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Serum uric acid can predict higher C-reactive protein levels in apparently healthy men

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Abstract

Introduction: **Epidemiological studies have shown an association between coronary heart disease and emerging cardiovascular risk factors, such as, levels of fibrinogen and high-sensitivity C-reactive protein (hs-CRP).**

Objectives: **To verify the ability of biochemical indicators in discriminating changes in the levels of hs-CRP and fibrinogen, in apparently healthy adult men.**

Methods: **Were evaluated 130 apparently healthy men (20-59 years), having measurement of weight and height. Biochemical measurements (lipid profile, fasting glucose, uric acid, hs-CRP and fibrinogen) were performed. Body mass index, total cholesterol/HDL-c and LDL-c/HDL-c ratios were calculated. It was considered as the cutoff point for hs-CRP values ≥ 0.12 mg/dL and for fibrinogen the 50th percentile of the evaluated sample.**

Results: **The uric acid showed the best correlation (r = 0.325) and the higher area under the ROC curve (0.704 ± 0.054), showing greater ability to discriminate higher levels of hs-CRP (p < 0.01). The total cholesterol/HDL-c ratio (r = 0.222) and the LDL-c/HDL-c ratio (r = 0.235) showed the best correlations and the higher areas under the ROC curves (0.624 ± 0.049 and 0.624 ± 0.049) in identify higher levels of fibrinogen (p < 0.05).**

Conclusion: **The uric acid and the total cholesterol/HDL-c and the LDL-c/HDL-c ratios showed greater ability to identify changes in the levels of hs-CRP and fibrinogen, respectively. It was suggested the use of biochemical markers in the clinical practice, in order to establish preventive action for cardiovascular disease in apparently healthy adult men.**

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Key words: *Lipoproteins. Uric Acid. Fibrinogen. C-reactive protein. Inflammation.*

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ÁCIDO ÚRICO SÉRICO PUEDE PREDECIR MAYORES NIVELES DE PROTEÍNA C-REACTIVA EN HOMBRES ADULTOS SANOS

Resumen

Introducción: **Los estudios epidemiológicos han demostrado una asociación entre la enfermedad coronaria y nuevos factores de riesgo cardiovascular, como, los niveles de proteína C-reactiva ultrasensible (PCR-us) y fibrinógeno.**

Objetivos: **Evaluar la capacidad de los indicadores bioquímicos en discriminar cambios en los niveles de PCR-us y fibrinógeno, en hombres adultos sanos.**

Métodos: **Se evaluaron 130 hombres (20-59 años). Se midió peso y talla. Se realizó mediciones bioquímicas (perfil lipídico, glucosa en ayunas, ácido úrico, PCR-us y fibrinógeno). Se calculó el índice de masa corporal, la relación colesterol total/HDL-c y la relación LDL-c/HDL-c. Se consideró como punto de corte para los valores de PCR-us ≥ 0,12 mg/dL y para el fibrinógeno se utilizó el percentil 50 de la muestra evaluada.**

Resultados: **El ácido úrico mostró la mejor correlación (r = 0,325) y el área más alta bajo la curva ROC (0,704 ± 0,054), mostrando una mayor capacidad predictiva para detectar niveles más altos de PCR-us (p < 0,01). La relación colesterol total/HDL-c (r = 0,222) y la relación LDL-c/HDL-c (r = 0,235) mostraron una mejor correlación y el área más alta bajo la curva ROC (0,624 ± 0,049 y 0,624 ± 0,049) en la identificación de niveles más altos de fibrinógeno (p < 0,05).**

Conclusiones: **El ácido úrico y la relación colesterol total/HDL-c y la relación LDL-c/HDL-c mostraron una mayor capacidad predictiva para detectar cambios en los niveles de PCR-us y fibrinógeno, respectivamente. Se sugirió el uso de marcadores bioquímicos en la práctica clínica, a fin de establecer medidas preventivas para la enfermedad cardiovascular en hombres adultos sanos.**

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Palabras clave: *Lipoproteínas. Ácido úrico. Fibrinógeno. Proteína C-reactiva. Inflamación.*

Abbreviations

ANOVA: Analysis of variance.
AUC: Areas under the ROC curves.
BMI: Body mass index.
CI: confidence interval.
CRP: C-reactive protein.
HDL-c: HDL cholesterol.
hs-CRP: high-sensitivity C-reactive protein.
LDL-c: LDL cholesterol.
ROC: Receiver Operating Characteristic.
WHO: World Health Organization.

