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Original Article

Association between nonalcoholic fatty liver disease and carotid atherosclerosis: a meta-analysis

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Abstract: Objective: We carried out a meta-analysis about non-alcoholic fatty liver disease, carotid artery intima-media thickness and carotid artery plaque to explore the association between nonalcoholic fatty liver disease (NAFLD) and carotid atherosclerosis. Methods: We searched for case-control studies about the relationship between NAFLD and carotid intima-media thick (IMT) published from 2004 to 2014 according to inclusion and exclusion criteria and extracted the relevant data. Statistical analysis was processed by RevMan 5.2 software. Results: 9 studies were involved totally, including 2446 subjects (925 patients and 1521 controls). We found that there was a significant heterogeneity between NAFLD and carotid IMT. By the random effects model we calculated and combined the mean value of carotid IMT. The mean difference was 0.16 mm with 95% confidence interval (0.11, 0.21). Studies showed that there was also heterogeneity between carotid artery plaque and NAFLD. By the random effects model the calculated and combined OR value was 3.73 with 95% confidence interval (2.42, 5.74). The publication bias of the included studies did not exist. Conclusion: The IMT in NAFLD patients increased 0.16 mm compared with the control group, and risk of carotid plaque was 3.73 times than that of the controls. It is necessary for NAFLD patients to carry out routine carotid ultrasound detection to predict the occurrence of carotid atherosclerosis and assess the risk of cardiovascular disease.

Keywords: Non-alcoholic fatty liver disease, carotid artery, atherosclerosis, carotid intima-media thickness, meta-analysis

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the liver disease characterized by excessive accumulation of fat, which is caused by the factors excepting of alcohol and other specific-liver-damage factors [1]. In Europe and America, the prevalence of NAFLD was 20-30% [2]; in 2005, the incidence of adult NAFLD was 17.3% in Shanghai [3]. NAFLD is closely related with abdominal obesity, hyperlipidemia and type 2 diabetes. Several epidemiological investigations have shown that cardiovascular disease is the leading cause of death in patients with NAFLD [4-5]; the mortality rate is much higher than that in non-NAFLD patients, and the more severe NAFLD severity, the higher cardiovascular mortality [6].

Carotid intima-media thickness (IMT) is one of the subclinical markers of atherosclerosis, and is closely related to coronary heart disease [7]. IMT can be measured by noninvasive carotid artery ultrasound; it can clear the presence of carotid atherosclerotic plaque and can be used to evaluate the risk of cardiovascular disease [8]. In recent years, researchers have found that, compared with non-NAFLD patients, average IMT of NAFLD patients was significantly increased, and this relationship was independent of classical cardiovascular risk factors [9], indicating that NAFLD may play a promoting role in early atherosclerosis.

However, in independent studies, mean IMT value of NAFLD patients ranged from 0. 64 ± 0.1 mm to 1.18 ± 0.14 mm, with great differences [10-18]. Therefore, Whether IMT is suitable for screening the risk of cardiovascular disease in patients with NAFLD has become questionable. In this study, Meta-analysis method was used to evaluate the relationships between NAFLD and mean IMT value and increased carotid artery plaque, in order to

Table 1. The characteristics of included studies

Authors	Publication Year	Sex	Case/Control	Case	Control	Case	Control
Aygun	2008		40/40	0.65±0.10	0.544±0.067	11	3
Brea	2005		40/40	0.70±0.20	0.54±0.13	20	10
Fracanzani	2008		125/250	0.89±0.26	0.64±0.14	26	15
Kang	2012		320/313	0.79±0.18	0.73±0.13	109	59
Mishra	2013		101/544	0.592±0.109	0.49±0.132	20	12
Mohammadi	2011		84/65	0.64±0.096	0.55±0.075	-	-
Ramilli	2009		90/64	0.84±0.10	0.72±0.10	52	24
Targher	2004		40/45	1.18±0.14	0.94±0.12	-	-
Targher	2006		85/160	1.14±0.20	0.82±0.10	59	55

obtain the evidence for the relationship between NAFLD and cardiovascular disease.

Materials and methods

Searching strategy

We used the computer to retrieve references on the relationship between NAFLD and IMT from MEDLINE, EMBASE, The Cochrane Library, Medical Network, CNKI and other literature databases. Searching terms included the following: non-alcoholic fatty liver fatty liver; carotid atherosclerosis or carotid plaque or IMT.

Inclusion and exclusion criteria for literatures

Literature inclusion criteria: (1) The case concerned the relationship between NAFLD and IMT-control studies; (2) The group classification standard was based on whether the patients were NAFLD and the subjects were adults; (3) The amount of sample cases, mean IMT values, detected number of carotid plaque and other relevant indicators both in case groups and control groups can be extracted; (4) Diagnostic criteria and the determination of relevant indicators in case group and control group should be consistent; (5) Statistical methods were correct in literatures.

