ORIGINAL ARTICLE

Relationship of the low-density lipoprotein (LDL)/high-density lipoprotein (HDL) index with antioxidant enzymes and with the oxLDL/HDL index

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Abstract

Introduction: *The low-density lipoprotein (LDL)/high-density lipoprotein (HDL) index is a predictive factor for atherosclerosis, which is associated with oxidative modifications.* **Objective:** *To assess the association of the index with oxidative stress markers.* **Methods:** *444 subjects were included and were clinically, anthropometrically and biochemically characterized; superoxide dismutase, glutathione peroxidase 3 (GPx3), magnesium and oxidized LDL (oxLDL) index (oxLDL/HDL) were quantified.* **Results:** *A decrease of 1.014 units in the LDL/HDL index was associated with a superoxide dismutase increase of 1 unit/mL ($p = 0.030$), while a decrease of 0.023 units was associated with a GPx3 increase of 1 nmol/min/mL ($p < 0.0005$). An increase of one unit in the index was associated with an increase of 0.831 in the oxLDL/HDL index ($p < 0.05$). After controlling for the effect of gender, age, smoking, obesity and insulin resistance, a reduction of 0.001 per index unit was associated with an increase of 1 µg/g of magnesium in the nails ($p = 0.020$).* **Conclusions:** *The LDL/HDL index shows an inverse relationship with the antioxidant status and a direct relationship with oxidation status, regardless of other cardiovascular and oxidative stress risk factors.*

KEY WORDS: *Low-density lipoprotein/high-density lipoprotein index. Antioxidants. Oxidized low-density lipoprotein/high-density lipoprotein index.*

Introduction

Lipid oxidation is one of the main causes of atherosclerosis, and it involves low-density lipoprotein (LDL), which is the main oxidative lipoprotein, high-density lipoprotein (HDL) and lipoprotein with antioxidant activity.[1-3] Recently, the oxidized LDL (oxLDL)/HDL index has been proposed as a predictor of oxidative stress in dialyzed patients and as a biomarker of cardiovascular disease (CVD).[4,5]

Increased lipid oxidation has been linked to myeloperoxidase (MPO)[6] and magnesium deficiency.[7] On the other hand, the reduction of oxidative stress by antioxidant enzymes superoxide dismutases (SOD) and glutathione peroxidase 3 (GPx3) is inversely associated with CVD.[8,9]

Currently, the LDL/HDL index has been proposed as an indicator of cardiovascular risk (CVR) with higher predictive value than the lipoproteins that form it;[10-12] however, to our knowledge, its relationship with oxidative stress biomarkers has not been explored, in

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order to establish whether it could be considered an early reference for oxidative state.

In general, this study had the purpose to assess the association of the LDL/HDL index with SOD, GPx3, MOP, magnesium and oxLDL/HDL, after controlling for the effect of gender, age, smoking, obesity and insulin resistance, which are parameters that have been associated with CVD or oxidative stress.[13]

Method

The study was conducted in accordance with the Declaration of Helsinki. The participants gave their written informed consent. The results are part of protocol 342, approved by the Research Committee of the Faculty of Medicine, *Benemérita Universidad Autónoma de Puebla*. We designed a cross-sectional study in male and non-pregnant female volunteers, aged 18 to 65 years, from January to December 2017. Subjects with cigarette[14] and/or alcohol dependence[15] and/or with vitamin supplement consumption within the previous year, and/or with intake of steroids or medications that interfere with lipid metabolism were excluded, as well as subjects with CVD, kidney disease, liver disease or inflammatory disease.

Clinical and anthropometric characterization

A standardized history was taken. With the subject in fasting conditions, with light clothes and without shoes, height and weight were measured, whereby the body mass index (BMI) was calculated as a parameter of obesity (weight in kilograms/height in m^2). Low, moderate and high cigarette consumption was considered.[14]

Assays

Blood samples were taken at the University Hospital of Puebla laboratory, by venous puncture after 12 hours of nocturnal fasting. Glucose, insulin, triglycerides, total cholesterol, LDL-cholesterol, HDL-cholesterol and serum magnesium were determined with standardized methods. Very low density lipoprotein (VLDL) cholesterol was estimated by dividing triglycerides by 5. Insulin resistance was quantified using the homeostatic model assessment for insulin resistance (HOMA-IR) based on fasting glucose (mmol/L) x fasting insulin (μU/mL)/22.517, using the HOMA© calculator.[16] SOD, GPx3, MPO and oxLDL were determined following commercial kits' instructions. Magnesium concentration of feet and hand nail samples was measured by atomic absorption spectrometry.

