



Revista da ASSOCIAÇÃO MÉDICA BRASILEIRA

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Review article

Association between nonalcoholic fatty liver disease and coronary artery disease[☆]

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ARTICLE INFO

Article history:

Received 27 September 2012

Accepted 23 November 2012

Available online 16 May 2013

Keywords:

Fatty liver

Cardiovascular diseases

Nonalcoholic fatty liver disease

Coronary artery disease

ABSTRACT

Objective: Although some investigations have shown a relationship between nonalcoholic fatty liver disease (NAFLD) and cardiovascular diseases, there are few studies analyzing the relationship between NAFLD and coronary artery disease (CAD). The aim of this article was to review the relationship between NAFLD and CAD and the methods of diagnosis used to assess such relationship.

Methods: A review was performed using search engines of indexed scientific material, including MEDLINE (by PubMed), Web of Science, IBECs, and LILACS, to identify articles published in Portuguese, English, and Spanish until August, 2012. The studies were eligible if they included the following data: place and year of publication, prevalence and methods used to diagnose NAFLD (ultrasound, computed tomography, nuclear magnetic resonance, or biopsy) and CAD (coronary angiography, or computed tomography), and the exclusion of patients due to alcohol consumption greater than 20 g/day.

Results: Ten articles were selected, most of which were cross-sectional studies. The studies mostly observed the association between NAFLD and the presence and severity of CAD.

Conclusion: The analysis of the review showed that evaluating the existence of NAFLD in patients with CAD from its subclinical form up to the symptomatic clinical form is important due to the higher risk of acute myocardial infarction and consequent increase of mortality.

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Associação entre doença hepática gordurosa não-alcoólica e doença arterial coronariana

R E S U M O

Palavras-chave:

Doença hepática gordurosa
Doenças cardiovasculares
Doença hepática gordurosa não
alcoólica
Doença arterial coronariana

Objetivo: Embora algumas investigações demonstrem uma associação entre a doença hepática gordurosa não-alcoólica (DHGNA) e doenças cardiovasculares, existem poucos estudos analisando a relação entre DHGNA e doença arterial coronariana (DAC). O objetivo deste artigo foi realizar uma revisão sobre a associação entre DHGNA e CAD e os métodos diagnósticos usados para avaliar esta associação.

Métodos: Foi realizada uma revisão da literatura utilizando métodos de busca de material científico indexado, incluindo MEDLINE (através do PubMed), Web of Science, IBECs e LILACS, para identificar artigos publicados em português, inglês e espanhol até agosto de 2012. Os estudos eram elegíveis se incluíam os seguintes dados: local e ano de publicação, prevalência e os métodos utilizados para o diagnóstico da DHGNA (ultrassonografia, tomografia computadorizada, ressonância nuclear magnética ou biópsia) e DAC (angiografia coronária ou tomografia computadorizada), e a exclusão de pacientes com consumo de álcool maior do que 20 g/dia.

Resultados: Dez artigos foram selecionados, predominando os estudos de corte transversal. Na maioria dos estudos foi observada a associação entre DHGNA e a presença e gravidade da DAC.

Conclusão: A análise da revisão mostra que é importante avaliar a existência de DHGNA em pacientes com DAC desde sua forma subclínica até a forma clínica sintomática, devido ao maior risco de infarto agudo do miocárdio e consequente aumento da mortalidade.

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Introduction

Some investigations have shown a relationship between nonalcoholic fatty liver disease (NAFLD) and cardiovascular diseases (CVDs),¹⁻³ with the latter being one of the main causes of morbidity and mortality in these patients. Although fatty liver is related to factors (such as dyslipidemia, central obesity, diabetes, and metabolic syndrome [MS]) that may cause CVDs including coronary artery disease (CAD), there are few studies analyzing the relationship between NAFLD and CAD, and they present controversial results.

