Risk factors for coronary artery disease: New vision in mendelian randomization studies

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Abstract

Objective: To collect information on risk factors for coronary artery disease in the adult population as evidenced by Mendelian randomization studies.

Methods: According to the recommendations of the Scale for the Evaluation of Narrative Review Articles (SANRA), a review was performed from the user of the Universidad Militar Nueva Granada in the databases of PubMed, EMBASE and BIREME.

Results: 757 articles were obtained, then inclusion and exclusion criteria were applied, and 29 articles investigating the association of coronary artery disease with apolipoprotein B, LDL cholesterol, triglycerides, total cholesterol, apolipoprotein C3, cholesterol ester transfer protein, HDL, omega 6, lipoprotein (a), obesity, hemoglobin A1C, type 2 diabetes mellitus, fasting glucose were chosen, smoking initiation, blood pressure, serum parathyroid hormone, serum phosphate levels, nonalcoholic fatty liver disease, polycystic ovary syndrome, sex hormone binding globulin, testosterone, circulating phylloquinone, inactive matrix gla protein, diet-derived circulating antioxidants, glycine, homocysteine, uric acid, inflammatory markers, hemoglobin, hematocrit, and red blood cell count.

Conclusion: This review suggests new studies with Colombian genetic information to support the risk factors presented here, taking into account that none of the studies evaluated used Latin American genetic information, which may limit the extrapolation of the results.

Key Words: Primary Prevention, Coronary Artery Disease, Coronary Disease, Mendelian Randomization Analysis

Resumen

Objetivo: recopilar información de factores de riesgo de la enfermedad arterial coronaria en población adulta evidenciados mediante estudios de aleatorización mendeliana.

Métodos: de acuerdo con las recomendaciones de la escala para la Evaluación de Artículos de Revisión Narrativa (SANRA), se realizó una revisión desde el usuario de la Universidad Militar Nueva Granada en las bases de datos de PubMed, EMBASE y BIREME.

Resultados: se obtuvieron 757 artículos, luego se aplicaron los criterios de inclusión y exclusión, y se eligieron 29 artículos en los que se investiga la asociación de la enfermedad arterial coronaria con la apolipoproteína B, colesterol LDL, triglicéridos, colesterol total, apolipoproteina C3, proteína de transferencia de ésteres de colesterol, HDL, omega 6, lipoproteína (a), obesidad, hemoglobina A1C, diabetes mellitus tipo 2, glucosa en ayunas, inicio del hábito de fumar, presión arterial, hormona paratiroidea sérica, niveles de fosfato sérico, enfermedad del hígado graso no alcohólico, síndrome de ovario poliquístico, globulina fijadora de hormonas sexuales, testosterona, filoquinona circulante, proteína gla de la matriz inactiva, antioxidantes circulantes derivados de la dieta, glicina, homocisteína, ácido úrico, marcadores inflamatorios, hemoglobina, hematocrito y recuento de glóbulos rojos.

Conclusión: esta revisión sugiere nuevos estudios con información genética colombiana para respaldar los factores de riesgo aquí presentados, teniendo en cuenta que en ninguno de los estudios evaluados se utilizó información genética latinoamericana, lo cual puede limitar la extrapolación de los resultados.

Palabras clave: prevención primaria, enfermedad arterial coronaria, enfermedad coronaria, análisis de aleatorización mendeliana

Introduction

Cardiovascular diseases (CVD) affect quality of life and are the leading cause of death worldwide (1), accounting for the loss of 1.9 million lives annually in the Americas (2), three quarters of which occur in low- and middle-income countries (3).

The reduction of CVD is one of the goals in the region. The sustainable health agenda for the Americas 2018-2030 proposes to reduce premature mortality from noncommunicable diseases (NCDs), including CVD, by one third through prevention and treatment (4). Colombia, in the 10-year health plan 2022-2031, presents as a goal for 2031 to reduce premature mortality from NCDs by 25% in the population aged 30 to 70 years (5).