Normality was tested using the Kolmogorov-Smirnov test. Between-group differences (CVR: LDL/HDL > 3.0)[17] were estimated using Mann-Whitney's U-test for numerical variables and Fisher's exact test for qualitative variables. Multivariate linear regression and partial correlation coefficient were used to determine associations adjusted for age (years), gender (female/male), smoker status (no/yes), BMI (kg/m^2) and HOMA-IR. The statistical program SPSS, version 23.0 was used; a p-value < 0.05 was considered statistically significant. Given that MPO, nail magnesium and oxLDL/HDL were measured in a smaller number of participants (74, 74 and 214, respectively), statistical power (1-β) was tested a posteriori, using the f2 effect size (based on r^2 adjusted values), using G * Power, version 3.0.10.

Results

Four-hundred and forty-four subjects participated in this study, with a higher participation of women than men (62.8 versus 37.2 %, p = 0.005). The characterization of the study population according to LDL/HDL (> 3.0 CVR) is shown in Table 1. The linear regression analysis and the partial correlation coefficient showed that SOD and GPx3 activity were negative predictors for LDL/HDL, as well as magnesium concentration in nails after adjusting for age, gender, smoking status, obesity and insulin resistance (Table 2).

The LDL/HDL index has been defined in an attempt to optimize the predictive capacity of the lipid profile, and thus the tendency of the index components was tested for variables with significant association. SOD was not associated with LDL (β coefficient [95 % confidence interval, CI = 5,662 {-25.84-37.17}], r_{123456} = -0.015, p = 0.724), but was positively associated with HDL (β coefficient [IC 95 % = 21.550 {12.237-30.864}], r_{123456} = -0.186, p < 0.0005). GPx3 was negatively associated with LDL (β coefficient [95 % CI = -0.360 {-0.545 to –0.174}], r_{123456} = -0.232, p < 0.0005) and positively associated with HDL (β coefficient [95 % CI = 0.294 {0.162-0.425}], r_{123456} = 0.265, p < 0.0005). Nail magnesium was not associated with LDL (β coefficient [95% CI = -0.019 {-0.079-0.41}], r_{123456} = -0.127, p = 0.520) or HDL (β coefficient [95% CI = 0.012 {-0.002-0.025}], R_{123456} = 0.333, p = 0.084). Finally, the LDL/HDL index was directly associated with the oxLDL/HDL index (Table 3).

Given that MPO, nail magnesium and oxLDL/HDL were measured in a smaller number of participants

Table 1. Clinical, anthropometric and biochemical characterization of the study population categorized by the LDL/HDL index (< 3.0, cardiovascular risk)

	LDL/HDL ≤ 3.0 (n = 165)	LDL/HDL > 3.0 (n = 279)	p
Gender (F/M, %)	64.9/35.1	48/52	0.075*
Smoker (Yes, %)	11.3	12.9	0.739*
	Mean ± SD	Mean ± SD	
Age (years)	40.14 ± 13.31	42.68 ± 11.75	0.035**
Weight (kg)	69.38 ± 13.68	75.86 ± 14.88	< 0.0005**
Height (m)	1.58 ± 0.085	1.59 ± 0.09	0.503**
BMI (kg/m^2)	27.72 ± 5.08	29.89 ± 5.08	< 0.0005**
Fasting glucose (mg/dL)	100.41 ± 28.20	107.76 ± 34.37	0.002**
Fasting insulin (μU/dL)	10.41±8.44	12.24±8.88	0.005**
HOMA-IR	1.37 ± 0.91	1.52 ± 0.96	0.009**
Triglycerides (mg/dL)	153.07 ± 95.57	192.34 ± 83.32	< 0.0005**
Total cholesterol (mg/dL)	185.91 ± 37.44	211.86 ± 37.76	< 0.0005**
HDL cholesterol (mg/dL)	47.96 ± 12.46	36.81 ± 8.56	< 0.0005**
LDL cholesterol (mg/dL)	88.04 ± 41.66	139.76 ± 28.96	< 0.0005**
VLDL cholesterol (mg/dL)	30.61 ± 19.11	38.47± 16.67	< 0.0005**

