ORIGINAL ARTICLE

Serum uric acid and markers of low-density lipoprotein oxidation in nonsmoking healthy subjects: data from the Brisighella Heart Study

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KEY WORDS

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ABSTRACT

INTRODUCTION Serum uric acid (SUA) levels, an inexpensive and standardized marker of systemic oxidative stress, has been recently associated with the risk of atherosclerotic cardiovascular events.

OBJECTIVES The main objective of the study was to evaluate the possible relationship between SUA, oxidized low-density lipoproteins (oxLDLs) and LDL susceptibility to oxidation in a sample of nonsmoking healthy subjects.

PATIENTS AND METHODS From the general database of the Brisighella Heart Study, we selected a sample of 354 nonsmoking and pharmacologically untreated adult subjects, in primary prevention for cardiovascular disease, with normal renal function, and without known allergic or rheumatic diseases, who were visited during the 2008 population survey. A full set of clinical and hematochemical parameters was evaluated together with oxidative susceptibility of LDL and oxLDL levels.

RESULTS In a multivariate analysis, the oxLDL level was positively correlated with apolipoprotein B (ApoB; B = 0.077; 95% confidence interval [CI], 0.015–0.139; P = 0.016), triglicerydes (B = 0.050; 95% CI, 0.032–0.069; P <0.001), LDL cholesterol (B = 0.102; 95% CI, 0.052–0.153; P <0.001) and SUA (B = 1.106; 95% CI, 0.405–1.807; P = 0.002). The diene level was positively correlated with the levels of LDL cholesterol (B = 0.685; 95% CI, 0.347–1.023; P <0.001), SUA (B = 2.201; 95% CI, 1.117–5.285; P <0.001), and ApoB (B = 0.717; 95% CI, 0.404–1.031; P <0.001). The LDL lag phase was inversely correlated with ApoB (P = 0.001) and fasting plasma glucose (P = 0.022). The propagation phase was positively correlated with age (P = 0.013) and inversely with triglycerides (P = 0.015).

CONCLUSIONS In a sample of healthy subjects, SUA is significantly associated to oxLDL and diene levels, but not to LDL lag phase and propagation phase.

INTRODUCTION Cardiovascular diseases are still the most common cause of death in developed countries.[1] The atherosclerotic process involves several oxidative reactions such as the development of oxygen and peroxyl radicals and oxidation of low-density lipoprotein (LDL) cholesterol, which is an important target of free radicals in blood.[2] Oxidative burst is an innate immune response to infection, the latter being also associated with marked changes in lipid and lipoprotein metabolism, aimed at neutralizing the endotoxin toxic effects. However, the oxidation of lipoproteins, resulting from an imbalance of the pro- and antioxidant equilibrium, is the main step in the development of atherosclerosis.[3] Lipid oxidation, induced by leukocyte-derived reactive oxygen species, can in fact amplify foam cell production through oxidized LDL (oxLDL) formation and uptake. OxLDLs are capable of inducing numerous proatherogenic processes, including the modulation of oxidative burst and modulation of stem cell proliferation.[4] OxLDLs may

TABLE 1 Clinical, laboratory, and low-density lipoprotein-related oxidation parameters in the study population

Parameter	Value	Parameter	Value
age, y	42.3 ±5.3	FPG, mg/dl	91.6 ±11.6
body mass index, kg/m²	26.2 ±4.6	GGT, U/l	24.5 ±5.6
SBP, mmHg	132.4 ±16.9	GOT, U/l	27.0 ±4.0
DBP, mmHg	83.3 ±11.1	GPT, U/l	29.7 ±6.1
heart rate, bpm	65.5 ±9.9	serum uric acid, mg/dl	5.1 ±1.4
total cholesterol, mg/dl	207.6 ±15.2	creatinine, mg/dl	0.8 ±0.2
HDL-C, mg/dl	47.2 ±11.8	eGFR, ml/min	74.3 ±6.3
TG, mg/dl	109.6 ±23.8	LDL lag phase, min	85.9 ±23.8
LDL-C, mg/dl	136.7 ±14.8	LDL propagation phase, min	39.9 ±12.7
apolipoprotein B, mg/dl	100.4 ±16.7	dienes, mcmol/dl	259.5 ±112.5
apolipoprotein A1, mg/dl	153.2 ±25.6	oxidized LDL, U/l	43.1 ±14.1

Data are presented as mean ± standard deviation.

