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健康体检人群血清尿酸与颈动脉粥样硬化斑块、10年心血管疾病风险的关系：随访研究

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【摘要】 目的 分析健康体检人群血清尿酸(SUA)与颈动脉粥样硬化(CAP)、10年心血管疾病风险的关系。方法 2013—2016年在西安交通大学第一附属医院健康医学科进行健康体检(包括SUA检查和颈动脉超声检查)者共74 539例,选取其中符合纳入与排除标准者34 473例。根据首次颈动脉超声检查结果将健康体检者分为CAP组($n=15\ 818$)和无CAP组($n=18\ 655$)。收集健康体检者的一般资料及实验室检查结果,以首次颈动脉超声检查为随访起点,以后续体检时发现CAP为随访终点事件,随访截止时间为2023-01-31。最后1次随访时,采用国人缺血性心血管病10年发病风险评估表对无CAP组中完成 ≥ 2 次颈动脉超声检查、年龄 >35 岁且有吸烟情况的2 352例健康体检者的10年心血管疾病风险进行评估。健康体检者发生CAP的影响因素分析采用多因素Logistic回归分析,SUA与健康体检者10年心血管疾病风险的相关性分析采用Spearman秩相关分析。结果 CAP组年龄大于无CAP组,男性占比、BMI、收缩压(SBP)、舒张压(DBP)、SUA、TC、TG、LDL-C、AST、球蛋白、空腹血糖、尿素氮、肌酐高于无CAP组,HDL-C、ALT、总蛋白、白蛋白低于无CAP组($P<0.05$)。多因素Logistic回归分析结果显示,年龄、男性、BMI、SBP、SUA、TC、TG、HDL-C、白蛋白、空腹血糖、尿素氮、肌酐是健康体检者发生CAP的独立影响因素($P<0.05$)。本研究对无CAP组中完成 ≥ 2 次颈动脉超声检查的3 308例健康体检者共随访了7~9年,结果显示,共1 530例健康体检者发生了CAP,CAP发生率为46.2%。根据基线SUA的四分位数将3 308例健康体检者分为Q1组($SUA \leq 259 \mu\text{mol/L}$, $n=829$)、Q2组($259 \mu\text{mol/L} < SUA \leq 316 \mu\text{mol/L}$, $n=830$)、Q3组($316 \mu\text{mol/L} < SUA \leq 379 \mu\text{mol/L}$, $n=824$)、Q4组($SUA > 379 \mu\text{mol/L}$, $n=825$)。随着SUA升高,健康体检者CAP发生率呈逐渐升高趋势($\chi^2_{趋势}=11.716$, $P=0.008$)。Q2组、Q3组、Q4组10年心血管疾病风险高于Q1组,Q3组、Q4组10年心血管疾病风险高于Q2组,Q4组10年心血管疾病风险高于Q3组($P<0.05$)。Spearman秩相关分析结果显示,SUA与健康体检者10年心血管疾病风险呈正相关($r_s=0.223$, $P<0.001$)。结论 SUA升高是健康体检人群发生CAP的危险因素,且SUA越高的健康体检人群CAP发生风险、10年心血管疾病风险越高。

【关键词】 斑块, 动脉粥样硬化; 尿酸; 心血管疾病风险; 随访研究

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Association of Serum Uric Acid with Carotid Atherosclerotic Plaque and 10-Year Risk of Cardiovascular Disease in the People Undergoing Health Examinations: a Follow-up Study YANG Yuhuan, WANG Jun, MIAO Jinjin, ZHANG Mingming, HAO Hua, SU Shi, MA Mao