Different methods can be applied to diagnose NAFLD and CAD. NAFLD can be diagnosed by ultrasound (US), computed tomography (CT), nuclear magnetic resonance (NMR), and liver biopsy. A recent meta-analysis showed that US has a sensitivity from 73.3% to 90.5% and a specificity from 69.6% to 85.2%. CT has a sensitivity from 46.1% to 72% and a specificity from 88.1% to 94.6%, but its cost is higher. NMR has a sensitivity from 82.0% to 97.4% and a specificity from 76.1% to 95.3%, and as a noninvasive technique, NMR is good at diagnosing, especially cases of steatosis < 25%.⁴ However, due to its high cost, NMR is not available to most patients. Liver biopsy is considered the gold standard for diagnosing steatosis, but it is an invasive method that may cause bleeding. US is relatively precise for the diagnosis of NAFLD; and since it is low-cost, risk-free, and widely available, it has been the most used method.

Although angiography is the gold standard exam for CAD diagnosis, the coronary calcification score identified by multislice computed tomography (MSCT) has been proposed as a potential method to improve the risk discrimination without invasive intervention, because it visualizes not only the

coronary artery stenosis but also the characteristics of the plaque.⁵ Thus, this method can be used to diagnose subclinical CAD.

The aim of this article was to review the relationship between NAFLD and CAD and the methods of diagnosis used to assess their relationship.

Methods

A review was performed using bibliographic databases MEDLINE (by PubMed), Web of Science, IBECs and LILACS, to identify articles published in Portuguese, English, and Spanish until August, 2012. The references of the articles were also surveyed and retrieved manually to find additional published investigations. During the search, the following strategy were used in PubMed: (Fatty Liver [MeSH] OR "Non-alcoholic Fatty Liver Disease"[Supplementary Concept] OR "Non-alcoholic Fatty Liver Disease"[All Fields] OR "nonalcoholic fatty liver disease"[All Fields] OR Steatohepatitis OR steatosis OR NASH OR NAFLD OR (fatty liver AND (non-alcoholic OR non-alcoholic))AND "coronary disease"[MeSH Terms] OR ("coronary"[All Fields] AND "disease"[All Fields]) OR "coronary disease"[All Fields] OR ("coronary"[All Fields] AND "artery"[All Fields] AND "disease"[All Fields]) OR "coronary artery disease"[All Fields] OR "coronary artery disease"[MeSH Terms]). Similar terms were used in other databases. From each investigation, the specified protocols were observed, including the place and year of publication, CAD diagnosis at the beginning of the investigation, inclusion and exclusion criteria, criteria for the diagnosis of NAFLD and CAD, maximum alcohol consumption, NAFLD and CAD prevalence, and the risk factors involved in the association between NAFLD

and CAD. The studies were eligible if they had included the following data: place and year of publication, prevalence and methods used to diagnose NAFLD (US, CT, NMR, or biopsy) and CAD (angiography or tomography), exclusion of patients due to alcohol consumption higher than 20 g/day, and other causes of fatty liver.

Results

Nineteen articles involving the relationship of CAD and NAFLD or steatosis were identified, and nine were excluded: three⁶⁻⁸ for not fulfilling the NAFLD criteria, five for using other methods to diagnose CAD,⁹⁻¹³ and one for not citing the diagnostic method for CAD.¹⁴

However, a global interpretation of the investigations selected (Table 1) was not allowed because they differ with respect to the design of the study, the size and selected samples, inclusion and exclusion criteria of patient in each study (Table 2), methods used to diagnose NAFLD and CAD, and the confounding factors included in the analysis. Thus, to evaluate the association of NAFLD and CAD, the studies were grouped according to the method used for CAD diagnosis.

Analysis of the selected articles

Type of study

The articles selected had different methods. The majority were characterized as prospective cross-sectional studies^{15,19,22} there was also one case-control study,²⁰ two retrospective cross-sectional studies,^{21,24} and a prospective cohort study.²³

Locale of the studies and sample size

Nine of the selected studies involved research with Asian patients. The samples varied from 61²⁰ to 4,023 patients.²⁴ In the investigations using the prospective cross-sectional model,^{15-19,22} a total of 2,585 patients were evaluated (Table 1).

Inclusion criteria used for the selection of samples

The studies used the following inclusion criteria: clinical suspicion of CAD;^{15,16,18} clinical suspicion of CAD in hospitalized patients;²² MS;¹⁷ evaluation of risk factors for CVD and cancer;¹⁹ low-intermediate risk for CAD and the presence of NAFLD without any other hepatobiliary disease;²⁰ the first coronary angiography (CAG);¹⁵ check-up for hepatobiliary disease and CAD in asymptomatic individuals;²¹ adults who received health evaluation²⁴ and age ≥ 18 years^{21,23} who underwent CAG.²³

Exclusion criteria

There were varied criteria (Table 2) and most investigations listed only alcohol consumption > 20 g/day and the presence of other liver diseases as common exclusion criteria.