Conversion factors to SI units are as follows: for glucose, 0.05551; cholesterol, 0.02586; and triglycerides, 0.0114.

Abbreviations: DBP – diastolic blood pressure, FGP – fasting plasma glucose, GGT – γ-glutamyltransferase, GOT – glutamic-oxaloacetictransaminase, GPT – glutamic-pyruvictransaminase, eGFR – estimated glomerular filtration rate, HDL-C – high-density lipoprotein cholesterol, LDL – low-density lipoprotein, LDL-C – LDL cholesterol, SBP – systolic blood pressure, TG – triglicerydes

also induce maturation of dendritic cells and regulate the shift from classical (M1) to alternative (M2) macrophage activation and from T helper 1 to T helper 2 response, suggesting that these could act as a bridge between innate and adaptive immunity, both involved in plaque development.[5]

On the other side, serum uric acid (SUA), an inexpensive and standardized marker of systemic oxidative stress, has been recently associated with the risk of atherosclerotic cardiovascular events.[6] In particular, recent data support the SUA role as a cardiovascular risk factor also in healthy subjects,[7] where SUA is associated with early markers of vascular stiffness.[8,9] Its detrimental effects on the cardiovascular system include mediating immune response upon cell injury,[10] increasing endotoxin-stimulated tumor necrosis factor α production, and hence, proinflammatory immune activation.[11] Therefore, high levels of SUA may contribute to increased cardiovascular damage through direct injury to the endothelium and alteration of cardiovascular function. Paradoxically, SUA may also provide protective antioxidant effects on the cardiovascular system, but these benefits may be overwhelmed by the negative effects.[12]

In this context, the aim of our study was to evaluate the possible relationship between SUA, oxLDLs, and LDL susceptibility to oxidation in a relatively large sample of nonsmoking healthy subjects.

PATIENTS AND METHODS The Brisighella Heart Study is a longitudinal population study started in 1972 and including a randomized sample representative of the population of Brisighella, a rural village in northern Italy. The full protocol and history of the study have been extensively described elsewhere.[13]

All available routine clinical and laboratory parameters have been sampled with standardized methods.[14,15] The study was conducted in agreement with the Declaration of Helsinki. The protocol was approved by the institutional ethical board of the University Hospital of Bologna, Italy.

For this substudy, we used the general database of the Brisighella Heart Study to select a sample of nonsmoking and pharmacologically untreated adult subjects (aged between 20 and 55 years), in primary prevention for cardiovascular disease, with normal renal function, without known allergic or rheumatic diseases (including gout), and not receiving antioxidant dietary supplements, who were visited during the 2008 population survey. Pregnant or nursing women and women taking estrogens or estrogen-progestin oral contraceptives were also excluded. Metabolic syndrome was defined according to the latest guidelines.[16]

Oxidative susceptibility of LDL was obtained using the method of Esterbauer et al.,[17] by monitoring the kinetics of LDL oxidation by changing the 234-nm diene absorption. The time-course shows 3 consecutive phases: 1) a lag phase during which no oxidation occurs, measured in minutes and proportional to LDL resistance to oxidation, 2) a propagation phase with a rapid increase of conjugated diene production and absorption, 3) a diene-decomposition phase characterized by a slow increase in absorbance when the conjugate diene on LDL (dienemol/LDL mg) is calculated. The lag time was used to evaluate the oxidative susceptibility of LDL after ultracentrifuge isolation.