Literature exclusion criteria: (1) The research method was non- case-control study; (2) The objectives of studies were special populations, such as: children, diabetes, identified liver disease, liver transplant patients, etc; (3) The patients were groups by liver enzyme levels, histological grade, gender and other indicators and lacked relevant experimental data in NAFLD group; (4) We took only one literature from repeated published literatures and the identical results from different literatures; (5) Experimental data were contradictory and statistical methods were error in literatures.

Data extraction

We extract the relevant data: first author, publication year, sample size, the mean IMT value of carotid plaque (Carotid plaque, CP) of the patients, average age, gender, body mass index, blood pressure, blood glucose, lipids, liver enzymes both in the case group and control group. Measurement data were expressed as mean ± standard deviation.

Statistical analysis

We carried out the heterogeneity test for the included literatures at first and calculated I^2. When I^2 value was 0-25%, it was for no heterogeneity, 26-50% for mild heterogeneity, 51-75% for moderate heterogeneity, and 76%-100% for the high degree of heterogeneity [19]. According to this standard, when I^2 was less than 50%, we took the fixed effect model to calculate and merge for the included studies. While I^2 was more than 50%, we used random-effects model. We conducted Begg's inspection and Egger's test to evaluate publication bias and draw the funnel plot. Meta-analysis software -Review Manager 5.2 were conducted in all computing applications. $P < 0.05$ was considered for difference and statistical significance.

Results

Basic information about literatures

114 relevant literatures were found by searching and a total of nine studies were included [10-18] with 2446 cases of cumulative sample size, 925 cases in patient group and 1521 cases in the control group (see **Table 1**). Nine

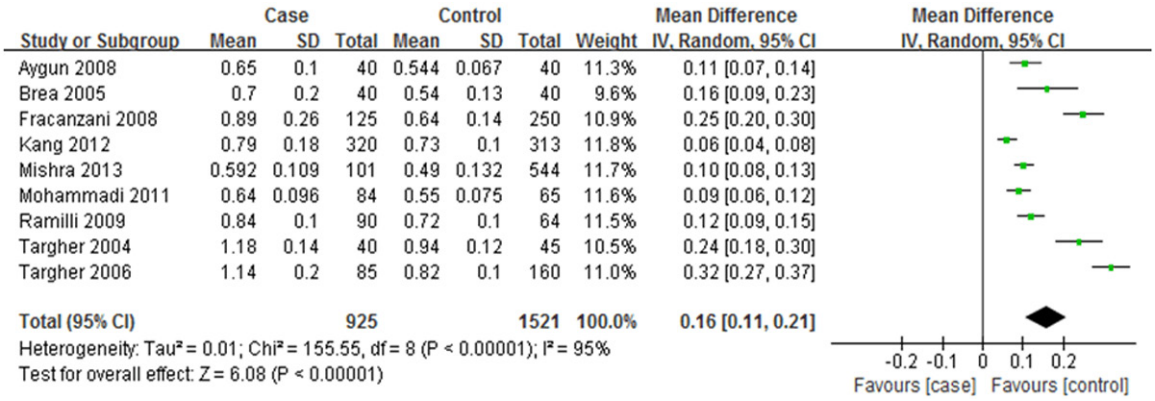

Figure 1. Forest plots of association of NAFLD with IMT between two groups.

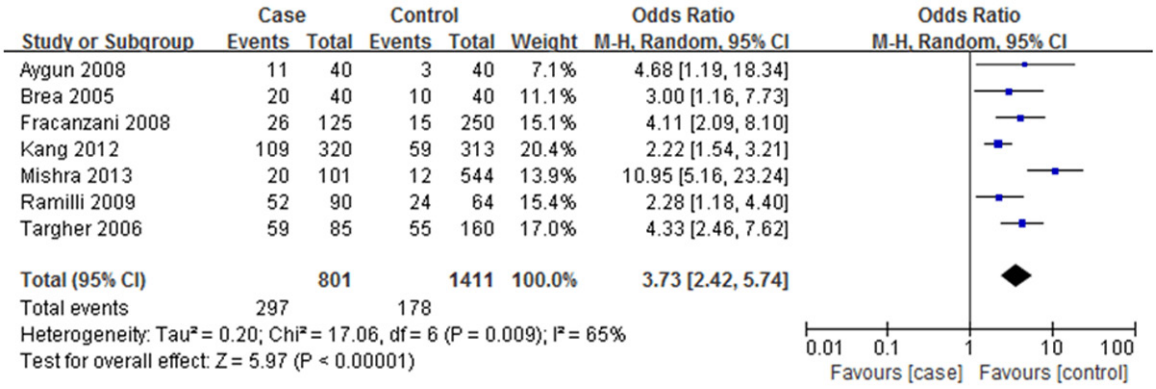

Figure 2. Forest plots of association of NAFLD with CP between two groups.

included literatures were all hospital population-based case-control studies. IMT data were complete in case group and the control group. We got the number of CP patients in seven literatures (**Table 1**). Carotid IMT values were measured by B-mode ultrasound in each literature, and bilateral carotid arteries were all measured.