The most common type of CVD is Coronary Artery Disease (CAD), a chronic dynamic pathological process secondary to the accumulation of atheromas in epicardial coronary arteries (6). Primary prevention of CAD requires the identification of risk factors to avoid the onset of the disease, and factors such as hypertension, type 2 diabetes mellitus (DM2), smoking, dyslipidemia, chronic kidney disease, obesity and metabolic syndromes have been recognized (7,8).

Mendelian randomization (MR) is a type of study that uses genetic variants to evaluate the causal relationship between a risk factor and an outcome of interest (9); it involves searching for variants associated with exposure and then testing for linkage with the results, avoiding confounding factors (10); thanks to this methodology, progress is made in the study of relationships between various modifiable exposures and CVD (11).

Based on the above, the present article aims to compile information on risk factors for coronary CAD in the adult population as evidenced in Mendelian randomization studies.

Methodology

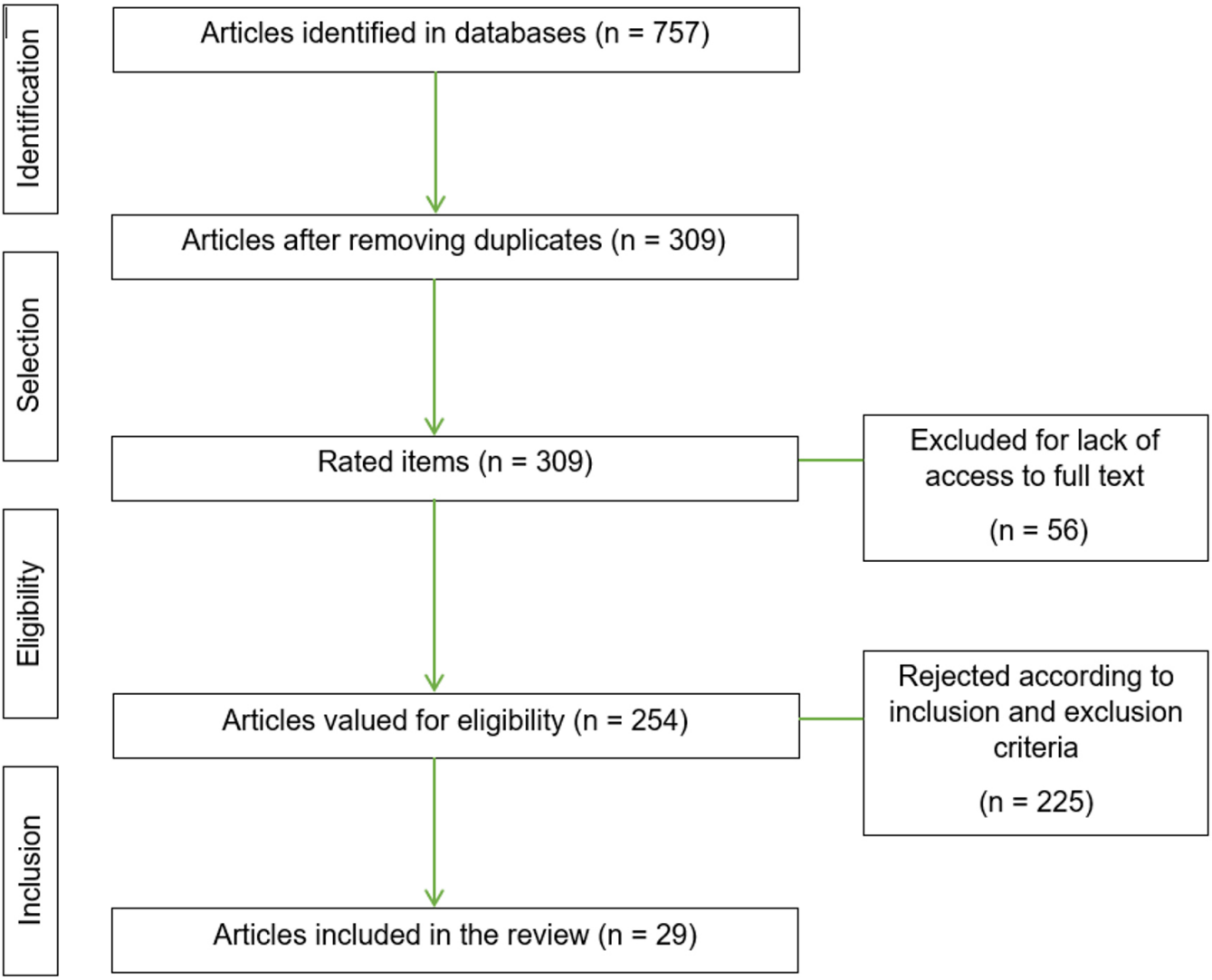
The PubMed, EMBASE and BIREME databases were searched. The DeCS/Mesh terms used in the search strategies are shown in Table 1:

Table 1. Search strategies

Database	Search terms	Results
PubMed	(((((((((Primary Prevention[MeSH Terms]) AND (Coronary Artery Disease[MeSH Terms])) OR (Coronary Disease[MeSH Terms])) AND (Mendelian Randomization Analysis[MeSH Terms])) NOT (Secondary Prevention[MeSH Terms])) NOT (Diagnosis[MeSH Terms])) NOT (Therapeutics[MeSH Terms])) NOT (Surgery[MeSH Terms])) NOT (Tertiary Prevention[MeSH Terms])) NOT (Rehabilitation[MeSH Terms])	125
Bireme	(Primary Prevention) AND (Coronary Artery Disease) OR (Coronary Disease) AND (Mendelian Randomization Analysis) AND NOT (Secondary Prevention) AND NOT (Diagnosis) AND NOT (Therapeutics) AND NOT (Surgery) AND NOT (Tertiary Prevention) AND NOT (Rehabilitation)	7
EMBASE	(Primary Prevention) AND (Coronary Artery Disease) OR (Coronary Disease) AND (Mendelian Randomization Analysis) NOT (Secondary Prevention) NOT (Diagnosis) NOT (Therapeutics) NOT (Surgery) NOT (Tertiary Prevention) AND NOT (Rehabilitation)	625

The result of the search showed 757 articles, 29 articles were included as shown in Figure 1. No studies with Latin American genetic information were found. For the selection of articles, the inclusion criteria were: (1) Mendelian studies (2) with free full access; and the exclusion criteria: (1) not performed in humans (2) that studied causality of a factor in a disease other than or in addition to coronary artery disease (3) bidirectional AM (4) written in the oriental language.

Figure 1. Item selection process



Results

1. Lipid metabolism:

1.1 Apolipoprotein B (ApoB): is shown to be important in CAD, the study by Richardson et al. (12) highlights its presence in every circulating atherogenic lipoprotein particle, including those containing low-density lipoprotein (LDL) cholesterol and triglycerides (TAG), recognizing it as the predominant lipid trait in CAD risk, compared with LDL cholesterol and TAG, OR=1.92(95% CI: 1.31-2.81;P<0.001) in multivariable AM and OR=1.73(95% CI:1.56-1.91;P<0.001) in univariable AM(12) . In the same line, the study by Zuber et al. (13) even refers to ApoB as the main lipid determinant of CAD because it represents the total number of liver-derived lipoproteins.

1.2. LDL cholesterol and TAGs: have a clear causal relationship with the risk of CAD, the study by Richardson et al. (12) shows that in univariate AM, an increase in 1 standard deviation (SD) of LDL cholesterol, OR=1.66 (95% CI: 1.49-1.86; P<0.001) and of TAG, OR=1.34 (95% CI: 1.25-1.44; P<0.001). Likewise, the study by Gordillo et al. (14), between LDL cholesterol, TAG and high-density lipoprotein (HDL) cholesterol, presents in multivariate MA LDL cholesterol, OR=1.53 (95% CI: 1.44-1.62) and TAG, OR=1.09 (95% CI: 1.01-1.17) as risk factors for CAD but does not state whether it is statistically significant. However, the study by Wang et al. (15) ratifies causal relationship, increase of 33.63 mg/dL LDL cholesterol, OR=1.80(95% CI:1.63 - 1.99;P=7.74 x10^(-31)), increase of 90.68 mg/dL TAG, OR=1.32(95% CI: 1.12-1.57;P=1.25x10^(-3)) and increase of 44.21 mg/dL total cholesterol, OR=1.35(95% CI:1.21-1.50;P=1.89x10^(-8)), presenting association of LDL cholesterol, TAG and total cholesterol with CAD.