The oxLDL dosage was obtained using a standardized enzyme-linked immunosorbent assay kit (Mercodia, Uppsala, Sweden), including monoclonal antibodies against specific antigenic

determinants on the oxidized apolipoprotein B100 (ApoB).[18]

A full descriptive analysis was conducted for the considered variables. A Kolmogorov–Smirnov normality test was used for all continuous variables. Nonnormally distributed parameters were then log-transformed before being used in further analyses. In the first step, we carried out a bivariate correlation analysis between SUA, oxLDL, dienes, and LDL lag phase and propagation phase. Then, we performed a univariate linear regression analysis using oxLDL, dienes, and LDL lag phase and propagation phase as dependent variables, and age, body mass index, LDL cholesterol, ApoB, SUA, and estimated glomerular filtration rate as independent variables, excluding at each step the single most extreme data by the Dunkan test to reduce possible interferences by extreme values. We repeated the analysis in men and women (without adjusting for sex). All tests were carried out using SPSS 21.0 for Windows (IBM, Massachusetts, United States). A *P* value of 0.05 was considered statistically significant.

RESULTS The final sample included 384 subjects (156 men and 228 women). Their main clinical characteristics, laboratory and LDL-related oxidation parameters are summarized in **TABLE 1**. Overweight was observed in 24% of the subjects; 29% of the patients had normal-high or first stage hypertension, 31% showed suboptimal LDL cholesterol levels (>115 mg/dl), and 28% had metabolic syndrome.

In the Pearson bivariate correlation analysis, SUA levels were significantly related to those of dienes (*r* = 0.178; *P* = 0.001) and oxLDL (*r* = 0.284; *P* <0.001), but not to LDL lag phase (*r* = 0.057; *P* = 0.285) and propagation phase (*r* = 0.016; *P* = 0.767).

In the univariate analysis, SUA levels were inversely correlated with LDL lag phase (*P* = 0.049) and positively with the levels of dienes (*P* = 0.001) and oxLDL (*P* <0.001). There was no significant association between SUA and the propagation phase (*P* = 0.614; **FIGURE**). The results of the univariate analysis are shown in **TABLE 2**.

In the multivariate analysis, the oxLDL level was positively correlated with ApoB (B = 0.077; 95% confidence interval [CI], 0.015–0.139; *P* = 0.016), triglycerides (B = 0.050; 95% CI, 0.032–0.069; *P* <0.001), LDL cholesterol (B = 0.102; 95% CI, 0.052–0.153; *P* <0.001), and SUA (B = 1.106; 95% CI 0.405–1.807; *P* = 0.002). The diene level was positively correlated with the levels of LDL cholesterol (B = 0.685; 95% CI, 0.347–1.023; *P* <0.001), SUA (B = 2.201; 95% CI, 1.117–5.285; *P* <0.001), and ApoB (B = 0.717; 95% CI, 0.404–1.031; *P* <0.001).

The LDL lag phase was inversely correlated with ApoB (B = –0.166; 95% CI, –0.259 to –0.073, *P* = 0.001) and fasting plasma glucose (B = –0.254; 95% CI, –0.471 to –0.037; *P* = 0.022). The propagation phase was positively correlated with age (B = 0.117; 95% CI, 0.025–0.209; *P* = 0.013) and

inversely with triglycerides (B = –0.021; 95% CI, –0.038 to –0.004; *P* = 0.015). Similar results were also obtained when the analysis was repeated in men and women (without adjusting for sex).

DISCUSSION Different hypotheses linked SUA levels with oxLDL levels in healthy subjects. We hypothesized that the common pathway is related to systemic oxidative stress. In fact, at normal levels, SUA exhibits some antioxidant properties acting as a strong peroxynitrite scavenger, accounting for up to 60% of serum free radical scavenging capacity[19] and being an important intracellular free radical scavenger during metabolic stresses,[20] including nitric oxide and peroxyl and hydroxyl radicals.[21] On the contrary, high SUA levels are considered as promoters of oxidative stress. The biochemical process leading to hyperuricemia increases the generation of free oxygen radicals in the proportion of 1 molecule of superoxide for each single molecule of SUA produced, with a negative impact on the microcirculation and the development of arteriolar disease, particularly at renal level.[22] Experimental evidence suggests that hyperuricemia can impair endothelial function by promoting an increased oxidative state, which in turn downregulates endothelial nitric oxide production, in a condition where nitric oxide has a central role in the modulation of vascular flow and blood pressure.[23] Hyperuricemia also inhibits endothelial cell proliferation and migration, and stimulates the release of inflammatory C-reactive protein, growth factors, and free oxygen radicals.[24] In addition, the negative effects of SUA also involve smooth muscle cells, where it is capable of stimulating cellular proliferation via the mitogen-activated protein kinase pathway and inducing the synthesis of proinflammatory substances such as chemokine, monocyte chemoattractant protein 1, and C-reactive protein. Finally, SUA has also been proved to strongly activate the renin–angiotensin system, promoting both AT1 and AT2 receptor and angiotensin II expression, with angiotensin II showing the ability to inhibit cell proliferation and promote endothelial senescence and apoptosis.[25]

