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Association of NAFLD with subclinical atherosclerosis and coronary-artery disease: Meta-analysis

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ABSTRACT

Background: Recent studies have associated non-alcoholic fatty liver disease (NAFLD) with increased risk of cardiovascular disease, using tests of subclinical atherosclerosis.

Aim: To evaluate the influence of NAFLD on subclinical atherosclerosis and coronary artery disease (CAD).

Methods: We reviewed Pubmed and EMBASE. According to inclusion and exclusion criteria, we selected 14 studies and were classified in two groups. Ten studies aimed the presence of subclinical atherosclerosis and four studies the presence of coronary artery disease. To assess subclinical atherosclerosis, we selected studies with pathological carotid intima-media thickness (CIMT) and with presence of carotid plaques. We considered coronary artery disease when patients showed at least 50 % stenosis at one or more major coronary arteries. NAFLD was assessed by ultrasound (US) and liver biopsy.

Results: NAFLD showed a higher prevalence of pathological CIMT [35.1 % (351/999) vs. 21.8 % (207/948); $p < 0.0001$], with OR 2.04 (95 % CI: 1.65-2.51). Similarly, the presence of carotid plaques was higher in NAFLD diagnosed by US [34.2 % (101/295) *vs.* 12.9 % (51/394); $p < 0.0001$] [OR 2.82 (95 % CI: 1.87-4.27)] and diagnosed by liver biopsy [64.8 % (70/108) *vs.* 31.3 % (59/188); $p < 0.0001$] [OR 4.41 (95 % CI: 2.63-7.40)]. On the other hand, four studies assessed CAD in patients underwent coronary angiogram. Subjects with NAFLD showed 80.4 % (492/612) of CAD, while it was detected in 60.7 % (356/586) ($p < 0.0001$) in patients without NAFLD. Therefore, NAFLD was associated with a remarkably higher likelihood of CAD, using random effects model [OR 3.31 (95 % CI: 2.21-4.95)] or fixed effects model [OR 3.13 (95 % CI: 2.36-4.16)].

Conclusions: NAFLD increases the risk of subclinical atherosclerosis and coronary artery disease. The right management of these patients could modify the natural history both liver and cardiovascular disease.

Key words: Non-alcoholic fatty liver disease. Cardiovascular disease. Subclinical atherosclerosis. Steatohepatitis. NASH.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a pathologic spectrum related to metabolic syndrome (MetS), ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), progressing to endstage liver disease with cirrhosis and hepatocellular carcinoma (1). Prevalence rates are rising because of overweight and obesity. In fact, NAFLD is the most common cause of chronic liver disease in Western countries with a prevalence of 20 %-30 %, which is increased up to 70 % in obese and diabetic subjects (2). NAFLD is closely associated with abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance and impaired glucose tolerance, which are all features of the MetS. Approximately 90 % of patients with NAFLD have, at least, one of the features of MetS and about 33 % present the complete diagnosis (3). Thus, NAFLD shares multiple potential risk factors with vascular disease (4).

Atherosclerosis is the main trigger of overall vascular disease and different methods are used to detect it in subclinical stage. Endothelial dysfunction is the first stage

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of subclinical atherosclerosis, and is defined as an imbalance between vasodilating and vasoconstricting substances produced by the endothelium, especially nitric oxide (5). Carotid disease is measured according to carotid intima-media thickness (CIMT) and the presence of carotid plaques by ultrasound (US), which are important markers of vascular disease. In fact, they have been considered as independent stroke predictor (6) and related to cardiovascular events (7). Furthermore, other methods have been developed with the same proposal –i.e. coronary artery calcium scoring by computed tomography (8), left ventricular hypertrophy by electrocardiogram and echocardiogram (9) or peripheral arterial disease by ankle-brachial pressure index (10), but they are not so extended in clinical practice for different reasons.

Interestingly, cardiovascular disease (CVD) is the main cause of complications in NAFLD, while the chronic liver disease is the responsible of most of morbidity and mortality in NASH (11). In fact, NAFLD was linked to increased overall mortality, deriving from liver-related and cardiovascular disease and a 2-fold risk of diabetes, in a meta-analysis (12). In particular, different studies assessing CVD by the presence of higher carotid-femoral pulse wave velocity (13), left ventricular dysfunction (14) or atrial fibrillation (15) have found an independent association with NAFLD. Therefore, this meta-analysis focuses on the clinical evidence about the influence of NAFLD on subclinical atherosclerosis and coronary artery disease (CAD).