Studies with CAD diagnosis by MSCT

Five investigations assessed CAD by MSCT,^{16,19-21,24} but the CAD criteria varied among the investigations. Most of these studies^{19,21,24} evaluated the coronary artery calcium (CAC) score. Two of these investigations^{21,24} quantified the total calcium score according to a scoring system proposed by Agatston et al.²⁵ In two articles,^{19,21} a CAC score > 100 was considered to indicate a moderate-high risk of CAD. In another,²⁴ CAC presence (CAC > 0) was considered as evidence of calcification. Two studies analyzed the characteristics of coronary lesions in MSCT: Akabame et al.¹⁶ classified the lesions of coronary arteries as calcified plaques, non-calcified plaques, low-density plaques, and positive remodeling vessels, and they observed that all major arteries had a diameter > 2.0 mm using enhanced images. The lipid pool was defined as having a plaque density of < 60 Hounsfield units (HU), and positive remodeling as having a remodeling index (RI) > 1.1 . A calcified plaque was considered severe if > 180 HU, and as mild if < 180 HU. Assy et al.²⁰ used the degree of stenosis of the coronary artery ($> 50\%$) as the CAD criterion. The plaques were classified as calcified or non-calcified on a segmental basis according to plaque features, including volume, attenuation, and calcification pattern. A calcified lesion was defined as a minimum of two pixels (area, 0.52 mm^2) with a minimum attenuation of 130 HU.

Methods and diagnostic criteria of NAFLD: In two of these studies, steatosis was diagnosed by CT^{16,20}. In the study by Akabame et al.,¹⁶ hepatic and splenic attenuation values were measured on non-contrast CT scans using 16 circular region-of-interest (ROI) cursors in the liver and four in the spleen. The calculation of the relationship between the liver and spleen was made by the division between the average value of the liver attenuation (16 points) and the average value of the splenic attenuation (4 points). The cut-off value for the liver to spleen ratio to diagnose NAFLD was defined as < 1.1 . Assy et al.²⁰ defined hepatic steatosis as the result of an attenuation of ≥ -10 HU (calculated as the liver attenuation minus the spleen attenuation).

Two studies used US for diagnosis of steatosis. In the study by Jung et al.,¹⁹ subjects were diagnosed with steatosis if at least two of the following three findings were present: increased liver echogenicity, deep attenuation, and vascular blurring. In Kim et al.²⁴ steatosis diagnosis was made based on ultrasound feature characteristics consisting of "bright liver" and evident contrast between hepatic and renal parenchyma, vessel blurring, focal sparing, and narrowing of the lumen of the hepatic veins.

One study²¹ diagnosed steatosis using US (218 patients) or CT (77 patients). In CT the following parameters were used: a liver attenuation lower than the spleen attenuation, pronounced contrast attenuation between the liver and spleen with blurred intrahepatic vessels, or markedly reduced attenuation of the liver with evident contrast between the liver and the intrahepatic vessels. In patients that had the US exam, the following parameters were considered: a diffuse increase in liver echogenicity with clear contrast between the liver and kidney, liver echogenicity diffusely increased with undefined intrahepatic vessels or diaphragm, or bright liver echogenicity with little penetration in the posterior

Table 1 – Selected studies about the association of CAD and NAFLD.