The peroxidation of lipids in membranes and lipoproteins proceeds through the classical free radical sequence encompassing initiation, propagation, and termination phases, which are expressed by the lag phase, in which little oxidation occurs, followed by a rapid increase in autocatalysis by chain-propagating intermediates, and, finally, by a decrease in the rate of oxidation. Hence, the lag phase in lipid peroxidation processes reflects the antioxidant status of membranes and lipoproteins and, as a corollary, their resistance to oxidation. The propagation phase represents the rate of lipid peroxidation.[26] Beyond their pathophysiological role in the development of atherosclerosis, oxLDLs are also associated with the upregulation of AT2 receptors, thus contributing to the development of hypertension similarly to SUA.[27]

FIGURE Linear regression between serum uric acid (SUA) levels and low-density lipoprotein (LDL)-related oxidation parameters
Abbreviations: oxLDL – oxidized LDL
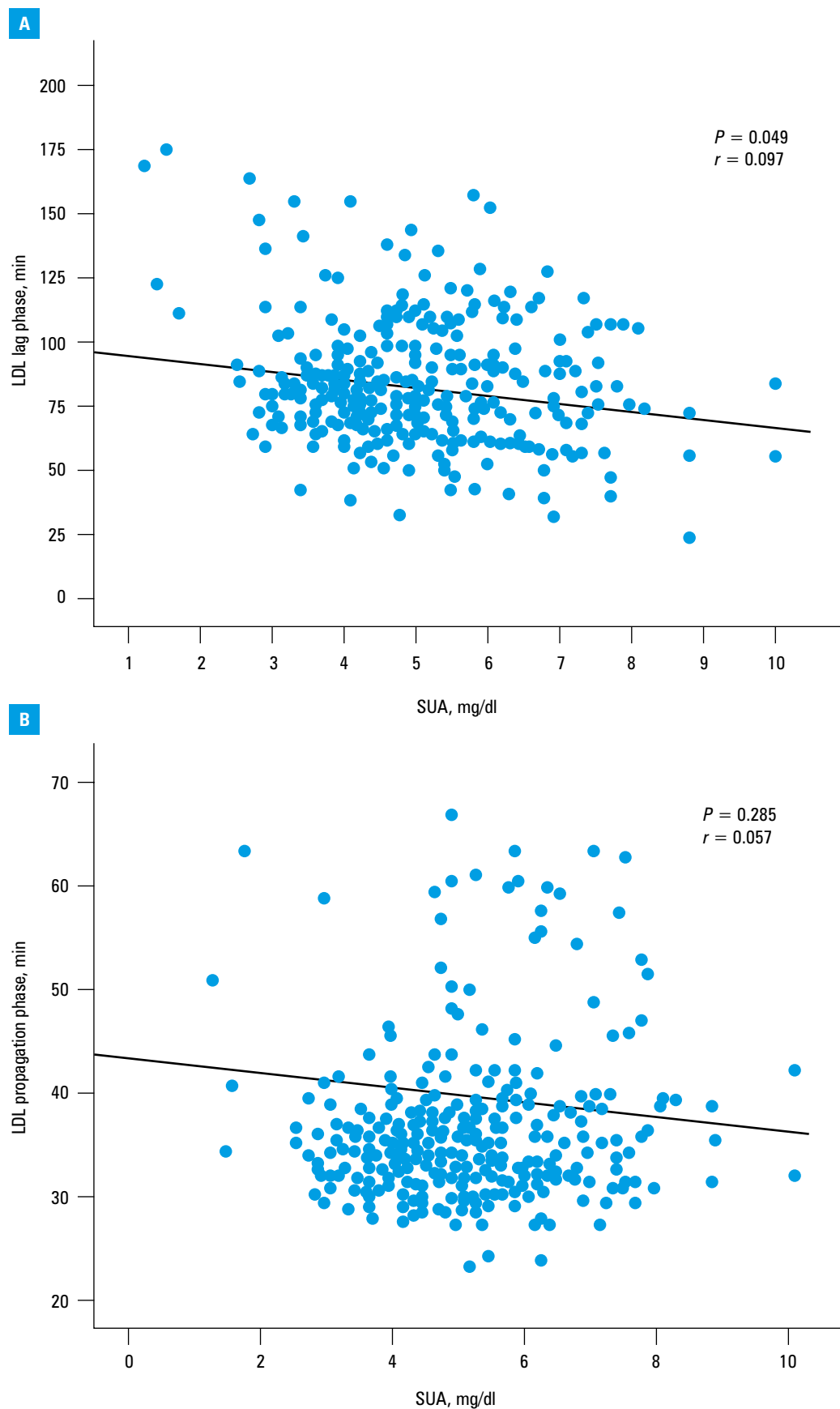
In our study, we observed that SUA was associated with the level of oxLDL in a relatively large sample of generally healthy elderly men and women. These data are in agreement with those reported by Barbosa et al.[28] in a smaller sample of younger subjects and by Ruíz-Hernández et al.,[29] who limited their study to overweight women. We also observed that SUA was associated with the diene level, but not with the length of the LDL lag phase and propagation phase. The formation of conjugated dienes is an early event of lipid peroxidation taking place soon after the initiation of