Introduction

Obesity, insulin resistance and atherosclerotic disease are closely linked and may all be determinants of an increased acute-phase response[1]. Over fifty percent of coronary heart disease occurs in individuals without traditional risk factors, such as, hypertension, hypercholesterolemia, smoking, diabetes mellitus, obesity and physical inactivity, in Western countries[2,3]. Danesh et al.[4], in meta-analysis study, verified that several epidemilogical studies have shown an association between coronary heart disease and emerging cardiovascular risk factors, such as, leukocyte count, albumin, fibrinogen and C-reactive protein (CRP) levels.

High levels of CRP have been associated with increased risk of mortality due to myocardial infarction, stroke, peripheral arterial disease and ischemic heart disease in healthy men[5]. Strong correlation between cardiovascular risk fator, low HDL cholesterol (HDL-c), high levels of CRP and fibrinogen has been observed, suggesting that inflammation may play a important role in the development of atherosclerosis and other cardiovascular diseases[6]. Adding, young obese with insulin resistance exhibited higher CRP and fibrinogen levels compared with those without insulin resistance[7]. Fibrinogen has been recognized as an independent risk factor for atherosclerosis and its thrombotic complications in adults[8]. Furthermore, fibrinogen levels were positively associated with hypertension prevalence and incidence of hypertension in five years, in men, independent of other cardiovascular risk factors[9].

Serum uric acid levels have been an important marker for cardiovascular risk fators, such as, hypertension, obesity, dyslipidemia, hyperinsulinemia and physical inactivity[10,11]. Moreover, higher serum uric acid levels were positively associated with the presence of metabolic syndrome in Korean males and females[12]. Adding, Ioachimescu et al.[13] found that serum uric acid levels were predictors of mortality in patients with high risk of cardiovascular disease.

Few studies have considered the association between biochemical indicators and inflammatory biomarkers. In this study, we evaluated the ability of biochemical indicators in discriminating higher levels of high-sensitivity C-reactive protein (hs-CRP) and fibrinogen in apparently healthy adult men.

Methods

Participants and data collection

A cross sectional study was conducted on apparently healthy adult (20-59 years old) men using a convenience sampling method. Data were collected in the Nutrition Sector of the Universidade Federal de Viçosa, Brazil. Exclusion criteria of the participants included in this study were: body mass index (BMI) ≤ 18.5 kg/m^2 or ≥ 35 kg/m^2 [14], self-reported hypertension or treatment with antihypertensive medication, type 1 or type 2 diabetes[15], osteoarthritis, treatment with drugs that could interfere with the expression of inflammatory biomarkers (i.e.: hormonal and nonhormonal anti-inflammatory, statins, steroids, cyclosporine, anticonvulsants and diuretics), current smokers, bacterial infections at the time of collection (leukocyte count >11.000/mm^3)[16], individuals with levels of hs-CRP above 1.0 mg/dL suggesting the presence of inflammation and/or infection[17,18].

Anthropometric measurements

The anthropometric assessment was performed by a single trained examiner. The participants wore light clothes and were barefoot during the evaluation. The weight was measured in a digital electronic balance and the height was perfomed using a stadiometer, according to the techniques recommended by the World Health Organization (WHO)[19]. The BMI was calculated as the weight (kg) divided by the square of the height (m) and classified according to criteria established by the WHO[14,19,20].

Biochemical analysis

The blood samples were collected at the Clinical Analysis Laboratory of the Universidade Federal de Viçosa after a 12 hours overnight fasting. The determination of complete blood count was performed by flow cytometry, in order to detect the presence of bacterial infections at the time of collection (leukocyte count > 11.000/ mm^3)[16].