*The difference between groups was analyzed with Fisher's exact test. Statistical significance with $p < 0.05$.
**The difference between groups was analyzed using Mann-Whitney's U-test. Statistical significance with $p < 0.05$.
BMI = body mass index, HOMA-IR = homeostasis model assessment of insulin resistance, HDL = high-density lipoprotein, LDL = low-density lipoprotein, VLDL = very low density lipoprotein.

(74, 74 and 240, respectively) a posteriori we tested the statistical power of the analyses, which was satisfactory for all results (1-β of 0.94, 0.99 and 0.80, respectively).

Discussion

Using a cross-sectional study, we analyzed the association of the LDL/HDL index with oxidative stress markers, demonstrating that it is inversely related to SOD and GPx3 activity and directly related to the oxLDL/HDL index, a relationship that is not altered by the effect of age, gender, smoking, obesity or insulin resistance.

Our study demonstrated for the first time that an increase of 1 unit/mL in SOD activity reduces the index by 1.01 unit, apparently depending on an additional antioxidant modulation effect between SOD and HDL. Our results are consistent with others where a positive correlation has been reported between SOD and ester hydrolase paraoxonase (PON) 1, an enzyme that is present in HDL nucleus and has a protective effect against oxidation, and between SOD and HDL in overweight or obese subjects and in patients with diabetes mellitus[18-21] and low SOD activity in patients with diabetes mellitus with HDL low levels.[22,23]

Moreover, we demonstrated that an increase of 1 nmol/minute/mL in GPx3 activity decreases the index by 0.023 units, which is a consequence of GPx3 being negatively related to LDL and positively related to HDL. Like us, a previous study demonstrated the inverse relationship of GPx3 activity with LDL/HDL in ischemic male patients.[24] These results could be explained because GPx3 prevents phospholipid oxidation,[25,26] and thus it might prevent LDL oxidation, with LDL affinity to its receptor being maintained,[27] and given that PON1 and GPx are associated,[19] an additional modulation effect between GPx3 and HDL might occur. Like our results, different studies have reported an association of GPx3 with LDL and HDL.[20,22,23,28,29]

On the other hand, several studies have proposed that the oxLDL/HDL index represents CVR-associated lipid oxidation.[30-32] In our population, the increase by one unit in the LDL/HDL index translated into a 0.831 increase in the oxLDL/HDL index; therefore, the LDL/HDL index adequately represents the presence of oxidative abnormalities in lipoproteins.

Another relevant result of this study was that the increase of 1 μg of magnesium per gram of nail was associated with a decrease in the index of 0.001 per unit. Magnesium is a cofactor of lecithin cholesterol acyltransferase and lipoprotein lipase, and thus it is involved in LDL decrease and HDL increase. According to this, oral magnesium therapy significantly increases the HDL/LDL ratio.[33] In our study, this association did not depend on the nail magnesium to lipoprotein ratio, but on other physiological mechanisms. In this sense, the essential role of magnesium in glucose uptake in insulin-sensitive tissues is a known phenomenon,[34] and a positive correlation between serum magnesium and HDL levels has been reported in patients with type 2 diabetes.[35] On the other hand, serum magnesium was not associated with the LDL/HDL index. These controversial results could be justified by the fact that nail samples are better for the analysis of oligoelements than serum samples;[36] however, it is necessary to carry out

Table 2. Analysis of LDL/HDL index association as a dependent variable with oxidative stress markers