C

diene, mcmol/dl vs SUA, mg/dl

P = 0.001
r = 0.178

D

oxLDL, U/l vs SUA, mg/dl

P = 0.001
r = 0.284
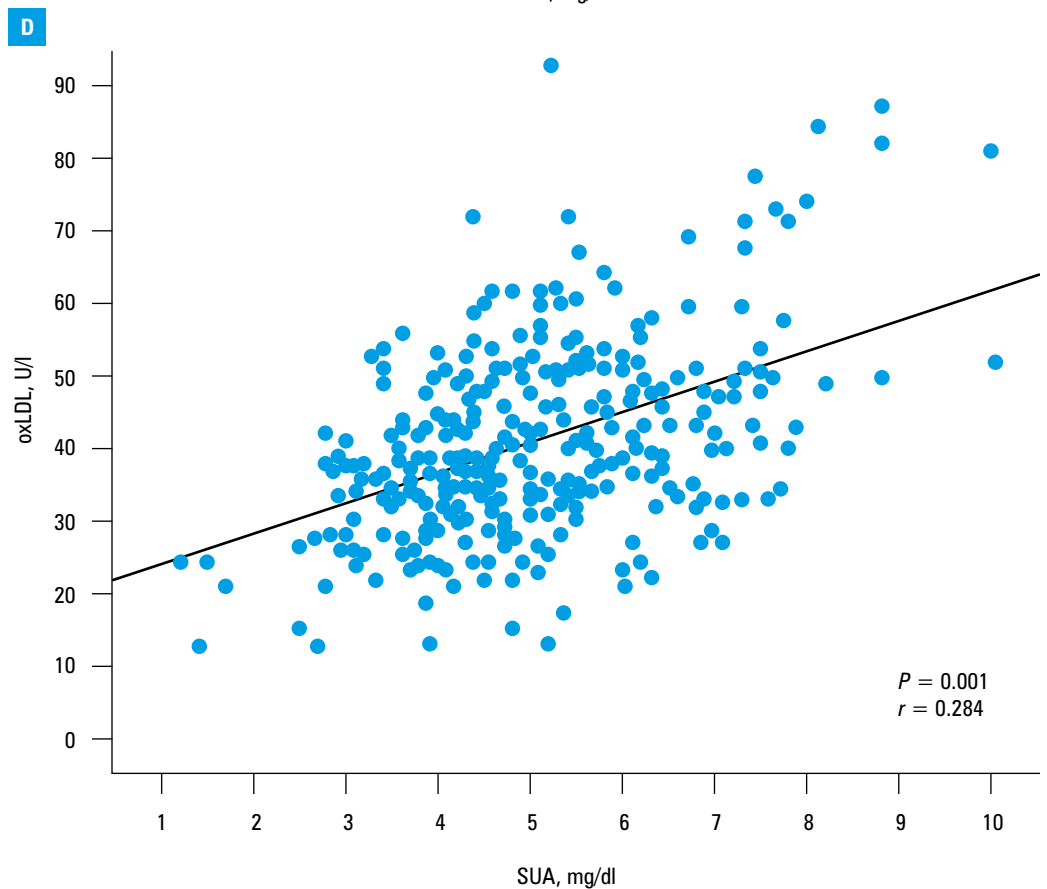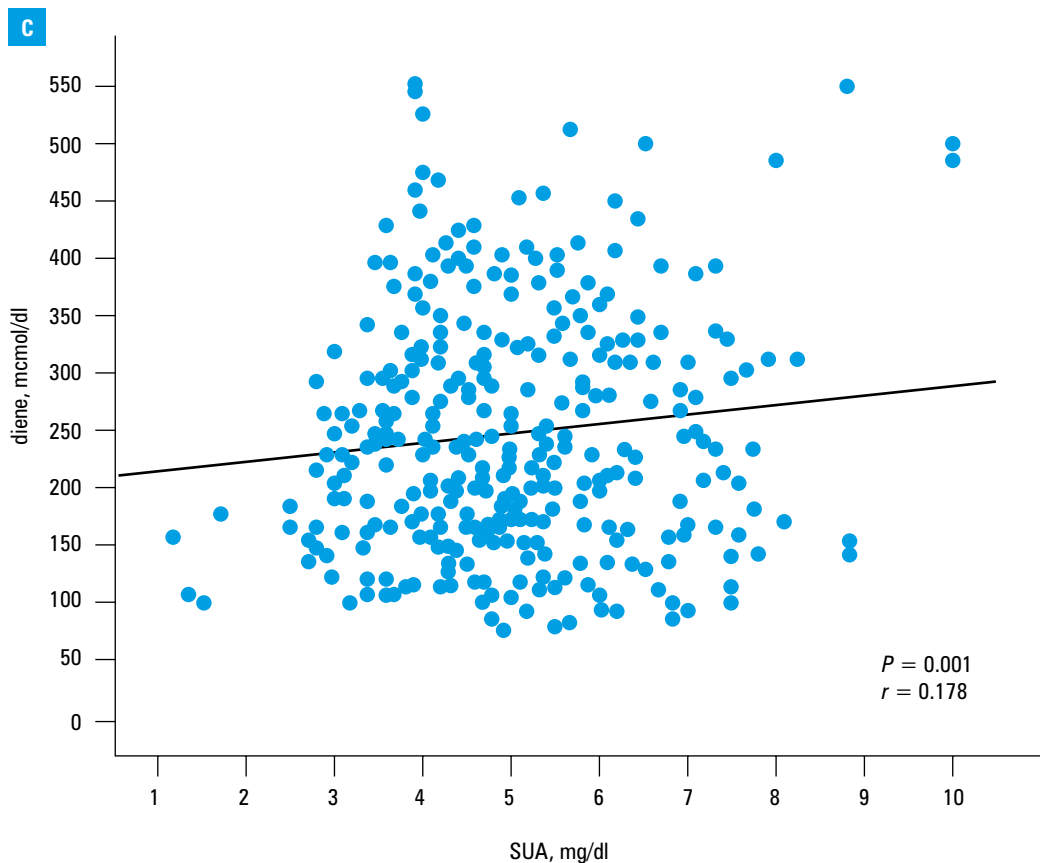
the chain reaction,[30] and the oxidation-induced increase of diene conjugation in LDL lipids is well documented.[31] In vitro, Patterson et al.[32] demonstrated that SUA rapidly reduces Cu^{2+} to Cu^+, and the decreased concentration of Cu^{2+} would inhibit tocopherol-mediated peroxidation in native LDL, while the generation of Cu^+ would promote the rapid breakdown of lipid hydroperoxides in mildly oxLDL into lipid radicals.[32] To the best of our knowledge, there are no clinical studies in the available literature about the cause and effect relationship between SUA and lipid peroxidation,