Author	Locale	year	N	Population	CAD prevalence	NAFLD prevalence	CAD and NAFLD association
Arslan et al. ¹⁵	Turkey	2007	92	Suspicion of CAD	43 (46.7%)	65 (70.7%)	NAFLD is predictor of CAD (OR: 6.73; 95% CI: 1.14-39.61; p= 0.035)
Akabame et al. ¹⁶	Japan	2008	298	Suspicion of CAD	Remodeling lesions: 56 (18.8%); lipid core plaques: 50 (16.8%); calcified plaque: 165 (55.4%); coronary lumen narrowing: 165 (55.4%)	60 (20.1%)	In NAFLD patients: Remodeling lesions: 19/60 (31.7%), p=0.01; lipid core plaques: 17/60 (28.3%), p=0.01; calcified plaque: 36/60 (60.0%), p=0.47; coronary lumen narrowing: 47/60 (78.3%), p=0.47
Alper et al. ¹⁷	Turkey	2008	80	MS (ATP III) + suspected CAD	63 (78.8%)	43 (53.8%)	NAFLD patients had higher vessel (2.5 ± 0.9 vs. 1.1 ± 1.0) and CAD severity scores (90.0 ± 40.0 vs 36.4 ± 28.9), than patients without NAFLD (p < 0.0001)
Açikel et al. ¹⁸	Turkey	2009	355	Suspicion of CAD	250 (70.4%); Gensini score: ≤ 36: 178 (50.1%); >36: 177 (49.9%)	Fatty liver: 215 (60.5%); fatty liver grades 2-3: 115 (32.4%)	Fatty liver grades 2-3 and CAD: 93/115 (80.9%), p=0.003; fatty liver grades 2-3 and Gensini score > 36: 67/115 (58.3%), p=0.041
Jung et al. ¹⁹	Korea	2010	1,218	Subject submitted to evaluation of risk factors for CVD and cancer	CCS >100: 110 (9.0%)	514 (42.2%)	Steatosis and ALT > 30 U/L predict CCS > 100 (OR: 2.12; 95% CI: 1.08-4.20; p<0.05), but not steatosis alone (OR: 1.24; 95% CI: 0.68-2.26)
Assy et al. ²⁰	Israel	2010	61	Low or intermediate risk of CAD + fatty liver or healthy	Cases: 11 (38%) Controls: 4 (14%)	Cases: 29	NAFLD vs. controls: non-obstructive lesions: 38% vs. 14%; Obstructive lesions: 10% vs. 14%. Fatty liver is predictor of coronary atherosclerosis (OR: 2.0; 95% CI: 1-4; p < 0.04)
Chen et al. ²¹	Taiwan	2010	295	Asymptomatic adults who received a check-up	CAC score: 0: 179 (60.7%); >100: 38 (12.9%)	121 (41%)	NAFLD was an independent factor that increased the risk of CAC >100: 23/38 (60.5%); (OR: 2.462; 95% CI: 1.065-5.691; p = 0.035)
Sun and Lu ²²	China	2011	542	High suspicion of CAD in hospitalized patients	Significant stenosis (≥ 70%): 382 (70.5%); mild or moderate injury: 136 (25.1%)	248 (45.7%)	Prevalence of NAFLD was associated with significant CAD: 222/382 (58.1%); (OR: 7.585; 95% CI: 4.617-12.461; p < 0.0001)
Wong et al. ²³	China	2011	612	Aged ≥ 18 years who underwent CAG	465 (76%)	356 (58.2%)	Fatty liver was associated with CAD: 301/465 (64.7%); (OR: 2.31; 95% CI: 1.46-3.64; p < 0.001); the association was independent of other metabolic factors
Kim et al. ²⁴	Korea	2012	4,023	Adults who visited health screening centers for a health evaluation (including CAC)	CAC score > 0: 1,286 (32%)	1,617 (40.2%)	NAFLD was associated with CAC > 0: 649/1,617 (40.1%); (OR: 1.35; 95% CI: 1.15-1.59; p < 0.001)

ALT, alanine aminotransferase; ATP, Adult Treatment Panel; CAC, coronary artery calcium; CAD, coronary artery disease; CAG, coronary angiography; CCS, coronary calcium score; CI, confidence interval, CVD, cardiovascular disease; MS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.

Table 2 – Exclusion criteria used in the selected studies.