MATERIALS AND METHODS

Data sources and search

The search strategy was in accordance with the recommendations of the meta-analysis of observational studies in epidemiology (MOOSE) group. We searched in MEDLINE (to April 2013), EMBASE (to April 2013) and Cochrane Library databases (to April 2013) to identify potentially relevant publications in English language. Search terms were: "non-alcoholic fatty liver disease", "non-alcoholic steatohepatitis", "NAFLD", "NASH", "fatty liver", "cardiovascular disease", "coronary artery disease", "carotid disease", "ischemic heart disease", "metabolic syndrome", "pathogenesis". The preceding terms were combined with appropriate Boolean logic. Manual search of cited bibliographies was also performed. Only fully published articles were considered. Duplicated publications were deleted. Two researchers independently performed the literature search and data abstraction with regard to the inclusion and exclusion criteria by reading titles and abstracts. When reading titles and abstracts did not allow identification of eligible studies, articles were read in full. Relevant reviews and letters to the editor were excluded from the analysis, but read in full to identify potential relevant original studies. Disagreements between two observers were resolved by discussion.

Study selection criteria

Observational studies must provide information about diagnosis of NAFLD, CIMT, presence of carotid plaques and findings in coronariography. Inclusion and exclusion criteria (studies involving pediatric population) were defined prior to commencement of the literature search. Fourteen studies were included and classified in two groups (Fig. 1). Ten studies aimed the presence of subclinical atherosclerosis and four studies the presence of CAD. To assess subclinical atherosclerosis, we selected studies when data of CIMT (when it was a qualitative variable, not quantitative) or carotid plaques could be extracted (measured in all of cases by US). To determine CAD, we selected studies with coronary artery disease as end-point, which were represented by pathological findings in coronariography (significant CAD was defined as the presence of at least 50 % stenosis at one or more major coronary arteries) following clinical symptoms (angina pectoris, fatal or non-fatal acute myocardial infarction). Consequently, these patients underwent coronary angiogram prior to diagnosis of NAFLD. On the other hand, NAFLD was determined by US and by liver biopsy, when it was possible. They were reported in the English language as full papers.

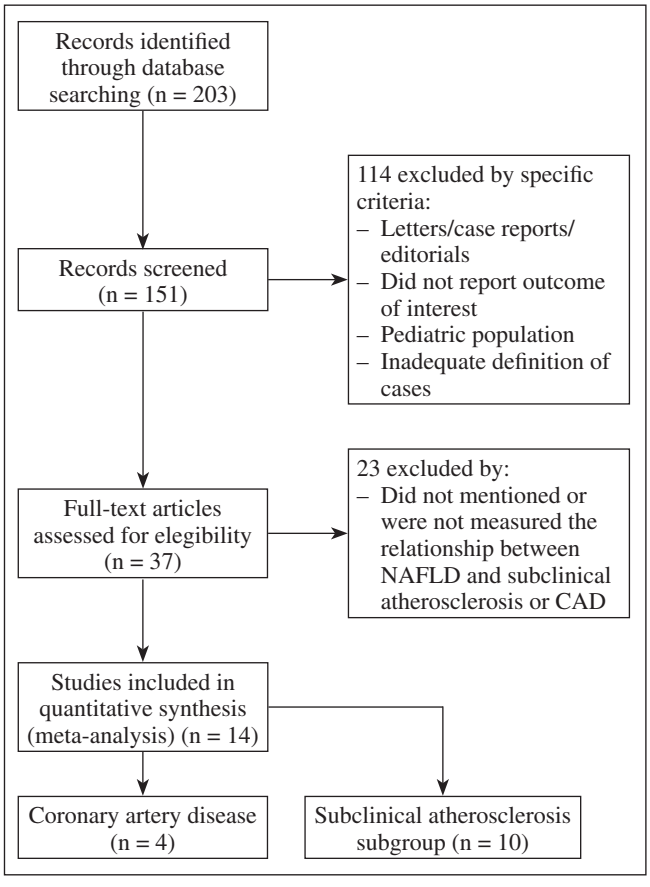

Fig. 1. Flow chart of studies screened and included in meta-analysis.