TABLE 2 Relationship between the main study variables and parameters related to low-density lipoprotein oxidation in the selected population sample in the univariate analysis

OxLDL	B	95% Confidence interval	Sig.	Dienes	B	95% Confidence interval	Sig.
age, y	0.041	−0.058 to 0.140	0.414	age, y	−0.708	−1.750 to 0.334	0.182
sex (F vs. M)	−2.097	−5.060 to 0.866	0.165	sex (F vs. M)	−1.328	−4.212 to 0.934	0.238
BMI, kg/m²	0.026	−0.240 to 0.292	0.848	BMI, kg/m²	0.079	−2.726 to 2.884	0.956
FPG, mg/dl	0.145	0.034 to 0.255	0.010	FPG, mg/dl	−0.027	−1.193 to 1.138	0.963
HDL-C, mg/dl	−0.059	−0.161 to 0.042	0.252	HDL-C, mg/dl	1.033	−0.041 to 2.108	0.059
LDL-C, mg/dl	0.069	0.030–0.107	0.001	LDL-C, mg/dl	0.901	0.494–1.309	<0.001
TG, mg/dl	0.873	0.231–1.045	0.011	TG, mg/dl	0.043	−0.345 to 0.988	0.456
ApoB, mg/dl	0.211	0.159–0.262	<0.001	ApoB, mg/dl	0.562	0.183–0.898	0.031
eGFR, ml/min	−3.179	−7.846 to 1.488	0.162	eGFR, ml/min	−3.521	−8.660 to 1.119	0.096
SUA, mg/dl	1.511	0.409–2.613	<0.001	SUA, mg/dl	9.99	2.368–21.612	0.001

Lag Phase	B	95% Confidence interval (upper–lower limit)	Sig.	Propagation phase	B	95% Confidence interval (upper–lower limit)	Sig.
age, y	0.234	0.036–0.432	0.021	age, y	−6.873	−0.050 to 0.187	<0.001
sex (F vs. M)	−3.955	−5.889 to −2.022	<0.001	sex (F vs. M)	−1.328	−10.422 to −3.325	0.238
BMI, kg/m²	−0.184	−0.716 to 0.349	0.498	BMI, kg/m²	.217	−0.098 to 0.539	0.175
FPG, mg/dl	−0.089	−0.394 to −0.041	0.011	FPG, mg/dl	−0.027	0.084–0.349	0.001
HDL-C, mg/dl	−0.201	−0.405 to 0.003	0.054	HDL-C, mg/dl	0.87	0.035–0.209	0.164
LDL-C, mg/dl	0.066	−0.011 to 0.143	0.095	LDL-C, mg/dl	0.016	−0.030 to 0.062	0.499
TG, mg/dl	0.132	−0.499 to 1.111	0.499	TG, mg/dl	−0.099	−0.164 to −0.002	0.017
ApoB, mg/dl	−0.131	−0.235 to −0.028	<0.001	ApoB, mg/dl	0.062	−0.483 to 0.608	0.822
eGFR, ml/min	−1.227	−9.584 to 8.129	0.889	eGFR, ml/min	−2.829	−7.209 to 2.551	0.361
SUA, mg/dl	−0.743	−0.950 to −0.003	0.049	SUA, mg/dl	−1.452	−2.172 to 0.132	0.285

For conversion factors, see **TABLE 1**.

Abbreviations: ApoB – apolipoprotein B100, BMI – body mass index, F – female, M – male, SUA – serum uric acid, others – see **TABLE 1**

but the explanation of our results could be that high SUA levels promote oxidative stress trough the generation of free oxygen radicals, thus inducing an increase in circulating oxLDL, or more simply, it is an indirect marker of systemic oxidation or exposition to oxidative stress, but probably does not directly affect LDL's resistance to oxidation. Therefore, it could be argued that the inhibition of xanthine-oxidase could improve the level of systemic oxidative stress and, consequently, also the level of circulating oxLDL, followed by positive effects on arterial walls and hypertension development. However, this hypothesis has to be confirmed in future studies. We are aware that this could be only one of the possible interpretations of our data and that other mechanisms could be responsible for a link between SUA and oxLDL levels in healthy humans.