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【Abstract】 Objective To analyze the association of serum uric acid (SUA) with carotid atherosclerotic plaque (CAP) and 10-year risk of cardiovascular disease in the people undergoing health examinations. **Methods** There were 74 539 people undergoing health examinations (including SUA examination and carotid ultrasonography) in the Department of Health Medicine of the First Affiliated Hospital of Xi'an Jiaotong University from 2013 to 2016, among which 34 473 people met the inclusion and exclusion criteria were selected. According to the first results of carotid ultrasonography, the people undergoing health examinations were divided into CAP group ($n=15\ 818$) and non-CAP group ($n=18\ 655$). The general data and laboratory examination results of people undergoing health examinations were collected, the first carotid ultrasonography was used as the starting point of follow-up, and CAP was found during follow-up physical examination as the end point event of follow-up. The follow-up deadline was 2023-01-31. The 10-year risk of cardiovascular disease of 2 352 people undergoing health examinations who completed ≥ 2 carotid ultrasonography, aged >35 years, and had smoking history in the non-CAP group was assessed using

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the 10-year risk assessment table for ischemic cardiovascular disease in Chinese. Multivariate Logistic regression analysis was used to analyze the influencing factors of CAP in people undergoing health examinations. Spearman rank correlation analysis was used to analyze the correlation between SUA and 10-year risk of cardiovascular disease in people undergoing health examinations.

Results The age of CAP group was older than that of non-CAP group, the male proportion, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), SUA, TC, TG, LDL-C, AST, globulin, fasting blood glucose, urea nitrogen and creatinine were higher than those of non-CAP group, and HDL-C, ALT, total protein and albumin were lower than those of non-CAP group ($P < 0.05$). Multivariate Logistic regression analysis showed that age, male, BMI, SBP, SUA, TC, TG, HDL-C, albumin, fasting blood glucose, urea nitrogen and creatinine were independent influencing factors for CAP in people undergoing health examinations ($P < 0.05$). A total of 3 308 people undergoing health examinations in non-CAP group who completed ≥ 2 carotid ultrasonography were followed up for 7-9 years in the study, the results showed that 1 530 people undergoing health examinations occurred CAP, and the incidence of CAP was 46.2%. According to the baseline SUA quartile, the 3 308 people undergoing health examinations were divided into Q1 group ($SUA \leq 259 \mu\text{mol/L}$, $n=829$), Q2 group ($259 \mu\text{mol/L} < SUA \leq 316 \mu\text{mol/L}$, $n=830$), Q3 group ($316 \mu\text{mol/L} < SUA \leq 379 \mu\text{mol/L}$, $n=824$) and Q4 group ($SUA > 379 \mu\text{mol/L}$, $n=825$). With the increase of SUA, the incidence of CAP in people undergoing health examinations showed an increasing trend ($\chi^2_{\text{trend}}=11.716$, $P=0.008$). The 10-year risk of cardiovascular disease in Q2 group, Q3 group and Q4 group was higher than that in Q1 group, the 10-year risk of cardiovascular disease in Q3 group and Q4 group was higher than that in Q2 group, and the 10-year risk of cardiovascular disease in Q4 group was higher than that in Q3 group ($P < 0.05$). Spearman rank correlation analysis showed that SUA was positively correlated with 10-year risk of cardiovascular disease in people undergoing health examinations ($r_s=0.223$, $P < 0.001$).

Conclusion Elevated SUA is a risk factor for CAP in people undergoing health examinations. The higher SUA, the higher risk of CAP and 10-year risk of cardiovascular disease.

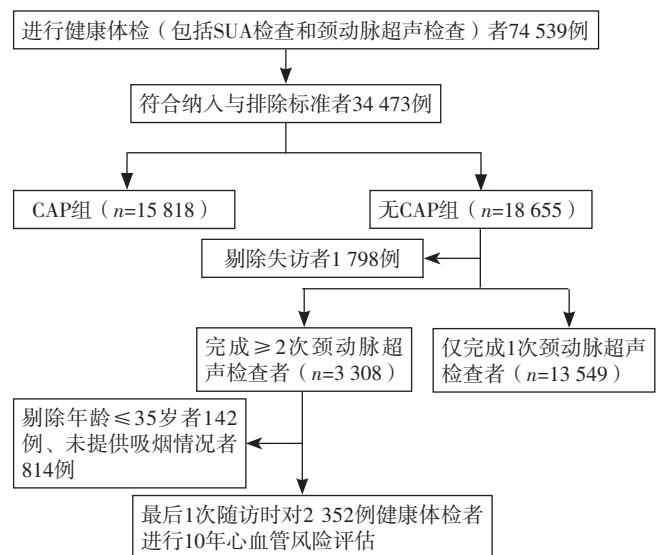
【Key words】 Plaque, atherosclerotic; Uric acid; Cardiovascular disease risk; Follow-up studies