The recognition of TAG as a causal factor of CAD is recent; the study by Ference et al. (16) found a relationship between lower risk of CAD with TAG-lowering variants in the lipoprotein lipase (LPL) gene, OR=0.771(95% CI: 0.741-0.802;P=3.9x10^(-38)) and with LDL cholesterol-lowering variants in the LDL receptor (LDLR) gene, OR=0.773(95% CI: 0.747-0.801;P=1.1x10^(-46)), suggests by reduction of TAG and LDL cholesterol, lower risk of CAD, with a similar clinical impact to the 10 mg/dl decrease of ApoB-containing lipoproteins.

According to the study by Jansen et al. (17), the increase in 1 SD in LDL cholesterol in <50 years has more impact as a risk factor for CAD, OR=1.16(95% CI:1.06-1.22) than in >70 years OR=1.02(95% CI:0.97-1.08; P=4.0x10^(-5))(17) so that control of LDL cholesterol in middle age has a relevant role in preventing CAD(17). The same phenomenon is observed in TAG, higher risk of CAD in <50 years than in >70 years, however, the results were not statistically significant (P=0.23).

1.3 Apolipoprotein C3: The role of common and rare variants of Apolipoprotein C3 (APOC3) is not clear, in the study by Sjaarda et al. (18) APOC3 is presented as a risk factor for CAD, OR=1.17 (95 CI: 1.08-1.26; P=0.0000345). However, the study by Goyal et al. (19) is inconclusive regarding the relationship between common APOC3 variants with increased TAG, due to inhibition of LPL, the enzyme responsible for hydrolysis of intermediate density lipoproteins, chylomicron remnants and very low-density lipoproteins rich in TAG; and rare APOC3 with decreased TAG as a cardio protector of CAD.

1.4. Cholesteryl ester transfer protein (ChETP): has been studied, in the research of Blauw et al. (20), PTEC favors transfer of cholesterol esters from HDL to LDL, together with transfer of TAG from LDL to HDL, contributing to the increase of LDL cholesterol, an increase of 1 mcg/ml in PTEC concentration is associated with risk of CAD, OR=1.08 (95% CI: 0.94-1.23). However, the study does not show whether it is statistically significant.

On the other hand, transfer of TAG to HDL may also be a risk factor for CAD. The study by Prats-Uribe et al. (21) questions the protective factor of HDL against CAD, because drugs such as fibrates, niacin and PTEC inhibitors, which increase HDL levels, fail to reduce the risk of CAD. However, the study by Wang et al. (15) identifies a 14.80 mg/dL increase in HDL, OR=0.89 (95% CI: 0.82-0.97; P=5.29x10^ (-3)), as a protective factor.

The study by Prats-Uribe et al. (21) states that the protective role does not depend only on the level of HDL cholesterol but also on the quality and function of the HDL cholesterol molecule, HDL molecules with a higher TAG content either transferred by PTEC or by aging of HDL that increases its TAG composition, have an Apolipoprotein A1 (ApoA-1) in an unstable conformation, this can alter the function of the molecule, the increase in TAG, if all other variables are held constant, increases the OR by 1.150 of EAC (β=0.14; 95% CI: 0,040-0,25;P=0,00684). The study shows that the protective effect of HDL also depends on the size of the molecule, when cholesterol is not transported in large HDL molecules but in smaller and even medium-sized molecules, the risk of CAD is reduced, very large HDL, if all other variables are held constant, increases the OR by 1.336 of CAD (β=0.29;95% CI:0.17-0.40;P= 0. 000000890) and has higher OR of CAD by 1.08 than medium-sized HDL cholesterol (β=-0.076;95% CI: -0.10-0.052; P=0.0000000000455).

This depends on the initial health conditions, in prooxidative and proinflammatory pathological states, small molecules of HDL, poor in lipids and rich in proteins, could be dysfunctional due to post-translational modifications of proteins and their enrichment in proinflammatory mediators, thus giving importance to the level, quality and functionality of HDL to fulfill a protective effect against CAD (21).

