Postprint: Study on the Effect of Longitudinal Trajectory of Serum Uric Acid on New-Onset Hypertriglyceridemia

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Abstract

Background Elevated serum uric acid (SUA) levels may be associated with hypertriglyceridemia; however, prospective cohort studies investigating the impact of longitudinal SUA trajectory changes on new-onset hypertriglyceridemia remain scarce. Objective To investigate the association between longitudinal SUA trajectory changes and new-onset hypertriglyceridemia. Methods A total of 3871 construction workers who underwent physical examinations at Shiyan Tiejian Hospital from 2015 to 2020 were enrolled as study participants. General information, physical examination data, and laboratory test results were collected. A group-based trajectory model (GBTM) was constructed to categorize participants' uric acid trajectories. Linear trend ^{2} test was applied to examine the linear trend of hypertriglyceridemia incidence density across SUA strata. Generalized estimating equation model (GEE) was utilized to analyze the relationship between various indicators and hypertriglyceridemia. Results GBTM classification revealed that Group 1 trajectory displayed low SUA fluctuation levels (250~350 mol/L), Group 2 displayed medium SUA fluctuation levels (>350~450 mol/L), and Group 3 displayed high SUA fluctuation levels (>450 mol/L). Based on trajectory characteristics, the three groups were sequentially designated as low-fluctuation group (n=1103), medium-fluctuation group (n=2141), and high-fluctuation group (n=627). Linear trend ^{2} test results demonstrated that hypertriglyceridemia incidence density increased with ascending uric acid fluctuation levels (2=146.728, P<0.001). Comparisons among the three groups revealed statistically significant differences in age, total cholesterol (TC), triglycerides (TG), SUA, creatinine (Cr), systolic blood pressure (SBP), diastolic blood pressure (DBP), and BMI (P<0.05). GEE analysis results indicated that TC, Cr, SBP, DBP, fasting blood glucose, and BMI were influencing factors for hypertriglyceridemia development (P<0.05). Using the low-fluctuation group as reference, both the medium-fluctuation group [RR=2.294, 95%CI (1.834, 2.868)] and high-fluctuation group [RR=3.012, 95%CI (2.295, 3.953)] exhibited increased risk of hypertriglyceridemia (P<0.05). Conclusion Hypertriglyceridemia incidence density increases with elevated uric acid trajectories, and elevated uric acid trajectory represents a risk factor for hypertriglyceridemia development. Maintaining SUA fluctuations within the normal range may help reduce the risk of developing hypertriglyceridemia.

Full Text

Effect of Longitudinal Trajectory of Serum Uric Acid on New-onset Hypertriglyceridemia

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Abstract

Background
High serum uric acid (SUA) levels may be associated with hypertriglyceridemia, but prospective cohort studies examining the effect of longitudinal trajectory changes in SUA on new-onset hypertriglyceridemia remain scarce.

Objective
To investigate the correlation between longitudinal SUA trajectories and new-onset hypertriglyceridemia.

Methods
A total of 3,871 construction workers who underwent physical examinations at Shiyan Tiejian Hospital between 2015 and 2020 were enrolled as study subjects. General demographic data, physical examination results, and laboratory test findings were collected. Group-based trajectory modeling (GBTM) was employed to categorize SUA trajectories. Linear trend ^{2} tests were used to examine the linear trend in hypertriglyceridemia incidence density across SUA strata. Generalized estimating equation (GEE) models were applied to analyze relationships between various indicators and hypertriglyceridemia.

Results
GBTM identified three distinct trajectory groups: Group 1 exhibited low SUA fluctuation levels (250–350 mol/L), Group 2 showed medium SUA fluctuation levels (>350–450 mol/L), and Group 3 displayed high SUA fluctuation levels (>450 mol/L). Based on these trajectory characteristics, the groups were designated as the low-fluctuation group (n=1,103), medium-fluctuation group (n=2,141), and high-fluctuation group (n=627). Linear trend ^{2} tests revealed that hypertriglyceridemia incidence density increased with rising SUA fluctuation levels (^{2}=146.728, P<0.001). Significant differences were