Serum levels of uric acid, total cholesterol, HDL-c and triglycerides were determined by enzymatic colorimetric method. The LDL cholesterol (LDL-c) levels was performed by the Friedewald formula[21]. It was calculated the total cholesterol/HDL-c and LDL-c/HDL-c ratios. Fasting glucose was analyzed by glucose oxidase method.

The hs-CRP was determined by nephelometry. Participants with hs-CRP levels above the 3rd quintile of the population distribution (≥ 0.12 mg/dL) were considered at higher relative risk of cardiovascular events[22,23].

Fibrinogen was estimated by the Clauss method. It was considered as the cutoff point for fibrinogen the 50th percentile of the evaluated sample.

Statistical analysis

Variables with normal distribution were analyzed with Student's t-test, analysis of variance (ANOVA) with Tukey's post hoc test and Pearson's correlation coefficient. Non-parametric variables were analyzed with Mann-Whitney test, Kruskal-Wallis test with Dunn's post hoc test and Spearman's correlation coefficient.

The areas under the Receiver Operating Characteristic (ROC) curves (AUC) were calculated for each biochemical indicator and risk condition. It was adopted a confidence interval (CI) of 95%[24].

The statistical analyses and ROC curves were performed by using SPSS for WINDOWS (version 15.0, SPSS Inc, Chicago, IL) and MedCalc (version 9.3). $P < 0.05$ was considered as statistically significant.

Ethical aspects

The general design of research was explained before the study began and all participants provided written informed consent. The protocol has been approved by the Ethics Committee on Human Research of the Universidade Federal de Viçosa (ref no. 006/2008), in accordance with the principles of the Helsinki Declaration[25].

Results

The characteristics of the study sample according to BMI are summarized in table I. Were evaluated 152 adult men, of which 130 filled out the inclusion criteria. The group with BMI ≥ 25 Kg/m^2 showed lower HDL-c levels, higher values for total cholesterol/HDL-c and LDL-c/HDL-c ratios and higher levels of triglycerides, fasting glucose and uric acid. No statistical diferences were found between age, blood pressure, levels of total cholesterol, LDL-c, hs-CRP and fibrinogen, comparing the group of eutrophic participants and those with overweight.

The group with hs-CRP levels ≥ 0.12 mg/dL had higher value for total cholesterol/HDL-c ratio, higher serum levels of uric acid and lower HDL-c levels ($p < 0.05$) (data not shown).

The distribution of biochemical indicators according to quartiles of fibrinogen levels found no statistical differences between them (table II).

There was a significant correlation between HDL-c, total cholesterol/HDL-c and LDL-c/HDL-c ratios with hs-CRP and fibrinogen levels. On the other hand, blood pressure and serum uric acid levels showed a significant correlation only with hs-CRP levels (table III).

After partial correlation analyzis, adjusted for BMI, only the uric acid levels remained significantly correlated with hs-CRP levels ($r = 0,281$; $p < 0,001$) and only the total cholesterol/HDL-c ($r = 0,190$; $p < 0,05$) and the LDL-c/HDL-c ($r = 0,211$; $p < 0,05$) ratios remained significantly correlated with fibrinogen levels (data not shown).

In agreement with the correlation analysis that detected the best correlation between the uric acid and the hs-CRP levels, the highest absolute value for AUC, in the ROC analysis (table IV), was represented by the serum uric acid, showing higher predictive ability for detecting higher hs-CRP levels. The application of the