颈动脉粥样硬化斑块 (carotid atherosclerotic plaque, CAP) 是冠心病发病的重要诱因。研究表明, 血清尿酸 (serum uric acid, SUA) 水平与多种心血管疾病危险因素密切相关^[1-2], 但其与CAP、心血管疾病之间的关系仍存在争议^[3-5]。有研究报道, SUA升高是动脉粥样硬化、心血管疾病的独立预测因子^[4]; 但也有流行病学研究显示, SUA与CAP、心血管疾病之间无直接的因果关系^[5-6]。基于此, 本研究分析了健康体检人群SUA与CAP、10年心血管疾病风险的关系, 旨在为降低颈动脉粥样硬化发病风险提供参考依据。

1 对象与方法

1.1 纳入与排除标准 纳入标准: (1) 年龄 ≥ 18 岁; (2) 完成体格检查和实验室检查。排除标准: (1) 有心血管疾病史者; (2) 正在服用别嘌醇、呋塞米、噻嗪类药物者; (3) 合并肿瘤者; (4) 有急、慢性肾衰竭史者。

1.2 研究对象 2013—2016年在西安交通大学第一附属医院健康医学科进行健康体检 (包括SUA检查和颈动脉超声检查) 者共74 539例, 选取其中符合纳入与排除标准者34 473例, 其中男22 080例、女12 393例; 平均年龄 (53.4 ± 12.5) 岁。根据首次颈动脉超声检查结果将健康体检者分为CAP组 ($n=15 818$) 和无CAP组 ($n=18 655$)。本研究设计流程见图1。本研究符合西安交通大学第一附属医院伦理委员会伦理审查要求, 所有健康体检者对本研究知情并同意参加。



注: SUA=血清尿酸, CAP=颈动脉粥样硬化斑块

图1 本研究设计流程

Figure 1 Design process of this study

1.3 一般资料收集与实验室检查 收集健康体检者的一般资料, 包括年龄、性别、体质量、身高、收缩压 (systolic blood pressure, SBP)、舒张压 (diastolic blood pressure, DBP), 并计算体质指数 (body mass index, BMI), $BMI = \text{体质量} / \text{身高}^2$ 。所有健康体检者禁食10~12 h后采集其肘静脉血, 使用化学自动分析仪检测SUA水平、血脂指标 (TC、TG、HDL-C、LDL-C)、肝功能指标 (ALT和AST)、总蛋白、白

蛋白、球蛋白、空腹血糖及肾功能指标(尿素氮和肌酐)。以颈动脉超声检查显示颈动脉内膜中膜厚度(intima media thickness, IMT) ≥ 1.0 mm或分叉处IMT ≥ 1.2 mm判定为CAP^[7-8]。

1.4 随访 所有健康体检者以首次颈动脉超声检查为随访起点,以后续体检时颈动脉超声检查显示CAP为随访终点事件,随访截止时间为2023-01-31。

1.5 10年心血管疾病风险评估 最后1次随访时,采用国人缺血性心血管病10年发病风险评估表对3 308例健康体检中年龄 >35 岁且有吸烟情况的2 352例健康体检者进行10年心血管疾病风险评估^[9-10]。