observed among the three groups in age, total cholesterol (TC), triglycerides (TG), SUA, creatinine (Cr), systolic blood pressure (SBP), diastolic blood pressure (DBP), and BMI ($P<0.05$). GEE analysis demonstrated that TC, Cr, SBP, DBP, fasting blood glucose, and BMI were influencing factors for hypertriglyceridemia development ($P<0.05$). Using the low-fluctuation group as reference, both the medium-fluctuation group [RR=2.294, 95%CI (1.834, 2.868)] and high-fluctuation group [RR=3.012, 95%CI (2.295, 3.953)] showed elevated risks of hypertriglyceridemia ($P<0.05$).

Conclusion
Hypertriglyceridemia incidence density increases with elevated SUA trajectories, and rising SUA trajectories represent a risk factor for new-onset hypertriglyceridemia. Maintaining SUA fluctuations within the normal range may help reduce the risk of developing hypertriglyceridemia.

Keywords: Hypertriglyceridemia; Hyperuricemia; Dyslipidemias; Group-based trajectory model; Risk factors

Introduction

Hypertriglyceridemia is an extremely common form of dyslipidemia characterized by elevated serum triglyceride levels. It represents a significant risk factor for metabolic syndrome components including hypertension, coronary heart disease, atherosclerosis, and diabetes, as well as acute pancreatitis. However, hypertriglyceridemia often presents without obvious symptoms and is frequently overlooked, underscoring the importance of identifying predictive factors. Uric acid is the final product of purine metabolism, though whether elevated serum uric acid (SUA) promotes hypertriglyceridemia development remains inconclusive. An early cross-sectional study identified an association between SUA and hypertriglyceridemia but could not establish causality [1]. Two recent cohort studies examined SUA' s effect on new-onset hypertriglyceridemia using baseline SUA quartiles from single time-point measurements, finding that elevated SUA levels may increase hypertriglyceridemia risk [2-3]. However, single time-point measurements fail to capture how SUA fluctuations over time affect outcome accuracy.

Group-based trajectory modeling (GBTM) is a longitudinal data analysis technique that identifies and groups individuals following similar trajectories in repeated measures data. GBTM overcomes single-measurement limitations, and its scientific validity and feasibility have been demonstrated in other medical cohort studies [4-6], though it has not yet been applied to research on SUA and hypertriglyceridemia associations. This study utilized 6-year physical examination data from construction workers at Shiyan Tiejian Hospital to construct a prospective cohort and investigate the impact of dynamic SUA changes on hypertriglyceridemia.

Methods

Study Population

Construction workers undergoing health examinations at Shiyan Tiejian Hospital between 2015 and 2020 were enrolled. Inclusion criteria were: (1) age $ $18 years; (2) participation in at least three examinations between 2015 and 2020 with complete data for primary study variables; and (3) no hypertriglyceridemia at the first examination. Exclusion criteria included: (1) hypertriglyceridemia at baseline or presence of cardiovascular/cerebrovascular disease, severe hepatic/renal disease, or malignant tumors; and (2) use of lipid-lowering medications or SUA-modulating drugs during the study period. After applying these criteria, 3,871 individuals were included in the study cohort. The study was approved by the Ethics Committee of Hubei University of Medicine (Approval No.: 2019-TH-101).

Data Collection

General Information

Medical staff recorded participants' identity information, age, and sex, and inquired about medication use in the previous month and medical history. All participants provided informed consent.

Physical Examination and Blood Sampling

Participants wore light clothing without shoes or hats for height and weight measurements (height to 0.1 cm precision, weight to 0.1 kg precision), from which BMI was calculated. After resting for 5 minutes, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured on the left upper arm using an Omron electronic sphygmomanometer, with the average of three readings recorded. Participants fasted for at least 8 hours before venous blood collection between 6:00–9:00 AM for laboratory testing.

Laboratory Tests

A Mindray BS-2000M automatic analyzer was used to measure serum total cholesterol (TC), triglycerides (TG), fasting blood glucose (FPG), blood urea nitrogen (BUN), SUA, and creatinine (Cr).