Data extraction

The following data were extracted: a) Study: Year of publication, number of patients, location, design; b) patients: Mean age, gender, type 2 diabetes mellitus; c) evaluation of NAFLD: US or liver biopsy; d) evaluation of subclinical atherosclerosis: Pathological CIMT or presence of carotid plaques; and e) evaluation of CAD: Presence of at least 50 % stenosis at one or more major coronary arteries. Any discrepancies in data quantification were resolved by discussion among the investigators.

Objective

Influence of NAFLD on subclinical atherosclerosis (evaluated by pathological CIMT and presence of carotid plaques) and coronary artery disease.

Statistical analysis

Statistical analysis was performed using the Meta-Disc software 1.4 (Zamora J, et al., BMC Medical Research Methodology 2006;6:31), considering: a) A summary of data from individual studies; b) an investigation of the studies homogeneity graphical and statistically; and c) calculation of clustered indexes; and d) exploration of heterogeneity. Our assumption of heterogeneity was tested for each planned analysis using the Cochran-Q heterogeneity and I^2 statistics (low, moderate, and high heterogeneity according to I^2 values of 25 %, 50 %, and 75 %, respectively) (16). Random effects model using Der Simonian and Laird method and fixed effects model were used. Meta-regression, including as covariables age and BMI, was analyzed using a generalization of Littenberg and Moses Linear model weighted by inverse of the variance or study size or unweighted. To check for publication bias, we used the Begg test and Egger test. Only two-sided tests with a significance level of 0.05 were used. Confidence intervals (CIs) of individual studies were determined or approximated from the available data. A sensitivity analysis was also conducted, in which each study was omitted in turn. On the other hand, we assessed the quality of the studies using the "Quality Assessment of Diagnostic Accuracy Studies" (QUADAS) tool, which consists of a set of 14 items (scored as yes, no or unclear). Studies showing a score ≥ 10 were considered as high-quality studies (17).

RESULTS

Effect of NAFLD on subclinical atherosclerosis

We evaluated ten studies that met the selection criteria and that were identified using the search strategy described. Studies characteristics are shown in table I. Pooled data included 2,932 patients. The meta-analysis including all 10 studies demonstrated that NAFLD was associated with subclinical atherosclerosis, using random effects model [OR 2.42 (95 % CI: 1.98-2.96)] or fixed effects model [OR 2.36 (95 % CI: 1.98-2.81)]. We did not find heterogeneity between these studies (Cochran-Q = 10.29; df = 9; p = 0.3277; inconsistency I^2 = 12.5 %, and τ^2 = 0.0131), as well as to seem that there was no publication bias [(Begg test: Kendall's tau 1.43; p = 0.15); (Egger test: 1.66; p = 0.14)]. Sensitive analysis showed similar results. Furthermore, we divided these studies in three subgroups, according to diagnosis of NAFLD and subclinical atherosclerosis.

NAFLD diagnosed by US and subclinical atherosclerosis by pathological CIMT

We included four studies in this subgroup. Pooled data included 1,947 patients. Data analysis showed subjects with NAFLD presented 35.1 % (351/999) of pathological CIMT. However, in patients without NAFLD, subclinical atherosclerosis was detected in 21.8 % (207/948); p < 0.0001. Three of four studies found a relationship between NAFLD and pathological CIMT. The meta-analysis including all 4 studies demonstrated that NAFLD was associated with a remarkably higher likelihood of pathological CIMT, using random effects model [OR 2.04 (95 % CI: 1.65-2.51)]. The test of heterogeneity (Cochran-Q = 1.08; df = 3; p = 0.7826) inconsistency I^2 = 0.0 %, and τ^2 = 0.0001 (Fig. 2A). In meta-regression, age [dOR 0.96 (95 % CI: 0.31-2.95); p = 0.744] and BMI [dOR 0.69 (95 % CI: 0.01-63.53); p = 0.488] did not influence on the results.