1.5. Omega 6: some studies have attributed omega 6 as a protective factor for CAD, however, the study by Liao et al. (22) shows the circulating metabolite as a risk factor, specifically, it presents how the metabolic alteration of arachidonic acid -one of the four main types of omega 6-, an

essential component of cell membranes, produces an increase in the formation of proinflammatory eicosanoids and decreases the production of anti-inflammatory factors, having a role in the regulation of inflammation that may be associated with the risk of CAD.

Another proposed mechanism involves linoleic acid, another type of omega-6, which promotes oxidative stress, and oxidation of LDL cholesterol increasing atherogenesis. The study found a causal association of omega 6 on the causal factors of CAD: total cholesterol, LDL cholesterol and TAG, OR=1.239(95% CI:1.125 -1.364; P=0.000) and evidenced a causal association of omega 6 on CAD, OR=1.418(95% CI:1.087-1.851; P=0.050) (22).

On this same factor, the study by Park et al. (23) shows the analysis of each omega 6 subtype and its causal association with CAD, where arachidonic acid is evidenced as a risk factor, OR=1.012(95% CI:1.000-1.024; P=0.042), but not all types of omegas 6 were considered risk factors.

1.6. Lipoprotein (a): the study by Lamina and Kronenberg (24), shows a causal association between a reduction of 10 mg/dL of lipoprotein (a) with a decrease in the risk of CAD, OR=0.941, showing the reduction of lipoprotein (a) as a protective factor, the study shows a decrease of 65.7 mg/dL (95% CI:46.3-88.3) comparable with the clinical benefit of reducing 38.67 mg/dL of LDL cholesterol(24) but does not show if its results are statistically significant. However, Sjaarda et al. (18) in their research does evidence lipoprotein (a) as a risk factor for CAD, OR=1.22(95% CI:1.20-1.25; P<1.00 x10^ (-50)). Therefore, further studies are required to elucidate the relationship of middle-aged and elderly TAG, APOC3, PTEC, omega-6 subtypes with CAD for future recommendations.

2. Obesity:

The study by Zhang et al. (25) presents obesity as a risk factor, due to secondary metabolic disease due to general adiposity that can produce insulin resistance, increased activity in the renin-angiotensin-aldosterone axis, subclinical inflammation and low levels of natriuretic peptide that can increase the risk of CAD.

Increased body mass index (BMI), OR=1.37(95% CI:1.15-1.63; P= 0.000474), waist circumference, OR=1.39(95% CI:1.06-1.84; P=0.018) and waist-to-hip ratio, OR=1.46(95% CI:1.17-1.91; P=0.006), measures related to obesity are causal factors of CAD (25).

The study by Lv et al. (26) reaffirms these interactions, posits the as-

sociation between adiposity traits independently of blood pressure, dyslipidemia and glycemic traits as risk factors for developing CAD, by mechanisms such as low-grade inflammation, endothelial dysfunction and altered endothelial vasodilator responses, the study shows increase in 1 SD in BMI, OR=1.50(95% CI: 1.30-1.75;P=1.3x10^(-8)), waist-to-hip ratio, OR=1.44(95% CI:1.11-1.87;P=0.005) and BMI-adjusted waist-to-hip ratio, OR=1.32 (95% CI:1.08-1.62;P=0.009), supporting overall obesity measured by BMI and central obesity measured by waist-to-hip ratio and BMI-adjusted ratio as risk factors for CAD.

The relationship of BMI may not be equal across the population, according to the study by Jansen et al. (17), 1 SD increase in BMI in < 50 years has a greater impact as a risk factor for CAD, OR=1.22 (95% CI:1.17-1.28) than in > 70 years, OR=1.02(95% CI:0.97-1.08; P=3.4 x10^(-6)). Thus, BMI control has a relevant role in middle age.

