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Review Article

Nonalcoholic fatty liver disease is associated with coronary artery calcification: A systematic review and meta-analysis

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ABSTRACT

Background: Nonalcoholic fatty liver disease (NAFLD) is associated increased cardiovascular events and mortality. Coronary artery calcium scanning (CAC) is the robust predictor of coronary events in the asymptomatic individuals. Several recent studies have investigated the association between NAFLD and this surrogate marker. Thus, we conducted a systematic review and meta-analysis to better characterize the association between NAFLD and CAC.

Methods: MEDLINE and EMBASE were searched through May 2016. Primary outcome was the association between NAFLD and CAC. Pooled odds ratio (OR) and 95% confidence interval (CI) from multivariable-adjusted estimates were calculated using a random-effects model. The between-study heterogeneity of effect-size was quantified using the Q statistic and I^2.

Results: Data were extracted from 16 studies (all cross-sectional studies) involving 16,433 NAFLD patients and 41,717 controls. NAFLD is significantly associated with CAC score >0 and CAC score >100 with pooled OR of 1.41 (95%CI 1.26–1.57, $P_{heterogeneity} = 0.07$, $I^2 = 66\%$) and 1.24 (95%CI 1.02–1.52, $P_{heterogeneity} = 0.10$, $I^2 = 42\%$).

Conclusions: NAFLD is associated with increased coronary artery calcification independent of traditional risk factors. The assessment of coronary artery calcium may be useful in identifying NAFLD patients at risk of future cardiovascular events.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease with the global prevalence of 25% [1]. It ranges from simple steatosis to nonalcoholic steatohepatitis (NASH) that could progress to cirrhosis and hepatocellular carcinoma [2,3]. Metabolic comorbidities including insulin resistance, obesity and hyperlipidemia could themselves increase the risk of cardiovascular disease in patients with NAFLD without surprise [4]. The role of NAFLD as an independent risk for cardiovascular disease has become topic of interest. Growing body of evidence suggests that the presence of fatty liver is associated with greater cardiovascular risks in both structural and functional abnormalities independent of traditional cardiometabolic risk factors [5–8]. Recent meta-analysis also supported these findings that NAFLD is a strong independent predictor of cardiovascular disease [9].

Coronary artery calcification (CAC) is the well-established non-invasive surrogate index of prevalent coronary artery disease that represents the atherosclerotic burden in arterial beds. It is correlated strongly with the extent of atherosclerosis, the incident of coronary heart disease and long-term mortality independent of conventional risk factors [10–13] and the use of CAC scores may improve cardiovascular risk prediction in asymptomatic individuals [14].

Several recent studies have investigated the association between NAFLD and CAC. Therefore, to better characterize this association, we conducted a systematic review and meta-analysis of all published observational studies regarding the association of

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NAFLD and CAC after adjustment to other known risk factors for cardiovascular disease.

2. Methods

This systematic review and meta-analysis was conducted and reported according to the Meta-analysis Of Observational Studies in Epidemiology statement [15] and was registered in PROSPERO (registration number: CRD42015029696).

2.1. Search strategy

Two authors (SU and VJ) independently searched published studies indexed in PubMed/MEDLINE and EMBASE databases from inception to May 2016 using the search strategy that comprised terms for NAFLD and coronary calcium as detailed in Item S1 in Supplementary material without language restriction. References of selected retrieved articles were also manually reviewed.

2.2. Eligibility criteria

Our inclusion criteria were (i) published observational studies investigating NAFLD and CAC in adult participants, (ii) multivariable-adjusted estimates were provided, (iii) participants without NAFLD were used as a reference group, (iv) NAFLD was diagnosed based on the detection of hepatic steatosis by imaging studies including ultrasonography (USG), computed tomography (CT) and magnetic resonance imaging with the exclusion of other causes of hepatic steatosis and significant alcohol consumption based on each study's definition, (v) Coronary calcium score was measured by cardiac CT scan using Agatston's method [16]. To assess the quality of all studies, review articles, case reports, abstracts, and unpublished studies were excluded.

Two authors (SU and VJ) independently reviewed titles and abstracts of all citations that were identified. After all abstracts were reviewed, data comparisons between the two investigators were conducted to ensure completeness and reliability. The inclusion criteria were independently applied to all identified studies. Differing decisions were resolved by consensus between the two authors.