Exclusion criteria	Arslan et al. ¹⁵	Akabam et al. ¹⁶	Alper et al. ¹⁷	Açikel et al. ¹⁸	Jung et al. ¹⁹	Assy et al. ²⁰	Chen et al. ²¹	Sun and Lu ²²	Wong et al. ²³	Kim et al. ²⁴
CAD documented in CAG	●									
Previous CAD						●				●
AMI	●							●		●
History of CVD					●					
Coronary bypass grafting						●				
Prior percutaneous revascularization	●					●			●	
Acute coronary syndrome	●		●				●	●		●
Alcohol consumption(>20g/day)	●	●	●	●	●	●	●	●	●	●
Use of drugs that induce steatosis		●		●		●	●	●	●	●
Hepatitis B and/or C	●	●	●	●		●	●	●	●	●
History of liver diseases known		●		●		●	●	●	●	●
Systemic diseases that cause steatosis	●						●			
Pregnancy				●						
Congestive heart failure			●	●				●		●
Severe pulmonary disease				●		●				
Cor pulmonale				●						
Renal insufficiency				●		●	●	●		
Active infection(chronic or acute)				●						
Surgery for weight reduction							●			
Cancer				●	●	●				
Positive serology for HIV and syphilis				●						
Severe obesity(BMI>35)						●				
DM2			●							
Drugs that improve NAFLD	●									
History of recent acute disease						●				
History of Cerebrovascular or IHD					●	●				
Typical chest pain						●				
Specific exclusion criteria for cardiac CT						●				
Incomplete test				●			●			
Contraindications to coronary angiogram									●	
Antinuclear antibody title >1/160									●	
History of heart attack										●

NOTE: AMI, acute myocardial infarction; BMI, body mass index; DM₂, diabetes mellitus type 2; CAD, coronary artery disease; CAG, coronary angiography; CVD, cardiovascular disease; CT, computed tomography; HIV, Human immunodeficiency virus; IHD, Ischemic heart disease; NAFLD, nonalcoholic fatty liver disease.

segment and the intrahepatic vessels or invisibility of the diaphragm.

Regarding the prevalences of CAD and NAFLD, in the investigation that evaluated the total calcium score (CAC), 9% to 12.9% of the individuals had a moderate-high risk of CAD (CAC > 100), while the NAFLD prevalence ranged from 20.1% to 42.2% (Table 1).

Regarding the relationship between CAD and NAFLD, in those investigations that used MSCT to diagnose CAD, Chen et al.²¹ observed a prevalence of NAFLD of 41% (121/295), while a moderate-high risk of CAD (CAC > 100) was observed in 12.9% (38/295). The prevalence of NAFLD increased as the CAC score increased (p = 0.003). The results indicated that NAFLD is related to a moderate-high risk of coronary artery disease (CAC > 100), but NAFLD is not guaranteed to be an independent risk factor or an epiphenomenon of CAD. In Jung et al.,¹⁹ hepatic steatosis was found in 42.2% (514/1,218), and coronary calcium score (CCS) > 100 with moderate-high risk of CVD was found in 9% (110/1,218) of subjects. An association was observed among the simultaneous presence of steatosis and elevated alanine aminotransferase (odds ratio [OR] = 2.12; 95% CI: 1.08-4.20; p < 0.05) and CSS > 100, but not with steatosis alone (OR = 1.24; 95% CI: 0.68-2.26). In the study by Kim et al.,²⁴ the presence of

NAFLD was 40.2% (1,617/4,023) and that of CAC > 0 was 32% (1,286/4,023). In the univariate analysis, the presence of CAC (score > 0) was significantly associated with NAFLD. Increasing CAC scores (0, < 10, 10-100, ≥ 100) were associated with higher prevalence of NAFLD (OR, 1.84; 95% CI: 1.61-2.10; p < 0.001).

Akabame et al.¹⁶ observed the existence of a relationship between NAFLD and the presence of remodeling lesions (OR = 2.41; 95% CI: 1.24-4.67; p = 0.0009) and lesions with a lipid core (OR = 2.29; 95% CI: 1.15-4.56; p = 0.0018), but they did not observe a correlation with calcified plaques or luminal stenosis. Assy et al.²⁰ found relationship of NAFLD with a higher prevalence of calcified and non-calcified plaques and nonstenotic lesions (38% vs. 14%). Although the presence of obstructive lesions was more frequent in the controls than in the patients with NAFLD (14% vs. 10%), the multivariate analysis showed the association of NAFLD with more severe coronary atherosclerosis.