NAFLD diagnosed by US and subclinical atherosclerosis by carotid plaques

In this subgroup, four studies were included. Pooled data included 689 patients. Subjects with NAFLD showed 34.2 % (101/295) of carotid plaques, while in patients without NAFLD, it was detected in 12.9 % (51/394); p < 0.0001. Three of four studies found an association between NAFLD and the presence of carotid plaques. The meta-analysis demonstrated that NAFLD patients showed a remarkably higher likelihood of carotid plaques, using random effects model by Der Simonian and Laird method, odds ratio was 2.82 (95 % CI: 1.87-4.27). The test of heterogeneity (Cochran-Q = 0.92; df = 3; p = 0.8207) inconsistency I^2 = 0.0 %, and τ^2 = 0.0001 (Fig. 2B). In meta-regression, age [dOR 1.33 (95 % CI: 0.02-86.82); p = 0.54] and BMI [dOR 0.83 (95 % CI: 0.07-9.59); p = 0.519] did not influence on the results.

Table I. Studies included in meta-analysis, according to subclinical atherosclerosis

Author	*Year*	*Country*	*Study design*	*Age (NAFLD vs. non-NAFLD)*	*Gender distribution (male vs. female sex)*	*T2DM*	*Patients*	*NAFLD evaluation*	*Carotid phenotype*	*OR (95 % IC)*	*QUADAS score ≥ 10*
Kim (28)	2009	South Korea	Cross-sectional study	52 *vs.* 51.5 yo	62 % *vs.* 47 %*	Disbalanced	1021	Ultrasound	CIMT	2.15 (1.56-2.95)	Yes
Wang (29)	2009	Taiwan	Prospective cohort study	51.7 *vs.* 53.1 yo	N/A	Disbalanced	169	Ultrasound	CIMT	1.45 (0.67-3.15)	Yes
Agarwal (30)	2011	India	Prospective cohort study	57 *vs.* 61 yo	58 % *vs.* 62 %	Balanced (all patients)	124	Ultrasound	CIMT	2.48 (1.075.76)	Yes
Kang (31)	2012	South Korea	Cross-sectional study	53.5 *vs.* 52.8 yo	60 % *vs.* 47 %	Balanced (none)	663	Ultrasound	CIMT	1.98 (1.44-2.73)	Yes
Brea (32)	2005	Spain	Prospective matched-cohort study	53.2 *vs.* 51.6 yo	50 % *vs.* 50 %	Disbalanced	80	Ultrasound	Carotid plaques	3.0 (1.16-7.73)	Yes
Fracanzani (33)	2008	Italy	Prospective case-control study	50.5 *vs.* 52 yo	87 % *vs.* 87 %	Balanced	375	Ultrasound	Carotid plaques	3.16 (1.57-6.38)	Yes
Ramilli (34)	2009	Italy	Cross-sectional study	59.3 *vs.* 60.1 yo	51 % *vs.* 45 %	Balanced	154	Ultrasound	Carotid plaques	2.28 (1.18-4.40)	Yes
Thakur (35)	2012	India	Cross-sectional study	42.1 *vs.* 41.9 yo	67 % *vs.* 67 %	Disbalanced	80	Ultrasound	Carotid plaques	4.75 (0.94-23.98)	Yes
Targher (36)	2006	Italy	Prospective matched-cohort study	45 *vs.* 45 yo	59 % *vs.* 59 %	Balanced	245	Biopsy	Carotid plaques	4.45 (2.53-7.84)	Yes
Vlachopoulos (37)	2010	Greece	Prospective matched-cohort study	55.4 *vs.* 51.5 yo	Matched	Balanced	51	Biopsy	Carotid plaques	4.22 (1.19-14.97)	Yes

NAFLD: Non-alcoholic fatty liver disease; OR: Odds ratio; CIMT: Carotid intima-media thickness; T2DM: Type 2 diabetes mellitus; N/A: Not applicable; yo: Year-old. *p < 0.05.

NAFLD diagnosed by liver biopsy and subclinical atherosclerosis by carotid plaques

We found two studies that assessed NAFLD by liver biopsy. Pooled data included 296 patients. Data analysis showed subjects with NAFLD presented 64.8 % (70/108) of subclinical atherosclerosis. However, in patients without NAFLD, subclinical atherosclerosis was detected in 31.3 % (59/188); p < 0.0001. The meta-analysis demonstrated that NAFLD was associated with a remarkably higher likelihood of subclinical atherosclerosis, using random effects model by Der Simonian and Laird method, odds ratio was 4.41 (95 % CI: 2.63-7.40). The test of heterogeneity (Cochran-Q = 0.01; df = 1; p = 0.9382) inconsistency I^2 = 0.0 %, and τ^2 = 0.0001 (Fig. 2C).