Diagnostic Criteria

(1) Hypertriglyceridemia was diagnosed as TG $ $2.3 mmol/L [7].

(2) Hyperuricemia was diagnosed as SUA $ $420 mol/L on two separate measurements [8].

Statistical Analysis

STATA 17 software was used to construct GBTM models. The Traj program was installed into STATA 17, and GBTM commands were used to explore trajectory groupings. The Bayesian Information Criterion (BIC) and average posterior probability (AvePP) were used to select appropriate grouping results. After multiple fitting attempts, the model with the smallest absolute BIC value and AvePP>0.7 for each group was accepted as the standard [9]. SPSS 22.0 was used for data analysis. Normally distributed continuous variables were expressed as ($\bar{x}\pm s$) and compared among groups using one-way ANOVA. Non-normally distributed continuous variables were expressed as M(P25, P75) and compared using Kruskal-Wallis H tests. Categorical variables were expressed as relative frequencies. Linear trend ^{2} tests were used to examine linear trends in hypertriglyceridemia incidence density across SUA strata. Generalized estimating equation (GEE) models were used to analyze relationships between various indicators and hypertriglyceridemia, with an exchangeable working correlation matrix and binary logistic link function. Statistical significance was defined as α=0.05, with $P<0.05$ considered statistically significant or allowing entry into the model.

Results

GBTM Grouping for Hypertriglyceridemia

GBTM model fitting was performed. The 3-group model yielded a BIC value of -80,745.82, with AvePP values of 0.92640, 0.91807, and 0.92069 for the three groups, all exceeding 0.7, indicating reasonable GBTM grouping. Group 1 trajectory showed low SUA fluctuation levels (250–350 mol/L), Group 2 showed medium SUA fluctuation levels (>350–450 mol/L), and Group 3 showed high SUA fluctuation levels (>450 mol/L). Based on trajectory characteristics, the groups were sequentially named low-fluctuation group (n=1,103), medium-fluctuation group (n=2,141), and high-fluctuation group (n=627).

Participant Characteristics

A total of 3,871 participants were included, aged 18–69 years with a median age of 28 (24, 40) years, including 3,416 males and 455 females. The study enrolled 1,704, 930, 762, and 475 participants in 2015–2018, respectively. Using the first examination as baseline, participants were followed up 2–5 times over a median follow-up duration of 4.39 years, totaling 14,487 person-years. Between 2016 and 2020, 913 new hypertriglyceridemia cases occurred, yielding an incidence density of 62.88 per 1,000 person-years. The low-, medium-, and high-fluctuation groups contributed 4,130, 8,039, and 2,318 person-years, respectively, with 137, 541, and 235 incident cases and incidence densities of 33.17‰, 67.30‰, and 101.38‰. Linear trend ^{2} tests revealed that hypertriglyceridemia incidence density increased with rising SUA fluctuation levels (^{2}=146.728, $P<0.001$).

Baseline Data Comparison Among Three Groups

Significant differences were observed among the three groups in age, TC, TG, SUA, Cr, SBP, DBP, and BMI ($P<0.05$). No significant differences were found in BUN or FPG among the three groups (P>0.05) .

GEE Analysis Results for Hypertriglyceridemia Influencing Factors

Using hypertriglyceridemia occurrence (assignment: 0=no, 1=yes) as the dependent variable, SUA fluctuation level as the independent variable, and age, TC, TG, SUA, Cr, SBP, DBP, and BMI as control variables, GEE analysis showed that TC, Cr, SBP, DBP, FPG, and BMI were influencing factors for hypertriglyceridemia development (P<0.05). Using the low-fluctuation group as reference, both the medium-fluctuation group [RR=2.294, 95%CI (1.834, 2.868)] and high-fluctuation group [RR=3.012, 95%CI (2.295, 3.953)] demonstrated elevated hypertriglyceridemia risk (P<0.05) .

Discussion

Previous studies have identified TC, BMI, FPG, and Cr as risk factors for hypertriglyceridemia, consistent with our findings [3,10-11]. However, because the third quartile of age among our participants was <40 years with a relatively young overall population, we did not find an association between age and hypertriglyceridemia. Notably, acute pancreatitis caused by hypertriglyceridemia has shown a trend toward younger onset [12-13], suggesting high hypertriglyceridemia prevalence among young and middle-aged adults, which our results also support.