Studies with CAD diagnosis by CAG

Five studies assessed CAD through angiography. Once again, the CAD criteria were different. Three studies defined CAD as the presence of at least 50% stenosis in at least one major

coronary artery.^{15,22,23} Two studies^{17,22} assessed CAD severity by the number of vessels affected (vessel score), the degree of coronary artery stenosis, and by use of the Gensini severity score.²⁶ The vessel scores ranged from 0 to 3, depending on the vessels involved. Significant stenosis was defined as a reduction of 70% or greater in the luminal diameter in any view compared with the nearest normal segment. The Gensini score considers the number of vessels affected, the importance

of these vessels, the degree of stenosis, and its localization in the artery. The cut-off was set as the average value of Gensini score = 36. The patients were divided into two groups, those with a Gensini score \leq 36 points (absent or mild coronary atherosclerosis) and those with a Gensini score $>$ 36 points (medium to severe coronary atherosclerosis). One study¹⁸ considered CAD if the stenosis was \geq 50% in the epicardial coronary arteries or their major branches. In this investigation, to assess the severity of the coronary atherosclerosis, a modified Gensini score and the number of vessels affected (one, two, or three vessels) were used.

Regarding the methods and diagnostic criteria of NAFLD, four studies used US for NAFLD^{15,17,18,23} diagnosis. Arslan et al.¹⁵ defined the presence of hepatic steatosis as the diffuse increase in the echogenicity of the liver compared with the kidney according to the conventional criteria. In Aıkel et al.,¹⁸ the right kidney echogenicity was used to determine the echogenicity of the hepatic parenchyma, and the liver was considered normal if it presented echogenicity equal to that of the kidney (degree 0). Fatty infiltration of the liver was described in three levels: mild (degree 1), when there was a minimum diffuse increase in the hepatic echogenicity, contours of the diaphragm and intrahepatic vessels with normal appearance; average (degree 2), when there was a moderate diffuse increase in the hepatic echogenicity and a slight deterioration in the image of the vessels of the liver and diaphragm; and severe (degree 3), when there was an apparent increase in the echogenicity. The posterior segment of the right lobe of the liver was difficult to visualize, and the structure of the intrahepatic vessels and contours of the diaphragm were smeared or not viewed.

Alper et al.¹⁷ described the US criteria to diagnose steatosis, including the hyperechoic appearance of the liver parenchyma with fine, tightly packed echoes and posterior beam attenuation. Steatosis was classified as mild, moderate, or severe when using the following parameters: normal liver – a normal hepatic echotexture and normal beam attenuation; mild hepatic steatosis – presence of a minimum increase in the echogenicity of the liver parenchyma, with a slight decrease in the definition of the portal vein walls, and minimal or no posterior beam attenuation; severe steatosis – a grossly increased hepatic parenchyma echotexture, allowing only for the visualization of the main portal vein walls and a strikingly increased posterior beam attenuation; moderate steatosis – the characteristics of these parameters (hepatic echogenicity, portal venous definition, and beam attenuation) fall between mild and severe. In the case of a confounding coexistence, the grade was assigned according to the most predominantly abnormal finding. The study by Wong et al.²³ was based on ultrasonographic features of diffusely increased liver echogenicity greater than that of the kidney or spleen, vascular

blurring, and deep attenuation of the ultrasound signal. In the study by Sun and Lu,²² NAFLD was investigated by CT. They used the same criteria as Chen et al.²¹

CAD and NAFLD prevalence: CAD prevalence by CAG varied from 46.7% to 95.6%. In these patients, NAFLD prevalence varied from 32.4% to 70.7% (Table 1)

Regarding the relationship between CAD and NAFLD, Arslan et al.¹⁵ found a prevalence of NAFLD of 70.7% (65/92), while significant CAD was observed in 46.7% (43/92) of the patients. The probability of detecting the presence of CAD was 6.73 times higher in patients with NAFLD than in patients without it ($p = 0.035$). The presence of NAFLD was independently related to the presence and extent of CAD. Alper et al.¹⁷ observed NAFLD and CAD in 53.8% (43/80) and 78.8% (63/80), respectively, of the patients with MS. Patients with NAFLD had significantly higher scores for affected vessels (2.5 ± 0.9 vs. 1.0 ± 1.0) and for the severity of CAD as evaluated by the Gensini score (90.2 ± 40.0 vs. 36.4 ± 28.9) than patients without NAFLD ($p < 0.001$). The presence of NAFLD, the degree of NAFLD, and the patient's age were significantly correlated with the severity score of CAD. Aıkel et al.¹⁸ found a prevalence of NAFLD of 32.4% (115/355), while CAD was present in 70.4% (250/355) of the patients. They concluded that the presence of steatosis in the US and its severity may represent an independent effect in both the presence and severity of CAD. Sun and Lu²² showed that the prevalence of CAD was 95.6% (518/542) and significant CAD was 70.5% (382/542), while that of NAFLD was 45.7% (248/542). Patients with NAFLD had significantly higher vessel scores (1.5 ± 0.6 vs. 1.4 ± 0.8 , $p = 0.001$) and more severe CAD scores. Wong et al.²³ found fatty liver prevalence of 58.2% (356/612) while significant CAD was observed in 76.0% (465/612) of subjects. Their study concluded that fatty liver is associated with CAD independently of other metabolic factors. However, fatty liver cannot predict cardiovascular mortality and morbidity in patients with established CAD.