Likewise, there may be a differentiation by population group, according to the study by Wang et al. (15) for an increase in BMI of 4.8 kg/m2, in the East Asian population the risk is higher, OR=1.67 (95% CI: 1.48-1.89; P=4.04x10^(-16)), with respect to the European population, OR=1.38 (95% CI: 1.29-1.47; P=2.20x10^(-20)), this last study in terms of anthropometric measures presents the 9.3 cm increase in **height** as a protective factor for CAD, OR=0.85(95% CI:0.82-088;P=1.65x10^(-23)). Further research will shed light on the role of height in CAD.

3. Glucose:

To assess the relationship of glucose to CAD risk, the study by Burgess et al. (27) used hemoglobin A1C (HbA1c) because it represents the average glucose level over approximately 120 days, which is equivalent to the erythrocyte half-life, avoiding time-dependent variability of glucose recording, each 1 mmol/mol increase in HbA1c is associated with an 11% increased risk of CAD, HR=1.11(95% CI:1.05-1.18;P=2x10^(-4))(27).

Likewise, in the study by Leong et al. (28), increased HbA1c levels per % unit are associated with increased risk of CAD, OR=1.61(95% CI:1.40-1.84; P=6.9x10^ (-12)). Meanwhile, in the study by Wang et al. (15), a 0.60% increase in HbA1C, OR=1.26(95% CI:1.19-1.34; P=8.26x10^ (-14)), the presence of DM2, OR=1.10(95% CI:1.07-1.13; P=1.48x10^ (-11)) and the increase of 21. 82mg/dL in fasting glucose, OR=1.23(95% CI:1.13-1.35; P=4.48x10^ (-6)) are evidenced as risk factors for CAD. The reduction of blood glucose levels and thus prevention of DM2 are part of the strategies to avoid CAD.

4. Smoking:

The study by Chen et al. (29) exposes nicotine as a cause of damage to the cardiovascular system by increasing free radicals and toxic substances that can affect the arterial wall, through lipid oxidation, proliferation of vascular smooth muscle cells, expression of inflammatory factors and thrombogenesis, the research reveals that in patients with diabetes the onset of smoking is a risk of CAD, OR=1.322 (95% CI:1.114-1.568; P=0.001). So, in patients with diabetes CAD prevention includes avoiding smoking initiation.

5. Blood pressure (BP):

The study by Wang et al. (15) found an increase of 18.67 mmHg in systolic blood pressure, OR=1.87(95% CI:1.66-2.10; P=1.74x10^ (-25)) and an increase of 10.14 mmHg in diastolic blood pressure, OR=1.83(95% CI:1.59-2.10; P=9.47x10^ (-18)), are presented as risk factors.

The increase in BP may have a different effect according to age, the study by Jansen et al. (17) shows a higher risk of CAD, with increased BP in < 50 years than in > 70 years, but the results were not statistically significant (P = 0.22)(17).The study by Gill et al. (30) presents CAD risk at older age with an increase in BP in middle age, measured by an increase of 10 mmHg in mean arterial pressure in ≤55 years, OR=1.43(95% CI:1.16-1.77;P=0.001); with elevated blood pressure having a cumulative lifelong effect on CAD risk new studies will clarify this relationship, however BP control throughout life and not only focused on advanced age may be part of CAD prevention.

6. Serum parathyroid hormone:

The study by Melhus et al. (31) does not present increased concentrations of serum parathyroid hormone, which regulates the concentration of extracellular calcium and phosphorus, as a risk factor for CAD, OR=1.01 (95% CI: 0.93-1.09; P=0.88), the association is not statistically significant.

7. Serum phosphate levels:

Not only hyperphosphatemia causes CAD, the study by Campos et al.(32) shows increased serum phosphate levels but within normal ranges as a risk factor, mainly in men, associated with the role of phosphate in arterial calcification, by active induction of osteoblastic differentiation of vascular cells or passive deposition of calcium phosphate, the study presents increased serum phosphate levels by 1 SD, i.e. 0.16 mmol/L=0.49 mg/dL, in the absence of: Hyperphosphatemia (>1.45 mmol/L=4.5 mg/dL), chronic kidney disease defined as glomerular filtration rate <60 ml/min per 1.73 m^2 and CVD, as a risk factor by increasing the OR of CAD by 3.421-fold (β =1.23;95% CI:0.17-2.28;P=0.023).