1.6 统计学方法 应用SPSS 23.0统计学软件进行数据处理。符合正态分布的计量资料以($\bar{x} \pm s$)表示,两组间比较采用成组t检验;不符合正态分布的计量资料以M(QR)表示,多组间比较采用Kruskal-Wallis检验,组间两两比较采用非参数检验;计数资料以相对数表示,两组间比较采用 χ^2 检验,多组间比较采用趋势 χ^2 检验;健康体检者发生CAP的影响因素分析采用多因素Logistic回归分析;SUA与健康体检者10年心血管疾病风险的相关性分析采用Spearman秩相关分析。以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 CAP组与无CAP组一般资料和实验室检查结果比较

CAP组年龄大于无CAP组,男性占比、BMI、SBP、DBP、SUA、TC、TG、LDL-C、AST、球蛋白、空腹血糖、尿素氮、肌酐高于无CAP组,HDL-C、ALT、总蛋白、白蛋白低于无CAP组,差异有统计学意义($P < 0.05$),见表1。

2.2 健康体检者发生CAP的影响因素 以健康体检者是否发生CAP为因变量(赋值:未发生=0,发生=1),以表1中差异有统计学意义的项目为自变量,进行多因素Logistic回归分析,结果显示,年龄、男性、BMI、SBP、SUA、TC、TG、HDL-C、白蛋白、空腹血糖、尿素氮、肌酐是健康体检者发生CAP的独立影响因素($P < 0.05$),见表2。

2.3 SUA与健康体检者发生CAP的关系 本研究对无CAP组中完成 ≥ 2 次颈动脉超声检查的3 308例健康体检者共随访了7~9年。结果显示,共1 530例健康体检者发生了CAP,CAP发生率为46.2%。根据基线SUA的四分位数将3 308例健康体检者分为Q1组($SUA \leq 259 \mu\text{mol/L}$, $n=829$)、Q2组($259 \mu\text{mol/L} < SUA \leq 316 \mu\text{mol/L}$, $n=830$)、Q3组($316 \mu\text{mol/L} < SUA \leq 379 \mu\text{mol/L}$, $n=824$)、Q4组($SUA > 379 \mu\text{mol/L}$, $n=825$)。Q1组、Q2组、Q3组、Q4组随访期间CAP发生率分别为41.74%(346/829)、45.54%(378/830)、

表1 CAP组与无CAP组一般资料和实验室检查结果比较

Table 1 Comparison of general data and laboratory examination results between CAP group and non-CAP group

项目	无CAP组 (n=18 655)	CAP组 (n=15 818)	t (χ^2) 值	P值
年龄($\bar{x} \pm s$, 岁)	47.4 \pm 10.2	60.4 \pm 11.1	-112.877	<0.001
男性[n(%)]	10 669 (57.2)	11 411 (72.1)	830.673 ^a	<0.001
BMI($\bar{x} \pm s$, kg/m ²)	24.4 \pm 3.2	24.7 \pm 3.0	-8.846	<0.001
SBP($\bar{x} \pm s$, mm Hg)	118 \pm 16	127 \pm 18	-49.897	<0.001
DBP($\bar{x} \pm s$, mm Hg)	77 \pm 11	80 \pm 11	-22.250	<0.001
SUA($\bar{x} \pm s$, $\mu\text{mol/L}$)	330 \pm 88	345 \pm 83	-16.253	<0.001
TC($\bar{x} \pm s$, mmol/L)	4.63 \pm 0.86	4.69 \pm 0.97	-5.873	<0.001
TG($\bar{x} \pm s$, mmol/L)	1.68 \pm 1.37	1.74 \pm 1.24	-4.154	<0.001
HDL-C($\bar{x} \pm s$, mmol/L)	1.27 \pm 0.31	1.21 \pm 0.29	18.436	<0.001
LDL-C($\bar{x} \pm s$, mmol/L)	2.81 \pm 0.75	2.90 \pm 0.86	-10.007	<0.001
ALT($\bar{x} \pm s$, U/L)	25.5 \pm 21.7	24.5 \pm 16.5	3.291	0.001
AST($\bar{x} \pm s$, U/L)	22.4 \pm 11.1	22.8 \pm 9.3	-2.575	0.010
总蛋白($\bar{x} \pm s$, g/L)	74 \pm 4	73 \pm 4	13.402	<0.001
白蛋白($\bar{x} \pm s$, g/L)	46 \pm 3	45 \pm 3	29.923	<0.001
球蛋白($\bar{x} \pm s$, g/L)	28 \pm 3	28 \pm 4	-6.052	<0.001
空腹血糖($\bar{x} \pm s$, mmol/L)	4.8 \pm 1.1	5.2 \pm 1.6	-14.804	<0.001
尿素氮($\bar{x} \pm s$, mmol/L)	5.0 \pm 1.2	5.4 \pm 1.4	-28.771	<0.001
肌酐($\bar{x} \pm s$, $\mu\text{mol/L}$)	63 \pm 17	68 \pm 23	-19.576	<0.001