Our study has some limitations. First, the study population was small and the strict selection of patients migth have made the sample unrepresentative of the general population. However, the exclusion of smokers and people with inflammatory diseases or those receiving drugs potentially affecting the oxidation status of LDL cholesterol was needed to avoid confounding factors on oxLDL levels. Similarly, the exclusion of subjects affected by chronic renal disease was needed to rule out the main secondary causes of an increase in SUA levels. Moreover, we did not strictly evaluate all the antioxidant power of the diet of the subjects we enrolled; however, the dietary habits of the Brisighella Heart Study rural cohort are usually constant and homogenous, and the cohort has been well characterized during the many years of investigation.[33,34] Finally, the statistical relationship between SUA and LDL oxidation-related parameters was not shown to be particularly significant, and its clinical relevance has to be more clearly defined in further studies.

On the basis of our findings, we may conclude that SUA is significantly associated with the level of oxLDL and dienes, but not with the length of the LDL lag phase and propagation phase. It remains to be investigated whether the reduction in the synthesis of SUA by xanthine-oxidase inhibition is itself associated with a decrease in oxLDL levels. Further studies on larger population samples are needed to confirm these preliminary observations.

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Stężenie kwasu moczowego w surowicy a markery oksydacji LDL u niepalących, zdrowych osób: dane z Brisighella Heart Study

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SŁOWA KLUCZOWE

epidemiologia, oksydacja LDL, osoby zdrowe, kwas moczowy w surowicy

STRESZCZENIE

WPROWADZENIE Stężenie kwasu moczowego w surowicy (*serum uric acid* – SUA), niedrogi i wystandaryzowany marker systemowego stresu oksydacyjnego, zostało ostatnio powiązane z ryzykiem wystąpienia incydentów sercowo-naczyniowych związanych z miażdżycą.

CELE Głównym celem badania była ocena możliwego związku między SUA, utlenionymi LDL (*oxidized low-density lipoprotein* – oxLDL) i podatnością LDL na oksydację w próbie niepalących zdrowych osób.

PACJENCI I METODY Z głównej bazy danych Brisighella Heart Study wybraliśmy próbę 354 niepalących, nieleczonych farmakologicznie dorosłych, w prewencji pierwotnej chorób sercowo-naczyniowych, z prawidłową czynnością nerek i bez znanych chorób alergicznych lub reumatologicznych, których odwiedzono podczas badania populacyjnego w 2008 r. Ocenialiśmy pełny zestaw parametrów klinicznych i biochemicznych oraz podatność LDL na oksydację i poziom oxLDL.

WYNIKI W analizie wielowariantowej poziom oxLDL wykazywał dodatnią korelację z apolipoproteiną B (ApoB; B = 0,077; 95% CI 0,015–0,139; p = 0,016), trójglicerydami (B = 0,050; 95% CI 0,032–0,069; p <0,001), cholesterolem LDL (B = 0,102; 95% CI 0,052–0,153; p <0,001) i SUA (B = 1,106, 95% CI 0,405–1,807, p = 0,002). Stężenie dienów korelowało dodatnio z cholesterolem LDL (B = 0,685; 95% CI 0,347–1,023; p <0,001), SUA (B = 2,201; 95% CI 1,117–5,285; p <0,001) i ApoB (B = 0,717; 95% CI 0,404–1,031; p <0,001). Czas opóźnienia oksydacji LDL (*lag phase*) wykazywał odwrotną korelację z ApoB (p = 0,001) i stężeniem glukozy na czczo (p = 0,022). Faza propagacji dodatnio korelowała z wiekiem (p = 0,013) i odwrotnie z trójglicerydami (p = 0,015).

WNIOSKI W próbie zdrowych osób SUA jest znamiennie związane z poziomem oxLDL i dienów, ale nie z opóźnieniem i propagacją oksydacji LDL.