in a significant between-group difference of -0.40 mg/dL (95% CI -0.69 to -0.12, n 134) – see Figure 1. Four participants in each group experienced serious adverse events; no deaths were observed.

Conclusion: This secondary analysis of the LOSE-IT trial suggests that liraglutide provides a potential novel serum urate lowering drug mechanism in obese patient populations, with potential implication for gout treatment.