注: CAP=颈动脉粥样硬化斑块, SBP=收缩压, DBP=舒张压, BMI=体质指数, SUA=血清尿酸; ^a表示 χ^2 值; 1 mm Hg=0.133 kPa

表2 健康体检者发生CAP影响因素的多因素Logistic回归分析

Table 2 Multivariate Logistic regression analysis of the influencing factors of CAP in people undergoing health examinations

变量	赋值	β	SE	Wald χ^2 值	P值	OR值	95%CI
年龄	实测值	0.113	0.002	4 941.521	<0.001	1.119	(1.116, 1.123)
男性	否=0, 是=1	-0.739	0.036	413.697	<0.001	0.478	(0.445, 0.513)
BMI	实测值	-0.022	0.005	19.515	<0.001	0.978	(0.968, 0.988)
SBP	实测值	0.009	0.001	51.475	<0.001	1.009	(1.006, 1.011)
DBP	实测值	0.001	0.002	0.628	0.428	1.001	(0.998, 1.005)
SUA	实测值	0.000	0.000	4.015	0.045	1.000	(1.000, 1.001)
TC	实测值	0.270	0.084	10.430	0.001	1.310	(1.112, 1.544)
TG	实测值	-0.088	0.023	14.631	<0.001	0.916	(0.875, 0.958)
HDL-C	实测值	-0.730	0.102	51.676	<0.001	0.482	(0.395, 0.588)
LDL-C	实测值	-0.032	0.080	0.157	0.692	0.969	(0.828, 1.134)
ALT	实测值	0.000	0.001	0.017	0.896	1.000	(0.998, 1.002)
AST	实测值	0.000	0.002	0.021	0.885	1.000	(0.996, 1.005)
总蛋白	实测值	0.002	0.011	0.022	0.882	1.002	(0.980, 1.024)
白蛋白	实测值	-0.036	0.018	3.897	0.048	0.964	(0.930, 1.000)
球蛋白	实测值	0.202	0.187	1.166	0.280	1.224	(0.848, 1.767)
空腹血糖	实测值	0.068	0.010	44.409	<0.001	1.070	(1.049, 1.092)
尿素氮	实测值	0.033	0.011	8.905	0.003	1.033	(1.011, 1.056)
肌酐	实测值	-0.003	0.001	13.855	<0.001	0.997	(0.995, 0.999)
常量	-	-5.974	0.455	172.427	<0.001	0.003	-

注: -表示无相关数据

49.39% (407/824)、48.36% (399/825)；随着SUA升高，健康体检者CAP发生率呈逐渐升高趋势 ($\chi^2_{趋势}=11.716, P=0.008$)，见表3。

表3 3 308例健康体检者随访期间CAP发生情况(例)

Table 3 Incidence of CAP in 3 308 people undergoing health examinations during follow-up period

组别	例数	第1年	第2年	第3年	第4年	第5年	第6年	第7~9年
Q1组	829	0	80	65	75	54	50	22
Q2组	830	0	106	81	80	43	43	25
Q3组	824	0	133	106	95	40	25	8
Q4组	825	0	163	101	61	60	5	9