Table I
Characteristics of the study sample according to body mass index

Variables	*BMI < 25 kg/m^2 (n = 71)*	*BMI ≥ 25 kg/m^2 (n = 59)*	*Total (n = 130)*
Age (years)	35 (20-59)	35 (20-54)	35 (20-59)
SBP (mmHg)	120 (100-150)	120 (100-150)	120 (100-150)
DBP (mmHg)	80 (60-100)	80 (60-100)	80 (60-100)
Total cholesterol (mg/dL)	185.69 ± 38.77	190.63 ± 35.99	187.93 ± 37.47
HDL-c (mg/ dL)	48 (29-105)	44 (24-89)†	46 (24-105)
LDL-c (mg/ dL)	117.94 ± 34.63	121.85 ± 32.49	119.71 ± 33.61
Total cholesterol / HDL-c	3.92 ± 1,20	4.49 ± 1,19†	4.18 ± 1,22
LDL-c/ HDL-c	2.52 ± 0.98	2.87 ± 0.96*	2.68 ± 0.98
Triglycerides (mg/dL)	75 (17-333)	111 (25-383)‡	84.5 (17-383)
Fasting glucose (mg/dL)	86.75 ± 7.98	90.8 ± 8.12†	88.58 ± 8.26
Uric acid (mg/dL)	3.9 (1.7-6.5)	4.6 (2.6-8.0)‡	4.0 (1.7-8.0)
hs-CRP (mg/dL)	0.08 (0.07-0.55)	0.10 (0.07-0.74)	0.08 (0.07-0.74)
Fibrinogen (mg/dL)	279.62 ± 43.7	287.19 ± 47.21	283.06 ± 45.31

Student's t-test for variables presented as mean ± standard deviation; Mann-Whitney test for variables presented as median (range).
*$p < 0.05$.
†$p < 0.01$.
‡$p < 0.001$.
BMI: Body Mass Index, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, HDL-c: HDL Cholesterol, LDL-c: LDL Cholesterol, hs-CRP: high-sensitivity C-reactive protein.

Table II
Distribution of biochemical indicators according to quartiles of fibrinogen levels

Variables	*1.º Quartile (n = 31) Fibrinogen ≤ 251.8 mg/dL*	*2.º Quartile (n = 34) Fibrinogen 251.9-277.5 mg/dL*	*3.º Quartile (n = 33) Fibrinogen 277.6-304.7 mg/dL*	*4.º Quartile (n = 32) Fibrinogen ≥ 304.8 mg/dL*
Total cholesterol (mg/dL)	174.1 ± 26.52	193.18 ± 43.20	195.18 ± 40.93	188.28 ± 34.18
HDL-c (mg/dL)	48 (29-105)	48.5 (24-89)	43.0 (31-75)	45 (27-83)
LDL-c (mg/dL)	107.04 ± 27.13	122 ± 36.46	126.37 ± 34.74	122.71 ± 33.22
Total cholesterol/HDL-c	3.72 ± 0.98	4.19 ± 1.40	4.32 ± 0.89	4.46 ± 1.44
LDL-c/HDL-c	2.33 ± 0.87	2.66 ± 1.07	2.79 ± 0.75	2.93 ± 1.15
Triglycerides (mg/dL)	78 (22-172)	79.5 (25-383)	92 (30-349)	86 (17-298)
Fasting glucose (mg/dL)	87.32 ± 7.41	87.85 ± 8.72	90.36 ± 9.78	88.75 ± 6.74
Uric acid (mg/dL)	4.07 ± 0.82	4.12 ± 1.04	4.41 ± 1.28	4.45 ± 1.28

ANOVA with Tukey's post hoc test for variables presented as mean ± standard deviation; Kruskal-Wallis test with Dunn`s post hoc test for variables presented as median (range). Comparisons between columns.
HDL-c: HDL Cholesterol, LDL-c: LDL Cholesterol.

Table III
Correlation between blood pressure, biochemical indicators and inflammatory biomarkers

Variables	*hs-CRP (95% CI)*	*Fibrinogen (95% CI)*
SBP (mmHg)	0.196 (0.024 to 0.356)*	0.084 (-0.090 to 0.252)
DBP (mmHg)	0.182 (0.010 to 0.343)*	0.066 (-0.107 to 0.235)
Total cholesterol (mg/dL)	0.059 (-0.114 to 0.229)	0.070 (-0.103 to 0.240)
HDL-c (mg/ dL)	-0.181 (-0.342 to -0.009)*	-0.191 (-0.351 to -0.019)*
LDL-c (mg/ dL)	0.093 (-0.080 to 0.261)	0.136 (-0.037 to 0.301)
Total cholesterol / HDL-c	0.191 (0.020 to 0.352)*	0.222 (0.052 to 0.380)*
LDL-c/ HDL-c	0.194 (0.022 to 0.354)*	0.235 (0.066 to 0.392)†
Triglycerides (mg/dL)	0.107 (-0.066 to 0.274)	0.076 (-0.098 to 0.245)
Fasting glucose (mg/dL)	0.065 (-0.108 to 0.235)	0.072 (-0.102 to 0.241)
Uric acid (mg/dL)	0.325 (0.162 to 0.471)†	0.142 (-0.031 to 0.307)