Quality of each study was independently evaluated by two authors (SU and VJ) using the Newcastle–Ottawa quality assessment scale which assessed each study in three areas: (i) the selection of the study groups; (ii) the comparability of the groups; and (iii) the ascertainment of the exposure or outcome of interest for case–control or cohort studies respectively [17]. Discrepant opinions between authors were resolved by consensus.

2.3. Data extraction

Full-text versions of potentially relevant papers identified in the initial screening were retrieved. If multiple articles from the same study were found, only the article with the most complete data was included. Data concerning author, year of publication, study design, study location, participant characteristics, diagnostic method of NAFLD, CAC measurement, confounder adjustment, and quality assessment were independently extracted by two authors. We contacted the authors of the primary reports to request any unpublished data. If the authors did not reply, we used the available data for our analyses.

2.4. Statistical analysis

Adjusted point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird. For studies with several multivariable-adjusted estimates, we extracted those reflecting the greatest degree of control for potential confounders. In light of the high likelihood of between-study variance, random-effects model was used. Sensitivity analysis was performed to evaluate the robustness of results, in which pooled estimates were computed omitting one study in each turn. The heterogeneity of effect size estimates across these studies was quantified using the Q statistic, its p-value, and I^2 ($P < 0.10$ was considered significant). A value of I^2 of 0–25% indicates insignificant heterogeneity, 26–50% low heterogeneity, 51–75% moderate heterogeneity and 76–100% high heterogeneity [18]. Publication bias was assessed using funnel plot, Egger's regression test and the trim and fill methods [19]. Data analysis was performed using Comprehensive Meta-Analysis 3.3 software from Biostat, Inc.

3. Results

The initial search yielded 291 articles; 268 articles were excluded based on title and abstract review. A total of 23 articles underwent full-length review. Seven articles were excluded (2 articles were not observational studies, 2 articles had no control group, and 3 articles did not report outcome of interest). Sixteen observational studies (all cross-sectional studies [20–35]) involving 16,433 NAFLD patients and 41,717 controls were included in the meta-analysis. Item S2 outlines the search methodology and selection process. Table 1 describes the detailed characteristics and quality assessment of included studies.

3.1. Effects of NAFLD on CAC score

All the included studies assessed the effect of NAFLD on CAC score. In the group with NAFLD compared with the group without NAFLD, the pooled OR for CAC score >0 was 1.41 (95%CI 1.26–1.57, $P_{heterogeneity} = 0.07$, $I^2 = 66\%$) from 12 studies [22,23,25,27–35] (Fig. 1) and the pooled OR for CAC >100 was 1.24 (95%CI 1.02–1.52, $P_{heterogeneity} = 0.10$, $I^2 = 42\%$) from 8 studies [20,24,21,31,26,22,32,35] (Fig. 2). In order to assess the stability of the results of the current meta-analyses, we performed a one-study removed sensitivity analysis. Statistically similar results were obtained after sequentially excluding each study in both the studies of CAC score >0 (Item S3) and the studies of CAC score >100 (Item S4), suggesting the results were robust.

3.2. Subgroup analysis

We stratified the odds of CAC score >0 based on participants' gender. The OR of CAC score >0 in NAFLD patients was not significantly difference between men (pooled OR = 1.27, 95%CI 1.11–1.45, $P_{heterogeneity} = 0.17$, $I^2 = 36\%$) and women (pooled OR = 1.64, 95%CI 1.32–2.03, $P_{heterogeneity} = 0.29$, $I^2 = 20\%$) compared with non-NAFLD subjects ($P_{sex\ difference} = 0.09$) (Fig. 3). The studies were too small to compare the gender difference on the odds of CAC score >100.

3.3. Evaluation of publication bias

To investigate potential publication bias, we examined the contour-enhanced funnel plot of the included studies that assessed OR of CAC score >0 (Item S5). The vertical axis represents study size (standard error by log odds ratio) while the horizontal axis represents effect size (log odds ratio). For assessing the studies for OR of CAC score >0, publication bias is present as there are more studies that favor positive log odds ratio (positive results) and P-value for Egger's regression test is significant ($P < 0.01$). For assessing the studies for OR of CAC score >100 (Item S6), the plot excludes bias since there is symmetrical distribution of studies on both sides of the mean. The Egger's test was non-significant ($P = 0.62$). Using the

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