Evaluation of other risk factors

Two studies^{15,21} evaluated the relationship between CAD and risk factors, three^{16,17,20} made a similar evaluation concerning NAFLD, and five evaluated the risk factors associated with these two conditions.^{18,19,22-24}

The researchers observed relationships between CAD and increased age,^{15,18,19,21-24} male gender,^{18,21-24} previous myocardial infarction (MI),^{18,22} hypertension,^{19,21,24} body mass index (BMI),²⁴ waist circumference,²⁴ diabetes mellitus (DM),^{18,21,24} smoking,^{18,19,24} dyslipidemia,¹⁸ lower levels of high-density lipoprotein (HDL) cholesterol,^{18,23,24} high levels of low-density lipoprotein (LDL) cholesterol,²² triglycerides,²⁴ fasting plasma glucose (FPG),^{19,21,24} total cholesterol (TC),²² aspartate aminotransferase (AST),^{18,21,22,24} alanine aminotransferase (ALT),^{19,22-24} gamma-glutamyltranspeptidase (GGT),^{18,24} and the use of lipid-lowering drugs²⁴ ($p < 0.05$, respectively). However, other investigations did not relate CAD to male gender,¹⁵ hypertension,^{15,18,22} DM,²² smoking history,^{15,21-23} high levels of LDL cholesterol,^{15,23} lower levels of HDL cholesterol,¹⁵ TC,^{18,21} triglycerides,^{15,18,21,22} ALT,^{18,21} obesity,^{18,22} waist circumference,¹⁵ MS,^{18,22} or BMI.^{15,18,22}

NAFLD was related to age in three studies,^{19,22,24} but this relationship was not observed in four others.^{16,17,20,23} NAFLD was also related to DM,²²⁻²⁴ male gender,^{23,24} waist circumference,^{17,20,22-24} smoking,²⁴ obesity,²² hypertension,^{23,24} MS,²² higher levels of triglycerides,^{17,20,22-24} ALT,^{20,24} AST,²⁴ GGT,²⁴ TC²⁴ homeostasis model assessment (HOMA),²⁰ lower HDL-cholesterol levels,^{17,22-24} and Gensini score.^{17,22} There was a relationship with BMI in five studies^{16,17,22-24} but not in a different investigation.²⁰ NAFLD severity(grades 2-3) was associated with the male gender, dyslipidemia, BMI, obesity, MS, triglycerides, and Gensini score ($p < 0.05$).¹⁸

There were no relevant differences between patients with and without NAFLD regarding male gender^{16,17,22} smoking^{16,17,22,23} hypertension,^{16,17,22} DM,^{16,20} dyslipidemia¹⁶ family history of CAD^{17,22} biochemical parameters of glucose during fasting,^{16,17} TC,^{17,22,23} HDL-cholesterol,²⁰ LDL-cholesterol,^{17,20,22} AST,²² and ALT.^{17,22}