Using GBTM, we categorized the study population into low-, medium-, and high-fluctuation groups with SUA fluctuation ranges of 250–350 mol/L, >350–450 mol/L, and >450 mol/L, respectively. The medium-fluctuation group progressed from normal to hyperuricemia (fluctuating between >350–450 mol/L), while the high-fluctuation group remained hyperuricemic throughout follow-up (fluctuating >450 mol/L). Follow-up revealed hypertriglyceridemia incidence densities of 33.17‰, 67.30‰, and 101.38‰ in the low-, medium-, and high-fluctuation groups, respectively (P<0.001). Although all three groups developed hypertriglyceridemia, the medium- and high-fluctuation groups showed incidence densities 2.03 and 3.06 times that of the low-fluctuation group, respectively, demonstrating that hypertriglyceridemia incidence density increases with elevated SUA trajectories.

A cross-sectional study of 36,663 examinees found that higher SUA was associated with hypertriglyceridemia risk [14]. A 5-year cohort study in Japanese populations showed that both higher baseline SUA and sustained uric acid elevation increased hypertriglyceridemia probability [15], while another cohort study in Chinese middle-aged and older populations found that each 100 mol/L increase in SUA elevated hypertriglyceridemia risk by 13% [2]. Our study, using SUA fluctuation trajectory grouping, demonstrated that compared with the low-fluctuation group, both the medium-fluctuation group [RR=2.294, 95%CI (1.834, 2.868)] and high-fluctuation group [RR=3.012, 95%CI (2.295, 3.953)] had elevated hypertriglyceridemia risk (P<0.05). Elevated SUA may serve as an important predictor of hypertriglyceridemia, and controlling SUA fluctuations within the normal range may help reduce hypertriglyceridemia risk.

The mechanisms underlying SUA' s effect on TG levels remain unclear. One hypothesis suggests that high uric acid induces NADPH oxidase 4 translocation, causing increased mitochondrial oxidative stress that promotes citrate release into the cytoplasm and stimulates TG synthesis [16]. Another proposes that uric acid induces overexpression of lipid metabolism-related enzymes to promote hepatic lipogenesis [17]. Our study further elucidates the epidemiological association between SUA and hypertriglyceridemia from a population perspective, while molecular mechanism research on how elevated SUA affects hypertriglyceridemia will contribute to disease diagnosis, treatment, and drug development.

This study has several limitations. First, our participants were predominantly young males, limiting population representativeness and potentially introducing bias. Second, smoking, alcohol consumption, and dietary habits all influence hypertriglyceridemia, but we did not include these factors as control variables, which may have affected our results. In conclusion, based on dynamic SUA trajectory changes and GBTM construction, this study compared hypertriglyceridemia incidence among populations with different SUA fluctuation levels, further demonstrating the importance of uric acid control for hypertriglyceridemia management.

Author Contributions: HE Yingmei was responsible for data collation, statistical analysis, figure and table preparation, and manuscript writing. JIA Xue and ZHU Guojun were responsible for data collection and review. LIU Bing was responsible for quality control and review of the article, overall responsibility, and supervision.

Conflict of Interest: The authors declare no conflict of interest.

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Table 1 Comparison of baseline data among three groups of subjects

Table 2 GEE analysis results of influencing factors for hypertriglyceridemia

References

[1] ZHAO L J, ZHAO D, LIU J, et al. Population study on the relationship between serum uric acid levels and triglycerides [J]. Chinese Journal of Internal Medicine, 2005, 44(9): 664-667. DOI: 10.3760/j.issn:0578-1426.2005.09.008.

[2] LI Y Z, TIAN L, ZHENG H, et al. Serum uric acid and risk of incident hypercholesterolaemia and hypertriglyceridaemia in middle-aged and older Chinese: a 4-year prospective cohort study [J]. Ann Med, 2020, 52(8): 479-487. DOI: 10.1080/07853890.2020.1795918.