Effect of NAFLD on coronary artery disease

Four studies assessed CAD in patients underwent coronary angiogram (Table II). Pooled data included 1,198 patients. Subjects with NAFLD showed 80.4 % (492/612) of CAD, while it was detected in 60.7 % (356/586) (p < 0.0001) in patients without NAFLD. The meta-analysis including all 4 studies demonstrated that NAFLD was associated with a remarkably higher likelihood of CAD, using random effects model [OR 3.31 (95 % CI: 2.21-4.95)] or fixed effects model [OR 3.13 (95 % CI: 2.36-4.16)]. The test of heterogeneity (Cochran-Q = 4.86; df = 3; p = 0.1827) inconsistency I^2 = 38.2 %, and τ^2 = 0.0631 (Fig. 3). In meta-regression, age [dOR 0.85 (95 % CI: 0.23-3.20); p = 0.37] and BMI [dOR 1.33 (95 % CI: 0.17-10.39); p = 0.33] did not influence on the results.

DISCUSSION

To date, conclusions about the relationship between non-alcoholic fatty liver disease and vascular disease have been difficult due to the small sample size and heterogeneity of available studies. In this meta-analysis, we have wanted to sought the influence of NAFLD on vascular disease in two different stages: First one, when the risk factor is present but not the pathological entity (subclinical atherosclerosis); and second one, when the clinical entity is established (coronary artery disease). Thus, we included four studies which searched the relationship between NAFLD and subclinical atherosclerosis, diagnosed by pathological CIMT. We found a prevalence of 35.1 % of pathological CIMT in patients with NAFLD, while it was