Association of NAFLD with IMT

Heterogeneity test was conducted for the seven included studies, the results showed that I^2 was 96% with P < 0.00001, indicating that there was a high degree of heterogeneity among the results. The calculated and combined statistical results by random effects model showed that: the averaged mean- IMT difference was 0.16 mm with 95% confidence interval [0.11, 0.21] (**Figure 1**).

Association of NAFLD with carotid plaque (CP)

We carried out the heterogeneity test for the number of CP patients in the included seven literatures and the results showed that I^2 was 65% and P was 0.009, indicating that there was heterogeneity among the results. The calculated and combined statistical results by random effects model showed that: the combined OR value was 3.73, and 95% CI was [2.42, 5.47], indicating that risk of CP for NAFLD patients was 3.73 times than that of non-NAFLD patients (**Figure 2**).

Publication bias

Begg's rank correlation and Egger linear regression method were used to analyze the publication bias for the nine included studies. We also draw the funnel plot that illustrated the nine literatures were all in the confidence interval and appeared roughly symmetrical distribution (**Figure 3**), indicating that there was no publication bias in the included studies.

Discussion

In recent years, some prospective cohort studies show that the increased incidence of coro-

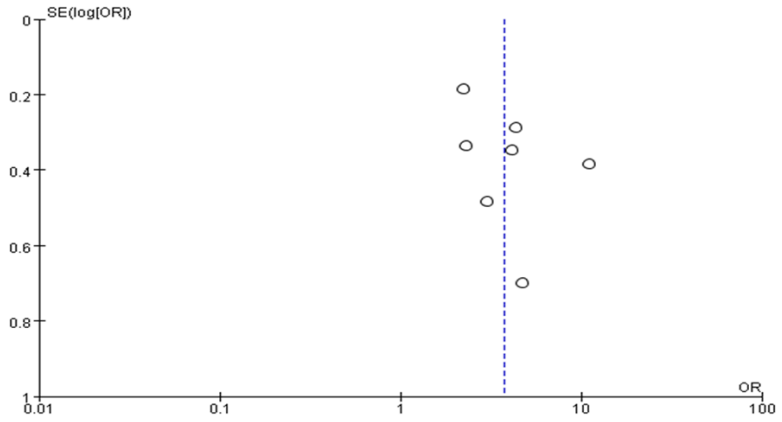

Figure 3. Funnel plot for publication bias.

nary heart disease is associated with NAFLD, and this association is independent of classic risk factors for coronary heart disease [20-22]. This provides epidemiological evidence for NAFLD promoting cardiovascular disease.

Bloodstream regulated vessel diastolic dysfunction is also one subclinical markers of atherosclerosis; studies have shown that it has a strong correlation with NAFLD, and the heavier histological severity of NAFLD (simple steatosis, necrotic inflammation, fibrosis), the more severe bloodstream regulated vessel diastolic dysfunction [23, 24]. Although previous studies have shown that NAFLD also has some relevance with IMT and CP, due to the greatly varied IMT measurements in different studies, researchers have not reach an agreement on the issue of whether IMT is suitable for screening cardiovascular disease risk in patients with NAFLD.

Meta-analysis of seven studies on the relationship between NAFLD and IMT was conducted in this study; the results showed that NAFLD can promote the increase of IMT; it also illustrated that the increased IMT was related with the severity of NAFLD. A Meta-analysis of prospective studies on GGT and cardiovascular events [25] showed that elevated GGT levels can increase the incidence of cardiovascular events. This conclusion can be used as an explanation for the higher incidence of cardiovascular events in patients with NAFLD than in non-NAFLD patients. Meta-analysis on the relationship between NAFLD and CP was also carried out in this paper, which directly explained that NAFLD patients had a higher incidence of CP, providing statistical evidence for NAFLD promoting carotid atherosclerosis.

The nine studies included in this paper were case-control studies on the relationship between adult NAFLD and IMT; the sample size of each study is not large (from 80 to 645), and the matching mode in the control group, IMT value definition and CP definition were different. Corresponding averages of IMT in case and control groups varied in each study. The forest plot of meta-analysis for IMT and NAFLD showed that the coincidence degree of confidence interval was small.

The heterogeneity was from experimental methods and background. The overall heterogeneity of these nine studies was up to 96%, including clinical heterogeneity, methodological heterogeneity and statistical heterogeneity. While each study lacks the raw data of liver enzyme levels or liver biopsy and grouping-related information by severity, so the accordingly subgroup analysis cannot be performed.

In addition, a meta-analysis for the relationship between NAFLD and CP was also conducted; there was heterogeneity among the included seven studies; the risk of CP in NAFLD patients was 3.73 times of that in non-NAFLD patients, suggesting that NAFLD was strongly related with carotid atherosclerosis and indirectly indicating that NAFLD was related with the increased incidence of cardiovascular disease.

In conclusion, there is association of NAFLD with carotid atherosclerosis, therefore, routine carotid ultrasonography is recommend for them to help predict carotid atherosclerosis occurrence and assess their risk of cardiovascular disease, thus achieving timely intervention to benefit NAFLD patients in the prevention of cardiovascular disease.

Disclosure of conflict of interest

None.

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