	β coefficient(95% CI)	Partial correlation coefficient	p	Adjusted r^2
SOD (U/mL)	−1.153 (-2.109 a − 0.197)	−0.098	0.018	0.008
SOD* (U/mL)	−1.014 (-1.930 a − 0.099)	−0.090	0.030	0.094
GP x 3 (nmol/minute/mL)	−0.024 (-0.036 a − 0.013)	−0.255	< 0.0005	0.065
GP x 3* (nmol/minute/mL)	−0.023 (-0.035 a − 0.012)	−0.255	< 0.0005	0.104
MPO[a] (pg/dL)	< 0.0005 (< 0.0005 a 0.0005)	0.408	< 0.0005	0.167
MPO[a]* (pg/dL)	< 0.0005 (< 0.0005 a 0.0005)	0.235	0.052	0.278
Serum Mg (mg/dL)	−0.243 (−0.634 a 0.148)	−0.058	0.222	0.003
Serum Mg* (mg/dL)	−0.339 (−0.732 a 0.054)	−0.081	0.090	0.055
Nail Mg[a] (µg/g)	−0.001 (−0.003 a < 0.0005)	−0.309	0.085	0.065
Nail Mg[a]* (µg/g)	−0.001 (−0.003 a < 0.0005)	−0.437	0.020	0.351

Multivariate linear regression. *Adjusted for age (years), gender (female/male), smoker status (no/yes), BMI (kg/m²) and HOMA-IR. Statistical significance at $p < 0.05$. [a]n = 74
CI = confidence interval, LDL/HDL = low-density lipoprotein/high-density lipoprotein index, SOD = superoxide dismutase, GP×3 = glutathione peroxidase 3, MPO = myeloperoxidase, Mg = magnesium.

Table 3. Analysis of oxLDL/HDL association as a dependent variable with the LDL/HDL index and antioxidant enzymes

	β coefficient (95% CI)	Partial correlation coefficient	p	Adjusted r^2
LDL/HDL	0.365 (0.271 a 0.459)	0.532	< 0.0005	0.283
LDL/HDL*	0.831 (0.640 a 1.022)	0.582	< 0.0005	0.348
SOD (U/mL)	−2.648 (-3.713 a − 1.584)	−0.383	< 0.0005	0.146
SOD* (U/mL)	−2.760 (-3.837 a 0.148)	−0.059	< 0.0005	0.144
GP×3 (nmol/minute/mL)	−0.014 (-0.022 a − 0.006)	−0.280	0.001	0.078
GP×3* (nmol/minute/mL)	−0.016 (-0.024 a − 0.008)	−0.317	0.047	0.092

Multivariate linear regression. *Adjusted for age (years), gender (female/male), smoker status (no/yes), BMI (kg/m²) and HOMA-IR. Statistical significance at $p < 0.05$. n = 214
CI = confidence interval, oxLDL/HDL = oxidized low-density lipoprotein/high-density lipoprotein index, LDL/HDL = low-density lipoprotein/high-density lipoprotein index, SOD = superoxide dismutase, GP×3 = glutathione peroxidase 3.

studies to determine the relationship between nail and serum magnesium in different populations in order to clarify their association.

Finally, we observed no association between MPO and the LDL/HDL index after controlling for the effects of age, gender, smoking, obesity and insulin resistance. In patients with CVD, an increase in the MPO/HDL index has been reported not to be accompanied by an increase in LDL levels,[37] which might justify our results; in addition, the association of MPO with CVR appears to be modulated by the effect of other metabolic factors; for example, in diabetic patients, the association of MPO with CVD is modulated by blood glucose concentration.[38] In addition to this, a correlation of MPO with age, height, weight and BMI has been reported in obese subjects without CVD.[39]

Our study has some limitations: it is a cross-sectional study that does not allow establishing a cause-effect relationship; in addition, other confounding variables such as diet and exercise, which could have modified study subjects' oxidative stress status, were not taken into account. The sample size is adequate for a satisfactory statistical power in the analyses with smaller population numbers; however, it would be convenient carrying out additional investigations in independent and larger samples for future application in the population.

Conclusions

The LDL/HDL index was inversely associated with antioxidants (SOD, Gpx3) and positively associated with lipoprotein oxidation (oxLDL/HDL) after controlling for the effect attributable to age, gender, smoking, obesity and insulin resistance. Together, these findings suggest that the index can be considered an early reference for the oxidation state that is independent of other CVR factors and oxidative stress, in

addition to contributing to the understanding of the complex relationship between the lipid profile and antioxidant state balance, regardless of other risk factors.

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