8. Non-alcoholic fatty liver disease (NAFLD):

The casual association between NAFLD and CAD was studied by Ren et al (33). The research enunciates NAFLD as the main cause of chronic liver disease worldwide, secondary to mechanisms such as increased free fatty acid flux and increased rates of de novo lipogenesis, however, in most cases with absence of alteration in the VLDL secretion pathway.

The study shows genetically predicted NAFLD after exclusion of genetic variants involved in altered VLDL secretion as a risk factor for CAD, even when NAFLD is confirmed by biopsy, OR=1.113(95% CI:1.041-1.189), but does not present whether it is statistically significant (33). Further research may reaffirm this causal relationship.

9. Polycystic Ovarian Syndrome (PCOS):

The study by Simons et al. (34) in relation to PCOS, the main syndrome in premenopausal women, does not show a causal relationship with CAD, OR=0.99 (95% CI: 0.89-1.11; P=18.5), it associates a possible relationship between a higher BMI with PCOS and CAD, the results presented are not statistically significant and therefore are not conclusive.

10. Sex Hormone Binding Globulin (SHBG) and Testosterone:

The study by Li et al. (35) investigates the association of SHBG, a testosterone transporter glycoprotein that reduces its free fraction by binding to testosterone and testosterone, a hormone that decreases in men with age due to decreased adrenal and testicular function, with CAD. In univariable AM evidence that the increase of 1 SD of SHBG, decreases the risk of CAD by approximately 14%, OR=0.86(95% CI:0.76-0.97;P=0.02), and the increase of total testosterone (includes free testosterone and testosterone bound to proteins) decreases the risk of CAD approximately 8 %, OR=0.92(95% CI:0.85-0.99;P=0.03), in multivariable AM is not statistically significant (P=0.053).

11. Circulating phylloquinone and inactive Matrix Gla Protein (MGP:

The study by Zwakenberg et al. (36) exposes phylloquinone and menaquinone as biologically active forms of vitamin K, which activates MGP, low levels of inactive MGP, i.e. dephosphorylated and non-carboxylated MGP (dp-ucMGP), indicate higher levels of long-term vitamin K intake, reflecting bioavailability of phylloquinone and menaquinone intake over weeks.

Vitamin K has been described to have a beneficial role in the prevention of CVD risk, the study presents for each 10**µ**g/L decrease in dp-ucMGP reduction in CAD risk, RR=0.96(95% CI:0.93-0.99; P=0.02), found no dif-

ference between circulating concentrations of phylloquinone and CAD risk, RR=1. 00(95% CI:0.98-1.04) however it does not present if statistically significant, further studies are required for the clarification of the role of phylloquinone and menaquinone intervention in CAD (36).

12. Circulating diet-derived antioxidants:

According to the research of Luo et al. (37) despite the fact that antioxidants scavenge free radicals counteracting oxidative stress and thus macromolecular damage and endothelial dysfunction, most absolute levels of diet-derived antioxidants have no protective relationship against CAD, by increasing b-carotene unit, OR=1.03(95% CI: 0.97-1.10), retinol, OR=0.94(95% CI:0.63-1.10), 1 mg/dl lycopene, OR=1.02(95% CI:0.99-1.06) and 1 mmol/l ascorbate, OR=1.00(95 % CI: 0.99 to 1.00), this research does not show whether the results were statistically significant.

13. Amino acids:

The protective role of glycine in CAD is not clear, in the study by Jia et al. There is no evidence of a protective relationship between alleles that increase glycine and a lower risk of CAD, although a reduction in platelet levels, platelet aggregation and an antihypertensive effect have been attributed to glycine (38). Further studies are needed.

The research by Xu et al. shows that homocysteine could affect the arterial wall through endothelial damage and dysfunction and could increase thrombogenicity, however, in people with diabetes the study does not show a causal association between homocysteine and CAD, OR=1.14(95% CI:0.82-1.58; P=0.43) is not statistically significant, this does not support a causal relationship (39). But further research will clarify the association of diet-derived homocysteine in CAD.