[3] ZHENG R J, REN P, CHEN Q M, et al. Serum uric acid levels and risk of incident hypertriglyceridemia: a longitudinal population-based epidemiological study [J]. Ann Clin Lab Sci, 2017, 47(5): 597-602.

[4] DU X, ZHANG R Y, ZHANG Y, et al. Relationship between longitudinal trajectory of systolic blood pressure and atrial fibrillation [J]. Chinese Circulation Journal, 2017, 32(6): 584-588. DOI: 10.3969/j.issn.1000-3614.2017.06.013.

[5] WANG S, ZHANG J, ZHANG J, et al. Cohort study on the relationship between body mass index trajectory and new-onset non-alcoholic fatty liver disease [J]. Chinese Journal of Hepatology, 2020, 28(7): 597-602. DOI: 10.3760/cma.j.cn501113-20190629-00230.

[6] HUANG J J, LI J J, ZHANG X L, et al. Effect of longitudinal trajectory of systolic blood pressure on new-onset chronic kidney disease [J]. Medical Journal of Chinese People' s Liberation Army, 2021, 46(1): 49-56. DOI: 10.11855/j.issn.0577-7402.2021.01.09.

[7] ZHU J R, GAO R L, ZHAO S P, et al. Chinese guidelines for the prevention and treatment of dyslipidemia in adults (2016 revision) [J]. Chinese Circulation Journal, 2016, 31(10): 937-953.

[8] Chinese Society of Endocrinology. Chinese guidelines for the diagnosis and treatment of hyperuricemia and gout (2019) [J]. Chinese Journal of Endocrinology and Metabolism, 2020, 36(1): 1-13. DOI: 10.3760/cma.j.issn.1000-6699.2020.01.001.

[9] LÜ Y C, ZHAO R. Group-based trajectory model: a new method for intervention research [J]. Psychological Exploration, 2018, 38(1): 91-96.

[10] LIU S J, LU F, HU Z B, et al. Epidemiological survey of hyperlipidemia among elderly people in Wujin District, Changzhou City [J]. Chinese Journal of Disease Control & Prevention, 2013, 17(1): 13-16.

[11] HUANG Y H, GAN M, QIN Y Y, et al. Survey on detection rate and risk factors of dyslipidemia among Zhuang population in Nanning City [J]. China Medical Herald, 2022, 19(20): 41-44, 61.

[12] GAN J Y, LIU Y M, WANG Q, et al. Construction of an early prediction model for severe hypertriglyceridemia-induced acute pancreatitis [J]. Chinese Journal of Critical Care Medicine, 2022, 42(11): 975-981. DOI: 10.3969/j.issn.1002-1949.2022.11.010.

[13] PETROV M S, YADAV D. Global epidemiology and holistic prevention of pancreatitis [J]. Nat Rev Gastroenterol Hepatol, 2019, 16(3): 175-184. DOI: 10.1038/s41575-018-0087-5.

[14] XU J, LIU C C, FU L, et al. The association of serum uric acid with metabolic syndrome and its components-From a single-clinical centre in China [J]. Int J Clin Pract, 2021, 75(4): e13845. DOI: 10.1111/ijcp.13845.

[15] KUWABARA M, BORGHI C, CICERO A F G, et al. Elevated serum uric acid increases risks for developing high LDL cholesterol and hypertriglyceridemia: a five-year cohort study in Japan [J]. Int J Cardiol, 2018, 261: 183-188. DOI: 10.1016/j.ijcard.2018.03.045.

[16] LANASPA M A, SANCHEZ-LOZADA L G, CHOI Y J, et al. Uric acid induces hepatic steatosis by generation of mitochondrial oxidative stress: potential role in fructose-dependent and-independent fatty liver [J]. J Biol Chem, 2012, 287(48): 40732-40744. DOI: 10.1074/jbc.M112.399899.

[17] CHOI Y J, SHIN H S, CHOI H S, et al. Uric acid induces fat accumulation via generation of endoplasmic reticulum stress and SREBP-1c activation in hepatocytes [J]. Lab Invest, 2014, 94(10): 1114-1125. DOI: 10.1038/labinvest.2014.98.

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