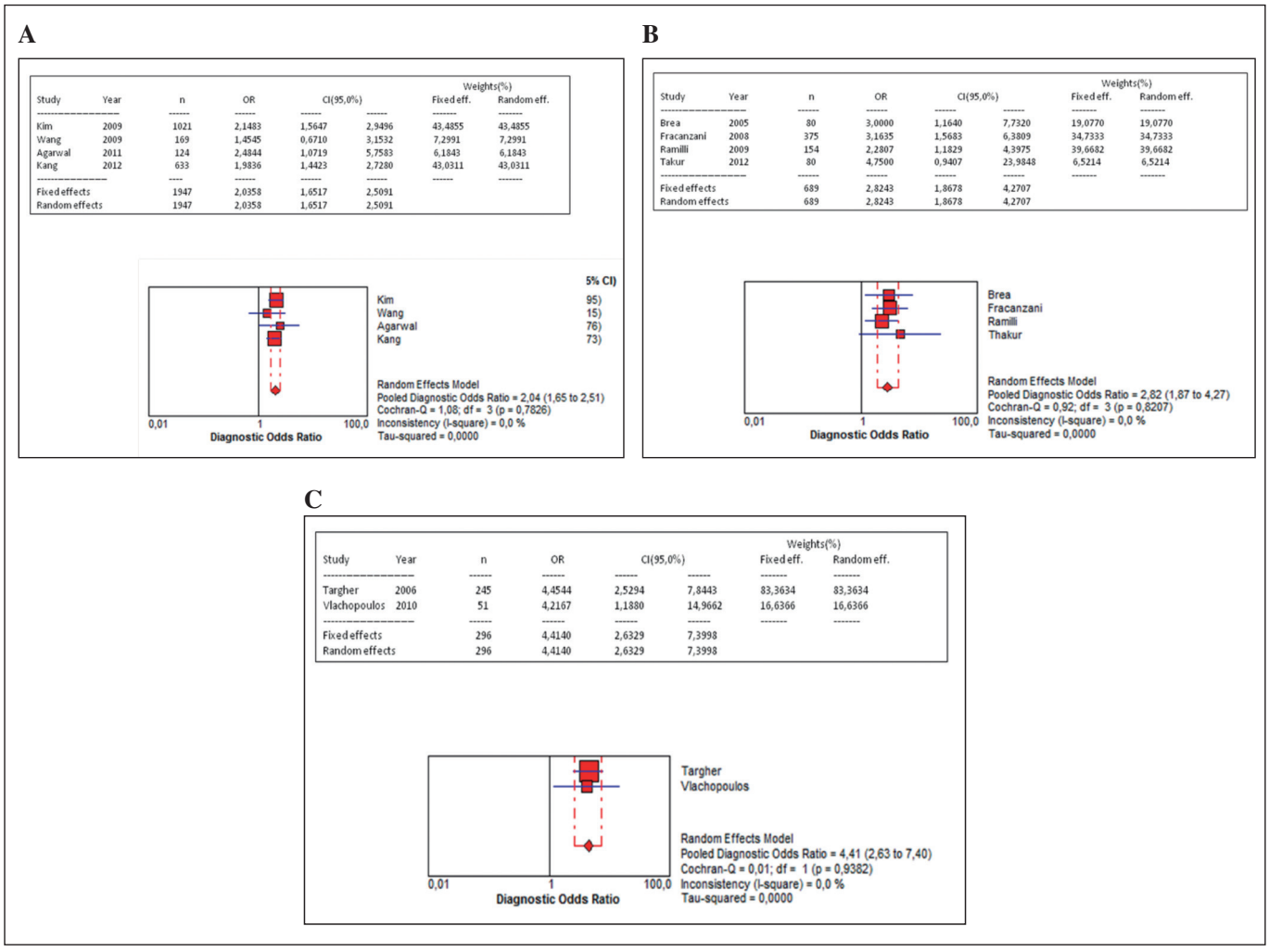

Fig. 2. Association between NAFLD and subclinical atherosclerosis (by subgroups). A. Odds ratio (95 % CI) for the association between NAFLD (US) and subclinical atherosclerosis (CIMT). B. Odds ratio (95 % CI) for the association between NAFLD (US) and subclinical atherosclerosis (carotid plaques). C. Odds ratio (95 % CI) for the association between NAFLD (biopsy) and subclinical atherosclerosis (carotid plaques).

Table II. Studies included in meta-analysis, according to coronary artery disease

Author	*Year*	*Country*	*Study design*	*Age (NAFLD vs. non-NAFLD)*	*Gender distribution (male vs. female sex)*	*T2DM*	*Patients*	*NAFLD evaluation*	*OR (95 % IC)*	*QUADAS score ≥ 10*
Alper (38)	2008	Turkey	Prospective cohort study	62 *vs.* 63 yo	48 % *vs.* 38 %	Balanced	80	Ultrasound	8.12 (2.11-31.25)	Yes
Açikel (39)	2009	Turkey	Cross-sectional study	56 *vs.* 59 yo	73 % *vs.* 66 %	Disbalanced	355	Ultrasound	2.23 (1.31-3.82)	Yes
Wong (40)	2011	China	Prospective cohort study	63 *vs.* 63 yo	74 % *vs.* 66 %*	Disbalanced	612	Ultrasound	3.07 (2.09-4.51)	Yes
Arslan (41)	2012	Turkey	Prospective cohort study	N/A	N/A	Balanced (none)	151	Ultrasound	4.95 (2.32-10.58)	Yes

NAFLD: Non-alcoholic fatty liver disease; OR: Odds ratio; T2DM: Type 2 diabetes mellitus; yo: Year-old. *p < 0.05.

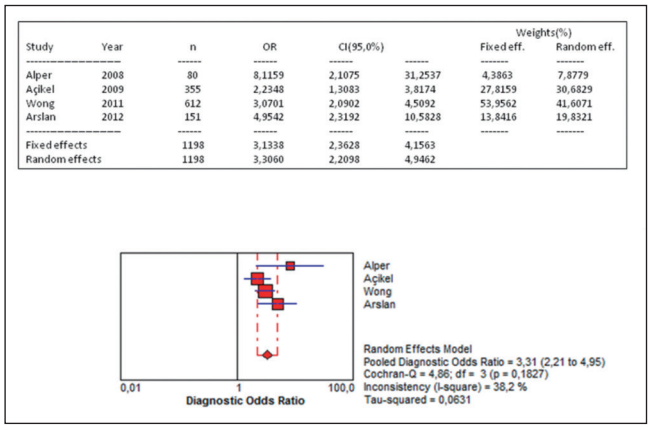

Fig. 3. Odds ratio (95 % CI) and Forest plot for the association between NAFLD (US) and CAD.