Pearson's correlation coeficiente for variables with normal distribution; Spearman's correlation coefficient for non-parametric variables.
*P < 0.05.
† p < 0.01.
hs-CRP: high-sensitivity C-reactive protein, CI: Confidence Interval, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, HDL-c: HDL Cholesterol, LDL-c: LDL Cholesterol.

Table IV
Areas under the ROC curves for biochemical indicators according to high-sensitivity C-reactive protein and fibrinogen levels

Variables	*hs-CRP AUC ± SE (IC 95%)*	*Fibrinogen AUC ± SE (IC 95%)*
Total cholesterol (mg/dL)	0.520±0.057 (0.408 to 0.631)	0.577±0.051 (0.478 to 0.676)
HDL-c (mg/dL)	0.617±0.052 (0.528 to 0.701)*	0.586±0.049 (0.497 to 0.672)
LDL-c (mg/dL)	0.517±0.056 (0.407 to 0.627)	0.599±0.050 (0.502 to 0.697)
Total cholesterol/HDL-c	0.590±0.057 (0.479 to 0.702)	0.624±0.049 (0.527 to 0.721)*
LDL-c/HDL-c	0.585±0.056 (0.475 to 0.695)	0.624±0.049 (0.527 to 0.720)*
Triglycerides (mg/dL)	0.583±0.056 (0.473 to 0.693)	0.544±0.051 (0.444 to 0.644)
Fasting glucose (mg/dL)	0.478±0.053 (0.373 to 0.583)	0.567±0.050 (0.468 to 0.666)
Uric acid (mg/dL)	0.704±0.054 (0.598 to 0.809)‡	0.575±0.050 (0.476 to 0.674)

* p < 0.05.
‡ p < 0.001.
hs-CRP: high-sensitivity C-reactive protein, AUC: Areas under the ROC curves, SE: Standard Error, CI: Confidence Interval, HDL-c: HDL cholesterol, LDL-c: LDL cholesterol.

Z test comparing AUC indicated that the uric acid levels had higher areas in relation to fasting glucose, LDL-c and total cholesterol ($p < 0.05$). In the ROC analysis, comparing different biochemical indicators and fibrinogen levels, the total cholesterol/HDL-c and the LDL-c/HDL-c ratios had the highest absolute values for AUC (table IV), indicating higher predictive ability for detecting higher fibrinogen levels. According to the Z test that compared the AUC, there were no statistically significant diferences ($p > 0.05$).

By assessing the cutoff points with greater accuracy for each biochemical indicator, the serum uric acid, the total cholesterol/HDL-c ratio and the LDL-c/HDL-c ratio reached the highest sum among the values of sensitivity and specificity for the cutoff points 4.4 mg/dL, 4.14 and 2.83, respectively (data not shown).

Discussion

Among the biochemical indicators assessed, the uric acid levels showed higher correlation with hs-CRP levels. It was observed positive significant correlation between total cholesterol/HDL-c and LDL-c/HDL-c ratios and hs-CRP and fibrinogen levels, and negative significant correlation between HDL-c and both inflammatory biomarkers. According to this, study with Brazilian population (14-74 years old) showed positive correlation between total cholesterol/HDL-c ratio and hs-CRP levels[26]. Imperatore et al.[27] verified negative correlation between fibrinogen levels and HDL-c ($r = - 0,110$; $p < 0,001$) and it was not observed significant correlation between fibrinogen levels and fasting glucose ($r = 0,0164$; $p > 0,05$).