2.4 SUA与健康体检者10年心血管疾病风险的关系
对3 308例健康体检者中年龄>35岁且有吸烟情况的2 352例健康体检者进行10年心血管疾病风险评估，其中Q1组631例、Q2组605例、Q3组579例、Q4组537例，其10年心血管疾病风险分别为0.5% (1.3%)、1.5% (1.8%)、2.1% (2.1%)、2.1% (2.8%)。四组10年心血管疾病风险比较，差异有统计学意义 ($H=345.726, P<0.05$)；Q2组、Q3组、Q4组10年心血管疾病风险高于Q1组，Q3组、Q4组10年心血管疾病风险高于Q2组，Q4组10年心血管疾病风险高于Q3组，差异有统计学意义 ($P<0.05$)。Spearman秩相关分析结果显示，SUA与健康体检者10年心血管疾病风险呈正相关 ($r_s=0.223, P<0.001$)。

3 讨论

近年越来越多的流行病学和临床证据表明，SUA与许多心血管疾病危险因素密切相关，如肥胖、高血压、高脂血症、糖尿病、代谢综合征和亚临床动脉粥样硬化^[11-12]。CAP是动脉粥样硬化的一种典型表现，而SUA升高是不同人群发生动脉粥样硬化、心血管疾病和死亡的独立预测因子^[11]。但目前关于SUA与CAP、心血管疾病关系的研究结果仍存在争议^[3-5]。本研究旨在分析健康体检人群SUA与CAP、10年心血管疾病风险的关系，结果显示，CAP组SUA高于无CAP组；多因素Logistic回归分析结果显示，SUA升高是健康体检者发生CAP的危险因素；本研究对无CAP组中完成≥2次颈动脉超声检查的3 308例健康体检者共随访了7~9年，结果显示，随着SUA升高，健康体检者CAP发生率呈升高趋势，提示SUA升高是健康体检人群发生CAP的危险因素，SUA越高的健康体检人群CAP发生风险越高。URRAH研究^[13]结果表明，SUA升高可被视为额外的心血管疾病危险因素。本研究对3 308例健康体检者中年龄>35岁且有吸烟情况的2 352例健康体检者进行10年心血管疾病风险评估，结果显示，SUA与健康体检者10

年心血管疾病风险呈正相关，提示随着SUA升高，健康体检人群10年心血管疾病风险逐渐升高。但SUA导致心血管疾病风险逐渐升高的具体机制尚未完全阐明，可能原因如下：高尿酸血症与脂代谢紊乱、氧化应激、胰岛素抵抗/糖尿病、内质网应激有关，进而可能导致血管损伤^[14-15]；尿酸易沉积于血管壁，可刺激血管平滑肌细胞增殖；高尿酸可激活肾素-血管紧张素系统，抑制一氧化氮产生，进而诱导内皮细胞功能障碍^[16]；此外，尿酸升高可能导致炎症反应加重，进而造成血管损伤^[17]。因此，SUA升高可能影响血管功能，形成动脉粥样硬化，导致健康体检人群10年心血管疾病风险逐渐升高。

综上所述，SUA升高是健康体检人群发生CAP的危险因素，且SUA越高的健康体检人群CAP发生风险、10年心血管疾病风险越高，这为SUA与心血管疾病之间的关系提供了有力证据。但本研究纳入的健康体检者年龄偏大、男性占比偏高，导致其CAP潜在风险和10年心血管疾病风险高于一般人群，故本研究结论的推广性受限。此外，本研究未考虑SUA与其他心血管疾病危险因素之间的复杂关系。

作者贡献：杨玉环负责研究实施、论文撰写；王军负责统计学分析；缪瑾瑾、蒿花进行数据收集、整理；张明明、苏石负责文章的质量控制及审校；马茂对文章整体负责、监督管理。

本文无利益冲突。

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