Discussion

Due to differences concerning the selection criteria of the samples, methods, and parameters for CAD and steatosis in most of the investigations, it is difficult to compare the results. In investigations that used MSCT to diagnose CAD, two studies analyzed the characteristics of coronary plaques and their association with NAFLD and found different results. While Assy et al., in a small study, found an association of NAFLD with coronary stenosis of at least 50%, the results of Akabame et al. indicate that patients with NAFLD might have a risk factor for vulnerable plaque rather than coronary stenosis. This result, therefore, suggested that NAFLD was related to the initial phase of CAD, but not with CAD severity. These observations highlighted the importance of evaluating NAFLD in individuals with subclinical CAD to establish strategies to prevent the evolution of the disease. The study by Chen et al.²¹ identified a correlation between NAFLD and CAC > 100. However, in the selection of the 295 participants, 1,391 individuals were excluded. In this study, individuals aged ≥ 18 were included, and the exams, which are expensive, were paid by the patients. This may have caused the selection of individuals with fewer risk factors and higher socioeconomic class. Jung et al.¹⁹ considered CCS > 100 as moderate to severe risk of CAD, and identified a correlation among steatosis and elevated alanine aminotransferase and CAD. However, their sample only excluded patients with alcohol intake > 20 g/day and positive virus B and C. They did not exclude other secondary causes of steatosis such as autoimmune diseases and use of hepatotoxic drugs, which may constitute an important bias. Kim et al. considered CAC values > zero as positive, but most of the patients have positive values between 0 and 100 and therefore, low or very low risk for CAD. It was a retrospective study involving a large number of subjects conducted in two health screening centers. Due to the study design, information about patients may have been affected.

Regarding the studies involving angiography to evaluate the relationship between NAFLD and CAD, such relationship may be a consequence of the selection. The studies considered CAD to be the presence of stenosis $\geq 50\%$, representing the

existence of moderate to severe obstruction of the coronary arteries. Nevertheless, these studies do not consider the initial phases of the disease when obstructions < 50% are observed, confirming the presence of mild CAD. Taking into account that coronary occlusion and myocardial ischemia may frequently be due to mild or moderate stenosis, the identification of such levels of obstruction in patients with NAFLD might be important for the risk stratification and therapeutic orientation, in addition to demonstrating such relationship more reliably. In the study by Arslan et al., NAFLD was observed in 70.7% of the patients, while coronary disease was present in only 46.7%, since only patients submitted to the first angiography could take part, and those individuals with previously diagnosed CAD were excluded. Wong et al.²³ also evaluated the effects of the presence of NAFLD for outcomes, and found no association of NAFLD and cardiovascular mortality in patients with confirmed CAD. These researchers concluded that NAFLD correlates with incident CAD, but cannot be used as a prognostic marker in patients with established CAD. In the latter case, the prognosis may be governed by other factors. Their study included patients referred for CAG by causes other than CAD.

Some comments can be made concerning the investigations that used the Gensini score,^{17,18,22} which was used to establish the severity criterion because it evaluates lesions from mild to 100% obstruction. The score is determined according to the importance of the vessel affected, and has a cut-off value of 36 (Gensini score ≤ 36 points: absent or mild coronary atherosclerosis; > 36 points: moderate to severe coronary atherosclerosis). Acikel et al.,¹⁸ used the Gensini score in a different form, and no justification for such a modification was presented, although the results were similar to other studies^{17,22}. In the study by Sun and Lu,²² the prevalence of CAD was 95.6%, with 70.5% (382/542) of the individuals presenting significant stenosis, taking into account the hospitalization of the patients. In their study, a Gensini score > 36 was established, indicating moderate to severe coronary atherosclerosis. However, even in the comparison between patients with significant and non-significant CAD, the average Gensini score (23.2 ± 12.1 vs. 10.1 ± 7.0 , $p < 0.001$) was lower than the cut-off point. When the relationship of NAFLD with the CAD severity score was evaluated, the average value was again lower than the cut-off point, although the average score was higher in patients with NAFLD compared with patients without NAFLD (24.5 ± 12.6 vs. 14.9 ± 10.4 , $p < 0.001$).

Finally, all selected studies involved Asian patients, and this should be noted because they have different epidemiological characteristics, lifestyles, and eating habits compared with Western individuals. The contribution of these characteristics to the association between CAD and NAFLD should not be neglected.

Conclusion

The studies reviewed in the present article point to the relevance of evaluating CAD in patients with NAFLD, since it may prevent higher risk of acute myocardial infarction and consequent increase in mortality. However, there are limitations in this review: the majority of the studies evaluated were cross-sectional and have a low level of scientific evidence. Most of

the studies were performed in Asian patients, and further trials using other study designs are needed, especially involving Western patients.

Conflicts of interest

The authors declare no conflicts of interest.

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