14. Uric acid:

The study by Wang et al (15) identifies an increase of 1. 35 mg/dL **uric acid** as a risk factor for CAD in East Asians, OR=1.27(95% CI:1.13-1.42;P=3.27x10^(-5)), which may be given by higher prevalence of hyperuricemia and gout in East Asians with respect to Europeans, uric acid could involve endothelial dysfunction, vascular smooth muscle cell proliferation and inflammation that are related to causal mechanisms of CAD.

15. Inflammatory markers:

The study by Zhao et al. (40) investigates the association of white blood cells (WBC) with CAD, presents them as acute or chronic inflammatory markers, and recognizes atherosclerosis as a complex chronic inflammatory

disorder mediated by both adaptive and innate immunity, in which leukocytes can interact with structurally intact but dysfunctional arterial endothelium, and develop a proinflammatory and prothrombotic environment and following endothelial dysfunction generate increased recruitment of leukocytes, lipids, smooth muscle cells, fibroblasts, and platelets into the arterial wall, leading to intimal proliferation and atheroma formation.

The study shows that atherosclerotic lesions and arterial thrombi in both humans and mice contain structures of neutrophil extracellular traps (NET) which have proteins of nuclear, granular and cell membrane origin, as well as chromatin, so that when neutrophils come into contact with cholesterol, they generate NET, and these NET trigger the release of cytokines from macrophages, activating helper T cells, thus stimulating the recruitment of immune cells for atheroma formation (40).

WBC count is associated with increased risk of CAD, OR=1.07(95% CI:1.01-1.14) and neutrophil count also, OR=1.09(95% CI:1.02-1.16) both statistically significant (P<0.05). There was no significant association between monocytes, basophils, lymphocytes, eosinophils and CAD (P>0.05) (40). The study by Wang et al. (15) shows no significant association between WBC, neutrophils or other leukocytes including C-Reactive Protein with CAD in European or East Asian population.

On the other hand, the study by Sjaarda et al. (18) shows other inflammatory markers and risk factors for CAD, such as macrophage colony-stimulating factor-1 (CSF-1), OR=1.18 (95% CI: 1.08-1.30; P=0.000207) and macrophage colony-stimulating factor-1 (CSF-1). 000207) and stromal cell-derived factor-1 (SDF-1 or CXCL12), OR=1.69(95% CI:1.40-2.05; P=6.16x10^ (-8)), the research shows that CSF-1 participates in recruitment and survival of monocytes in atheroma, likewise CXCL12 has been expressed in smooth muscle cells and endothelial cells of the atherosclerotic plaque. Further research will help to clarify the relevance of inflammatory processes in CAD.

16. Red blood cells (RBC):

The study by Wang et al. (15) identifies 1.23 g/dL increase in hemoglobin, OR=1.28 (95% CI:1.11-1.47; P=4.29x10^(-5)) and 3. 53% increase in hematocrit, OR=1.31 (95% CI:1.16-1.48; P=4.59x10^(-8)) as risks for CAD, secondary to possible vasoconstriction by elimination of nitric oxide by hemoglobin; and stimulation or activation of platelet adhesion by increased hematocrit.

It also presents an increase of 40.94×10^4/µL of RBC as a risk factor for CAD in the East Asian population, OR=1.21(95% CI:1.10-1.33; P=9.46x10^(-5)), due to the possible participation of normal RBC in thrombin generation and the effect of its elevation in arterial and venous thrombosis due to increased blood viscosity. The study clarifies that anemia can exacerbate cardiovascular complications and suggests a cautious interpretation of the extremes of RBC indices (15). These results give a new perspective to future CAD prevention measures.

Conclusions

This review finds greater approval in studies of AM to DM2 and smoking initiation in patients with diabetes and increase in: ApoB, lipoprotein (a), LDL cholesterol, TAG, total cholesterol, TAG-rich HDL, HDL large molecules, obesity, glycemia, blood pressure, serum phosphate levels, hemoglobin, hematocrit, CSF-1 and CXCL12 as risk factors for CAD. Therefore, systematic reviews are invited to clarify these results; and new studies with Colombian genetic information are suggested to support the risk factors presented here, taking into account that none of the studies used Latin American genetic information, limiting their extrapolation.

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