the 21.8 % in absence of it, resulting in an increase 2.04 fold the risk of subclinical atherosclerosis. Similar results were obtained when we analyzed the effect of NAFLD on the presence of carotid plaques, due to NAFLD diagnosed by US showed a higher prevalence of carotid plaques (34.2 % *vs.* 12.9 %; OR 2.82), as well as when NAFLD was diagnosed by liver biopsy (64.8 % *vs.* 31.3 %; OR 4.41). According to CAD, in 4 studies (1,198 patients), a higher prevalence of CAD was observed in patients with NAFLD (80.4 % *vs.* 60.7 %), with OR 3.31. Probably, the fact of these patients underwent coronariography prior to detect NAFLD is the reason to detect these raised percentages. Our results are consistent with other studies previously published. In 2008, Sookoian et al. performed a meta-analysis and observed that CIMT (as quantitative variable) and carotid plaques were related to NAFLD. Furthermore, an association between liver enzymes and carotid atherosclerosis was obtained, suggesting a potentially relation between ALT and GGT with CIMT (18).

Visceral adipose tissue inflammation, insulin resistance, atherogenic dyslipidemia, oxidative stress and genetic factors seem to be the major contributors to NAFLD, MetS and atherosclerosis. Visceral adipose tissue can secrete pro-inflammatory cytokines, adipokines and hormones causing chronic low-grade inflammation and insulin resistance that, in turn, affect atherosclerosis and CAD risk factors (19). Insulin resistance promotes atherogenic dyslipidemia, which is strongly linked to CAD (20), and fatty acid accumulation in the liver, resulting in increased β-oxidation and oxidative stress (21). On the other hand, increased mitochondrial fat oxidation produces reactive oxygen species (ROS) and upregulates the nuclear factor kappa-B (NF-κB), which activates the transcription of several pro-inflammatory genes and the production of pro-inflammatory cytokines (TNF-α, IL-6 and IL-8) (22). Therefore, oxidative stress appears to be important in both the early and later stages of the atherosclerotic process. On the other hand, common genetic variants are known to influence on the risk of NAFLD (23). Whether the association between these genes and NAFLD could impact on the risk of developing CVD remains elusive. Therefore, accumulating evidence indicates that CVD is a growing cause of morbidity and mortality in patients with NAFLD (24). Important implications for screening and surveillance strategies are derived from this association. To deepen in the increased risk of CVD in patients with NAFLD is probably the best strategy to improve the prognosis of these patients.

These data should be interpreted with caution. First, the diagnosis of NAFLD is mainly based on US, which shows a limited capacity in the diagnosis because is an explorer-dependent technique and only detects steatosis when the fat is higher than 33 % in liver biopsy. However, the two studies included with liver biopsy showed a strong relationship between NAFLD and subclinical atherosclerosis (O.R. 2.82 *vs.* 4.41). Second, we selected studies with pathological CIMT and presence of carotid plaques as end-points because are the methods most widely used. There are more diagnostic criteria of subclinical atherosclerosis, such as lipid and glicidic biomarkers, ultrasound and computerized-tomography markers of endothelial dysfunction or genetic factors (25). However, they have shown worse reproducibility. Third, it is thought that type 2 diabetes mellitus (T2DM) is the main reason to increase vascular disease in NAFLD. We took into account this aspect and up to eight studies showed similar distribution of T2DM, ranging from all patients with T2DM to none. Interestingly, all studies showed similar results. Furthermore, there are more published studies in which T2DM is similarly distributed in NAFLD and non-NAFLD patients with vascular disease. Bonapace et al. included all patients with T2DM and the conclusion was NAFLD (*versus* non-NAFLD) was associated with left ventricular diastolic dysfunction (other diagnostic criteria of subclinical atherosclerosis) (26). Assy et al. did not find difference between NAFLD and non-NAFLD patients, according to T2DM, and concluded that NAFLD increased the risk of atherosclerosis, evaluated by coronary computed tomography (27).

In conclusion, our results provide new evidences of the relationship between non-alcoholic fatty liver disease and cardiovascular disease. Accordingly, we should be alert about an increased risk of coronary artery disease in subjects with non-alcoholic fatty liver disease and to be more aggressive in the searching of primary prevention with the performance of tests of detection of subclinical atherosclerosis. The right management of this kind of patients will enable to modify the natural history both liver and cardiovascular disease.

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