In the presente study, total cholesterol, LDL-c, triglycerides and fasting glucose showed no significant correlation with hs-CRP and fibrinogen levels. Nevertheless, Aronson et al.[28] identified significant positive correlation between fasting glucose and CRP levels in adults. Individuals in the higher quartile of fasting glucose had higher CRP levels compared with those in the lowest quartile ($p < 0.05$). Whereas, Gui et al.[29] verified by multiple linear regression analysis that LDL-c was determinant of hs-CRP levels. Forouhi et al.[30] evaluated 113 healthy men and women from South Asia and Europe and showed that CRP levels were significantly associated with triglycerides and HDL-c in both groups ($p < 0.05$), by regression analysis adjusted for age, sex and smoking. However, Lemieux et al.[31] assessed 159 men (22-63 years old) and found no association between hs-CRP and lipid profile.

Blood pressure showed significant correlation only with hs-CRP levels in the presente study. Study with 150 participants from the Chennai Urban Rural Epidemiology Study (CURES) observed strong correlation between hs-CRP and systolic blood pressure ($r = 0.216$), fasting glucose ($r = 0.338$), total cholesterol ($r = 0.413$), triglycerides ($r = 0.201$), LDL-c ($r = 0.336$) and total cholesterol/HDL-c ratio ($r = 0.354$) ($p < 0.05$)[32]. Nakamura et al.[33] evaluated 262 Japanese healthy men and identified that triglycerides ($r = 0.20$), HDL-c ($r = -0.28$) and fasting glucose ($r = 0,15$) were significantly associated with hs-CRP levels ($p < 0.05$), whereas blood pressure did not show the same behavior ($p > 0.05$). On the other hand, Dupuy et al.[34] showed that the componentes of metabolic syndrome, such as, fasting glucose, triglycerides, HDL-c and blood pressure were significantly associated with CRP levels only in women. Hak et al.[1] found a significant association between CRP levels and variables related to insulin resistance syndrome, such as, blood pressure, insulin, HDL-c and triglycerides. However, no correlation were found between CRP levels and glucose, total cholesterol and LDL-c. In this same study, after adjustment for BMI, the association between CRP levels and variables related to insulin resistance syndrome disappeared.

Despite the present study did not found correlation between blood pressure and fibrinogen levels, Shankar et al.[9] found positive association with increasing tertiles of fibrinogen and prevalence of hypertension in men. Individuals in the highest tertile of fibrinogen showed odds ratio (OR) of 1.95 (1.03 to 3.68) compared with those in the lowest tertile. Imperatore et al.[27], in order to determine if the hyperfibrinogenemia (fibrinogen levels ≥ 350 mg/dL) representes a component of the metabolic syndrome, assessed 1,252 nondiabetic men (35-64 years old) and found significant positive association between fibrinogen levels and blood pressure, total cholesterol, LDL-c and triglycerides.

In the presente study, after partial correlation analyzis, adjusted for BMI, only the serum uric acid remained significant correlated with hs-CRP levels, whereas only the total cholesterol/HDL-c and the LDL/HDL-c ratios remained significant correlated with fibrinogen levels. The ROC analysis identified the serum uric acid as the best biochemical indicator to detect changes in hs- CRP levels, since this indicator showed the higher AUC. Whereas the total cholesterol/HDL-c and LDL-c/HDL-c ratios, in the ROC analysis, were the best indicators for detecting changes in fibrinogen levels. Ioachimescu et al.[13], in a study with 2,003 men (18-78 years old), observed that the uric acid significantly improved the predictive accuracy of a model that included Framingham Heart Study score factors, components of metabolic syndrome and fibrinogen levels. Niizeki et al.[35] suggested that the combination of biomarkers, such as, uric acid, sodium, hemoglobin, creatinine, creatinine clearance and hs-CRP, could potentially improve the risk stratification of patients with chronic heart failure in predicting cardiac events with low cost and wide availability.

Conclusion

The serum uric acid levels and the total cholesterol/HDL-c and the LDL-c/HDL-c ratios were the biochemical indicators more suitable for detecting

changes in hs-CRP and fibrinogen levels, respectively, in apparently healthy men. The results of the presente study suggest the use of these biochemical indicators in the clinical practice in order to improve the assessment of cardiovascular risk and establish measures to prevent cardiovascular diseases in adult males.

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